Optimising Individual Treatment Regimes and Patient Outcomes through the Use of Patient-Reported Toxicity Assessments in Patients treated with Pelvic Radiotherapy

Alexandra Jane Gilbert

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The candidate confirms that the work submitted is her own, except where the work which as formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapters 1 and 2 have sections taken from ‘Gilbert A, Sebag-Montefiore D, Davidson S, Velikova G. Use of patient reported outcomes for symptom and health related quality of life assessment in clinical practice. Gynecol Oncol. 2014 Nov 28. pii: S0090-8258(14)01536-4.’ I completed the literature review and authored the paper. Comments on the article were provided by my three supervisors prior to submission.

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Abstract

The primary objectives of this thesis are to develop a systematic method for patients to self-report pelvic radiotherapy adverse events (AE) using electronically collected patient reported outcomes (PROs) in clinical practice and to evaluate patient-reported toxicity in association with radiotherapy dosimetric data and clinical factors.

Before testing the research objectives in two observational studies, important practical and methodological issues were addressed. Analysis from systematic and literature reviews, content analysis of three validated PRO systems and interviews with health professionals found the European-Organisation-for-Research-and-Treatment-of-Cancer-Quality-of-Life-Questionnaires (EORTC-QLQ) C30 and cancer-specific modules to have the most effective coverage of acute and late AE for patient treated with radiotherapy for anal, rectal, endometrial and cervical cancer. Qualitative analysis of patient cognitive interviews found the EORTC-QLQ system was acceptable to patients and revealed discrepancies in toxicity grading between patient and clinician (using the Common-Terminology-Criteria-of-Adverse-Events (CTCAE)) might be due to inherent differences in the grading descriptions between the scoring systems. Electronic methods for collection and presentation of PRO data were developed alongside technology to improve clinical data capture from electronic health records (EHR). A pilot study of 31 patients proved it was feasible to collect electronic and paper PRO data and integrate results into individual EHRs. A protocol for organ at risk (OAR) contouring and methods used for dose-volume-histogram (DVH) export were developed.

The cross sectional (n=315) and prospective studies (n=129) found bowel urgency and sexual dysfunction to be the late AE most commonly reported by patients. The cross sectional study piloted the application of principal component analysis to describe DVH data from patients treated with multiple radiation techniques and demonstrated associations between PRO late toxicity and dosimetric and clinical data. The prospective study interim analysis found resolution of many treatment-related symptoms by six-months and provided encouraging findings for the use of longitudinal PRO collection in routine practice.

Abbreviations and Definitions

Acute/ early AE	Side effects during treatment and present in the first 3 months post completion of radiotherapy treatment
Adjuvant	Applied after initial treatment for cancer
AE	Adverse events
Chronic/late AE	Side effects present greater than 3 months post completion of radiotherapy treatment
Concurrent	Treatment given at the same time as another treatment
EORTC	European Organization for Research and Treatment of Cancer
HRQOL	Health related quality of life
IMRT	Intensity Modulated Radiotherapy
NCI	National Cancer Institute
NIHR	National Institute of Health Research
OAR	Organs at risk
Palliative	Not for curative treatment
PCORG	Patient centred outcomes research group
PPM	Patient pathway manager (electronic health records)
PRO	Patient reported outcome
RTOG/EORTC	Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer
VMAT	Volume Modulated Arc Therapy

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Chapter 1 Introduction and overview of the project

1.1 Introduction

1.1.1 Radiotherapy as a curative treatment

Radiotherapy forms part of the management of around 40% of patients cured of their cancer with around 65,000 patients treated with curative (radical) radiotherapy each year in England(1). Radiotherapy may be used with curative potential in patients with loco-regional disease as a sole treatment modality or in combination with other treatments such as chemotherapy and surgery. Progress in cancer treatments have led to improvements in cancer survival, however, this has also led to an increasing number of patients with significant long term adverse events or toxicities as a result of their cancer treatment(2). Long-term side effects following radiotherapy may not manifest until many months or years following treatment. Symptomatic adverse events may arise when the normal tissue adjacent to the tumour is irradiated as a consequence of delivering sufficient dose to the tumour. Subsequently, the maximum tolerated dose for radiation treatments is usually limited by the tolerance of the normal tissues, or organs at risk, to the late effects rather than the acute side effects of the treatment.

Modern external beam radiotherapy (EBRT) techniques were introduced in the 1950s and enabled patients to be treated using parallel opposing field techniques to improve the homogeneity of dose delivered to the tumour. Two-dimensional (2D) x-ray images enabled visualisation of the bony landmarks. However, because of limited capabilities to image the soft tissue of the tumour a wide area or margin around the tumour was treated, with a large area of the normal tissue adjacent to the tumour receiving the prescribed target dose. Advances in radiotherapy technology have led to changes in radiation treatment delivery. Computed tomography (CT) based diagnosis and radiotherapy planning, developed throughout the 1980s and 1990s, enabled more accurate tumour delineation and facilitated treatment planning using three-dimensional (3D), multiple field techniques (conformal radiotherapy) to ensure effective dose delivery to the tumour or ‘target volume’. CT planning allowed more accurate visualisation of soft tissue enabling accurate delineation of the visible tumour (gross tumour volume – GTV), the incorporation of margins around the visible tumour to include areas of potential local and regional tumour spread (clinical target volume – CTV) and additional margins to allow for movement of the tumour and normal tissue (internal target volume – ITV) and variations in patient positioning between treatments (planning target volume – PTV) (Figure 1.1). Further advances have led to the

introduction of techniques such as Intensity Modulated Radiotherapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT), a type of IMRT, to routine practice(3). These techniques aim to improve the precision of radiation dose delivered to the tumour, enabling the delivery of near uniform doses to the target volume (Figure 1.1). Whilst these techniques reduce the volume of normal tissue exposed to high doses of irradiation an important consequence is that more tissues are exposed to a low dose of irradiation than in 3D conformal treatments. This has an unknown impact on late toxicity.

Along with the technological advances, radiotherapy is increasingly used in combination with other treatment modalities such as surgery and chemotherapy. These different treatment combinations are used to improve cancer-related outcomes however they are known to increase the risk of side effects in both the short and long term and may be associated with considerable impairment in quality of life (4-7). Understanding the complex balance between the possible increase in toxicity through combining radiation with systemic therapies or dose escalation and potentially reducing toxicity through improving dose distributions, using techniques such as IMRT or VMAT, is increasingly relevant as the use of these techniques is becoming more widespread in clinical practice. As yet this important area remains under researched(8).

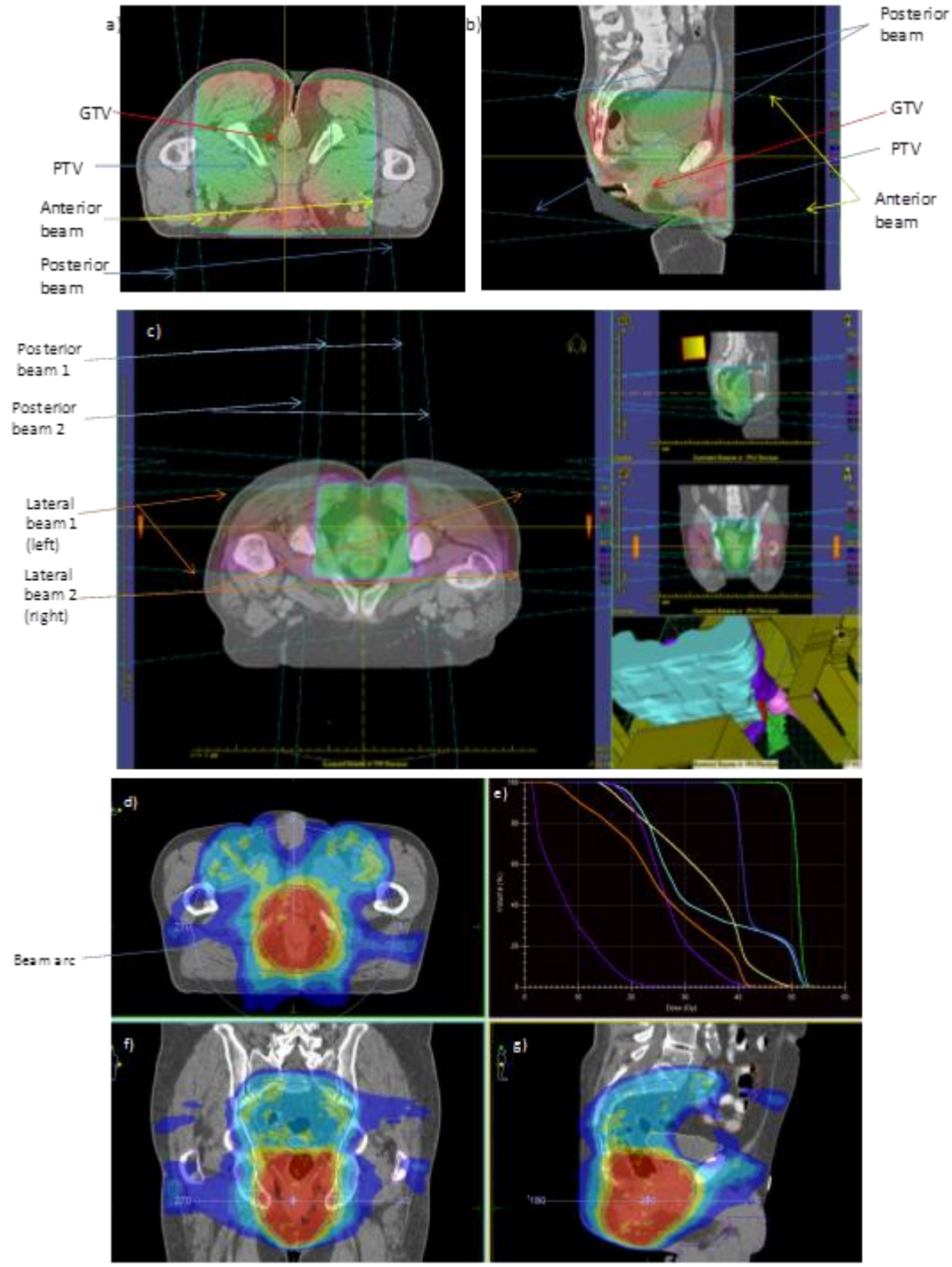


Figure 1-1 Treatment planning example

a-b: Example of a 3D CT planning scan in a male anal cancer patient treated with (phase 1) a parallel opposed pair of beams in the prone position (face down). a) Axial and b) Sagittal CT images showing treatment dose delivery across all tissues between the two opposing beams (anterior and posterior). GTV and PTV labelled. c) Example of a female rectal cancer patient treated with four-beam technique in a prone position. Image show dose coverage to a 'box' region covering the PTV. d-f) Example of a male patient treated with VMAT for anal cancer in a supine position. d) Axial image showing the beam arc. Images d, f (coronal) and g (sagittal) show the treatment dose region highlighted in red/orange with low doses shown in the green/blue areas showing the ability to significant reduce the high dose area treated with IMRT. e) Shows the DVH calculated for this patient and illustrates the graphical representation of dose and volume treated (targets and organs at risk).

1.1.2 Pelvic Radiotherapy and incidence of pelvic malignancies

In the UK, an estimated 17,000 patients are treated annually with radical radiotherapy for pelvic cancer, more than in any other tumour site(9, 10). The proximity of many normal tissues in the pelvis to the primary tumour or lymph node regions can lead to multiple long-term toxicities. Despite a relative paucity of research in some areas, findings suggest patients report more gastrointestinal (GI) and urinary symptoms as well as sexual dysfunction following treatment(10, 11). Symptoms may persist for many years and may adversely affect the quality of life of survivors(12-14). The prevalence rates of adverse events following pelvic radiotherapy vary widely in the literature with the diversity in part attributable to differences in methodological approaches to data collection including differences in the assessment and measurement of adverse events.

The main cancer sites treated in the pelvis are prostate, rectal, endometrial, cervical, anal, bladder, penile, vaginal and vulval cancers. Prostate cancer is the commonest site for EBRT within the pelvis, however, radiotherapy related toxicity and dose-related adverse events have already be extensively studied and therefore this cancer site was not included in the current study(15). We decided to select two GI cancers, rectal and anal and two gynaecological cancers, endometrial and cervical cancer for this project. EBRT and concurrent chemotherapy is the main stay of treatment for patients treated with anal and locally advanced cervical cancer leading to potentially worse toxicity. For endometrial and rectal cancer patients, EBRT is used in combination with surgery complicating the adverse event profile further. Irradiation of the four tumour sites included in this project involves coverage of the involved lymph node regions as well as the primary tumour. This leads to a more extensive radiation field and therefore a greater volume of normal tissue treated than for prostate EBRT. Penile, vaginal and vulval cancers are rare and were therefore not included due to the relatively small numbers treated annually in our institution. The following sections briefly describe the prevalence and treatment methods delivered for each cancer site.

1.1.2.1 Rectal cancer

Rectal cancer is diagnosed in over 14000 people annually in the United Kingdom (16). Surgery is the key procedure in curative treatment. Improvements in surgical techniques have reduced loco-regional failure rates(17). Several surgical procedures are used in rectal cancer management – anterior resection (AR), abdominoperineal excision (APE), or Hartmann’s procedure (HP). APR and, in most cases, HP will lead to

permanent stoma formation. AR is a sphincter preserving surgery, although temporary stomas may be required to protect the anastomosis.

Whilst the addition of preoperative (chemo)radiotherapy has reduced the loco-regional failure rates further, studies have found a minimal impact on overall survival with a potential increase in toxicity(18, 19). In Leeds Cancer Centre, patients with resectable disease (T1-3 with a predicted clear circumferential resection margin (CRM)) are offered neoadjuvant short course radiotherapy (25Gy in 5 fractions over 5 days) followed by surgery within 7-10 days. Long course chemoradiotherapy (45Gy in 25 fractions over 5-6 weeks with either capecitabine on the days of radiotherapy treatment or 5-flurouracil (5FU) weeks 1 and 5) is offered to patients whose CRM is predicted to be threatened with the aim of downsizing the tumour prior to resection. Surgery in this case is delayed for six weeks following an MRI scan to assess response.

1.1.2.2 Endometrial cancer

Endometrial cancer is the commonest gynaecological malignancy in the UK with around 8500 cases diagnosed in 2011(16). Surgery is the main stay of treatment and patients are treated with radical or total hysterectomy with bilateral sapingo-oophrectomy (BSO) with or without pelvic lymphadenectomy depending on stage and grade of the tumour. EBRT (45Gy in 25 fractions over 32-34 days) may be used postoperatively to reduce local recurrence rates. It is recommended in patients with FIGO stage 1B or 2 tumours with serous/cell cell histology or grade 3 endometrioid histology and in all patients with stage 3 disease with or without vaginal brachytherapy.

The Post Operative Radiotherapy in Endometrial Carcinoma (PORTEC) randomised clinical trials (RCTs) have influenced and reduced the use of EBRT to high-risk patient groups. PORTEC-1 trial found a significant reduction in the rates of local regional recurrence with the addition of post-operative EBRT to standard surgical treatment of endometrial cancer, with an associated increase in patient-reported gastrointestinal and urinary toxicity(20, 21). As the majority of disease recurrences in PORTEC-1 were located in the vagina in patients whohad surgery alone, PORTEC-2 compared the efficacy of EBRT to vaginal brachytherapy to establish which treatment provided optimal local control without significant adverse events. The results found few vaginal recurrences in both treatment groups but an increase in acute and late gastrointestinal toxicity in the EBRT arm(22, 23). These findings have lead to a move towards treatment with vaginal brachytherapy alone in the intermediate risk group, with the consequence that fewer patients are treated with EBRT in clinical practice.

1.1.2.3 Cervical cancer

Patients with cervical cancer account for approximately 2% of all new cancers diagnosed in women in the UK, with 3000 new cases diagnosed in 2011(16). In patients with locally advanced disease, the addition of platinum-based chemotherapy to radiotherapy alone was found to improve overall survival and local and distant recurrence rates, with an associated increase in acute haematological and GI toxicity(24). Current practice recommends FIGO stage 2b-4 disease is treated with a combination of concurrent chemotherapy (weekly cisplatin) and EBRT (48Gy in 24 fractions over 32-34 days) followed by intracavity brachytherapy (ICBT) 21Gy in 3 fractions over 14 days (usually starting in week four of EBRT treatment). Recent clinical studies have evaluated the use of image-guided adaptive brachytherapy to improve dose optimisation and have found improvements in disease free survival and local control with associated reductions in toxicity(25, 26). A multi-centre international prospective clinical trial, EMBRACE, is evaluating these findings further(27).

1.1.2.4 Anal cancer

Anal cancer is more uncommon, although incidence is rising, with around 1200 cases diagnosed in the UK in 2011 (16, 28). A small minority of patients with very early anal margin cancer may be treated with local surgery. Otherwise, the standard of care in the UK is concurrent chemoradiotherapy (typically 50-54Gy in 25-28 fractions) with chemotherapy (Mitomycin (MMC) on day 1 and 5 and 5FU days 1-5 and 29-33). Recent RCTs have evaluated alternative treatment regimes but the outcomes have not altered the standard of care (29-31). A systematic review of efficacy and toxicity related to anal cancer treatment found poor reporting quality of radiation dose delivered, chemotherapy compliance rates and few studies reporting on late toxicity(32).

RTOG 0529 is the first multi-centre phase II trial evaluating the use of IMRT with concurrent MMC and 5FU in anal cancer treatment(33). Early results found significant reductions in acute haematological, GI and skin toxicity using IMRT compared to historical trials (RTOG 9811) using conventional radiotherapy techniques(33). Future trials are exploring alterations in radiotherapy dose and fractionation, stratifying by risk to reduce local regional failure rates (personal communication DSM).

1.2 Current reporting of adverse events in radiotherapy

The terms adverse events (AE), side effects and toxicity will be used interchangeably throughout this thesis. Adverse events are defined as '*An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or* procedure'(page1;(34)).

Acute radiotherapy AE are defined as side effects present during or up to three months post radiotherapy treatment. Late AE are those symptoms that continue to worsen (consequential effects) or manifest after a latent period greater than three months after radiotherapy(13). A uniform classification system for clinician reporting of late radiotherapy-related toxicity was initially proposed in 1995(35). By 2003 the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) morbidity criteria and the Late Effects on Normal Tissues–Subjective Objective Management and Analytic (LENT-SOMA) scale were incorporated into version 3 of the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 3)(36). More recently the CTCAE (now version 4) has been chosen through international consensus as the clinician-reported AE recording system of choice for all cancer clinical trials, including radiotherapy(9, 34, 37, 38).

This international consensus for clinician AE reporting was founded from concerns regarding a lack of clear standards for the clinical application of toxicity measurements and wide variation in the methods, completeness and frequency of toxicity reporting(39). This issue was also raised by the international committee, QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) in relation to the monitoring of AE following radiotherapy in clinical practice(40). The aim of the committee was to help clinicians and treatment planners to determine acceptable dose/volume constraints to minimise toxicity to OAR(40). QUANTEC highlighted two key deficiencies in the data available to accurately describe dose/volume constraints and relate this to toxicity outcomes; 1) The lack of data on the incidence of toxicity and uneven standards of reporting and 2) challenges to defining clinically relevant endpoints and the lack of a standardised toxicity grading system. One of the key recommendations was the inclusion of patient reported outcomes (PROs) in toxicity assessments alongside clinician-reporting in routine clinical practice.

1.3 Patient Reported Outcomes (PROs) in radiotherapy

In preparation for my PhD thesis I conducted and published a review on the "Use of patient-reported outcomes to measure symptoms and health related quality of life in the clinic" in *Gynecologic Oncology*(41). The key findings and recommendations originating from my paper are modified for the following sections 1.3 and 1.4.

Clinician reporting of patient's symptoms as a grade of toxicity has been the usual source of AE reporting in clinical trials and routine practice in all areas of medicine. However, clinician reporting of AE relies on the clinician's interpretation of AE and focuses on 'safety' issues rather than patient experiences(42). Clinicians have also routinely been found to under-report toxicity as compared to patients even within RCTs(43). Over the past decade in cancer clinical trials the research community has shifted to include patient reported outcomes (PROs), as a standard data source to capture patient's subjective experience, usually as a secondary endpoint(44). PROs are standardised, validated questionnaires that are completed by patients and measure a broad range of health-related constructs including symptom assessment, evaluation of function and health-related quality of life (HRQOL)(45). It is increasingly recognised that inclusion of validated PRO assessments within clinical trials can provide important data for clinicians to inform treatment decision-making. Within the clinical trial literature there are numerous examples of where clinical decision-making has been influenced by the outcomes of the PRO assessment(46).

Whilst a number of validated radiotherapy PRO instruments exist there is no consensus as to which is the best PRO instrument to use for radiotherapy AE reporting. A number of PROs have been adapted from the CTCAE to allow patients to self-report their AE and these have been introduced in clinical trials reporting. For example, the NCI commissioned a programme (PRO-CTCAE) to adapt the CTCAE grading into a format suitable for patients to self-report (Figure 1.2)(34).

CTCAE v4 Term	Grade 1	Grade 2	Grade 3	Grade 4
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated

Two PRO-CTCAE v1 items	Responses
What was the severity of your MOUTH OR THROAT SORES at their worst?	None/Mild/Moderate/Severe/Very Severe
How much did MOUTH OR THROAT SORES interfere with your usual activities?	Not at all/ A little bit/ Somewhat/Quite a bit/Very much

Figure 1-2: Example of NCI PRO-CTCAE item

The EORTC Quality of Life Questionnaires (EORTC-QLQ) are also used commonly in the cancer clinical trial setting including radiotherapy trials. Whilst the questionnaires were developed for patients to report on health related quality of life (HRQOL) increasingly the disease-specific modules in particular, which were developed to report on treatment- and disease-related symptoms, have been used as a surrogate for toxicity reporting (see figure 1.3). The PORTEC-1 trial in endometrial cancer described previously provides a clear example where the patient reported toxicity outcomes using the EORTC-QLQ system impacted on clinical decision-making(20, 21).

EORTC-QLQ EN24	Responses
When you felt the urge to move your bowels, did you have to hurry to get to the toilet?	Not at all/A little/Quite a bit/Very much

Figure 1-3: EORTC-QLQ EN24

1.4 Using PROs in clinical practice

In addition to their use in clinical trials, PROs have also been found to provide patient benefits when used in routine care. PROs may be used flexibly to achieve multiple objectives in clinical practice depending on the goal of the intervention(47). At an individual level, PRO data may be collected as a one off screening for AE or used as a method of monitoring changes in problems over time (47). Feeding back the PRO information in a structured format to the clinician can promote patient-centred care by highlighting an individual's concerns(48). Improvements in symptom or function monitoring, and patient-physician communication have also been found(48-50). At an organisational level, individual's PRO information may be collated and used within or across organisations to look at the impact of treatment on cohorts of patients and as a performance measure to assess quality of care(51). Although the research evidence for the benefits of using PROs in clinical practice is increasing, some results are conflicting and wider implementation has not been achieved.

Benefits of integrating PROs to measure symptoms and HRQOL in routine practice

Cancer treatment, including treatment for pelvic cancers, increasingly involves multiple treatment modalities used in combination. The combination of treatments aims to improve cancer outcomes without significantly increasing the toxicity experienced. The treatment modalities commonly used– surgery, radiotherapy and systemic therapy - are often managed by a different set of clinicians, who may or may not reside within the

same organisation. This organisational complexity, in addition to the multiple different PRO instruments available, creates an almost infinite range of possibilities of how to integrate PRO data collection in an organisation. However, widespread, systematic use of PRO data collection across specialities and organisations has the potential to significantly impact on the quality of information regarding acute and long-term AE despite organisational challenges.

The most extensive literature has been on the use of PRO assessments in the monitoring of AE and HRQOL associated with systemic treatments. Measuring the acute AE associated with systemic treatments such as chemotherapy provides the opportunity for regular collection of PRO data to inform dose reductions, treatment modification, supportive care and educational support based on symptom and quality of life (QOL) assessment(52). In radiotherapy and surgery, whilst patients experience acute side effects or complications from treatment, other AE may not manifest until months or years later and may cause greater problems(53). The integration of prospectively collected PROs into routine practice may provide consistency in long-term follow up between different clinicians and organisations for the long-term AE of radiotherapy and surgery, as well as chronic chemotherapy-induced symptoms such as fatigue and neuropathy. By using standardised and validated PRO tools and baseline assessments clinically important differences over time may be evaluated. This may allow empirical identification of AE in patients who may benefit from an active intervention in the short and long-term following treatment and allow cohort assessment of PRO data in association with treatment details to evaluate performance to improve future treatments(8, 54).

The inclusion of symptom and HRQOL PROs into routine care may offer additional benefits to the collection of clinician AE data. The CTCAE is often used in routine care in oncology to guide treatment decisions despite its development specifically for use in clinical trials(55). However, despite widespread availability of clinician-reported tools, such as the CTCAE, research into symptom reporting in both clinical practice and trials has found systematic under-reporting of symptoms by clinicians when compared to patients(56-58). When a clinician reports on a subjective symptom this requires clinical interpretation and then requires the clinician to decide on the severity of the problem. This may lead to poor inter-rater reliability and well as incomplete reporting of symptoms(55, 57). Other research has highlighted that most clinicians screen for side effects through history-taking rather than using formal tools(2). This inevitably leads to heterogeneity in the methods of reporting on the presence or absence of an AE. Clinical audit in our organisation has shown that this variability is dependent on the

organisation of the clinic and training of clinicians. Symptoms were recorded via dictation following the consultation and documented in letter (text) format but clinicians rarely referred to grades of symptom severity(59). This lack of systematic data collection through clinician reporting in routine practice has been highlighted as a barrier to future treatment optimisation(8, 39).

1.4.1.1 Benefits to patients and clinicians at an individual level:

The main focus of research into PRO implementation in clinical practice has been the improvement of patient care at an individual level. It was hypothesised that by asking patients to routinely complete questionnaires about their symptoms and level of functioning in a broad range of health constructs that this may improve the ability of patients to communicate concerns to inform the clinical consultation. The survey items may help provide patients with a different terminology and prompt patients about the potential side effects they may experience with aim of engaging patients more actively in their own care(52). Improvements in communication between physician and patient are the most commonly reported benefit of routine PRO collection. This was seen in 70% of 47 studies reviewed by Hayward et al.(60).

Table 1.1 provides an overview of RCTs in oncology evaluating improvements in individual patient care(48, 61-66). The RCTs show consistently that using PROs in daily oncology practice leads to improvements in patient-doctor communication with increased discussion of symptom and HRQOL issues. Some studies have also found reductions in distress and improvements in HRQOL through the use of PROs. However, the RCTs have consistently found no clear impact on decision-making or satisfaction with care. The results reflect the challenges often observed when conducting RCTs of complex interventions. The following sections evaluate these findings in more detail.

Table 1-1: Randomised controlled trials (RCTs) in oncology evaluating symptom and HRQOL based PROs in routine practice

AUTHORS	DESCRIPTION OF INTERVENTION PROCESS AND OUTCOMES	POSITIVE OUTCOMES	NO IMPACT	COMMENTS
McLachlan 2001 (27)	Patients (N=450) completed self-reported cancer needs (CNQ), HRQOL (EORTC-QLQ C30) and psychosocial information (BDI) using touch screen computers. (1) Intervention: 2/3 patients randomized to have PRO information fed back to clinical team with a coordinating nurse present to implement the referral pathway proposed following consultation or (2) Control: usual care. Primary outcome: Change from baseline psychological and information needs (from CNQ). Secondary outcomes: Other domains of CNQ, QOL, psychosocial functioning at 2 and 6 months and satisfaction with care (non-validated questionnaire) at 6 months	Patients with moderate to severe depression had significant benefit from intervention at 6months (p=0.001; secondary analysis). Patients endorsed touch screen computers.	No significant difference in primary and secondary outcomes.	No clinician training provided on the use of the PRO data. Patient satisfaction with care was high for all groups.
Detmar 2002 (26)	Routine HRQOL (EORTC-QLQ C30) screening (graphical paper report): Prospective randomized cross over trial. Patients (N=214) receiving palliative chemotherapy were randomized to (1) Intervention: completion of EORTC-QLQ C30 at 3 successive outpatient visits with results fed back to clinical team (2) Control: usual care. Clinicians switched to alternate arm of study mid way through study recruitment. Outcomes: Communication about HRQOL (content analysis of audio-recorded consultations); HRQOL, Satisfaction with care, patient management, physician awareness (COOP/WONCA),	Communication scores significantly improved in intervention arm (4.5 vs 3.7; p=0.01 effect size = 0.38). More patients in intervention group received counselling on how to manage health problems (23% vs 16%; p=0.05)	No differences in physicians' awareness (COOP/WONCA); Referral patterns or medication/test management; HRQOL scores; duration of consultation. Satisfaction with care was high in all groups.	All physicians and 87% of patients believed the intervention facilitated communication and expressed interest for continued use of intervention.
Velikova 2004 (5)	Routine HRQOL (EORTC-QLQ C30) and HADS assessment on touch screens +/- graphical paper feedback: N=286 patients randomized to (1) Intervention: completion of PRO measures with feedback; (2) Attention-control: completion of PRO measures no feedback; (3) Control: usual care for 3 consultations (over 6 months) Primary outcomes: HRQOL over time (FACT-G); physician-patient communication and clinical management (content analysis of audio-recorded consultations).	Improved HRQOL in intervention and attention-control vs control (p=0.006; SE = 2.84) and p=0.01). A larger proportion of patients in intervention arm had clinically meaningful improvement in HRQOL (NNT 4.2). Increased discussion of HRQOL issues in intervention arm (p=0.03).	No significant impact of intervention on patient management	Trial not primarily designed to look for difference between attention-control and control group.
Rosenbloom 2007 (28)	Routine HRQOL assessment (paper) followed by nurse-led interview. N=213 patients on chemotherapy randomized to (1) Intervention: HRQOL (FACT-G) completion followed by structured research nurse led interview fed back to treating nurse; (2) Assessment control: HRQOL with report fed back to treating nurse; (3) Control: usual care over 4 consultations (over 6 months). Primary outcome: FLIC; Brief-POMS-17; PSQ-III; clinical treatment changes		No significant differences between groups in HRQOL (FLIC), satisfaction (PSQ-III) or clinical treatment changes over time.	High QOL/PSQ scores reported at baseline (possible ceiling effect seen). Sensitivity of outcome measures questioned by authors.

Carlson 2010 (25)	Routine distress screening using hand held tablet: Patients with lung (N= 549) and breast cancer (N=585) were randomized to (1) Minimal screening - Distress thermometer (DT) assessment plus usual care; (2) Full screening - DT, problem checklist, psychological screen for cancer (PSSCAN) for anxiety and depression; report provided to patient and EHR; (3) Triage - As for (2) plus option of personalized phone call to access referral services. Primary outcome: Distress at 3 months measured using DT. Secondary outcome: anxiety and depression measured using PSSCAN	Triage group significantly lower distress at 3 months than minimal screening group (p=0.031)	Intervention had no impact on anxiety or depression measured	
Berry 2011 (24)	Routine electronic symptoms and QOL (ESRA-C): Patient with cancer diagnosis (N=660) randomized to (1) Intervention: ESRA-C completed on touch screens in clinic and graphical summary presented to clinical team; (2) Control: ESRA-C with no summary provided. Primary outcome: Communication of symptoms and QOL above predetermined threshold highlighted on summary report. Secondary outcome: duration of clinic visit and clinician evaluation of intervention.	29% increase in discussion of symptoms and QOL scored over predetermined threshold in intervention group (odds ratio 1.29; 95% CI 1.1 to 1.6). Greater discussion of sexual items (6.8% vs 2.4%) initiated by clinician.	No impact of intervention on duration of visit.	Clinicians reported the intervention as useful for guiding the interview and identifying problem issues.
Berry 2014 (66)	Routine electronic ESRA-C assessment in clinic or internet based with self-care education and coaching on symptom feedback to clinicians. Patients with cancer diagnosis (N=752) randomized to (1) Intervention: ESRA-C completed either using internet at home or in clinic. Self-care education and coaching provided to patients in real time and result summary of ESRA-C provided to clinicians. (2) Control: Completed ESRA-C and result summary provided to clinicians. Follow up 3-4 months Primary outcome: Symptom distress (SDS-15)	Lower symptom distress in intervention arm (SD-15 score reduced by estimated 1.21 (95% CI, 0.23 to 2.20; p=0.02).	Intervention effect was significant for older patients (p=0.01) but not younger (<50years) patients (p=0.2)	Benefit of the intervention greatest in patients >50 years

Key: CNQ: Cancer Needs Questionnaire; HRQOL: Health related quality of life; EORTC- QLQ C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; BDI – Beck Depression Inventory short form; COOP/WONCA: Dartmouth primary care cooperative information functional assessment and World organisation project of National colleges and academics; HADS: Hospital Anxiety and Depression scale; PRO: patient reported outcome; FACT – Functional Assessment of Cancer Therapy (General questionnaire); FLIC: Functional living index-cancer (QLQ); Brief POMS-17: Brief profile of mood states; PSQ-III: Medical outcomes study patent satisfaction questionnaire-III; DT: distress thermometer; PSSCAN: Psychological screen for cancer part C; EHR: electronic health records; SDS-15 (Symptom distress scale-15)

Provision of PRO results to the clinician prior to consultation appears to be a key part of integrating PRO data collection in routine practice. Our research group (Patient-reported Outcomes Group) conducted a RCT to evaluate the importance of the feedback process. In two of the trial arms patients receiving chemotherapy were asked to self-report on HRQOL (using the EORTC QLQ-C30(67) and Hospital Anxiety and Depression Scale (HADS)(68)) via touch screen computers before each clinic appointments for six months. One group of these patients had their responses fed back to their clinician prior to consultation (intervention group), the other (attention-control) group simply completed the questionnaires. The third control arm did not complete a questionnaire. The trial demonstrated that the process of shared communication with clinicians (in the intervention group) resulted in improved physician-patient communication, which was significant enough to be reported by patients(48, 69). The study also highlighted that patients demonstrated a clinically meaningful improvement in their HRQOL in the intervention arm when compared to the control arm and this was associated with explicit use of the HRQOL data in the consultation. Importantly, although the intervention increased the discussion of non-specific and chronic symptoms, this did not significantly increase the duration of the consultation(48).

Despite high-level agreement for many AE reported by patients and clinicians, research has been able to demonstrate that using PROs in clinical practice can provide data on a wider range of toxicities, including a greater number of mild AE(56, 70). Patients report on symptoms earlier and more frequently than clinicians, and clinicians were found to down grade or miss symptoms such as pain, dyspnoea and fatigue(56, 57, 70, 71). Higher-level agreement is seen with symptoms such as diarrhoea and vomiting, which may more easily be quantified(56).

Interestingly incorporating PRO assessment into routine care does not seem to improve patient's satisfaction with their care in oncology(52, 60, 72). Satisfaction may be more related to the overall experience of their treatment and influenced by a "ceiling effect" of high satisfaction typical for cancer patients. However, patient engagement and empowerment through improved communication, promotion of collaborative and informed decision-making, and improved education has been well documented(73). Patients report that the inclusion of PROs in their clinical follow up made them feel 'more in control of their care' ((page 3559)(52)). As many treatment decisions are based on a complex balance between the costs and benefits of treatment the inclusion of PROs to facilitate this process may help patients and clinicians understand the different priorities in a patient care(74).

The impact of PROs on management decisions is more complex to determine with conflicting conclusions reported in studies. Earlier reviews of the medical literature concluded that although clinicians report on the importance of HRQOL in their clinical decision-making, in reality the majority of their treatment decisions were based on biomedical factors(75). A more recent systematic review evaluated 137 trials (across all healthcare settings) considering interventions designed to enhance patient participation in the consultation process (including PROs)(60). The authors reported that 56% of the 32 studies using PROs reported a change in provider diagnosis and/or management of patient conditions. A systematic review of qualitative literature found clinicians conflicted on the positive impact the use of PROs in clinical practice had on care processes and outcomes(73). Improvements in communication, patient education, patient confidence and promotion of joint decision-making were described. But some professionals were concerned the PRO data provided them with no additional information and had the capacity to narrow the conversation potentially diverting discussion from important aspects of care(73). These conflicting findings highlight the challenges of identifying changes to decision-making in a clinical setting, and the importance of collaboration with clinicians when developing PRO interventions so the process is transparent and the data collected useful in guiding decision-making in individual patient care.

1.4.1.2 Benefits to patients and clinicians at an organisational or systemic level:

The organisational benefits of the integration of PROs into routine care have more recently been evaluated at the organisational level. Although overall survival has been the traditional outcome measure used to assess quality of care it has been argued that inclusion of measurements of improved health status, along with appropriate risk adjustment for case complexity, may capture important information regarding care quality(76). PROs have been suggested as one method of assessing patient's health status as a key outcome measure of healthcare(76). A number of recent reviews have considered the impact of introducing PRO collection into routine care on the cost effectiveness, overall economic benefits, and evaluation of healthcare quality improvements within and across healthcare providers and individual clinicians(51, 73, 76).

PROs may be used to assess a cohort of patients within a particular organisation to evaluate a particular disease outcome or review treatment efficacy. If standardised PROs are used, and as long as case-mix variables are carefully considered, this data may also be used to evaluate outcomes across different providers to review the quality

of care and assess provider performance(77). Combining PRO data with cancer registry data is feasible and may allow risk adjustment of PROs across organisations, however, it is not clear which variables are important for risk adjustment and further work in this area is needed(54, 78, 79).

Outside of cancer care the UK's National Health Service started the first nationwide routine collection of PRO data before and after elective surgery for hip and knee replacements, and hernia and varicose vein repairs(80).The pilot study established the feasibility of the nationwide project, with a cost of approximately £6.50 per person for postal PRO collection(81). The pilot study received positive feedback from stakeholders, and demonstrated high response rates between 80-90%(82). The systemic aims of this venture included measuring provider performance, linking payment to performance, improving referral between primary and secondary care and regulation of safety and quality(51). A recent report established that nationwide PRO data collection was feasible (66% response rate preoperatively and 74% postoperatively) for elective surgical procedures and, when adjusted for case-mix variables, it was possible to calculate quality adjusted life years (QALYs) for individuals and to establish the comparative cost effectiveness and technical efficiency of different hospitals(81). This approach could be used in oncology to evaluate similar goals.

Another possible systemic benefit to remote PRO data collection could be the potential to re-design follow up care for cancer patients after treatment. The traditional method of regular hospital visits predominates in clinical practice(83, 84). Discussion around the cost effectiveness of hospital-led follow up, and concern about the increased anxiety experienced by patients around their hospital appointments, has led to consideration of alternative models including the use of PROs(85, 86). The regular collection and evaluation of PRO data could reduce the intensity of routine clinical follow up and improve the identification of treatment-related toxicity and therefore be considered as an alternative to traditional hospital follow up. With the Internet accessed by 86% of the UK population (Office of National Statistics, 2015) using a web-based system to measure PROs remotely is attractive and may allow a more consistent method of monitoring late side effects and detection of symptomatic recurrences when patients do not routinely attend the hospital or are followed up by different specialty teams. Within gynaecological cancer surveillance evaluation of remote follow up using PROs has not been studied in RCTs(87) and in other cancer sites including colorectal cancer mainly telephone follow up has been evaluated as an alternative to hospital appointments(88).

PROs may also be used in clinical practice to inform treatment optimisation. Radiation treatment is an excellent modality to consider this potential benefit. As discussed earlier in this chapter, the dose limiting toxicities are late AE. This poses particular challenges for data collection in RCTs, including extra expense and attrition rates, in which the follow up to establish late effects may involve follow up for 10 years. Using high quality PRO data collected in clinical practice to evaluate the impact of radiation therapy on patients' toxicity profiles could enable institutions to evaluate their short and long-term AE outcomes, particularly with the introduction of newer precision radiation techniques. The PRO data may be also be considered in relation to information on patient comorbidities, medications known to impact on toxicity severity as well as information on the dose and volume of normal tissues treated with radiation(8, 15, 89). This high quality information could provide evidence for developing safe dose-volume constraints for normal tissues in the future. Within a clinical trial setting, Stenmark and colleagues(15) demonstrated the feasibility of this approach by using prospectively collected PRO data to establish the relationship between the dose and volume of rectal tissue irradiated and patient reported bowel symptoms in patients treated with EBRT for prostate cancer. It is this approach of combining patient-reported toxicity data with clinical and dosimetric information that will be explored within the cross sectional study of this project.

1.5 Using PROs collected in clinical practice to improve radiotherapy treatment

Currently there is poor recognition of the extent of acute and late AE following pelvic radiotherapy and minimal research to guide optimal management of patients(2, 90). Without information on the extent of the problem clinicians are unable to provide effective patient care or develop services to support patients adequately(2). Recent guidelines on the management of acute and chronic gastrointestinal problems following cancer treatment, including pelvic radiotherapy, describe effective multidisciplinary approaches to managing patient's symptoms(91). A systematic review of interventions for sexual dysfunction following pelvic radiotherapy also outlines a number of effective management options but highlights that the true incidence of these complications is unknown and further research into effective interventions require a unified grading system(90). By establishing the true extent of acute and late AE suffered by patients and describing associations between toxicity and individual treatment and patient-related information it will be possible to assess therapeutic benefit, plan treatment more effectively and implement effective management strategies to reduce the experience of acute and late treatment AE following pelvic radiotherapy for patients(92).

1.6 Overall Hypothesis

This project focuses both on the feasibility of routine PRO collection using electronic and paper methods in patients treated with pelvic radiotherapy and on the potential for patient-reported toxicity to be used to establish dose response relationships with the organs at risk in the pelvis in four chosen cancer sites – anal, rectal, endometrial and cervical cancer. I aim to establish the frequency, trajectory and severity of acute and late AE following pelvic radiotherapy as part of routine clinical care by collecting patient-reported responses using an electronic (or paper) toxicity questionnaire. The feasibility of introducing electronic PRO data collection into our organisation will be evaluated through consideration of patient recruitment rates, attrition, missing data and from feedback surveys from patients to explore the perceived impact on care.

To correlate PROs with radiotherapy dosimetric data, individual's self-reported toxicity data will be combined with dose-volume histograms (DVH) for the organs at risk taken from the individual EBRT treatment plan. The toxicity profiles will also be compared to potential confounding factors - treatment-related factors: concurrent chemotherapy, surgery and brachytherapy and patient-related factors, for example smoking and patient comorbidities - potentially enabling treatment modification for high-risk individuals in the future(8, 93).

1.7 Research Setting

Leeds Cancer Centre is one of the largest providers of cancer care within the UK supported by research led by St James's Institute of Oncology. Each year within the four chosen cancer sites (anal, rectal, cervical and endometrial) we treat approximately 365 patients. The Patient reported Outcomes Group (POG) within Leeds Cancer Centre is established internationally in PROs and toxicity monitoring in routine oncology clinical practice. Electronic health records (EHR) are widely adopted within the hospital enabling the successful development and implementation of QTool, a web-based questionnaire collection system developed for POG(94). The results from the QTool questionnaire are integrated with Patient Pathway Manager (PPM), Leeds and Yorkshire Cancer Network's EHR system enabling assessments to be analysed and viewed by clinicians for use in clinic(95). This project will use the QTool and PPM integrated system and evaluate its use in patients treated with pelvic radiotherapy.

1.8 Specific Objectives

An overview of the methods used in this thesis will be detailed in Chapter 2. The specific objectives of my thesis, details of how they will be addressed and an outline of each chapter is presented below. Figure 1.4 provides an overview of the process:

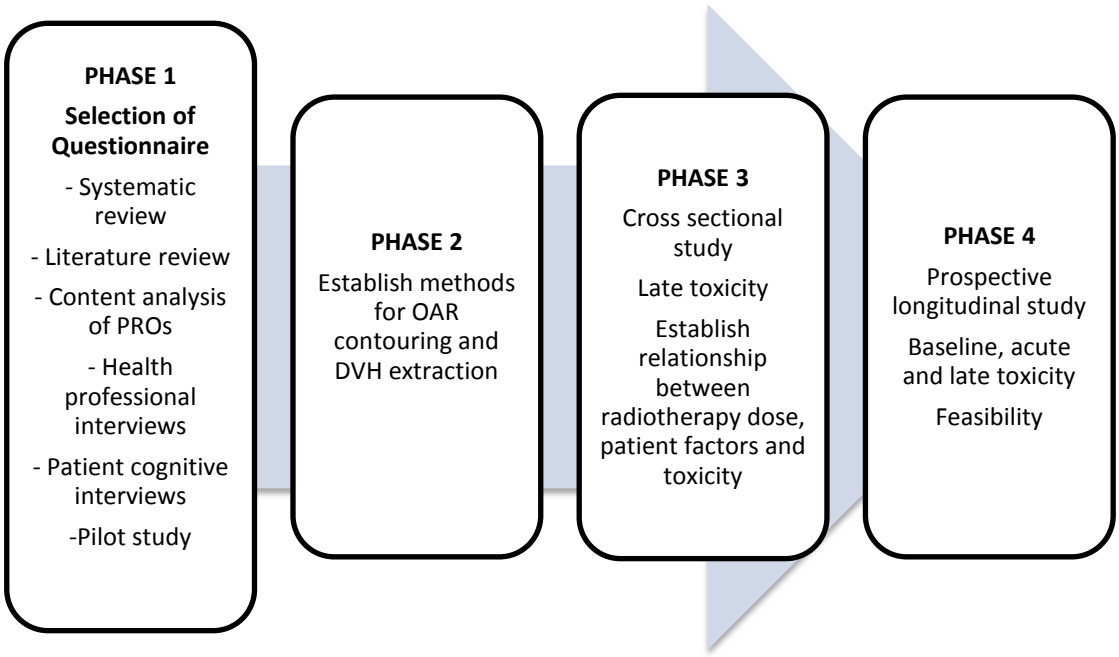


Figure 1-4: Flow diagram of project

1.8.1 Phase 1: Questionnaire Selection

The aim of the initial development phase is to select a questionnaire for patients to self-report acute and late toxicity during and after pelvic radiotherapy using a mixed methods approach. To implement a reliable tool for self-reporting AE, this phase reviews existing PRO measures used in clinical trials for patients treated with pelvic radiotherapy for anal, rectal, cervical and endometrial cancer. The instrument is required to evaluate all consequences of treatment, differences in treatment regimes, changes in AE over time and discriminate between different patient's toxicity scores. Best practice recommends reviewing clinical literature and obtaining information from clinicians and patients to ensure the instrument(s) selected is/are relevant to measurement aims(96). In addition, the use of an innovative inductive content analysis approach to evaluate item coverage in existing PRO measures will be piloted. The instrument(s) selected following the interviews with health professionals and content analysis of the questionnaires will be further refined following patient interviews and inputted into QTool. The chosen questionnaire(s) will be administered to patients in a pilot study to evaluate acceptability and usability with a feedback survey and modified further prior to use in the cross sectional and prospective studies.

Chapter 2 reports on the systematic review of toxicity reporting in RCTs of pelvic radiotherapy in rectal cancers and literature reviews of the PRO measures used in clinical trials in the three other chosen cancer sites: cervical, endometrial and anal cancer.

Chapter 4 presents the results of the health professional interviews and inductive content analysis of the PRO measures.

Chapter 5 reports the findings of the cognitive interviews with patients exploring the differences between the PRO measures selected and the CTCAE grading system.

Chapter 6 describes the methods and technology used to approach and track patients on the clinical studies, the set up and methods used to input the data effectively into QTool and EHR systems and finally, reports on the outcomes of the pilot study.

1.8.2 Phase 2: Establishing the methods for OAR contouring and DVH extraction

Chapter 7 focuses on developing rigorous contouring methods for OAR using the highest quality evidence from the literature and create a protocol, through working with a multi-disciplinary team of experts, which allows reproducibility of the OAR contours in the clinical studies and practice. This chapter also evaluates the use of image registration of the diagnostic magnetic resonance imaging (MRI) scan onto the planning computed tomography (CT) scan to assist OAR contouring. Chapter 7 also describes the processes used to extract the DVH data from the treatment planning system (TPS), where DVH describes the 2D graphical display of the relationship between the amount of dose delivered to each incremental volume of a particular tissue treated.

1.8.3 Phase 3: Cross sectional study

Chapter 8 evaluates the dosimetric, clinical and patient factors impacting on patient-reported late toxicity in patients treated with pelvic (chemo)radiotherapy for anal, rectal, cervical and endometrial cancer using a cross sectional study design. Eligible patients in the four chosen cancer sites, treated with pre or post operative or radical 3D conformal radiotherapy in the previous 1-5 years were invited to complete a single self-reported AE assessment, either online or on paper. As well as an overview of the socio-demographic and clinical data of the participants, the prevalence of patient-reported toxicity in the different cancer sites will be appraised. The use of principal component analysis (PCA) to evaluate the dosimetric (DVH) data for use within a

regression analysis will be critiqued. Finally the associations between patient-reported toxicity, patient's clinical data and radiotherapy dosimetric data will be evaluated to develop predictive models linking radiation treatment to toxicity severity.

1.8.4 Phase 4: Prospective study

Chapter 9 describes the interim analysis of the prospective study evaluating the use of electronic (or paper) PRO collection in routine practice with integration into patient EHR. This study prospectively measures acute and longer-term toxicities using an electronic (or paper) questionnaire for assessment of baseline, acute and (early) late radiotherapy toxicity in patients with anal, rectal, cervical and endometrial cancer during a one year follow up. This is the first prospective study to pilot the use of electronic integration of patient results into EHR and even at the stage of the interim analysis demonstrates the longest mean and median follow up of patients using electronic PRO data collection in a clinical setting. Descriptive analysis of the socio-demographic and clinical data will be presented along with provisional data evaluating the feasibility and acceptability of the intervention through consideration of recruitment and attrition rates, missing data and initial patient feedback. The trajectory of patient reported toxicity will be described and plans for future analysis of the data will be outlined.

The final chapter, Chapter 10, summarises the conclusions for all phases of the project, critiques the methodology and considers the implications for future research within clinical practice and clinical trials.

Chapter 2 Methodology

My thesis employs a mixed methods approach, which combines qualitative and quantitative methodological techniques within a series of connected study phases(97). Mixed methods studies aim to combine the complementary strengths of quantitative methods, which produce numerical data, with qualitative approaches, which tend to generate non-numerical data using techniques such as semi-structured interviews, to explore a particular research question more comprehensively that it may be using either method alone(97). The value of mixed methods approaches to research in a healthcare setting is increasingly recognised where questions are often multi-faceted and complex(97, 98). Qualitative research approaches allow the researcher to apply rigorous interpretative frameworks to analyse the data but allow for the questions explored to be open-ended or 'inductive' enabling hypotheses to develop from the data. This approach is particularly favourable when exploring complex social phenomenon to explore views and meaning behind the data(97). However, the small sample sizes used in qualitative work may limit the generalizability of the findings. In contrast, quantitative research often examines an *a priori* hypothesis and aims to measure an observed phenomenon objectively. In contrast to qualitative research, quantitative methods aim to reduce confounding within the analysis and include large enough sample sizes to be representative of a population and potentially generalizable to others. This 'deductive' research method however, may miss the beliefs, values and meaning behind complex social experiences and may be less suited to understanding why particular effects are seen and generating hypotheses(97). However, incorporating the strengths from the complimentary methodological strands may be particularly beneficial in healthcare research when the outcome of the research often has two objectives – research outcomes and application into practice(99). The qualitative strands aims to focus the project on developing research that is relevant to use in a practical setting and provide reasons to explain particular findings in the data. The quantitative elements aim to test out hypotheses and generate results that may be generalizable to other healthcare populations. In this chapter I describe the different methods employed and explore why each methods has been chosen for the different phases of my thesis.

2.1 Summary of research methods

Within this thesis I have employed the following methods:

- Synthesis of the evidence using systematic literature review methodology and structured literature reviews

- Qualitative methods including semi-structured interviews analysed using thematic framework analysis and inductive content analysis of existing patient reported outcome (PRO) measures
- Quantitative methods: Cross sectional study design and prospective, longitudinal study design with data analyses including descriptive statistics and regression analyses

As described in the thesis objectives in Chapter 1, this project was planned in four key phases. Ethics approval was sought for all studies from the Research Ethics Committee:

1. Selection and electronic implementation of PROs for use with patients treated with pelvic radiotherapy in clinical practice (Chapters 3-6)
2. Selection of relevant organs at risk (OAR) and establishing methods for OAR contouring and dose volume histogram (DVH) data extraction (Chapter 7)

Cross sectional study to establish prevalence of late toxicity in patients treated with pelvic radiotherapy and to establish the relationship between radiotherapy related late toxicity severity, radiotherapy dose delivered to organs at risk and confounding variables (Chapter 8)

3. Prospective study to establish the trajectory and prevalence of acute and early late toxicity (median 9 month follow up) in patients treated with pelvic radiotherapy (Chapter 9) and evaluate the feasibility and acceptability of longitudinal routine PRO data collection within our organisation

Each phase is discussed in this chapter offering:

- A critique of the purpose of each phase of the research
- A critical evaluation of the methods of data collection used
- A critical evaluation of the methods of analysis selected
- A consideration of the practical and organisational boundaries affecting each phase

2.2 Phase 1: Selecting a PRO for use in clinical practice

A modified version of sections 2.2.1, 2.2.2.1 and 2.2.2.2 originate from my paper “Use of patient-reported outcomes to measure symptoms and health related quality of life in the clinic” published in *Gynecologic Oncology(41)*.

Implementing the integration of PRO assessments into routine care may be considered as a complex intervention. Key components need to be addressed for the whole intervention to work(100). It is important to establish the effectiveness of an intervention in everyday practice, but this involves understanding the whole range of potential outcomes and how the effect of the intervention varies between patients and clinicians, between specialties, treatments and diseases and within and between organisations(101). This initial phase of questionnaire selection aims to evaluate the most effective PRO, using multiple methods, from existing measures for use in clinical practice in each of the cancer sites for both clinical studies.

2.2.1 Which PRO measure to choose?

The hypothesis and outcome of the research need to be established, as the choice of instrument will depend on the overall project aims. This thesis aims to evaluate patient reported toxicity in patients treated with multimodal treatment regimes including pelvic radiotherapy assessed through cross sectional and longitudinal study designs. The measure needs to include sufficient detail to establish dose response relationships with organs at risk and be sensitive to changes in toxicity reported over time.

In the clinical setting, the majority of studies have used a combination of a generic and a disease-specific questionnaire. This combination enables assessment of general health domains like physical or social functioning using questionnaires such as EORTC-QLQ-C30 or FACT-G, as well as symptom-specific instruments, which are related to the disease or treatment; for example, for patients with cervical cancer FACT-Cx or EORTC-QLQ-CX24(102). Selection of PROs covering clinically relevant issues that will be discussed at hospital follow up aims to avoid additional cognitive demands on clinicians but instead to act as a guide to support communication and work as a method for systematically recording clinically relevant data for future analysis.

It is important that all stakeholders involved in the research value the selected measure for the implementation to be a success(102). This may be challenging, particularly if the intervention involves different treatment specialties or organisations. Agreement on one particular instrument may be difficult but inclusion of more items may be burdensome. Some of the barriers to achieving the benefits of PRO interventions may be dispelled through consultation with health professionals and patients who will be involved in the intervention to establish relevant measures and keeping the objectives for PRO data collection transparent at all times(73).

To establish the content, coverage and relevance to clinical practice of pre-existing PRO measures, this phase uses a mixed methods approach similar to that used in questionnaire development (103, 104). This rigorous approach recommends literature reviews to establish potentially relevant items/instruments followed by interviews with clinicians and patients to ensure content validity and relevance to the clinical setting. In chapter 3, systematic and literature reviews of clinical trials in each of the four cancer sites will be used to establish the most commonly used PROs. The systematic review in rectal cancer also offers the opportunity for an in-depth analysis of radiotherapy AE reporting in RCTs comparing clinician and patient reporting and provides recommendations to improve future trials.

Chapter 4 aims to establish the most effective PRO to use in each of the cancer sites for the clinical studies, through semi-structured interviews with health professionals, an inductive content analysis of three PRO measures selected following the systematic/literature reviews and discussion with an expert review panel discussion. The semi-structured interviews allow for an open discussion of AE commonly experienced during and after pelvic (chemo)radiotherapy and a detailed assessment of the content of existing PROs to ascertain clinical preferences. The interview process with health professionals is also used to ensure the relevance and value of the PRO data to clinical practice for all stakeholders. The interviews explore the optimal timing of assessments in the prospective study to establish acute and late toxicity and explore current management pathways for side effects within Cancer Research UK Leeds Centre. The inductive content analysis of existing measures pilots a qualitative methodological technique to compare and contrast the content of three commonly used PRO measures to establish the measure(s) that most effectively cover the common AE experienced by patients treated with pelvic radiotherapy.

Chapter 5 considers a thematic framework analysis of cognitive interviews with patients completing the selected PRO. Cognitive interview techniques are used to develop and evaluate the content of questionnaires(105). The theory behind cognitive interviewing considers four key processes involved in the question-answering process: comprehension of the question, relevant information retrieval from memory, decision-making process and response processes(106). Participants are requested to describe their question-answering process either through ‘think aloud’ techniques during completion of the questionnaire or through probed questioning following questionnaire completion(107). These interviews explore the content validity of the selected PRO(s). Patient responses describing their reasons for selecting a particular response on the

PRO are used to establish the equivalent grading of the same AE using the CTCAE. This analysis aims to evaluate the similarities and differences between the subjective reporting of AE using clinician and patient reporting using a thematic framework analysis approach to explore methodological differences.

A thematic content analysis using a framework method was chosen to analyse the content of the health professional semi-structured interviews and the cognitive interviews with patients. The framework method is increasingly used in health research(108). The data collection is often more structured than other forms of qualitative analysis, favouring homogenous data sets such as semi-structured interviews, and is often guided by strong a priori principles(108, 109). The matrix output defines cases (rows), codes (columns) and 'cells' of short text descriptors providing clearly structured outputs enabling the researcher to summarise the data by case and code(110). Cases are often defined as the interviewee (as they are in the cognitive interview analysis) but may also be a predefined group (for example, a tumour site, as in the health professional interview analysis). The framework method can be adapted to allow a combination of both inductive and deductive analysis approaches(108). These different approaches determine how the themes are selected. In the deductive approach themes and codes are pre-determined based on a priori knowledge. In contrast the inductive approach allows themes and codes to be generated from open coding of the material and a process of refinement of the themes follows. Often a combination approach is favoured to allow a focus on key research outcomes whilst leaving open the possibility of allowing unexpected themes to emerge(108). Both inductive and deductive approaches using the framework method are used in the interview analyses and an inductive approach used in the content analysis of the PRO measures.

2.2.2 Developing the clinical study process: Setting up the clinical studies and Pilot study

Chapter 6 reports on the methods used to ensure effective integration of the electronic (and paper) PRO assessments using the EORTC-QLQ system within clinical practice and a pilot study evaluation. Following selection of the PRO measure(s) the presentation of PRO data in electronic format for clinicians and patients is considered within this chapter. The development of the scoring procedures for the PRO items and formatting of the graphical/tabular results for clinician viewing is described as well as the online patient experience, including an online consent form, supported by a member of our research advisory group to exemplify user involvement.

The approach methods for the cross sectional study and tracking technology used in the prospective studies are also outlined. This chapter also describes the innovative processes piloted in this study to export and validate existing clinical data from the electronic health records (EHR) system Patient Pathway Manager (PPM) for use within the analysis. Finally the approach methods and electronic integration processes are evaluated through a pilot study to consider the acceptability and usability of the measure (n=31). Patients complete the PRO symptom questionnaire, either online or on paper, and a feedback questionnaire on the process with further refinements made following patient feedback.

2.2.2.1 Methods for collection and presentation of PRO data

For the clinicians to be able to use PRO information effectively at the point of care with a patient, it is important that the data is collected, scored and presented before the consultation in a way that does not interrupt the clinical workflow or create significant cognitive demands on the clinician. Traditionally PRO data has been collected in clinical trials using paper methods, as found in the systematic review (Chapter 3). However, as described in Chapter 1 this thesis aims to evaluate the use of electronic PRO data collection in clinical practice. Electronic methods, using Internet-based questionnaires or touch-screen computers, may be best placed to enable a seamless pathway and integration with patient EHRs may further improve the usability of such an approach especially in organisations like ours in which EHRs are already well integrated(54). Our research group has developed the Internet-based questionnaire collection system, QTool (78). This system allows patients to self-report on symptoms during and after treatment at home or in clinic and has been integrated with Patient Pathway Manager (PPM), Leeds and Yorkshire Cancer Network's EHR system(111) (Figure 2.1).

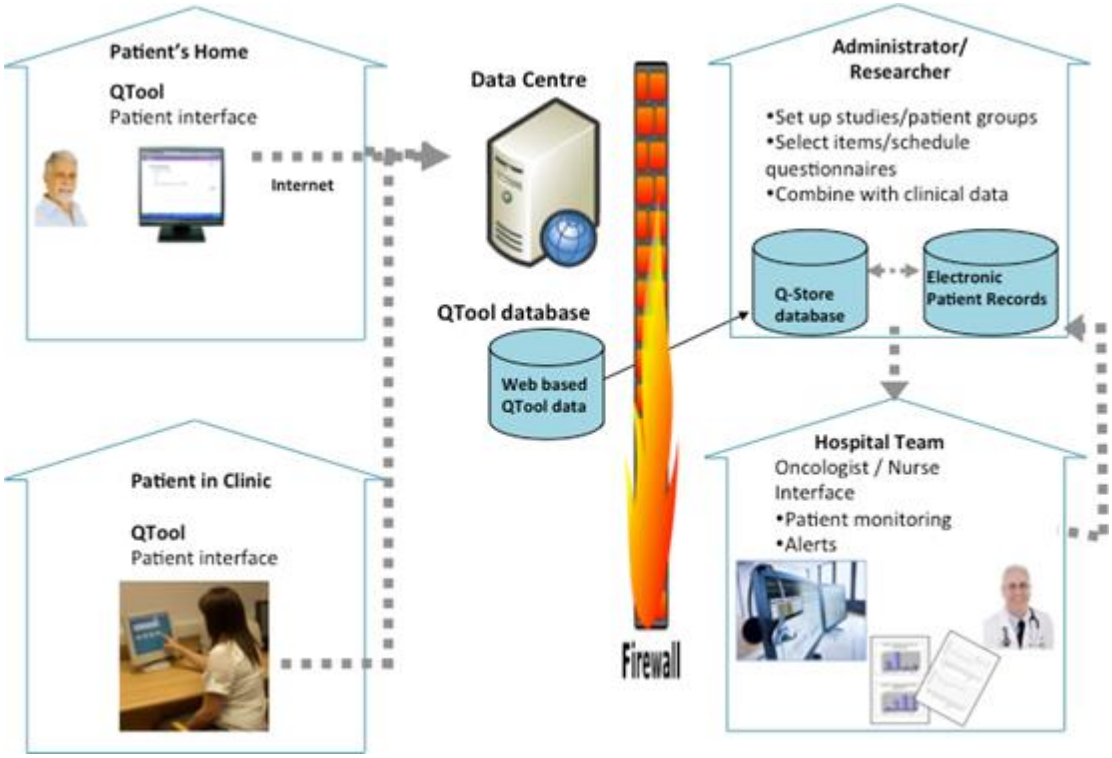


Figure 2-1: Overview of QTool

2.2.2.2 Electronic data collection and presentation of results

Electronic methods for patient reporting have been found to be acceptable to patients and provide better quality data than paper methods(52, 112). Using weekly email reminders to patients in one study led to an 83% monthly and a 62% weekly compliance rate with patients on chemotherapy over a mean eight month period(113). The high responses rates provide positive evidence for the use of electronic PRO data collection in routine practice. Within a RCT setting, a companion study (RTOG-0828) to the RTOG-0415 RCT comparing hypofractionated to conventionally fractionated prostate radiotherapy highlighted the benefits of electronic PRO systems using Internet-based PRO data collection in a subset of patients(114). The completion rates using the paper version of the PRO measure EPIC (Expanded-Prostate-Index-Composite), were 36% at one year as compared to 82% using Internet-based technology. This study also made use of real-time data collection and email reminders to patients when items or forms were incomplete.

Whilst electronic methods have many clear advantages for data collection and analysis this project incorporates paper collection alongside electronic methods within the clinical studies. Enabling paper completion increases the inclusivity of the project to all eligible patients within the clinical population and also enables faster recruitment, due to the limited timeframe for data collection within this project.

For long-term sustainability of PRO use in clinical practice research suggests that focussing on ease of use and clinically relevant issues are key(115). As EHRs are increasingly used in clinical practice, both within our institution and worldwide, ideally electronically collected PRO results should be integrated into them, as they will be within this project(54, 102). However, the research in this area is in its infancy with significant variability in the approaches used to achieve EHR integration in published research(116). A key issue lies in the fact there are no standard methods for how best to present the PRO data. Within chapter 6, the development and pilot work addresses how best to establish the formatting of the results ensuring that the PRO data makes sense to the viewing clinician(117). Ideally the presented PRO data should provide information about the clinical importance of an individual's scores or on what constitutes a clinically important change to aid decision-making(118).

The frequency and timing of administration of the PRO data collection must also be considered, weighing up the potential burden versus the usefulness of PRO completion by patients and evaluation by clinicians. Although frequent data collection could provide a more detailed picture of a patient's experience this may result in more variable scoring, which could be challenging to interpret(102). If completion of the PRO assessment becomes burdensome to patients, this may also lead to significant missing data. Whilst incomplete data sets are less of a concern when considering use in practice as compared to clinical trials, for the PRO data to be meaningful for the purposes of internal audit it is important that sufficient data is collected.

In radiation treatments, patients require more intense support for acute AE during treatment and in the few weeks after treatment. However, late toxicity may have an insidious onset and may not manifest until many months or years later(53). For AE developing months after treatment, association of the PRO data collection with follow up consultations may enable further discussion and support of any issues(54). The key timings for administration of the questionnaire in the prospective study were established following the analysis of the health professional interviews and the process of initial implementation explored during the pilot study.

2.2.2.3 Pilot study

Pilot study methods are used in this context to consider the feasibility of electronic data capture on a small scale before carrying out the larger studies (cross sectional and prospective studies) and pre-test the data collection methods and recruitment

processes in advance using the PRO selected(119, 120). The pilot study offers the opportunity for identification of practical problems in the research process so modifications can be made before starting the large-scale recruitment. Pilot study methods do have limitations; in particular, as the pilot study generally uses small numbers of participants the feedback received may not be representative of a larger population. Purposive sampling by cancer site was used to ensure a representative patient sample.

The feedback questionnaire for the pilot study was developed from pre-existing measures used in our organisation and reviewed by a member of our research advisory group (as a patient representative). The results were analysed using descriptive statistics and the qualitative free text responses reviewed for any modifications required.

A substantial amendment was submitted to the Research Ethics Committee at this point to clarify the processes for the Cross sectional and Prospective study recruitment. The amendment established the PRO measure(s) selected, the processes involved with finding and contacting eligible patients in the cross sectional study, the timings of follow up in the prospective study, and the methods used to manage the process of contacting patients.

2.3 Phase 2: Organs at Risk (OAR) and DVH extraction

2.3.1 Developing guidelines for OAR contouring

Pelvic irradiation is associated with significant acute and late toxicity affecting the normal tissues surrounding the tumour. Chapter 7 considers the choice of which organs at risk (OAR) to contour and the methods to approach the contouring based on current expert guidance and research. This will enable the relationship between the organ-specific patient-reported toxicity from the cross sectional study (Phase 2) and the DVHs for each OAR and treatment- and patient-related factors to be explored.

Prior to the introduction of precision radiotherapy techniques, such as IMRT, OAR were not routinely contoured as avoidance structures within the pelvis. The introduction of precision radiotherapy enables reduction of the radiation dose to critical OAR by conforming the high-dose to the target volume; however, this has not always translated to a clinical benefit to patients(121). This has led to deliberation amongst

clinical/radiation oncologists about the best approaches to OAR contouring and the dose constraints to apply to these critical structures.

The current published guidelines and research in this area are evaluated within this chapter, including a critique of OAR guidelines developed for clinical trials using precision radiotherapy techniques within the pelvis. OAR that may be relatable to symptomatic toxicity measureable using PRO methods were prioritised over OAR with no clear link to symptomatic toxicity. For OAR with no established contouring guidelines or where multiple methods are described consensus was achieved through:

(1) Consideration of the views in the research literature;

(2) Through achieving consensus through discussion with a multi-disciplinary team of experts in the area including medical and clinical oncology consultants, consultant radiologists, medical physicists, and dosimetrists;

(3) Through exploring the practicality of implementation.

Recent consensus guidelines for OAR contouring in the pelvis have developed guidelines through expert panels of doctors(122-124). This study pilots an innovative approach of incorporating multi-disciplinary team members to develop a contouring protocol with practical implementation in clinical practice in mind, including dosimetrists as well as clinicians within the contouring process. A number of quality assurance measures will be incorporated to ensure high quality OAR contouring accuracy including training and supervision.

This chapter also explores alternative methods for contouring such as computed tomography (CT) and magnetic resonance imaging (MRI) fusion or image registration. CT-based planning remains the most widely used modality for target volume delineation in clinical practice(125). However CT has limited contrast resolution for soft tissue delineation and commonly CT planning combines information from multiple imaging modalities including MRI and positron emission tomography-CT (PET-CT) to improve the target volume delineation. Image registration enables the alignment of two sets of images. The image registration software, Mirada, (Mirada Medical, Oxford UK) is used within our organisation to provide rigid registration of MRI and CT images in patients treated with head and neck cancer. In rigid registration the two images essentially overlay each other. This does not allow for differences in soft tissue displacement between images taken on different days and changes in positioning. This evaluation explores the use of Mirada RTx v1.4 (Mirada Medical, Oxford UK) to perform deformable image registration of the CT planning scan and the diagnostic MRI for a small sample of 20 patients. Deformable image registration aims to correct for

differences in set up between images taken on different days by mapping differences in volume between the two images. The software effectively moulds the diagnostic MRI image over the CT planning scan to find the best method to overlay the organ volumes. The benefits and challenges of using image registration with CT and MRI in a research context to improve normal tissue OAR contouring in the pelvis are reviewed qualitatively with a sample of 20 patients.

2.3.2 Developing guidelines for DVH data extraction

Finally this chapter considers the technical processes and methods for DVH data extraction and analysis. For patients treated in two or more phases a technical process to extract and recalculate patient's dosimetric information into standard equivalent dose in 2Gy fractions (EQD2) was developed based on methods previously described in the literature(126). The technical processes for combining dosimetric data and those involved in exporting the DVH information are outlined.

2.4 Phase 3: Cross sectional Study

Cross sectional evaluation of late toxicity using PROs has been a method commonly used in RCTs of radiotherapy(127). Within the time frame of a three year PhD this study design provides the best method to estimate the prevalence of late toxicity in each of the four cancer sites studied: anal/cervical/endometrial/rectal(53). Patients who had completed radical external beam radiotherapy treatment, following departmental guidelines, over the past 1-5 years in the four cancer sites were eligible. Patients were invited to complete a single PRO assessment either electronically or on paper, ideally prior to their hospital appointment. The relationship between the severity of the patient reported toxicity experienced following pelvic radiotherapy, the dose delivered to the organs at risk (extracted as dose volume histogram [DVH] data) and other potential confounding variables was then explored. Sample size calculations were performed in advance of recruitment into the clinical studies and are outlined in Chapter 8.

The cross sectional methodology does have a number of disadvantages(128). Although there is no loss of follow up as patients complete a single assessment at one time point, it is difficult to infer a temporal relationship between the radiotherapy exposure and the toxicity severity as both the exposure and the outcome are measured at the same time. For example, some patients may have pre-existing conditions or symptoms unrelated to the cancer treatment. This means that only an association/correlation may be described rather than a causal relationship. The study

may also be prone to non-response bias if the patients who chose to take part differ from the whole population of pelvic radiotherapy patients treated at Cancer Research UK Leeds Centre. However, this methodology allows an exploration of the prevalence of symptomatic late toxicity within these four patient groups treated with pelvic radiotherapy and provides an opportunity to evaluate the relationship with the radiotherapy dose delivered to the relevant organs at risk and other confounding factors.

Chapter 8 presents the findings from the cross sectional study. The overall summary PRO scores are presented using descriptive statistics(129). Principal component analysis (PCA) of the dosimetric data was used to describe and compress the correlated variability of the DVH data for each OAR(126, 130-132). PCA aims to explain the individual DVHs and their variability by a few 'principal components' (PCs). This reduction in the data to represent the DVH allows for more manageable modelling of the impact of the DVH in causing dose related symptoms in patients. The use of this method in normal tissue complication probability modelling is critiqued within Chapter 8. The PCs generated and other dosimetric data, such as mean dose, were evaluated alongside clinical factors within an exploratory linear regression analysis to evaluate the dosimetric relationship with toxicity outcomes. Three backward stepwise regression models were used to identify predictors of PRO scores for each symptom item or scaled item. Model 1 evaluated associations between PRO scores and clinical data (patient and treatment characteristics) using a significance level of 10% ($p<0.1$) to determine potentially significant covariates. Model 2 assessed dosimetric predictors using $p<0.1$ to determine significance. Model 3 included all significant dosimetric and clinical variables from models 1 and 2 retaining those where $p<0.05$.

To avoid repetition within the introduction and methods, Chapter 8 includes all data from the cross sectional study. The results section presents the overall patient characteristics of the sample and the results from the EORTC-QLQ C30(67). The results of each group of toxicity items – urinary, bowel, female and male sexual dysfunction and low back pain - and related OAR dosimetric analyses are then laid out in turn. The discussion evaluates the overall findings from the study and considers the models developed for each symptom group in turn.

2.5 Phase 4: Prospective Study

The prospective observational study aims to measure acute and longer-term toxicities over a one-year period in patients treated with pelvic radiotherapy for anal/cervical/endometrial/rectal cancer using PROs integrated into EHR to establish:

(1) The feasibility of electronic PRO implementation into routine practice and
(2) The trajectory, frequency and severity of toxicity reported.

As a complex intervention, the evaluation of PRO implementation in clinical practice is challenging. The aim of evaluation is to measure a process of social change, which involves a complex, non-linear and interpersonal system sensitive to multiple influences, such as different environments, leadership, and the details of the intervention(133). Although observational study designs are uncontrolled (unlike a randomised controlled trial) the methods can provide evidence of effectiveness and are often quicker and cheaper to run(102). Additional qualitative assessment to observe how the PRO is used by clinicians and patients and how it is integrated into the workflow may be employed to provide a more holistic view of the interventions application and use. This type of evaluation allows consideration as to how the change has occurred and what aspects are generalisable to other contexts by establishing the local conditions that have led to successful outcomes before consideration of wider implementation(133).

Previous research using electronic PRO systems in patients treated with radiotherapy has focused on use within a randomised clinical trial (RCT)(134). However in this particular trial patients were only followed up for 12 weeks post treatment. Most patients treated curatively for anorectal and gynaecological cancer will be followed up for five years for monitoring of disease recurrence within clinical practice. However, research into PROs has only followed up patients (treated with systemic therapies) outside of clinical trials for a mean duration of eight months(113). The use of Internet-based PROs in longer-term follow up may enable clinicians to re-design follow up care. For example, assigning remote regular PROs completion and monitoring of results, may potentially enable follow up through telephone consultations or email if patients report no significant problems(87). The duration of follow up within this study is innovative and could be used as a starting point to explore alternative models of long term follow up in clinical practice in future work.

Following on from the feedback from the pilot study (described in Chapter 6) this feasibility study implements and evaluates the complex intervention on a broader scale using an observational prospective cohort design. Currently there is no standard policy

for assessment of acute toxicity following (chemo)radiotherapy and so the timing of administration of the symptom questionnaire were implemented based on feedback from health professional interviews. The study involves multiple different treatment pathways managed using an electronic tracker system (described in chapter 6) designed to contact patients with invitations and reminders to complete an electronic or paper questionnaire. This tracker system has been used effectively within our organisation for a previous study(135). Participants are asked to complete an initial baseline assessment and then assessments invitations sent during and after treatment at selected time points using either electronic or paper methods.

The duration of follow up for the prospective study was limited by the timeframe of the PhD. Chapter 9 provides an interim analysis of the study after a mean/median nine-month follow up. This early analysis aims to evaluate the acceptability and feasibility through assessment of recruitment rates, attrition, missing data and early feedback in the form of questionnaires from patients. The final analysis, once follow up is complete in June 2016, will incorporate qualitative analysis in the form of interviews with patients and staff to assess the process in more detail. Early results on the trajectory, frequency and severity of symptoms for each cancer site are presented in Chapter 9 with some case study examples. The sample size calculations for the prospective study were based on estimated numbers of patients treated each year in Cancer Research UK Leeds Centre and calculated in advance.

The full future analysis will additionally evaluate the OAR contouring and dosimetric models developed within the cross sectional study in the prospective cohort, as an independent data set. Changes in toxicity over time will be evaluated with the dosimetric data, taking into account confounding factors (such as co-morbidities and medications taken) as in the cross sectional study analysis. Unlike the cross sectional study design the temporal relationship between the toxicity outcome and the treatment received can be evaluated using this methodology.

2.6 Conclusion

The overall project aims to select a questionnaire to report on side effects of pelvic radiotherapy through rigorous methods, including consultation with stakeholders, suitable for use in regular electronic PRO data collection in routine practice. The project pilots the integration of electronically collected PRO data into electronic health records (EHR) within CRUK Leeds Centre and develops an innovative technical

process to export and validate clinical data from the EHR for use within the research analysis. The project seeks to improve the detail provided for OAR contouring to improve reproducibility between multi-disciplinary users and develop guidelines for OAR without contouring definitions. The PRO results from the cross sectional study are evaluated in relation to patient related factors and treatment related factors, including OAR DVH data, as a method of evaluating treatment outcomes in a cohort of patients treated within our organisation. This project is the first to combine the dosimetric data from multiple pelvic radiotherapy treatment techniques and cancer sites using principal component analysis for use within a regression analysis. Finally, this project aims to expand on the limitations in current work with electronic PRO data collection over a short time frame by integrating regular PRO data collection in follow up over a yearlong period in routine practice in the prospective study. Early toxicity results are explored in an interim analysis along with assessment of feedback questionnaires and an evaluation of recruitment and attrition rates to provide early evidence of feasibility and acceptability of this intervention. The following chapter outlines the literature review process used as the initial step in selecting the most appropriate PRO instrument(s) for use in this study of patients treated with radiotherapy for anal, rectal, cervical and endometrial cancers.

Chapter 3 A comparison of patient-reported outcomes and clinician toxicity reporting in pelvic radiotherapy clinical trials

3.1 Introduction

A modified version of the systematic review originates from my paper “Systematic Review of Radiation Therapy Toxicity Reporting in Randomized Controlled Trials of Rectal Cancer: A Comparison of Patient-Reported Outcomes and Clinician Toxicity Reporting” published in *International Journal of Radiation Oncology, Biology and Physics(127)*.

This chapter aims to establish the most commonly used toxicity reporting measures in clinical trials of pelvic radiotherapy in the four chosen cancer sites using a systematic review and scoping review methods. In addition, within the systematic review of rectal cancer randomised controlled trials (RCTs), the differences in the methods of reporting between clinician and patient reported toxicity are explored to inform future use of patient reported outcomes (PRO) in rectal cancer trials.

Reliable collection and analysis of adverse event data in oncology is challenging as complex multimodal regimes involve not only different treatments but also variations in dose intensity and duration(136). Methods for toxicity data capture and reporting in oncology were developed from other disciplines which employ treatments with a different, and often less toxic profile, such as antibiotics(136). Adverse events (AE) in oncology may be inadequately captured by these methods and are often underreported(8). A number of international reports, including QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic), have highlighted that in order to optimise future radiation treatment regimes a systematic approach to the collection and publication of detailed toxicity data is required(8).

The clinician-reported Common Terminology Criteria for Adverse Events (CTCAE) version 4 has recently been accepted as the preferred instrument for collection of adverse event data in cancer trials(137). However, patient-reported outcomes (PROs) included in trials are increasingly used as a surrogate measure of late toxicity, usually as a secondary outcome. Using PROs has been found to increase the number and

variety of adverse events recorded and highlighted discrepancies between clinician and patient reporting(56, 70). The inclusion of PROs in clinical trials may therefore provide additional information to better inform clinical decision-making. However, a number of reviews of PROs in clinical trials have revealed concerns regarding the methodological quality and reporting of the results(138-140). Two recently published internationally developed guidelines highlight this area of concern(141, 142).

Rectal cancer was chosen as the main tumour site for a full systematic review for a number of reasons. Firstly, there has been considerable change in treatment practice in rectal cancer over the past two decades with many Phase III RCT carried out. Secondly, I am an author on a systematic review publication carried out in association with the EORTC PROMOTION (Patient Reported Outcome Measures Over Time In ONcology) project group for PROs used in RCTs for gynaecological cancers(46). I produced the first draft of the introduction and methods for this publication and have been involved in the data extraction for the lung cancer study. Finally, I am an author on a systematic review of trials reporting on QOL in anal cancer in association with the EORTC Quality of life group anal cancer module development(143). I am an active member of the development group for this module and have advised the first author and development team about the relevant findings from my thesis to support the project. Therefore for the purpose of my thesis I conducted a scoping review for the anal cancer, cervical and endometrial cancer sites to establish the PRO instruments used most commonly in the clinical trials literature.

Previous reviews of radiotherapy treatment in rectal cancer have focused on survival outcomes and descriptions of late adverse events or functional outcomes in a variety of different trial settings, including retrospective single centre studies(19, 144-147). The systematic review focuses on RCTs in rectal cancer, as the research gold standard, with the following objectives: (1) to establish the clinician and patient-reported toxicity instruments used; (2) to assess the methodological quality of the studies and quality of PRO reporting; and (3) to report a summary of the percentage of toxicity reported by treatment received and compare differences in clinician and patient reporting. The aim for the scoping reviews was to establish the most commonly used PRO instruments in (chemo)radiotherapy AE reporting in anal, cervical and endometrial (gynaecological) cancer and to ensure that the systematic review findings in rectal cancer are broadly replicated.

The questionnaires most commonly used in the clinical trials will be further evaluated for their content coverage in the health professional interviews and content analysis

explored in Chapter 4. The prevalence of toxicity reported in the rectal cancer RCTs may be used as a comparison for the late toxicity findings in the cross sectional study presented in this thesis (Chapter 8). This chapter concludes with recommendations for improving adverse event data collection from clinicians and PROs. Below I present first the systematic review in rectal cancer followed by the scoping literature reviews in endometrial, cervical and anal cancer.

3.2 Systematic review methods

3.2.1 Search strategy

Medline, EMBASE and the Cochrane Library were searched from January 1995 to July 2013 for RCTs reporting late toxicity in patients treated with regimens including preoperative (chemo)radiotherapy. The search followed Centre for Reviews and Dissemination recommendations for undertaking systematic reviews(148) and PRISMA guidelines(149). Only English language publications were included. Relevant studies listed as references were hand searched. The electronic search strategy is outlined below:

In MEDLINE (10/10/11):
1. ((rectum or rectal) adj2 (cancer* or carcinoma* or neoplasm* or tumo?r*)).mp.
MeSH term: Rectal Neoplasms/
2. radiation, radiotherap*, chemoradiation, chemoradiotherap*, irradiation,
MeSH terms: Radiotherapy/OR combined modality therapy.
3. adverse event*, dysfunction, function*, (late adj2 toxicit*), complication*, quality of life, patient reported outcome*
MeSH keyword: radiation injuries/

In COCHRANE: (10/10/11)
1. (adverse event*) or (complication*) or (late NEAR/2 toxicit*) or (dysfunction) or (function*) or (patient reported outcome*) or (quality of life)
OR MeSH descriptor Radiation Injuries
2. (radiation) or (radiotherap*) or (chemoradiation) or (chemoradiotherap*) or (irradiation) in Cochrane Reviews and Clinical Trials
OR MeSH descriptor Combined Modality Therapy
OR MeSH descriptor Radiotherapy
3. (rectum or rectal) NEAR/2 (cancer* or carcinoma* or neoplasm* or tumo?r*) in Cochrane Reviews and Clinical Trials
OR MeSH descriptor Rectal Neoplasms

3.2.2 Selection criteria

All Phase II and III RCTs in adult patients with a localised resectable rectal cancer were eligible if patients were randomised to at least one arm of preoperative radiation or chemoradiation. Studies of patients treated only with postoperative radiation were excluded unless in a comparison study with a preoperative radiotherapy arm. Studies of surgery alone, intraoperative radiation or brachytherapy were not eligible. Conference abstracts were excluded.

3.2.3 Outcome measures examined

Studies including clinician-reported toxicity and/or patient reporting on symptoms or some other aspect of health-related quality of life (HRQOL) as a primary or secondary outcome were considered. PROs were defined as any reports coming directly from the patient(45). Late toxicity was defined by side effects present from three months post radiotherapy treatment(53). Any secondary analysis papers of late toxicity were reviewed in conjunction with the original publication. Multi-dimensional PRO measures (for example a measure covering different aspects of functioning such as physical, emotional or cognitive function) or single-item health outcomes were included if patient-reported. Clinician conducted interviews, structured using PRO questionnaires, were considered as clinician-reported. Studies reporting post-operative complications or patient satisfaction were excluded.

3.2.4 Data extraction and type of information extracted

The identified RCTs were assessed using a predefined data extraction form adapted from a published checklist to include clinician-reported toxicity studies(139). Data on toxicity measures and detailed information on how toxicity was reported was extracted using QUANTEC recommendations(92). Three reviewers (Alex Gilbert (AG), Lucy Ziegler (LZ), Maisie Martland) independently screened the titles and abstracts of all retrieved studies. In cases of disagreement the full articles were revisited to reconcile differences and achieve consensus. AG and LZ independently extracted and analysed the data from all chosen articles. Differences were reconciled through discussion.

Data was extracted into a predefined database for each RCT on (1) basic trial demographics (e.g. publication year, trial phase, design); (2) clinical demographics (e.g. overall sample size, sample size for toxicity reporting, treatment regimens, primary endpoints); (3) adverse event reporting (e.g. toxicity measure(s) used, grade and percentage of toxicity reported) and (4) methodological quality (e.g. quality of PRO-reporting, risk of bias assessment, statistical analysis and presentation of results).

In trials with multiple publications the results are presented separately when data on different side effects and/or time points was presented or the methodological reporting quality varied.

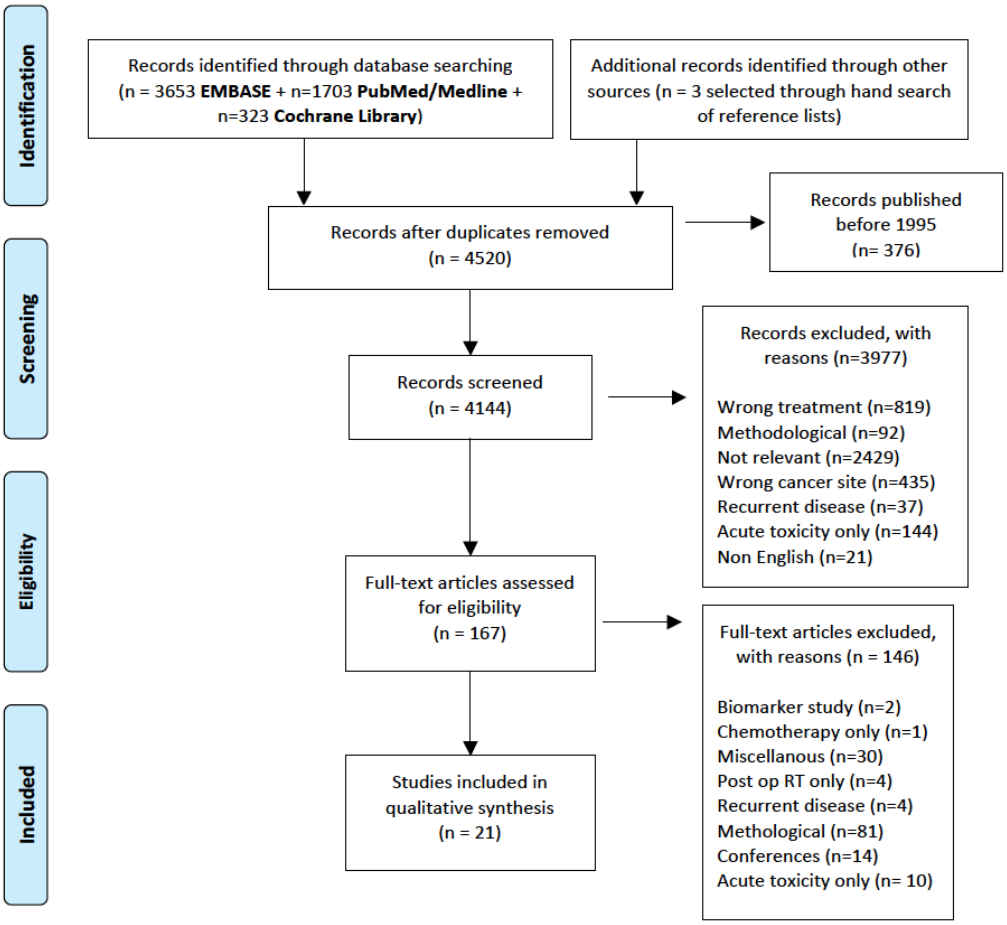
3.2.5 Quality assessment of RCTs and PRO reporting

Internal validity was assessed by applying the Cochrane Risk of Bias tool to evaluate: adequacy of sequence generation; allocation concealment; blinding; incomplete outcome data; selective reporting; and other potential threats to validity(150). PRO quality assessment was adapted from the recently published ISOQOL recommended standards (142).

3.3 Systematic review results

The search yielded 5682 records (Figure 3.1). 4144 records were screened after duplicates and articles published before 1995 were removed. 21 publications representing data from 13 different RCTs fulfilled the inclusion criteria (see Table 3.1). The median duration of follow up for all studies was 5 years (range 1-15 years). Toxicity was a secondary endpoint in all but one trial. Park et al(151) included toxicity as part of multiple primary endpoints. In the studies where statistically significant cancer outcomes were achieved (Stockholm/Swedish; Dutch Total Mesorectal Excision (TME) and CRO7 trials), these were associated with deterioration in some aspect of patient or clinician-reported late toxicity (see Table 3.1 for details)(152, 153). Only one trial disclosed industry funding/affiliations(154).

Figure 1: PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 3-1: PRISMA 2009 Flow Diagram

Table 3-1: Clinical trial demographics

Reference	Country	Years of study	Design of Toxicity measurement	Patient and/or clinician reported (P/C)	Design	Trial name	Participants in overall study (Participants in toxicity follow up)	Timing of toxicity follow up (median years)	Primary end point	Treatment arms	RT dose	Details of concurrent chemotherapy	Difference in primary outcome	Summary PRO/toxicity difference between treatment arms
Pollack et al 2006 (26)	Sweden	1980-1993	Cross sectional	P & C	Phase I&II	Stockholm trials	1406 (139)	15	Overall survival	Preop RT vs surgery alone	25Gy in 5#	Nil	Yes	Yes - Preop RT more late toxicity (mainly CVD, fecal and urinary incontinence) than surgery alone (69% vs 43%; p=0.002)
Pollack et al 2006 (27)	Sweden	1980-1993	Cross sectional	P & C	Phase I&II	Stockholm trials	1406 (64 – LAR patients only)	15	Overall survival	Preop RT vs surgery alone	25Gy in 5#	Nil	Yes	Yes - Preop RT more anorectal toxicity than surgery alone (Fecal incontinence 57% vs 26%; p=0.01; frequency of bowel movements per week 20 vs 10; p=0.02). No differences in overall HRQOL.
Dahlberg et al 1998 (28)	Sweden	1987-1990	Cross sectional	P	Phase III	Swedish Rectal Cancer Trial	1168 (171)	6.7	Local recurrence and OS	Preop RT vs surgery alone	25Gy in 5#	Nil	Yes	Yes - Preop RT more bowel toxicity than surgery alone (frequency of bowel movements per week 20 vs 10; p<0.001; fecal incontinence loose stools 50% vs 24%; p<0.001)
Bosset et al 2006 (29)	France	1993-2003	Longitudinal	C	Phase III	22921 EORTC	1011 (1011)	5.4	Overall survival	Preop CRT vs preop RT +/- postoperative chemotherapy	45Gy in 25#	5FU week 1 & 5 +/- 4 cycles of 3 weekly postoperative 5FU	No	No significant differences (fecal incontinence in 9% of patients following sphincter-sparing resection)
Tiv et al 2010 (30)	France	1993-2003	Cross sectional	P	Phase III	22921 EORTC	1011 (207)	4.6	Overall survival	Preop CRT vs preop RT +/- postoperative chemotherapy	45Gy in 25#	5FU week 1&5 +/- 4 cycles of 3 weekly postoperative 5FU	No	Yes – patients treated with addition of chemotherapy to preop or postop RT had worse diarrhea (RT 6.9 vs +chemotherapy 21.3*; p=0.001) and lower role (90 vs 83**, p=0.03) and social functioning (85 vs 75**; p=0.02) as well as worse global QOL scores (78 vs 71**; p=0.02). All patients reported low scores for sexual function (18.9**).
Taher et al 2006 (31)	Egypt	1994-1999	Longitudinal	C	Phase III	RCT	50 (50)	5.2	Local recurrence and OS	Preop RT vs post op CRT	Preop 46Gy in 23# vs post op 50Gy in 25# (5FU)	Post op CRT: Concurrent 5FU first 3 days of first and last week of RT	No	No significant differences in late radiation-related toxicity (Grade 3+ radiation-related toxicity reported in 1 patient). Acute grade 3+ radiation-related toxicity: post op CRT 34.6% vs 8.3%; p=0.039.

Reference	Country	Years of study	Design of Toxicity measurement	Patient and/or clinician reported (P/C)	Design	Trial name	Participants in overall study (Participants in toxicity follow up)	Timing of toxicity follow up (median years)	Primary end point	Treatment arms	RT dose	Details of concurrent chemotherapy	Difference in primary outcome	Summary PRO/toxicity difference between treatment arms
Sauer et al 2004 (32)	Germany	1995-2002	Longitudinal	C	Phase III	RCT	421 (421)	3.82	Overall survival	Preop CRT vs post op CRT	50.4 Gy in 28# (5FU)	Concurrent 5FU daily weeks 1 and 5	No	Yes - Worse acute and late grade 3+ toxicity in post op CRT vs preop CRT (Acute: 40% vs 27% ; p=0.001; Late: 24% vs 14%; p=0.01)
Braendengen et al 2011 (33)	Norway	1996-2003	Cross sectional	P & C	Phase III	RCT	207 (105)	6.7	Overall survival	Preop CRT vs preop RT	50Gy in 25 (+/- 5FU)	Concurrent 5FU days 1-2, 11-12 and 21-22.	No	Yes - More patients (without a stoma) in the CRT group had good anal function vs RT (using St Mark's score for fecal incontinence): 30% vs 11% (p=0.046). Severe erectile dysfunction reported in both groups (Mean 6.9 vs 10.4: using IIEF)
Braendengen et al 2012 (34)	Norway	1996-2003	Longitudinal	P	Phase III	RCT	207 (105)	6.7	Overall survival	Preop CRT Vs preop RT	50Gy in 25 (+/- 5FU)	Concurrent 5FU days 1-2, 11-12 and 21-22.	No	No statistically significant differences found in HRQOL. A clinically significant reduction in physical functioning found in both groups (CRT: 94 to 86*; RT: 94 to 87*)
Marijnen et al 2005 (35)	The Nether-lands	1996-1999	Longitudinal	P	Phase III	Dutch TME trial	1861 (786)	2	Local recurrence	Preop RT vs TME	25Gy in 5#	Nil	Yes	Yes - Preop RT worse sexual function than surgery alone (males: p=0.004; females: p <0.001). Preop RT slower recovery of bowel function and worse fecal incontinence (51.3% vs 36.5%; p= 0.002). No differences in overall QOL.
Peeters et al 2005 (36)	The Nether-lands	1996-2000	Cross sectional	P	Phase III	Dutch TME trial	1861 (597)	5.09	Local recurrence	Preop RT vs TME	25Gy in 5#	Nil	Yes	Yes – Preop RT worse fecal incontinence than surgery alone (62% vs 38%; p=0.001) with bowel function impacting on ADLs (34% vs 22%; p=0.01). No differences in urinary function or overall QOL.
Lange et al 2007 (37)	The Nether-lands	1996-1999	Longitudinal	P	Phase III	Dutch TME trial	1861 (399)	5	Local recurrence	Preop RT vs TME	25Gy in 5#	Nil	Yes	Yes - Preop RT worse fecal incontinence than surgery alone (61.5% vs 38.8%; p<0.001).
Lange et al 2008 (38)	The Nether-lands	1996-1999	Longitudinal	P	Phase III	Dutch TME trial	1861 (785)	5	Local recurrence	Preop RT vs TME	25Gy in 5#	Nil	Yes	No significant differences in urinary function. Incontinence reported in 38.1% of all patients (72% had normal function pre treatment).

Reference	Country	Years of study	Design of Toxicity measurement	Patient and/or clinician reported (P/C)	Design	Trial name	Participants in overall study (Participants in toxicity follow up)	Timing of toxicity follow up (median years)	Primary end point	Treatment arms	RT dose	Details of concurrent chemotherapy	Difference in primary outcome	Summary PRO/toxicity difference between treatment arms
Lange et al 2009 (39)	The Nether-lands	1996-1999	Longitudinal	P	Phase III	Dutch TME trial	1861 (526)	2	Local recurrence	Preop RT vs TME	25Gy in 5#	Nil	Yes	Yes – Preop RT was a risk factor for deterioration in male sexual function (p=0.003) and ejaculatory problems (p=0.026). Preop RT was the only risk factor for deterioration in female sexual functioning (p=0.033).
Stephens et al 2010 (40)	UK	1998-2005	Longitudinal	P	Phase III	CRO7	1350 (1208)	2	Local recurrence	Preop RT vs selective postop CRT	25Gy in 5# vs selective 45Gy in 25# (5FU)	Concurrent CVI 5FU or weekly bolus	Yes	Yes - Preop RT worse fecal incontinence than selective postop CRT (53.2% vs 37.3%; p=0.007). Deterioration in male sexual function following treatment in all groups (p<0.001).
Bujko et al 2006 (41)	Poland	1999-2002	Cross sectional	C	Phase III	RCT: phase III	316 (221)	1	Sphincter preservation of 15%	Preop CRT vs preop RT	25Gy in 5# or 50.4Gy in 28# (5FU)	Concurrent 5FU daily week 1 & 5	No	No significant differences in overall late radiation-related toxicity (CRT: 27% vs RT: 28.3%; p=0.81) or grade 3+ toxicity (CRT: 10·1% versus RT: 7·1%; P = 0·360). Acute radiation-related toxicity was higher in CRT group (18·2% vs 3·2%; p < 0·001).
Pietrzak et al 2007 (42)	Poland	1999-2002	Cross sectional	P	Phase III	RCT: phase III	316 (221)	1	Sphincter preservation of 15%	Preop CRT vs preop RT	25Gy in 5# or 50.4Gy in 28# (5FU)	Concurrent 5FU daily week 1 & 5	No	No significant differences in QOL (RT: 57* vs CRT: 61*; p=0.22) or anorectal function (estimated as good/very good RT: 41% vs CRT 37%; p=0.52) or sexual function (males: p=0.56; females: p=0.1)
Mohiuddin et al 2006 (43)	USA	2001-2003	Longitudinal	C	Phase II	RCT: Phase II	106 (106)	3	Pathologic complete response	Pre op CRT (5FU) vs preop CRT (5FU & irinotecan)	55.2 to 60Gy (5FU) in 1.2Gy bid vs 50.4 to 54Gy at 1.8Gy per day (5FU& irinotecan)	Concurrent CVI 5FU or CVI 5FU and weekly irinotecan	No	No significant differences in overall late radiation-related toxicity (CRT +irinotecan: 8% vs CRT: 4%) or acute chemotherapy or grade 3+ radiation-related toxicity (42% vs 31%).
Ngan et al 2012 (44)	Australia/NZ	2001-2006	Longitudinal	C	Phase III	RCT	326 (313)	5	Local recurrence	Preop CRT vs preop RT	25Gy in 5# and 50.4Gy in 28# (5FU)	Concurrent 5FU daily 7 days a week.	No	No significant differences in any grade 3+ toxicity late radiation-related toxicity (CRT: 8.2% vs RT: 5.8%; p=0.53) or grade 3+ small/large bowel toxicity (CRT: 5.1% vs RT 3.2%; p=0.53)

Reference	Country	Years of study	Design of Toxicity measurement	Patient and/or clinician reported (P/C)	Design	Trial name	Participants in overall study (Participants in toxicity follow up)	Timing of toxicity follow up (median years)	Primary end point	Treatment arms	RT dose	Details of concurrent chemotherapy	Difference in primary outcome	Summary PRO/toxicity difference between treatment arms
Park et al 2011 (45)	Korea	2004-2006	Longitudinal	C	Phase III	RCT: Phase III	240 (240)	4.3	OS, local control, sphincter preservation and toxicity	Preop CRT vs post op CRT	50Gy in 25# (CAP)	Capecitabine BD (without weekend breaks) daily during RT	No	No significant differences in any grade 3+ late radiation-related toxicity (preop CRT: 8% vs postop CRT: 3%; p=0.35) or acute toxicity (15% vs 16%; p=0.83).
Gerard et al 2012 (46)	France	2005-2008	Longitudinal	P & C	Phase III	ACCORD 12/0405 PRODIGE 2	598 (575)	3	Pathological complete response	Preop CRT (CAP45) vs Preop CRT (CAPOX50)	45Gy in 25# (CAP45) vs 50Gy in 25# (CAPOX50)	CAP45 - Capcitabine BD each radiation day. CAPOX50 - Capecitabine BD each radiation day. Plus oxaliplatin once a week for 5 weeks	No	No significant differences in any grade 3+ late radiation-related toxicity, over 3 year follow up (CAP45: 6.5% vs CAPOX50: 5.4%) or fecal incontinence (16% vs 20%). 71% of all patients reported erectile dysfunction following treatment (35% before).

Key 1: RCT - Randomised controlled trial; RT - radiotherapy; CRT - chemoradiotherapy; # - fraction; TME - total mesorectal excision; 5FU - 5 – flurouracil; CVI – continuous venous infusion; OS – overall survival; HRQOL – Health related quality of life; CVD – cardiovascular disease; ADL – activities of daily living. *EORTC-QLQ symptom mean scores: Scores range from 0-100 with higher scores indicating more symptoms. **EORTC-QLQ function mean scores: Scores range from 0-100 with higher scores indicating fewer functional problems. IIEF - International index of erectile function (Score ranges from 1-30 with lower scores indicating more functional problems.

3.3.1 Methods of toxicity reporting: Clinician-reporting versus PROs

Table 3.2 summarises the data extracted from the publications using QUANTEC recommendations for toxicity reporting. In total, 15 different PRO instruments were used in 14 publications and seven different clinician-reported instruments in 11 publications. RTOG/EORTC was used most commonly for late toxicity clinician-reporting (n=4) followed by the CTCAE (n=2). The EORTC-QLQ core questionnaire (C30) and colorectal cancer-specific module (CR38) were the most commonly used validated PROs (n=4/n=2 respectively). Baseline symptoms alongside acute and/or late PRO toxicity were reported in 6 out of the 7 longitudinal PRO studies (18, 154-158). The remaining eight PRO studies used a cross sectional design to assess late toxicity or HRQOL at a single time-point. Only one of the 11 longitudinal clinician-reported papers published baseline symptoms(154). In almost half of the clinician-reported papers only the more severe grades of toxicity, ≥grade 3, were reported (n=5; 45%). In comparison 79% (n=11) of the PRO publications, reported data on the full range of toxicities (from no symptoms to severe toxicity).

The most frequently reported late adverse event in any RCT was related to bowel toxicity (84% of publications) followed by urinary dysfunction (40%) (Table 2). *None* of the 11 clinician-reported papers reported on sexual dysfunction. 50% (n=7) of the PRO publications covered sexual dysfunction, 43% (n=6) also reported on HRQOL, mainly using the EORTC QLQ-C30 (n=4). Skin toxicity (n=5; 45% clinician-reported papers) and hematological toxicity (n=5; 45%) are reported in the clinician-reported papers and not in the PRO publications.

The majority of clinician-reported publications grouped symptoms referable to the bowel or bladder as a single organ, reporting on ‘small/large bowel’ or ‘bowel’ or ‘bladder’ toxicity or only reporting *all* ≥grade 3 toxicities (n=7; 64%). In comparison, all PRO studies (n=14; 100%) reported a breakdown of individual symptoms, for example fecal incontinence, or a combination of individual symptoms and a summary score of multiple items as implemented in the EORTC-QLQ system.

Table 3-2: Comparison between toxicity reported by clinician reported instruments and patient reported measure using QUANTEC recommendations for reporting*

	RCT PUBLICATIONS REPORTING ON TOXICITY WITH PATIENT REPORTING		RCT PUBLICATIONS REPORTING ON TOXICITY WITH CLINICIAN REPORTING	
TOTAL NUMBER OF RCT PUBLICATIONS INCLUDED (N=21)	14 (References: 26-28, 30, 33-40, 42, 46)		11 (References: 26, 27, 29, 31-33, 41, 43-46)	
Publications with both patient and clinician reporting N=4* (References: 26, 27, 33, 46)				
COCHRANE RISK OF BIAS				
Overall number of RCTs with a overall low risk of bias assessed	11		5	
TOXICITY INSTRUMENT USED				
	Modified or self created questionnaires	6	CTCAE v2	1
	ASCRS QOL questionnaire	1	CTCAE v3	1
	ASCT questionnaire	1	German Classification system	1
	EORTC QLQ C30	4	Interviews	3
	EORTC QLQ C38	2	RTOG/EORTC late radiation morbidity scoring criteria	4
	IIEF	1	St Marks score for faecal incontinence	1
	Rotterdam symptom checklist	1	WHO	1
	SF36	1	Not reported	1
	SVQ	1		
	Visual analogue scale QOL	2		
Total number of instruments used	15		7	
REPORTING OF TOXICITY				
Baseline symptom reporting	Yes	6	Yes	1
	No	8	No	10
Acute symptom reporting	Yes	6	Yes	9
	No	8	No	2
Are all grades of toxicity reported (from mild to severe symptoms)?	Yes, all grades	11	Yes, all grades	3
	No, more severe grades only (grade 3+)	1	No, more severe grades only (grade 3+)	5
	No, presence or absence of symptom	2	No, presence or absence of symptom	3
Most frequent type of toxicity reported	**Bowel**	**11**	**Bowel**	**10**
	Urinary	**5**	**Urinary**	**5**
	Sexual	**7**	Sexual	0
	HRQOL	**6**	HRQOL	0
	Skin	0	**Skin**	**5**
	Haematological	0	**Haematological**	**5**
Are various symptoms referable to a single organ grouped together (e.g. urinary frequency and incontinence grouped as 'bladder symptoms')?	Yes (grouped symptoms)	0	Yes (grouped symptoms)	5
	No (individual symptoms)	11	No (individual symptoms)	2
	Both	3	Both	2
	Unclear	0	Unclear	2

*For the four papers including data from both clinician-reporting and patient-reporting each of the different reports is considered separately.

KEY: HRQOL - Health related quality of life; ASCRS - American Society of Colon and Rectal surgeons QOL questionnaire; ASCT - Anal Sphincter-conserving treatment questionnaire; SF 36 – Short form health survey; EORTC QLQ - European Organisation for Research and Treatment of Cancer quality of life questionnaire; IIEF – International index of erectile function; SVQ – Sexual function-vaginal changes questionnaire; WHO – World Health organisation, CTCAE – Common Terminology for Common Adverse Events.

3.3.2 Frequency of symptomatic toxicity: Clinician-reporting versus PROs

Table 3.3 shows the frequency of toxicity reported as a range of percentages separated by treatment received. Higher rates of toxicity symptoms were described in the patient-reported papers in comparison with clinicians. In the clinician-reported papers ≥grade 3 bowel toxicity was reported at rates ranging from 1.4-9%. Faecal incontinence and diarrhoea were reported at rates of around 9%. Bladder toxicity ≥grade 3 was reported at lower rates between 1-2%.

In the patient-reported papers, faecal incontinence rates varied between 8-50% for solid stools and 24-72% for liquid (or non-specified) stools. Urinary incontinence rates were between 18-45%. None of the clinician-reported papers mentioned sexual dysfunction, which was reported in seven PRO papers. Between 70-80% of male patients reported a decline in sexual function, with 71% reporting erectile dysfunction in one study(154). Another study reported severe dysfunction scores using the International Index of Erectile Function questionnaire(159). EORTC-QLQ-CR38 mean scores for sexual dysfunction ranged from 40.8 to 65.7 (with a higher score, up to 100, indicating more problems). In women, 41-52% reported a decline in sexual function(160) and EORTC-QLQ-CR38 mean scores ranged from 29.9 to 50(18). 86-100% vaginal dryness and dyspareunia ranging between 50-86% was reported in one study(159). Two PRO studies were unable to report in detail on sexual dysfunction outcomes due to a paucity of response data(158, 161).

The results of the 22921-EORTC trial reveal the potential differences in clinician-reported toxicity and PRO data over and above the clear differences in symptom frequency reported. The clinician-reported paper did not detect/find any significant differences in toxicity between the four different treatment arms(162). However, the cross-sectional PRO study using the EORTC QLQ-C30/CR38 found an increase in diarrhoeal symptoms in patients treated with chemotherapy at any stage as well as lower social and role functioning and overall global QOL(161).

Table 3-3: Prevalence of toxicity reported by treatment type according to clinician or patient reports (PRO)

	RANGE OF TOXICITY REPORTED BY TREATMENT TYPE (References in parentheses)				
TYPE OF TOXICITY	Surgery alone	Short course RT (25Gy in 5)	Long course RT (45-50.4Gy in 25-28)	Long course 5FU CRT (45-50.4Gy in 25-28)	Long course 5FU CRT with additional chemotherapy (45-50.4Gy in 25-28)
CLINICIAN-REPORTED					
ANY GRADE 3+ TOXICITY (%)				**1.3-14** (31, 32, 43, 45, 46[†])	**1-8** (43, 46)
BOWEL SYMPTOMS					
Grade 3+ bowel toxicity (%)		**3.2-5.1** (41, 44)		**1.4-9** (32, 41, 43, 44)	**4** (43)
Faecal incontinence (%)				**9** (29)	**9** (29)
Diarrhoea (% Grade 2+)				**9.6** (29)	**9.6** (29)
URINARY SYMPTOMS					
Grade 3+ urinary toxicity (%)		**1.3-1.4** (41, 44)		**0.7-2** (32, 41, 43, 44)	**0** (43)
PATIENT-REPORTED					
BOWEL SYMPTOMS					
Fecal incontinence (%)	**24-38.8** (26, 27, 28, 35, 36, 37, 40)	**50-62** (26, 27, 28, 35, 36, 37, 40)			
Fecal incontinence (liquid stools) (%)		**72** (42)	**38** (33)	**58-66** (33, 42)	
Fecal incontinence (solid stools) (%)		**42** (42)	**13** (33)	**8-50** (33, 42)	
Frequency (median times per day)	**1.4-3** (27, 28, 36)	**2.8-4** (27, 28, 36, 42)		**5** (42)	
Urgency (unable to defer <10mins) (%)		**60 (Very often 7%)** (42)		**64 (Very often 8%)** (42)	
Urgency (median deferral time/mins)	**10** (28)	**5** (28)			
URINARY SYMPTOMS					
Urinary incontinence (%)	**27-38.1** (26, 36, 38)	**38.1-45** (26, 36, 38)	**18** (33)	**28** (33)	
SEXUAL DYSFUNCTION (MALES)					
Sexual function (EORTC-QLQ CR38 mean scores*)	**40.8- 57.4** (35, 40)	**47.4 - 65.7** (35, 40)			
Decline in sexual life (%)		**80** (42)		**70** (42)	
Erectile dysfunction (%)	**47.1** [(35)EORTC-QLQ CR38 mean scores]	**53.9** [(35)EORTC-QLQ CR38 mean scores]	**10.4** [(33) IIEF mean score**]	**71** (%)(42) **and 6.9** [(33) IIEF mean score**]	**71** (42)
Ejaculation dysfunction [EORTC-QLQ CR38 mean scores*]	**31.7** (35)	**42.5** (35)			

	RANGE OF TOXICITY REPORTED BY TREATMENT TYPE (References in parentheses)				
TYPE OF TOXICITY	Surgery alone	Short course RT (25Gy in 5)	Long course RT (45-50.4Gy in 25-28)	Long course 5FU CRT (45-50.4Gy in 25-28)	Long course 5FU CRT with additional chemotherapy (45-50.4Gy in 25-28)
SEXUAL DYSFUNCTION (FEMALES)					
Sexual function [EORTC-QLQ CR38 mean scores*]	**29.9** (35)	**50** (35)			
Decline in sexual life (%)		**41** (42)		**52** (42)	
Vaginal dryness (%)			**100** (33)	**86** (33)	
Dyspareunia (%)			**50** (33)	**86** (33)	

Key: References in parentheses; *EORTC-QLQ symptom mean scores: Scores range from 0-100 with higher scores indicating more symptoms. ** IIEF - International index of erectile function: Score ranges from 1-30 with lower scores indicating more functional problems (1 to 10 – severe dysfunction).

3.3.3 Quality assessment of RCTs and PRO reporting

The RCTs varied little in the Cochrane Risk of Bias tool assessment with 16 studies with an overall low risk of bias assessed (76%; table 3.2). The response rates for the studies including PROs varied widely. The response rates for single cross-sectional assessments (n=6) varied between 55 and 90% and from 49% to 89% in longitudinal studies with 2 to 5 year follow up (n=7). Paper data collection was used in seven studies and was not explicitly stated in the remaining seven studies.

Table 3.4 shows the evaluation of PRO quality using the recently published ISOQOL recommended standards(142). The quality of the reporting was highly variable. Three previously recommended key methodological criteria were considered(163): reporting of baseline data; statistical methodology for missing data; and the use of validated instruments. Only 43% of PRO studies presented baseline data(18, 155-158, 164)and 29% of studies described statistical methods for managing missing data (18, 155, 156, 158). One of the main difficulties was that eight of the PRO RCTs had used a cross-sectional design and thus could not provide baseline data (160, 165-168). 28% (n=4) studies did not use any psychometrically validated PRO instruments. The remaining studies either used solely psychometrically validated instruments(n=5; 36%) or a combination of validated and non-validated PROs or modified instruments (n=5; 36%).

Table 3-4: Overview of RCTs PRO quality of reporting

		TOTAL: n = 14 (%)
TITLE AND ABSTRACT		
The PRO should be identified in the abstract as a primary or secondary outcome (If PRO or QOL mentioned in the title/abstract this is sufficient for 'Yes')	No	2 (14)
	Yes	12 (86)
Note all included PRO studies reported on adverse events as a secondary outcome.		
INTRODUCTION, BACKGROUND AND OBJECTIVES		
Include background and rational for PRO assessment	No	1 (7)
	Yes	13 (93)
The PRO hypothesis should be stated and relevant domains identified, if applicable	No	2 (14)
	Yes	12 (86)
METHODS		
Participants: Not PRO-specific, unless the PROs were used in eligibility or stratification	No	0 (0)
	Yes	0 (0)
	N/A	14 (100)
Outcomes: Evidence of PRO instrument validity and reliability should be provided or cited if available (Both – includes a mix of validated and non validated instruments or validated instruments used methodologically in a non-validated way)	No	4 (28)
	Yes	5 (36)
	Both	5 (36)
Outcomes: States methods of data collection	Not stated	6 (43)
	Paper	5 (36)
	Paper or interview	3 (21)
	Electronic	0 (0)
Outcomes: States who completed the assessment	Patients	11 (79)
	Patient and clinician (through interviews)	3 (21)
Sample size: Not required for PRO unless it is a primary outcome	N/A	N/A
RANDOMIZATION		
Statistical methods: Statistical approaches for dealing with missing data are explicitly stated	No	10 (71)
	Yes	4 (29)
RESULTS		
Participant flow: The number of PRO outcome data at baseline and at subsequent time points should be made transparent	No	4 (29)
	Yes	10 (71)
Baseline data: Include baseline PRO data when collected	No	8 (57)
	Yes	6 (43)
Numbers analysed: Include number of participants (denominator) in each analysis and whether analysis was by original assigned group	No	0 (0)
	Yes	14 (100)

RESULTS		
Outcomes and estimations: For multidimensional PROs provide results and effect sizes from each domain and time point	No	0 (0)
	Yes	14 (100)
Outcomes and estimations: Report estimated effect size, and it's precision	No	9 (67)
	Yes	5 (33)
DISCUSSION		
Limitations: PRO-specific limitations	No	3 (25)
	Yes	11 (75)
Limitations: Implications for generalizability and implications for clinical practice	No	0 (0)
	Yes	14 (100)
Interpretation: PRO data should be interpreted in relation to clinical outcomes including survival data, where relevant	N/A	6 (43)
	No	1 (7)
	Yes	7 (50)

3.4 Scoping literature review methods in Gynaecological cancers and anal cancer

3.4.1 Search strategy and selection criteria

All electronic searches were conducted in Medline and included studies from 1995 to September 2013. The search strategy was restricted to studies that included PROs for clinical studies in the gynaecological cancers. In anal cancer the search strategy was expanded to include all toxicity studies, not just studies including patient reporting, due to small numbers of relevant studies in anal cancer. RCTs and clinical studies using a prospective or cross-sectional design reporting on radiotherapy toxicity, both acute and late toxicity, were included. Retrospective, case series or case-control studies were excluded. Studies reporting on surgery or brachytherapy alone were excluded. Conference abstracts were excluded. The PROMOTION review results were hand checked to ensure all relevant RCTs were included for the gynaecological cancer studies(46). The results of the systematic review completed by the anal cancer EORTC Quality of life group were checked to ensure all relevant studies were included in the anal cancer review(143). The electronic search strategies are presented below:

ENDOMETRIAL
1. ((endometri* or uter*) adj2 (cancer* or carcinoma* or neoplasm* or tumo?r*)).mp.
MeSH term: Uterine Cervical Neoplasms/ , Endometrial neoplasms
2. radiation, radiotherap*, chemoradiation, chemoradiotherap*, irradiation,
MeSH terms: Radiotherapy/OR combined modality therapy.
3. adverse event*, dysfunction, function*, (late adj2 toxicit*), complication*, quality of life, patient reported outcome*, survey*, questionnaire*
MeSH keyword: radiation injuries/
4. limit to English language

CERVIX
1. ((cervix or cervical) adj2 (cancer* or carcinoma* or neoplasm* or tumo?r*)).mp.
MeSH term: Uterine Cervical Neoplasms/

2. radiation, radiotherap*, chemoradiation, chemoradiotherap*, irradiation,
MeSH terms: Radiotherapy/OR combined modality therapy.
3. adverse event*, dysfunction, function*, (late adj2 toxicit*), complication*, quality of life, patient reported outcome*, survey*, questionnaire*
MeSH keyword: radiation injuries/
4. limit to English language

ANAL
1. ((anus or anal) adj2 (cancer* or carcinoma* or neoplasm* or tumo?r*)).mp.
MeSH term: Anus Neoplasms/
2. radiation, radiotherap*, chemoradiation, chemoradiotherap*, irradiation,
MeSH terms: Radiotherapy/OR combined modality therapy.
3. adverse event*, dysfunction, function*, (late adj2 toxicit*), complication*, quality of life, patient reported outcome*, survey*, questionnaire*
MeSH keyword: radiation injuries/
4. limit to English language

3.4.2 Data extracted

The identified studies were assessed using a predefined data extraction form. Data was extracted on trial design and the type and frequency of PRO measures used in all cancer sites to provide a quantitative assessment of the type of PROs in use in clinical trials. In addition, as a comparison to the rectal cancer systematic review results, in the anal cancer scoping review the type and frequency data on the clinician reported instruments was also extracted. One reviewer (AG) screened the titles and abstracts of all retrieved studies before reviewing the full articles. The data was extracted from the full text articles.

3.5 Scoping review results

3.5.1 Endometrial cancer

78 titles and abstracts were reviewed following removal of duplicate articles (n=2). 10 studies met the eligibility criteria and reported on radiotherapy AE using PROs (see table 3.5)(169-178). Only two studies used a RCT design, two were prospective and the remaining six were a cross-sectional study design. The most commonly used PROs were EORTC-QLQ-C30 (n=5) and supporting modules (n=7), SF36 (n=3) and Female-sexual-function-index (n=2). The EORTC supporting module varied significantly for the studies because the EORTC-EN24 (endometrial cancer module) was only fully validated for use in 2011(178). Only one cross sectional study used EN24(178) and the remaining six studies either used the cervical cancer module (CX24) as a complete module or combined CX24 with the ovarian cancer module (OX28) or the prostate cancer module (PR25). All of the studies used validated instruments for patient reporting. Only two studies included additional non-validated items(169, 171).

Table 3-5: Type and frequency of PRO instruments used in Endometrial cancer studies

REFERENCE	EORTC QLQ C30	EORTC EN24	EORTC CX24	EORTC OX28	EORTC PR25	FACT	FSFI	SF 36	QUESTIONNAIRES	STUDY DESIGN	VALID-ATED
Klee et al 2001(169)	1	0	0	0	0	0	0	0	EORTC QLQ-C30 and 80 additional questions.	Prospective	Mix
Herwig et al 2004(170)	0	0	0	0	0	0	0	0	Validated (urinary) incontinence questionnaire	Cross sectional	Yes
van de Poll-Franse et al 2007(171)	0	0	0	0	0	0	0	1	SF-36, and Quality of Life-Cancer Survivors (QOL-CS) instrument (45-item visual analogue scale), and four additional items on sexual activity	Cross sectional	Mix
Erekson et al 2009(172)	0	0	0	0	0	0	0	0	Three validated questionnaires were used: the Sandvik Severity Index, the Urinary Distress Inventory-6 (UDI-6), and Incontinence Impact Questionaire-7 (IIQ-7).	Cross sectional	Yes
Le et at 2009(173)	1	0	0	0	0	0	0	0	EORTC QLQ-C30	Prospective	Yes
Nout et al 2009(174)	1	0	0	1	1	0	0	0	EORTC QLQ-C30 and subscales from the prostate cancer module, PR25, and the ovarian cancer module, OV28.	RCT	Yes
Becker et al 2011(175)	1	0	1	0	0	0	1	0	EORTC QLQ-C30 and the cervical cancer module, CX24. Sexual function evaluated using the Female Sexual Function Index (FSFI).	Cross sectional	Yes
Nout et al 2011(176)	0	0	1	1	1	0	0	1	SF-36 and subscales from EORTC-QLQ PR25 module for bowel and bladder symptoms and the OV28 and CX24 modules for sexual symptoms	RCT	Yes
Damast et al 2012(177)	0	0	0	0	0	0	1	0	Female Sexual Function Index (FSFI)	Cross sectional	Yes
van de Poll-Franse, 2012(178)	0	1	0	0	0	0	0	1	SF-36 and the EORTC-QLQ EN24	Cross sectional	Yes
TOTAL	**4**	**0**	**3**	**2**	**2**	**0**	**2**	**2**			

Key: RCT - Randomised controlled trial; RT – Radiotherapy; EORTC QLQ - European Organisation for Research and Treatment of Cancer quality of life questionnaire; FACT -Functional Assessment of Cancer Therapy; FSFI - Female Sexual Function Index; SF-36 - Short-Form Health Survey;

3.5.2 Cervical cancer

54 titles and abstracts of cervical cancer studies were reviewed following the removal of duplicate studies (n=3). 29 eligible studies were found (26 from the electronic search and 3 from hand searching the literature) and the full text reviewed. 23 used a cross sectional methodology, three studies were prospective, three used a longitudinal design but did not include baseline data (179-181) and only two studies were RCTs, both of which reported only on acute toxicity although longer term follow up is planned for the EMBRACE study(57). The most commonly used PRO was EORTC-QLQ C30 (n=13) and cervical cancer module, CX24 (n=10). Seven studies used the Hospital Anxiety and Depression Scale (HADS), five studies used the short form health survey (SF-36) and 6 studies used patient-reported questionnaires developed from LENT-SOMA and CTCAE (developed by Dr Susan Davidson and updated in 2009 to create the 'Pelvic Symptom Questionnaire'). The two RCTs used both EORTC-QLQ C30 and CTCAE for clinician reporting.

Four studies combined patients treated with (chemo)radiotherapy for cervical and endometrial cancer in the same analysis(182-185). Two studies were prospective, with one study comparing clinician-reporting of acute toxicity using CTCAE and RTOG compared to patient-reporting using WHO QOL BREF(182). The other study followed up patients for one year using the EORTC-QLQ C30 and CX24 and the HADS(185). Two studies used a cross-sectional design and used validated instruments (one using the EORTC QLQ-C30)(183, 184). Table 3.6 provides a summary of the cervical cancer and the combined gynaecological cancer studies.

Table 3-6: Type and frequency of PRO instruments used in Cervical cancer studies and studies including both cervical and endometrial patients

REFERENCE	EORTQLQ C30	EORTC CX24	MFI	STAI	HADS	FACT	FSFI	Sexual activity questionnaire	SF-36	LENT SOMA	Anal incontinence	QUESTIONNAIRE	CERVIX OR BOTH (including endometrial patients)	STUDY DESIGN	VALIDATED
Bermark et al 1999(186)	0	0	0	0	0	0	0	0	0	0	0	Developed own questionnaire (Swedish)	Cervix	Cross sectional	No
Klee et al 2000(180)	1	0	0	0	0	0	0	0	0	0	0	EORTC QLQ-C30 and additional specific questions.	Cervix	Longitudinal post completion of treatment	Mix
Klee et al 2000(181)	1	0	0	0	0	0	0	0	0	0	0	EORTC QLQ-C30 and additional specific questions.	Cervix	Longitudinal post completion of treatment	Mix
Bermark et al 2002(187)	0	0	0	0	0	0	0	0	0	0	0	Developed own questionnaire (Swedish)	Cervix	Cross sectional	No
Bukovic et al 2003(188)	0	0	0	0	0	0	0	0	0	0	0	Non-validated questionnaire	Cervix	Cross sectional	No
Davidson et al 2003(189)	0	0	0	0	0	0	0	0	0	1	0	LENT SOMA questionnaire. Validation study.	Cervix	Cross sectional	Yes
Davidson et al 2003(190)	0	0	0	0	0	0	0	0	0	1	0	LENT SOMA questionnaire and the Franco-Italian glossary	Cervix	Cross sectional	Yes
Jensen et al 2003(179)	0	0	0	0	0	0	0	0	0	0	0	EORTC-QLQ C30, Sexual Function-Vaginal Changes Questionnaire and the Uro-Gynecological Morbidity Questionnaire.	Cervix	Longitudinal post completion of treatment	Yes
Routledge et al 2003(191)	0	0	0	0	0	0	0	0	0	1	0	LENT-SOMA questionnaire.	Cervix	Prospective	Yes
Frumovitz et al 2005(192)	0	0	0	0	0	0	1	0	1	0	0	12-Item Short-Form Health Survey (SF-12) , Brief Symptom Index-18 (BSI-18), Menopausal Survey. The Abbreviated Dyadic Adjustment Scale (A-DAS),Cancer Rehabilitation Evaluation System (CARES), Female Sexual Function Index (FSFI).	Cervix	Cross sectional	Yes
Kamau et al 2007(193)	1	0	0	0	0	0	0	0	0	0	0	EORTC C30	Cervix	Cross sectional	Yes
Nagy et al 2007(194)	1	0	0	0	0	0	0	0	0	0	0	C30 and CTCAE v2. Acute toxicity only measured	Cervix	RCT	Yes
Park et al 2007(195)	1	1	0	0	0	0	0	0	0	0	0	EORTC QLQ-C30, CX24, and additional sexual function items.	Cervix	Cross sectional	Mix
Vistad et al 2007(196)	0	0	0	0	1	0	0	0	1	0	0	HADS, SF-36 and fatigue questionnaire (FQ)	Cervix	Cross sectional	Yes
Vistad et al 2008(196)	0	0	0	0	0	0	0	1	0	1	0	LENTSOMA questionnaire and the Sexual Activity Questionnaire (SAQ)	Cervix	Cross sectional	Yes
Distefano et al 2008(197)	0	0	0	0	1	0	0	0	1	0	0	SF-36 and Hospital Anxiety and Depression Scale (HADS) questionnaire	Cervix	Cross sectional	Yes
Abayomi et al 2009(183)	0	0	0	0	0	0	0	0	0	0	1	Anal incontinence questionnaire	Both	Cross sectional	Yes
Hsu et al 2009(184)	1	0	0	0	0	0	0		0	0	0	EORTC C30	Both	Cross sectional	Yes
Greimel et al 2009(198)	1	1	0	0	0	0	0	1	0	0	0	EORTC-QLQ C30, CX24, and the Sexual Activity Questionnaire (SAQ).	Cervix	Cross sectional	Yes
Kobashi et al 2009(199)	0	0	0	0	1	1	0	0	0	0	0	Japanese version of the HADS, the Functional Assessment of Cancer Therapy (FACT)-General, and the Rosenberg Self-esteem Scale.	Cervix	Cross sectional	Yes
Korfage et al 2009(200)	0	1	0	1	0	0	0	0	1	0	0	SF-36, EQ-5D, CX24 and 6-item State Trait Anxiety (STAI) Inventory	Cervix	Cross sectional	Yes

REFERENCE	EORTQLQ C30	EORTC CX24	MFI	STAI	HADS	FACT	FSFI	Sexual activity questionnaire	SF-36	LENT SOMA	Anal incontinence	QUESTIONNAIRE	CERVIX OR BOTH (including endometrial patients)	STUDY DESIGN	VALIDATED
Vaz et al 2009(182)	0	0	0	0	0	0	0	0	0	0	0	WHO QOL abbreviated version plus RTOG also used to measure acute toxicity.	Both	Prospective	Yes
Farnell et al 2010(201)	0	0	0	0	0	0	0	0	0	0	0	Patient-reported toxicity developed from CTCAE (feasibility and reliability study)	Cervix	Cross sectional	Yes
Hazelwinkel 2010(202)	0	0	0	0	0	0	0	0	0	0	0	Urogenital Distress Inventory (UDI) and Incontinence Impact Questionnaire (IIQ). (DUTCH)	Cervix	Cross sectional (match cohort - surgery vs surgery plus RT)	Yes
Kim et al 2010(203)	1	1	0	0	1	0	0	0	0	0	0	HADS, EORTC C30 and CX24 and McGill quality of lift questionnaire	Cervix	Cross sectional (match cohort - cervical cancer survivors vs controls)	Yes
Ljuca et al 2011(204)	0	1	0	0	0	0	0	0	0	0	0	EORTC-QLQ CX24	Cervix	Prospective	Yes
Vistad et al 2011(205)	0	0	0	0	1	0	0	0	1	1	0	HADS, SF-36, LENTSOMA questionnaire, chronic pelvic pain questions	Cervix	Cross sectional	Mix
Bjelic-Radisic et al 2012(206)	1	1	0	0	0	0	0	0	0	0	0	EORTC-QLQ C30 and CX24	Cervix	Cross sectional	Yes
Ferrandina et al 2012(207)	1	1	0	0	1	0	0	0	0	0	0	The Global Health Status scale of EORTC QLQ-C30 (GHS), the EORTC QLQ-CX24 (CX24) and the Hospital Anxiety and Depression Scale (HADS) questionnaire	Cervix	Prospective	Yes
Hazelwinkel 2012(208)	0	0	0	0	0	0	0	0	0	0	0	Urogenital distress inventory and defaecatory distress inventory. (DUTCH)	Cervix	Cross sectional	Yes
Kirchheiner et al 2012(57)	1	1	0	0	0	0	0	0	0	0	0	C30 and CX24 and CTCAE. Compared clinician and patient reported acute side effects.	Cervix	RCT	Yes
Yavas et al 2012(185)	1	1	0	0	1	0	0	0	0	0	0	EORTC-QLQ C30, CX24 and HADS	Both	Prospective	Yes
Le Borgne et al 2013(209)	1	1	1	1	0	0	0	0	0	0	0	SF-36, EORTC-QLQC30, CX24, MFI fatigue questionnaire, STAI for anxiety, and a life condition questionnaire were used.	Cervix	Cross sectional (match cohort - cervical cancer survivors vs controls)	Yes
TOTAL	**13**	**10**	**1**	**2**	**7**	**1**	**1**	**2**	**5**	**5**	**1**				

Key: RCT - Randomised controlled trial; RT – Radiotherapy; EORTC QLQ - European Organisation for Research and Treatment of Cancer quality of life questionnaire; FACT-C -Functional Assessment of Cancer Therapy-Colorectal; WHO – World Health organisation; QOL – Quality of life; CTCAE – Common Terminology for Common Adverse Events; MOS -Medical Outcomes Study; RTOG - Radiation Therapy Oncology Group; MSKCC – Memorial Sloan Kettering Cancer Center; MFI –Multidimensional Fatigue inventory; STAI - State Trait Anxiety Inventory; HADS - Hospital Anxiety and Depression Scale; FSFI - Female Sexual Function Index; LENT-SOMA - late effects in normal tissues subjective, objective, management and analytic scales

3.5.3 Anal cancer

252 abstracts and titles were reviewed following removal of duplicate studies. 34 studies reported on anal cancer toxicity following radiotherapy. Seven studies used PROs in their study design; five used a cross sectional methodology, one prospective and one was a RCT. The most commonly used PRO was the EORTC-QLQ C30 (n=4), CR38 (n=3) and the FACT-C (n=2). The majority of the studies including PROs were published from 2008, with only one cross sectional study published prior to this in 1999. The remaining studies reported on toxicity using clinician reporting; eight RCTs, 18 prospective studies and two cross sectional studies. An additional retrospective evaluation of cancer outcomes following IMRT was included due to prospective collection of toxicity data(210). The most commonly used reporting instruments were RTOG/EORTC (n=17) and CTCAE (n=15). RTOG/EORTC was more commonly used for assessment of late toxicity and CTCAE for acute toxicity reporting with this pattern of reporting seen in seven out of the 34 studies. Only one cross sectional study evaluated the impact of long term clinician reported toxicity and quality of life assessed using the FACT-C questionnaire with a median 5.6 year follow up post (chemo)radiation(211). Table 3.7 shows a summary.

Table 3-7: Type and frequency of PRO instruments used in anal cancer studies

REFERENCE	PATIENT REPORTED /CLINICIAN REPORTED /BOTH	PATIENT REPORTED OUTCOMES					CLINICIAN REPORTED INSTRUMENTS					INSTRUMENT DETAILS	STUDY DESIGN	ACUTE OR LATE TOXICITY REPORTED
		EORTC C30	EORTC-CR29	FACT- C	AS CT	MOS	MSKCC	WHO	RTOG	LENT-SOMA	CTCAE			
Flam et al 1996(212)	C	0	0	0	0	0	0	0	1	0	1	Chemotherapy - CTCAE and radiotherapy - RTOG	RCT	Acute
John et al 1996(213)	C	0	0	0	0	0	0	0	1	0	0	RTOG/EORTC late toxicity criteria. Specific criteria to grade anal toxicity were devised.	Prospective	Late
Martenson et 1996(214)	C	0	0	0	0	0	0	0	0	0	1	CTCAE	Phase 2	Acute
UKCCCR 1996(215)	C	0	0	0	0	0	0	0	0	0	0	Morbidity rates reported but instrument not defined	RCT	Both
Bartelink et al 1997(216)	C	0	0	0	0	0	0	1	0	0	0	Acute - WHO and Late - not reported	RCT	Both
Gerard et al 1998(217)	C	0	0	0	0	0	1	0	1	0	0	RTOG acute and late and MSKCC sphincter function scoring system	Prospective	both
Allal et al 1999(218)	C	0	0	0	0	0	0	1	1	0	0	Acute chemotherapy - WHO toxicity criteria.	Prospective	Both
Allal et al 1999(219)	P	1	1	0	0	0	0	0	0	0	0	EORTC-QLQ C30 and CR29	Cross sectional	Late
Mitchell et al 2001(220)	C	0	0	0	0	0	0	0	1	0	1	Acute CTCAE late RTOG	Prospective	Both
Mai et al 2002(221)	C	0	0	0	0	0	0	0	1	1	0	Acute RTOG late LENTSOMA	Prospective	Both
Bosset et al 2003(222)	C	0	0	0	0	0	0	1	0	1	0	Acute - WHO and Late - LENT SOMA	Phase 2	Both
Chauveinc et al 2003(223)	C	0	0	0	0	0	0	0	0	0	1	Acute - NCI and Late - Rousseau classification system	Prospective	Both
Vuong et al 2003(224)	C	0	0	0	0	0	1	0	1	0	0	MSKCC sphincter function scoring system	Prospective phase 2	Both
Kouloulias et al 2005(225)	C	0	0	0	0	0	0	1	1	0	0	Acute chemotherapy - WHO toxicity criteria. Acute radiation toxicity - RTOG toxicity scale Late morbidity - EORTC/RTOG late toxicity criteria.	RCT	Both
Fallai et al 2007(226)	C	0	0	0	0	0	0	0	1	0	1	Acute CTCAE and late RTOG	Prospective	both
Salama et al 2007(227)	C	0	0	0	0	0	0	0	1	0	1	Acute - CTCAE and Late - RTOG	Prospective	Both
Stojanovic et al 2007(228)	C	0	0	0	0	0	0	1	1	0	0	Acute - WHO and Late - RTOG	Prospective	Both
Ajani et al 2008(29)	C	0	0	0	0	0	0	0	1	0	1	Acute - CTCAE and Late - RTOG	RCT	Both
Cho et al 2008(229)	C	0	0	0	0	0	0	0	0	0	1	CTCAE v1 or 2	Prospective	Both
Konski et al 2008(230)	C	0	0	0	0	0	0	0	1	0	0	Late - RTOG	RCT	Late
Saarilahti et al 2008(231)	C	0	0	0	0	0	0	0	1	0	0	RTOG acute and late	Prospective	Both
Tournier-Rangeard et al	P	1	0	0	1	0	0	0	0	0	0	EORTC QLQ-C30 and anal sphincter conservative treatment questionnaire (AS-CT).	RCT	Acute

REFERENCE	PATIENT REPORTED /CLINICIAN REPORTED /BOTH	PATIENT REPORTED OUTCOMES					CLINICIAN REPORTED INSTRUMENTS					INSTRUMENT DETAILS	STUDY DESIGN	ACUTE OR LATE TOXICITY REPORTED
		EORTC C30	EORTC-CR29	FACT- C	AS CT	MOS	MSKCC	WHO	RTOG	LENT-SOMA	CTCAE			
2008(232)														
Das et al 2010(233)	P	0	0	1	0	1	0	0	0	0	0	Functional Assessment of Cancer Therapy-Colorectal (FACT-C) and the Medical Outcomes Study (MOS) Sexual Problems Scale	Cross sectional	Late
Northover et al 2010(234)	C	0	0	0	0	0	0	0	0	0	0	From hospital reports	RCT	Late
Provencher et al 2010(235)	P	1	1	0	0	0	0	0	0	0	0	EORTC QLQ-C30 and CR29	Cross sectional	Late
Rabbani et al 2010(236)	C	0	0	0	0	0	0	0	1	0	0	RTOG late	Prospective	Late
Matthews et al 2011(237)	C	0	0	0	0	0	0	0	1	0	1	Acute CTCAE and late RTOG	Prospective	Both
Welzel et al 2011(238)	P	1	1	0	0	0	0	0	0	0	0	EORTC QLQ-C30 and CR29	Cross sectional	Late
Defoe et al 2012(239)	C	0	0	0	0	0	0	0	0	0	1	CTCAE	Prospective phase 2	Both
Kachnic et al 2012(210)	C	0	0	0	0	0	0	0	1	0	1	Acute CTCAE v3 and late RTOG (toxicity reported prospectively)	Retrospective	Both
Tomaszewski et al 2012(240)	C	0	0	0	0	0	0	0	0	0	1	Late toxicity – CTCAE v.4	Cross sectional	Late
Fakhrian et al 2013(211)	B	0	0	1	0	0	0	0	0	0	1	CTCAE v.4.0 and FACT-Colorectal questionnaire.	Cross sectional	Late
James et al 2013(241)	C	0	0	0	0	0	0	0	0	0	1	CTCAE	RCT	Acute
Kachnic et al 2013(33)	C	0	0	0	0	0	0	0	0	0	1	CTCAE	Phase 2	Acute
TOTAL		4	3	2	1	1	2	5	17	2	15			

Key: RCT - Randomised controlled trial; ASCT - Anal Sphincter-conserving treatment questionnaire; EORTC QLQ - European Organisation for Research and Treatment of Cancer quality of life questionnaire; FACT-C -Functional Assessment of Cancer Therapy-Colorectal; WHO – World Health organisation, CTCAE – Common Terminology for Common Adverse Events; MOS - Medical Outcomes Study; RTOG - Radiation Therapy Oncology Group; MSKCC – Memorial Sloan Kettering Cancer Center; LENT-SOMA - late effects in normal tissues subjective, objective, management and analytic

3.6 Discussion

3.6.1 General discussion of review findings

The EORTC-QLQ system measures are the most commonly used PROs in the clinical trials reviewed, followed by the LENTSOMA-based measure (now the Pelvic Symptom Questionnaire) in the gynaecological cancer review. The most commonly used clinician reported instruments are the RTOG/EORTC and the CTCAE. However, the RTOG/EORTC measure is no longer recommended for use in clinical trials and instead the CTCAE is the preferred gold standard for clinician reporting. The National Cancer Institute (NCI) have recently developed the patient reported outcome version of the CTCAE – the NCI-PROCTCAE, which is likely to be used in future clinical trials(242). Therefore, based on these findings the NCI-PROCTCAE, the EORTC-QLQ system and the Pelvic Symptom Questionnaire were selected for further evaluation in Chapter 4 to establish the measure with the best toxicity item coverage for use in the clinical studies.

The systematic review describes the toxicity outcomes for some 8800 patients enrolled in 13 different RCTs, with 21 papers considering the impact of radiotherapy toxicity following rectal cancer treatment over the past two decades. The outcomes of these trials have determined clinical practice and the summary of reported toxicities by clinicians and patients presented in this review is relevant to all clinicians treating rectal cancer. Analysis of these trials highlights the lack of standards for adverse event reporting, both patient and clinician-reported, in cancer clinical trials and raises a number of questions about how future treatment may be optimised on the basis of past RCT results. The results support the complementary nature of the two different methods of reporting. Detailed information is more readily available from validated PROs and information on observable adverse events, such as skin reactions, available only from clinician reports. The data on observable events was not included in the analysis in the clinical studies within this project.

The results of the scoping literature review confirm that the toxicity reporting measures, both clinician and patient reported are similar in the other pelvic cancer sites reviewed. The use of PROs in anal, cervical and endometrial trials cancer sites is not as extensive as in rectal cancer, which in part reflects the number of recent radiotherapy trials in these cancer sites.

In the systematic review, the clinician-reported papers tend to report only the more serious toxicities (≥grade 3) and group symptoms relating broadly to a single organ unit together. The frequency of adverse event symptom reporting was consistently lower than those reported using PROs. There was also a lack of clinician-reported data on sexual dysfunction (an important clinical issue) and baseline symptoms were rarely reported. Although the approach used in the clinician-reported papers allows an overview of the adverse events that may be expected following treatment, the details are lacking and may lead to a paucity of clinically meaningful information. The lack of detail on the adverse events experienced will not only impact on the knowledge of the true incidence of complications but may also impact research into improving treatment with radiation, effective interventions for symptoms and limit research in areas such as radiogenomics(90, 243).

“Mild” symptoms (such as a CTCAE grade 1/2 diarrhoea) experienced over a lifetime following treatment may have a significant impact on daily life and patients may benefit from intervention. Currently this data is rarely available in the clinician-reported papers. It not usual practice for clinician-reported RCTs to publish baseline symptom data, even if it has been collected pre-randomisation. This finding is of particular importance when modifications to dose-volume constraints using radiobiological modeling are based on the presence, or not, of complications in particular organs at risk. If baseline symptoms are not routinely reported or considered in the analysis it may not be clear if a patient’s symptoms were present prior to treatment and thus may not be a true ‘complication’. This precludes evaluation of deterioration or improvement in symptoms over time.

The international review of dose-volume-outcome data from the QUANTEC Group highlights challenges with the current systems of adverse event reporting. One of their key concerns was the impact of poor quality outcome data on the ability to improve future radiotherapy treatments by failing to provide sufficiently detailed information on which to define dose-volume constraints(92). To improve the quality of clinician-reported data published in future studies all grades of toxicity and individual toxicity symptoms, including sexual dysfunction should be published in clinician-reported papers using the CTCAE with consideration of the change from patients’ baseline symptoms in order that complications and improvements over time may be assessed.

Inclusion of prospectively collected PRO data in clinical trials may offer additional benefits. Information on a wider range and milder side effects including sexual dysfunction is reported. Many validated instruments also have data on what constitutes

a clinically important difference in symptom and function scores over time (e.g. EORTC-QLQ systems)(244). This feature of PROs may offer some benefits over the use of the CTCAE if PRO data is used in modeling normal tissue complication probability (NTCP), as the CTCAE is not formally validated as an instrument to measure differences in adverse event severity(245). By comparing a clinically meaningful change in PRO scores over time, true complications will be established and links between specific PRO items and pathophysiological changes following radiation treatment can be made.

3.6.2 Methodological considerations

The systematic review findings raise some important methodological issues that need to be addressed to ensure quality PRO data collection and presentation within this thesis. The CONSORT-PRO and ISOQOL guidelines provide details on reporting standards for trials with PROs as primary or important secondary outcomes(141, 142). Key recommendations include reporting on PRO psychometrics, statistical management of missing data, identification of the PROs in the abstract as primary or secondary endpoints; description of the PRO-related hypothesis; reporting on PRO-specific limitations and relating results to cancer outcomes and clinical practice. Within the development work of this project three key features were considered: (1) the choice of a validated PRO instrument; (2) methods of data collection; and (3) statistical methods to manage missing data. The methods used for data collection are described in detail in Chapters 1, 2 and 6.

3.6.2.1 Instrument choice

Chapter 2 covered the methodological considerations around the choice of a validated instruments and methods of data collection in detail. However, this review raises a couple of points. The key concern for instrument selection is that the validated PRO selected covers the adverse events expected with different treatment regimens. This issue is covered in detail in the following chapter, however methodologically it also raises interesting issues for recommending the incorporation of PRO data collection into all Phases of clinical trials research, including Phase I. Currently, Phase I trials in rectal cancer focus mainly on the maximum tolerated dose relating to the new agent and rarely focus on the radiation-related toxicity or incorporate PRO data. The number of trials evaluating novel agents alongside radiotherapy is likely to increase over the next few years. Using PROs could enable data collection of milder toxicities (providing a more accurate description of patient's subjective experience in all aspects of the treatment, including radiation), and enable the validation of new PRO symptom-related items/questionnaires for the new treatments evaluated. This may help alleviate one of

the challenges inherent with using a validated disease-specific instrument where toxicities related to newly introduced treatment may not be covered. Currently the EORTC-QLQ system recommends supplementing the existing modules with additional items taken from the item bank or whole subscales, as used in the PORTEC trials(21). The NCI-PROCTCAE uses a different approach and items are validated as single items and may be used to cover all expected toxicities within a clinical trial. Within this project, if additional items are required following the content evaluation in chapter 4, the ability to supplement existing questionnaire systems with additional items to cover all expected toxicities will be considered during the process of questionnaire selection.

3.6.2.2 Managing missing data

Only 29% of the RCTs evaluated in the systematic review reported on statistical methods for managing missing data. Various reasons for missing items or forms are reported: treatment or disease-related illness; being too busy; poor administration; or not wishing to complete data on sensitive issues(113, 246). Internet-based collection may improve questionnaire administration allowing patients to complete them at home, privately, at a convenient time(114). However, consideration for managing missing data should be given when establishing sample size (if patient-reported toxicity is an important endpoint) and during analysis, described in detail in previous papers(247). During analysis, 'imputing' is a commonly used method for managing missing items scored as part of a group of items (subscale). Provided over half of the items in the subscale have been reported the mean value of these items may be substituted for the missing item.

3.6.3 Strengths and limitations

The systematic review has limitations. Despite the use of a comprehensive search strategy, it is still possible that some eligible trials reporting on toxicity were missed. Articles published after the cut-off date of this literature search are not included in this review. To our knowledge only one eligible paper within the systematic review of RCTs in rectal cancer has been published since the electronic search was completed by Wiltink and colleagues (14) reporting on the 14 year HRQOL following the Dutch TME trial. The scoping literature reviews were similarly limited by the timing of the electronic search. The systematic review also has a number of strengths. PRO trials were evaluated using the most up to date methodological evaluation criteria(142) and the details and frequency of the toxicities reported were considered in relation to the consensus developed QUANTEC recommendations(92).

3.6.4 Conclusions

In conclusion, the results of the systematic review highlight the lack of reporting standards for adverse events in both clinician and patient-reported RCTs, and describe the inconsistency within and between clinician and patient reporting of toxicity. The results of the systematic review will help clinicians treating rectal cancer in designing future trials and support consultation with patients about expected toxicities in routine clinical practice. To significantly improve the quality of toxicity outcome data for future studies these findings recommend greater adherence to key guidelines in this area(141, 142) for the collection and reporting of PRO data and for more detailed publication of clinician-reported adverse event data using the CTCAE version 4 as the current gold standard.

For the purposes of questionnaire selection for further analysis within this thesis, the systematic review found the EORTC-QLQ C30 and CR38 were the most commonly used PRO instruments. The results of the literature reviews confirmed that similar toxicity reporting instruments are used to report on radiotherapy related toxicity in other pelvic malignancies - endometrial, cervical and anal cancer. Due to the recommendations to use the CTCAE as the gold standard for future trials using clinician reporting, the NCI-PROCTCAE was selected for further evaluation of content to assess suitability for use in patients treated with pelvic radiotherapy. The EORTC-QLQ system was selected for content evaluation as it was used most commonly in the trials in all cancer sites assessed in this chapter and the Pelvic Symptom Questionnaire as it was commonly used (in earlier formats) in the gynaecological cancer studies.

The following chapter will seek to further address the methodological considerations around the selection of the PRO instrument for the two main clinical studies to address the toxicities experienced by patients before, during and after pelvic radiotherapy for anal, cervical, endometrial and rectal cancers.

Chapter 4 A multi-method approach to identifying the most effective patient reported outcome questionnaires to use with patients treated with pelvic radiotherapy for anal, cervical, endometrial and rectal cancers

4.1 Introduction

This chapter aims to explore the main side effects of patients treated with radiotherapy for anal, cervical, endometrial and rectal cancer and to evaluate the content of the most frequently used generic and symptom based patient reported outcomes (PROs). Multiple qualitative methods are used to establish the most effective validated questionnaire(s)/items to evaluate (1) the prevalence and trajectory of radiotherapy-related toxicity and (2) the pathophysiological relationship between toxicity and dose delivered to different organs at risk.

A multi-method qualitative approach to the initial phase of questionnaire development in cancer research is replicated in two of the most commonly used questionnaire systems – EORTC QLQ (103) and Functional Assessment of Cancer Therapy (FACT) systems(104). An initial literature review to establish pre-existing measures and relevant items is then followed by structured interviews with patients and health professionals to confirm and search out important items. As validated questionnaires exist for patients treated with pelvic radiotherapy rather than develop a new questionnaire this rigorous approach is used to select the optimal questionnaire for this project. This chapter follows on from the systematic and literature reviews through exploring the content and coverage of relevant items from existing measures using qualitative research methods.

Three PRO measures - the EORTC-QLQ, Pelvic symptom questionnaire (PSQ) and National Cancer Institute's (NCI) PROCTCAE – were used in the inductive content analysis and health professional interviews to prompt discussion of missing items and to explore questionnaire preferences. The EORTC-QLQ system and the PSQs were selected for further analysis based on their frequency of use in the systematic/literature reviews in the four cancer sites evaluated. The NCI-PROCTCAE (the PRO version of the CTCAE) was selected due to widespread use of the CTCAE in cancer clinical trials and practice and the increasing inclusion of the NCI-PROCTCAE in clinical trials.

This chapter pilots the use of an inductive content analysis method of evaluating the content of existing validated PRO measures as part of an on going international collaboration with members of the EORTC Quality of Life working group and the NCI-PROCTCAE development team(248). This collaboration aims to ensure effective coverage of the newly developed NCI-PROCTCAE items in all areas of oncology treatments. However, the main focus of results and discussion in this thesis will be on the effective coverage of items for pelvic radiotherapy treatments in the four cancer sites.

Interviews with health professionals and patients are used in questionnaire development to improve content validity(103). Health professional interviews can be conducted prior to patient interviews (covered in Chapter 5) to avoid patient burden(103). An open style of interview questioning is recommended allowing an initial exploration of the issues before presenting the questionnaires or item lists(249). As discussed in Chapters 1, 2 and 3, it is essential that the selected questionnaire covers the adverse events expected with the different treatment regimes and that stakeholders involved in the research are engaged(102). The interview process was used to facilitate an active process of engagement between the existing clinical pathways and the ideas of the research project, aiming to develop clinical studies that incorporate a PRO measure and methodological processes that are relevant for the purposes of the research outcomes as well as clinically relevant.

A framework approach was used to analyse the semi-structured health professional interview data, exploring both inductive and deductive approaches to fit the data to the content analysis of the questionnaires, highlight missing items and reveal other areas relevant to the study intervention. The rationale for using the framework methodology is discussed fully in chapter 2(108). Finally the results of both analyses were presented to an expert multi-disciplinary clinical review panel and the final decision regarding the questionnaire for use in this project was made.

4.2 Methods

4.2.1 PRO inductive content analysis

4.2.1.1 Background on the PRO measures

Both the NCI-PROCTCAE and the male and female PSQ were developed initially from the content of the CTCAE. In contrast, the EORTC-QLQ system was developed independently from the CTCAE instead using the mixed methods approach described

in the introduction, involving patient interviews from an early stage(12, 103, 242). NCI-PROCTCAE and CTCAE are designed to cover multiple tumour site adverse events as well as generic symptoms experienced by all cancer patients. EORTC-QLQ C30 covers generic symptoms and quality of life items and each of the 17 validated (Phase IV) disease specific modules[1] covers the symptoms, side effects and quality of life associated with each tumour and treatment in more detail. In comparison, the PSQ was developed for use specifically in patients treated with pelvic radiotherapy in their longitudinal follow up and focuses on treatment/disease-specific items. It is important to recognise these differences when evaluating the results of this analysis.

Methodologically, the NCI-PROCTCAE was developed for all items to be used as single independently validated questions allowing any item to be selected for use within a clinical trial based on the clinically expected toxicities associated with each treatment. Conversely the EORTC-QLQ system and the PSQs are validated questionnaires, which involve grouped items creating a scale (e.g. urinary symptoms) as well as individual items scored separately. Within the EORTC-QLQ system there is the facility to use individual items or whole subscales from other existing validated questionnaires within an existing module to cover any clinically relevant missing items(21).

4.2.1.2 Design rationale

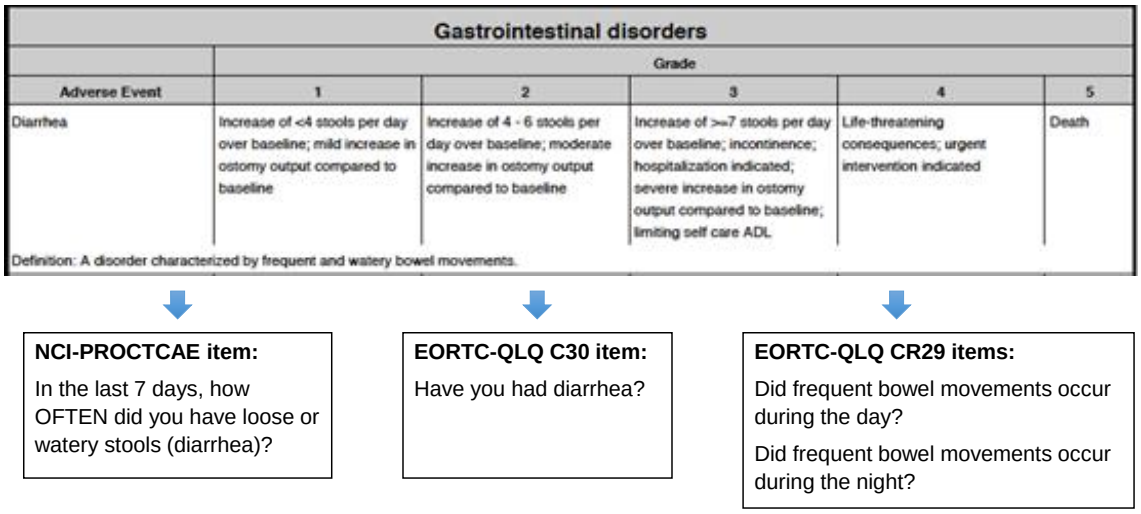
The analysis aims to reveal concordance and discrepancies between the different patient-reported questionnaires to aid questionnaire selection for this project. In addition, this analysis evaluates the relationship between the CTCAE, as the gold standard in cancer treatment reporting and the commonly used patient-reported toxicity instruments.

All items on the NCI-PROCTCAE, male and female PSQ, and EORTC-QLQ-C30 and all 17 validated (Phase IV) EORTC QLQ modules were coded using an inductive content analysis approach based on the symptom reported for each item. For example, the PROCTCAE question ‘In the last 7 days, how OFTEN did you lose control of bowel movements’, the EORTC-CR29 question ‘Have you had leakage of stools from your back passage?’ and the PSQ item ‘Have you had any difficulty controlling your bowels (e.g. any accidents)’ were coded as a domain code ‘*Bowel symptoms’* with a subcode (code) ‘*Incontinent of faeces/leakage of stool*s’. It was decided to focus only on the

[1] EORTC-QLQ validated, phase IV disease-specific modules (2014): BN20, BM22, BR23, CR29, CX24, EN24, GINET21, HCC18, HN35, LC13, LMC21, MY20, OES25, OG25, OV28, PR25, STO22

content of the questionnaire items rather than the severity scales of each toxicity items in this initial phase of piloting this qualitative method.

Data on the items from CTCAEv.4 was extracted in order to establish if all items from the selected patient-reported questionnaires were covered by the CTCAE. The initial step in this process involved a process of open inductive coding of all CTCAE items considered to be suitable for patient self-reporting following a process described by the NCI-PROCTCAE group(242). This inductive process was used as a method to familiarise with the CTCAE data. The second step involved a process of deductive coding where all items found in the patient reported modules were searched for within the CTCAE. Items were coded as present if described within the title, description or grading of a CTCAE adverse event. Figure 4.1 shows an excerpt from the CTCAE v4: diarrhoea was considered a symptomatic item suitable for patient self-report in the process of open inductive coding. In the second process of deductive coding the four items reporting on diarrhoea and bowel frequency were coded as present for the CTCAE diarrhoea adverse event item. Diarrhoea is present in the title and bowel frequency is described in the description and grading of the item.



Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					

Figure 4-1: Diarrhoea example from CTCAE V4 and PRO instruments

4.2.1.3 Data analysis

QSR NVivo10 software was initially used to manage the data before transferring to Microsoft Excel to summarise the data. I (AG) independently coded all items on the CTCAE, the NCI-PROCTCAE, the two PSQ and the EORTC QLQ-C30 and four EORTC modules (LC13, CX24, EN24, and CR29) into item codes and domains. Elaine O'Connell Francischetto (EOF) independently coded the NCI-PROCTCAE, EORTC-QLQ C30 and all 17 validated EORTC-QLQ modules. Both EOF and I then discussed

each code and domain in turn for all items to reach agreement, providing in many cases both a medical and lay description of each code/domain. Independent coding by two researchers with different professional backgrounds (clinical oncologist and psychologist) was used to maximise the consistency and reliability of the analysis(250). Any item disagreement was discussed and independent experts (Galina Velikova (GV) – medical oncologist and Jane Blazeby - surgeon) included in the discussion to achieve a consensus.

4.2.2 Health professional interviews

The interview process was used to assess (1) views on adverse events related to pelvic radiotherapy; (2) coverage and design of the different questionnaires; (3) highlight missing items on the questionnaires; (4) timing of when to record PRO data; and (5) management of side effects.

4.2.2.1 Design rationale

One to one semi-structured interviews were utilised to allow in-depth discussion of health professional experiences of adverse events associated with pelvic (chemo)radiotherapy as well as allowing the flexibility to explore other issues that the participants felt were important to this topic(251). Participants were provided with a letter/email explaining the rationale of the project and copies of the questionnaires in advance to review: NCI-PROCTCAE items related to pelvic radiotherapy; EORTC-QLQ CX24, EN24 and CR29; Male and female PSQ. In the interviews the CR29 (for colorectal cancer) was evaluated as the disease-specific questionnaire from the EORTC-QLQ system for patients with anal cancer as currently an anal cancer-specific module does not exist. This methodological choice was based on the findings from the literature review in which the CR29 was used most frequently in clinical trials of anal cancer patients as the PRO of choice.

4.2.2.2 Ethical approval

NRES Leeds East Committee approved the study (13-YH-0156) and all participants gave informed consent.

4.2.2.3 Participants recruitment

Eight health professionals were purposively recruited with a range of clinical backgrounds to ensure capture of a broad spectrum of experiences and views in the interviews of working with patients treated with pelvic radiotherapy. All eight

participants invited to take part in the study agreed to take part. Participants were contacted by email, explaining the objectives of the study, or by face-to-face invitations. All participants work as clinicians at St James' Oncology Centre, Leeds; a tertiary centre for cancer care. The participant's clinical backgrounds are summarised in table 4.1.

Table 4-1: Demographics of Health Professional interview participants

Role	Number interviewed	Cancer speciality area
Clinical oncologist	2	GI (n=1), Gynae (n=2)
Surgeon	2	GI (n=1); Gynae (n=1)
Clinical Nurse Specialist	2	GI (n=1); Gynae (n=1)
Nurse	1	All
Radiographer	1	All

Key: GI – gastrointestinal cancer; Gynae – gynaecological cancer

4.2.2.4 Interviews

I conducted all semi-structured interviews face-to-face. An interview guide was developed from the literature based on the aims of the project. Participants received an invitation to take part in the study along with a participant information sheet and copies of the questionnaire items. Interviews were arranged at a mutually convenient time and place. At the beginning of each interview participants were reminded about the rationale for the research and given the opportunity to ask any questions before signing a consent form. All interviews were audio-recorded and lasted between 38 and 75 minutes.

4.2.2.5 Data analysis

All interviews were transcribed verbatim by experienced medical secretaries. I reviewed all transcripts for inaccuracies before analysis. QSR NVivo10 software was initially used to manage the data. The data was transferred to Microsoft Excel to further summarise the data in conjunction with the inductive content analysis of the three PROs and CTCAE. A framework method was applied to the analysis. The transcripts were initially read and reread to familiarise the researchers (AG and Patricia Holch) with the data before coding took place. A process of both 'open coding' and deductive coding was applied to the transcripts(108). The interview topic guide was used to identify themes in the transcripts. The pre-defined broad areas of interest were (1) adverse events; (2) missing items; (3) management of symptoms; (4) timing of questionnaires; and (5) views on questionnaires. Open coding within these categories was explored and throughout the analysis the interpretations were compared to the verbatim transcript data. Inductive themes emerging regarding other aspects of the

complex intervention process such as multidisciplinary roles in the current management of symptoms were also explored. To enhance the validity of the analysis all transcripts were independently coded by the two researchers, AG and PH. Similarities and differences were discussed to reach consensus.

4.3 Expert review panel

The summary results from both the interview and questionnaire content analysis study were discussed in an expert review panel comprising of my three clinical supervisors (GV – medical oncologist; DSM – clinical oncologist [GI]; SD – clinical oncologist [gynaecology]) and the two clinical nurse specialists (CNS: GI and gynaecology) who took part in the interview study. The aim of this final review was to bring together the results from all of the development work to select a questionnaire for the remaining clinical studies suitable to evaluate adverse events in patients treated with pelvic radiotherapy.

4.4 Results

4.4.1 PRO inductive content analysis of all items

The summary of the domain coding spreadsheets for all items may be reviewed in Appendix A. Overall 49 different domains and 198 different codes were extracted from the analysis of the PROs and the symptomatic CTCAE items. Overall the CTCAE covers the greatest number of domains (n=44), followed by the EORTC-QLQ system (n=42) and the NCI-PROCTCAE (n=37). The PSQ focuses on the most common side effects of patients treated with pelvic radiotherapy and covers seven domains. Similar findings are seen within the codes for the questionnaires. However the EORTC-QLQ system covers more codes (n=168) than the other PROs (NCI-PROCTCAE n=78; PSQ n=33) with an additional focus on psychosocial/emotional impact of cancer diagnosis and treatment not covered by the other PROs or the CTCAE (n=153 codes); see table 4.2 and appendix A.

Table 4-2: Summary of domain and code frequency

System	NCI-PROCTCAE	EORTC-QLQ system	CTCAE	PSQ (Male and female)
Domains (n) Total n=49	37	42	44	7
Codes (n) Total n=198	78	168	153	33

4.4.2 Findings from the Health professional interviews

Eight interviews were carried out between 10th July 2013 and 16 April 2014. Six key themes were identified from the health professional interview analysis: (1) Adverse events (2) Missing items; (3) Views on different PROs; (4) Timing of questionnaires; (5) Specific interventions/treatment and provision of care; and (6) Improving the service. The first two themes, adverse events and missing items were also analysed in association with the summary findings from the content analysis of the questionnaires.

4.4.2.1 Adverse events

The most commonly reported adverse events following pelvic radiotherapy described in the interviews were bowel, urinary and sexual dysfunction. Other adverse event items commonly mentioned were fatigue, lymphoedema, pelvic insufficiency fractures, psychological and social issues, and body image concerns.

4.4.2.1.1 Bowel symptoms

Bowel symptoms were considered by all health professionals to be a dominant acute and late side effect of pelvic radiotherapy:

> *'Yes, during treatment, the most common side-effect apart from the treatment-related fatigue is bowel problems and they may or may not settle down soon after treatment but some may persist and will become chronic or settle and then recur. So that's a huge area.' (HP5.)*

Seventeen codes related to bowel symptoms were described. Problems ranged from bowel frequency and diarrhoea to erratic bowel function, urgency, incontinence, pain, bloating and the social impact of bowel dysfunction. One health professional described a common scenario in patients following pelvic radiotherapy treatment:

> *'The [bowel] frequency is less of the issue if it isn't associated with urgency. It's the urgency. Because if they have urgency and they're out and they don't know where the toilet is then obviously they can have an episode of incontinence and socially that's a huge taboo so that's one of the main concerns for our patients in terms of bowels… toilet dependency is quite anxiety making, it produces a lot of anxiety.'(HP1.)*

Stoma-related issues were also highlighted as important items to cover in anal and rectal cancer patients when patients may require a stoma (either temporarily or permanently) as part of their care:

> *'It's a different group [anal], than I think for the rectal's that have needed a defunctioning stoma pre-chemoradiotherapy. It's because they are having such bad symptoms before. I think for them it must be a relief, because it does improve their quality of life.' (HP2.)*

The psychological impact of having a stoma was considered an issue for all health professionals who discussed stoma related adverse events:

> *'It's a stoma. It goes into the bag, you don't have to deal with it and it's not ideal but equally it's a means to an end... I don't think any young people are happy with a stoma, it's all about the group of people you are dealing with.' (HP7.)*

4.4.2.1.2 Bladder symptoms

Aside from bowel-related issues, bladder dysfunction was a common theme. Many health professionals highlighted pre-existing bladder dysfunction as an important contributing factor for this adverse event particularly in the elderly population, stating *'so you need to differentiate from the normal to what is new or different.' (HP3.)*

In patients receiving both surgery and radiotherapy as part of their treatment – rectal and endometrial cancer patients - the impact of surgery and radiotherapy on bladder function were considered to lead to different symptoms:

> *'Bladder irritation tends to be radiotherapy and obstructive symptoms tend to be related to surgical issues with damaging the nerves.'(HP7.)*

The combination of the effect of multimodal treatments and pre-existing functional pathology (post-partum/post-menopausal and prostate hypertrophy-related obstructive bladder symptoms) highlights the importance of comparing post treatment PRO reporting to baseline PRO reporting and single modality treatment to multi-modality treatments within the clinical studies.

4.4.2.1.3 Sexual dysfunction

Clinicians discussed sexual dysfunction in terms of functional problems and their psychological impact. For women, the impact of pelvic irradiation on vaginal function

was highlighted as a common problem leading to problems with vaginal stenosis and dyspareunia:

> *'Some of them after radiotherapy find intercourse painful because there's some narrowing and shortening of the vagina.' (HP1.)*

> *'The things I'm frequently called out for from a specialist point of view by the doctors is the vaginal stenosis and painful sex.' (HP2.)*

Patient misconceptions regarding vaginal length following a total hysterectomy for endometrial cancer were also mentioned: '*Quite often, women think the vagina is being shortened to about a centimetre.' (HP3.)*

Issues of guilt and anxiety around the diagnosis and treatment of cervical cancer were also recurrent themes:

> *'So I think for younger women with the intact cervix following radical chemoradiotherapy and brachytherapy there are loads of issues that relate to their sexual functioning that we don't address… So for the intact cervix cancer patients they do get vaginal stenosis but a lot of these are younger women who then go on to HRT so they tend to maintain vaginal moistness etc. and they are sexually active but there's a lot of issues going on, psychologically some of them feel that they have been violated by brachytherapy....Yes, because it is pretty horrible. So psychologically some of them find that very difficult to get over, and I know that from talking to patients…And as I said I think the sexual contact and the sort of way the cervical cancers, the HPV [human papilloma virus] and the sexual contact and that link is a bit of an issue.' (HP1.)*

Modifying management of sexual problems for patients of different ages groups was also a recurrent theme with health professionals being careful to be open to discussions whilst keeping in mind potential disparate priorities of different patient groups:

> *'When you are talking about sexuality and sexual activity particularly you have got to be very careful with your wording and with knowing the patient and how far you can go with that advice and never ever ever assume anything about anybody's sexual life. Never. No matter age, colour, sex, creed, nothing. I have learnt that the hard way at times.' (HP3.)*

For male patients the key symptoms of sexual dysfunction related to impotence and ejaculation problems:

> *'Men though, obviously impotence is an issue, and again there will be a degree of underlining impotence anyway that would be useful to know.' (HP1.)*

As with bladder dysfunction, the additive impact on erectile function when pelvic radiotherapy is combined with surgery was also discussed:

> *'I think both play a role. It's difficult to know exactly which is more important but certainly both have played their part because the other issue you have with the radiotherapy is that it also affects the urinary tract or the genitourinary [GU] tract so you also have issues with, problems when they urinate, incontinence, obstruction and problems with getting impotence and retrograde ejaculation and that sort of thing which again it's difficult to unpick that from surgery and the procedure you have done where sometimes the nerves to the GU organs can be compromised and the battering they get from radiotherapy and again its very very hard to unpick it all to be certain about it, about what caused the problems.' (HP7.)*

This adverse event information was further analysed in reference to the outcomes of the content analysis of the PRO questionnaires to illuminate the PRO questionnaire(s) that covered the adverse event issues most extensively.

4.4.2.2 Adverse events and Missing items: Combining the PRO inductive content analysis with the health professional interviews

Of the 49 domains covered in the PRO content analysis 25 domains were discussed within the health professional interviews and out of the total 198 codes, 74 codes were covered in the interviews; see table 4.3 for a summary. The dominant domains in relation to code frequency were bowel symptoms with 13 different codes, and bladder and vaginal symptoms with seven codes.

The EORTC-QLQ system covered all domains discussed in the interviews except for the skin domain; missing items related to radiation skin reaction and palmar-planter erythema (PPE). The CTCAE covered the majority of domains discussed except those related to body image, psychosexual issues and social issues. As the NCI-PROCTCAE was developed from the CTCAE these domains were also missing. However, within the NCI-PROCTCAE adverse event domains relating to mobility problems and stoma-related symptoms were also found to be missing. As discussed previously, the PSQs focus on the key side effects – bowel and urinary symptoms, male and female sexual dysfunction, pain and menopausal symptoms - experienced by patients following pelvic radiotherapy and covers these domains effectively. However, the PSQs miss out a number of relevant toxicity domains necessary for detailed evaluation of pathophysiological processes involved with all organs at risk within the pelvis. This includes domains on lymphoedema, skin issues such as radiation skin reaction, muscle, bone or joint issues, and stoma-related symptoms.

Table 4-3: Summary of PRO and CTCAE content in relation to health professional interviews

Domain	Code	PROCTCAE	EORTC	CTCAE	PSQ	Interviews
Body Image	N=2					
	Masculinity and femininity					
	Perception of attractiveness					
Bowel symptoms	N=13					
	Abdominal discomfort/pain					
	Abdominal bloating					
	Bowel urgency					
	Anal area and rectum pain					
	Constipation					
	Embarrassment about bowels					
	Incontinent of faeces/leakage of stools					
	Unintentional release of gas/Incontinent of wind					
	Bowel frequency					
	Diarrhoea					
	Change in bowel Movement					
	PR bleeding/Blood in Stool					
	Treatment for bowels					
Emotional Issues	N=2					
	Feeling anxious					
	Low mood					
Fatigue	N=3					
	Fatigue					
	Tired					
	Lacking energy					
Hair loss	N=1					
	Hair loss					
Hearing	N=1					
	Hearing problems					
Impact on eating	N=1					
	Reduced appetite					
Lymphoedema/Swelling	N=1					
	Lymphoedema/Swelling					
(Male) sexual dysfunction	N=3					
	Ejaculation problems					
	Impotence/Erection Issues					
	Treatment for erectile function					
Mobility problems	N=4					
	Heavy legs					
	Ability to do leisure activities					

	Ability to travel					
	Ability to do normal routine					
Muscle, bone or joint issues	N=4					
	Bones and joints aches or pains					
	Muscle aches or pain					
	Pain in back					
	Pain in legs/hips					
Nausea and vomiting	N=2					
	Nausea					
	Vomiting					
Oral issues	N=1					
	Mouth sores					
Overall Health	N=2					
	Overall Health					
	Overall QoL					
Pain	N=2					
	Frequency and level					
	Medicine for pain					
Psychological sexual	N=2					
	Worrying sex would be painful					
	Feeling uncomfortable about sexual activity					
Sex life	N=4					
	Sexual desire/interest in sex					
	Sexual Enjoyment					
	Sexual Activity					
	Effect of treatment of sex life					
Skin Issues/Skin side effects	N=2					
	Rash/Hand and foot syndrome					
	Radiation skin reaction					
Social Issues	N=4					
	Effect on family life					
	Effect on finances					
	Social Isolation					
	Effect on social activities					
Stoma related symptoms	N=3					
	Presence of stoma					
	Bowel frequency stoma					
	Embarrassment about stoma					
Sweating	N=1					
	Hot flushes					
Tingling/numbness	N=1					
	Tingling/numbness					
Urinary/bladder symptoms	N=7					
	Cystitis/pain or burning when urinating					

	Incomplete emptying bladder					
Urinary/bladder symptoms						
	Nocturia/Urinary frequency (night)					
	Urinary frequency					
	Urinary incontinence/Ability to control bladder					
	Urinary urgency					
	Treatment for bladder problems					
Vaginal symptoms	N=7					
	Pain during sexual activity/Dyspareunia					
	PV bleeding					
	Vaginal discharge					
	Vaginal dryness					
	Vaginal inflammation					
	Vaginal stenosis					
	Treatment for vaginal symptoms					
Weight	N=1					
	Weight gain					
TOTAL						
DOMAINS (yellow)	25	7	1	3	18	25
CODES (green)	74	35	68	55	28	74
MISSING CODES (red)	-	39	6	19	46	-

The EORTC-QLQ system covers the majority of coded issues discussed by health professionals in the interviews. This system not only has the most comprehensive coverage of 'traditional' adverse event items relevant to pelvic radiotherapy but also includes the psychological and social aspects of the impact of adverse events and diagnosis. Although the EORTC-QLQ are developed to cover all aspects of quality of life affecting cancer patients one health professional described the complex psychosocial impact of sexual dysfunction as follows:

> *'…sexual activity, "was it enjoyable for you, were you interested in sex, were you sexually active, have you felt physically less attractive, less feminine [taken from the EORTC-QLQ CX24)"…I don't think they are quality of life I think they are a direct toxicity of treatment'. (HP1.)*

The EORTC modules however do have a number of missing items relevant for anal cancer patients' treatment that are covered by other PROs but not covered by existing validated modules, for example, radiotherapy skin reaction. The EORTC Quality of Life group are in the process of developing a new module for use in anal cancer patients(143). I am an active member of this group advising as both a clinician and researcher in this field. Other items that were considered 'missing' from the disease-specific modules (cervical, colorectal and endometrial modules) by health professionals were found in other validated modules within the EORTC-QLQ system and could therefore be added from the item bank as single items for use in an extended questionnaire(21).

The analysis reveals a number of omissions in the NCI-PROCTCAE, PSQ and CTCAE. For bowel symptoms the CTCAE, and therefore the NCI-PROCTCAE, miss out *bowel urgency*, a common patient-reported symptom post pelvic radiotherapy (252):

> *'Urgency is a really key thing. In terms of bowels you really want urgency in there which as you say they don't have in there [NCI-PROCTCAE].' (HP1.)*

Other relevant bowel symptom items missing in the NCI-PROCTCAE are rectal bleeding, an absence of stoma-related questions, change to bowel habits, pain in the anal/rectal area and embarrassment about bowels/stoma. The PSQ questionnaires do not include any stoma-related items but do include items on the use of medications to manage bowel symptoms (as well as sexual and bladder problems), which are not covered by the other PROs. The items on medication use will not only provide a measure of toxicity severity (as most grade 2 adverse events on the CTCAE involve the use of medical interventions) but will also provide information to clinicians on the number of patients post treatment receiving this intervention.

For sexual dysfunction symptoms, the NCI-PROCTCAE and female PSQ have missing items about vaginal stenosis. This is coded in the CTCAE as vaginal stricture and is reported in the EORTC CX24 and EN24 in the questions 'Has your vagina felt short and/or tight?'. The EORTC modules do not cover changes to orgasm, but include items on sexual enjoyment, sexual activity and worrying about sexual intercourse being painful. The PSQ covers the majority of male and female sexual dysfunction items but does not include questions on sexual enjoyment and libido. These items were originally included in earlier versions of the questionnaires however they were removed following feedback from patients who found the items intrusive or chose not to answer. The complexity of the wording for the sexual function items on the NCI-PROCTCAE was commonly criticised by the health professionals: *'What was the severity of your decreased sexual interest at its worst? [NCI-PROCTCAE]. I think that's a really mouthy question isn't it?' (HP3.)*

A number of areas discussed by the health professionals were not covered by any of the PRO measures. A number of these were specific to anal cancer treatments but some were more general. Table 4.4 summarises these issues along with the related quotes from the interviews. The table highlights items missing from existing whole validated questionnaires (the disease-specific EORTC modules and PSQs) that were felt to be relevant by the health professionals interviewed and would need to be considered for inclusion as additional items within the study. Other potential adverse events raised in the discussions not found in any of the PROs are also presented. In particular, one health professional highlighted that vaginal toxicity could be explored in non-sexually active patients post treatment that were using vaginal dilators. Vaginal dilators are ideally offered to all female patients post pelvic radiotherapy to stretch the vagina and protect against vaginal stenosis(90).

Table 4-4: Summary of missing items and additional items

DOMAIN	MISSING ITEM CODES	MISSING FROM PROs	HEALTH PROFESSIONAL QUOTES
POTENTIAL ANAL CANCER ITEMS	Lymphoedema	CR29, PSQ	HP1. Lymphoedema we do see. So the groups we see it in are the post op endometriums and the anal cancer a little bit.
	Stoma	PSQ, NCI-PROCTCAE	HP1. …and some of the anal cancers have stomas…. HP2. It's a different group that I think for the rectals, that have needed a defunctioning stoma pre chemo radiotherapy it's because they are having such bad symptoms before…Some of them mention a colostomy bag, that's not across the, but not here on this one.
	Incomplete bowel emptying	All	HP1. I think there's some difficulty in completely emptying, and I presume that's what it is and they just have to go back, and maybe they've lost a little bit of sensation as to if they have emptied their bowels, and that is typical of the anal cancer patients.
	Sensation loss perineal area	All	HP1. …they often lose some sensation around the anal canal, particularly if they've had a large tumour...I think there's some difficulty in completely emptying, and I presume that's what it is and they just have to go back, and maybe they've lost a little bit of sensation as to if they have emptied their bowels, and that is typical of the anal cancer patients....The only thing they sometimes get is a loss of sensation or pain.
	Skin reaction	CR29, PSQ	HP2. Pain due to skin reaction...So that's why you'd have skin reaction question..skin reaction of course, depending on how low down the tumour is so obviously that depends, that would go through all the anal patients the skin reaction, with severity at the end of treatment.
	Mucositis	CR29, PSQ	AG1. So the nausea and mucositis you think are the main chemo…HP2. Yeah for the AN1 and 2 [Mitomycin and 5FU]
POTENTIAL RECTAL CANCER ITEMS	Palmer Planter Erythema	EORTC-QLQ, PSQ	HP2. No and that's part of your grading checklist! And it's not one that AG1. Sorry that's not on the EORTC then the hand and foot syndrome, that's important isn't it, whereas its mentioned here [NCI-PROCTCAE], hair loss comes up here, it's in quite a few of them
POTENTIAL CERVICAL CANCER ITEMS	Weight gain	CX24, PSQ	HP1. that's a huge one the weight. Because they all gain weight, particularly the cervix cancer patients go on steroids, so I think that ups their appetite levels
IMPACT ON EATING	Food intolerance	All	HP1. …associated abdominal pain, sometimes related to food, some patients get intolerant of different food.
VAGINAL SYMPTOMS	Loss of vaginal or clitoral sensation	All	HP1. I'm sure there's loss of sensation, I can't believe there isn't some loss of sensation because the mucosa has changed.
	Vaginal dilators	All	HP3. Has your vagina felt dry, has your vagina felt sore, not during sexual activity because as you say it might be more they are using dilators … Yeah I think you're right I think you could have said that if you have been sexually active within the past weeks or using dilators…
EMOTIONAL ISSUES	Guilt	All	HP5. …and all that cancer means and particularly with cervical cancer and anything where it's HPV-related related and they've picked up on that. You've got feelings of guilt, can you pass it on, will it come back and all that and that is a huge thing that I don't think is explored very much for patients.....Yes, it's the guilt. So that's a huge area.
	Loss of dignity	All	HP3. …they lose a lot of dignity, they lose a lot of their femininity, but as they begin to build that back up again and we build up their confidence and they get better, then they start wearing the nice clothes again

Key: HP(Number) – Health professional quote; AG1. – Alex Gilbert quote; AN1 and 2 – chemotherapy regime; 5FU – 5-fluorouracil chemotherapy; HPV – Human Papilloma Virus

4.4.2.3 Views on the different PROs

The health professionals interviewed provided many conflicting comments on the content, format and wording of the different questionnaires. The themes arising relating to the coverage and formatting of the PROs were as follows:

- Missing adverse event items;
- Quality of item wording;
- Limitations of only asking about symptoms over the past week;
- Simplicity as a key feature;
- Quantifiable outcomes;
- The ability to relate the PRO items to clinician reporting systems;
- Keeping overall item burden to a minimum; and
- Familiarity with PROs used in previous studies.

Comments about the PROs were coded as either negative or positive and the frequency of comments was highlighted (Table 4.5).

Table 4-5: Summary of views

	Number of +/- comments	HP comments from	Example
Positive EORTC	41	HP1-5, HP8	HP2. I want to put myself in the patients shoes and think would I if I had preference, it would maybe that layout [EORTCs], just for simplicity, it doesn't look over complicated the way its set out you just have to choose one you know it's quite easy to read through really…
Negative EORTC	17	HP1-7	HP6. It asks if you urinate frequently during the day and I kind of thought that somebody's very much might be someone else's 'not at all' really... I feel it needs to quantify the number of times a day…
Positive NCI	12	HP2, HP3, HP4, HP5, HP6	HP6. See I like that, in that it looks at how often, how severe and how much that affected what you are doing
Negative NCI	44	All	HP5. Okay. There's a lot about interfering with normal daily activities. Some of them don't see it as interfering in daily activities; they see it as part of treatment. Because their daily activities are completely changed by coming for treatment in the first place…
Positive PSQ	26	All	HP8. Well, I like this one, not because it is coloured but it gives a scale 0,1,2,3 not all moderate or severe, so I do like this type of questionnaire. Cos it is for simple minds like mine, it is easy to see.
Negative PSQ	13	HP1-3, HP6	HP1. They [PSQ] cover less things in a way.

Key: HP – health professionals; ADL – activities of daily living; RT – radiotherapy; + Positive - Negative

Overall the comments were helpful for highlighting the missing items as discussed in detail in the previous section. However, the participants in the main described both positive and negative issues about each of the PROs with conflicting sentiments, particularly around item wording, described within one questionnaire system. In a clear

example of these conflicting views HP3 describes her opinion of the item wording in the NCI-PROCTCAE:

> *HP3. Oh, I don't like this one [referring to the NCI-PROCTCAE]. The thing about frequent I think… "were there times you had to urinate frequently", again what does that mean, "how much did frequent urination", that's not good English…*
>
> *HP3. I like the "at its worst" [referring to the NCI-PROCTCAE], I like that because it gives them…it's asking them to answer the question at their worst so it's giving you a proper answer.*

Limitations around only asking patients about their symptoms over the past week were highlighted by one health professional who preferred the flexibility of the two week time window provided by the PSQs:

> *'Because I think it is a pattern … when you question your patients there is a pattern of things slowly going wrong or changing, it's not usually a dramatic change and sometimes I find they don't report things for several months although you've asked them. Until it becomes a set pattern... So this one [NCI-PROCTCAE] at seven days I thought wouldn't … I didn't like it.' (HP5.)*

All three PRO systems were praised for their simplicity for different reasons. The simplicity of the format and wording of the EORTC-QLQ system was more favourable to some clinicians: '*I want to put myself in the patients shoes and think, if I had a preference, it would be that layout [EORTC-QLQ], just for simplicity, it doesn't look over complicated the way it's set out.' (HP2.).* Both the PSQs and the NCI-PROCTCAE were praised for quantifying the frequency of adverse events making the results more relatable to the CTCAE. In addition, the PSQs were praised for their brevity by one clinician for focusing only on the most common adverse events but this was a concern for one clinicians interviewed*: 'They [PSQ] cover less things in a way'. (HP1.)*

A number of clinicians mentioned that they are more familiar with using the EORTC-QLQ system as they have been used in a number of previous clinical trials within the cancer department.

4.4.2.4 Timing of questionnaires

All participants were in agreement that the most effective times to both request and view patient's self-reported adverse events would be in line with existing long term follow up schedules. This will enable patients to consider their symptoms prior to a clinic appointment and for clinicians to view the PRO results before seeing the patient

via electronic integration into each patient's electronic health record. One clinician describes how the process would fit into her practice:

> *'…if they were coming for a scan result you'd look at the scan result, if they were coming for a blood test result you look at the blood test result. Then in some ways being able to look at that [PRO results] would be really, really useful, that would very much inform and direct your consultation and it would speed consultations up and make them much more useful for you and the patient…Or even to say, which of these things do you think we should tackle first, it's going to be difficult to tackle everything at the same time. Sometimes you sort the bowels out and the sexual things might improve and vice versa.' (HP1.)*

For the anal, cervix, and endometrial cancer patients this would mean that after their initial 5-6 weeks of radiotherapy treatment patients are followed up initially at 6 weeks post treatment and then three monthly. In addition to following traditional follow up schedules a number of the clinicians also suggested measuring acute toxicity in more detail, recommending week 2 of treatment, week 5 and then week 7. During radiotherapy, patients are seen daily by the radiographers administering the treatment, and weekly (or bi-weekly) by clinical staff. Patients are not traditionally reviewed by clinicians at week 7 but a number of participants suggested that it would be interesting to review the extent to which acute toxicity increases or declines over the weeks following completion of treatment.

For the rectal cancer patients it was suggested that the follow up schedule should be altered to allow for changes in symptoms expected acutely following surgery and to allow for patient's spending a period of time as in-patients.

> *HP7. I am not sure. I think the danger with doing it anywhere near operations is that the operation can distort what you are measuring. You are measuring probably what it going on around the time of their operations and that's not what you want is it? You want to know what effect radiotherapy is having… So, I guess 3 months is as good a time as any. You may want to do 6 months because very few people will have had their ileostomy reversed at that point and it will have given the greatest possible chance for everything settling down and gives a true reflection of what, how things really are.*

4.4.2.5 Specific interventions/treatment and provision of care

This theme highlights the interventions recommended by the different participants to manage patients' adverse events and how members of the multi-disciplinary team provide this care. The interventions broadly fell into seven areas: (1) Self-management/lifestyle modifications; (2) Information provision; (3) Medical interventions; (4) Surgical interventions; (5) Screening; (6) Referral to specialist services; and (7) Counselling. Table 4.6 summarises the discussions, it is not an

exhaustive list of all management options for all adverse events following pelvic radiotherapy.

During the acute phases of pelvic radiotherapy treatment the interventions were supportive to enable patients to complete their full treatment schedule:

> *'If we could avoid a side effect, we would, but generally we can't, so what we do is we either delay the onset of a side effect if we can or mostly we minimise the severity and provide all the support mechanisms we have, and that in turn enables the patient to continue doing what they need to do, which is come in for treatment.' (HP4.)*

Table 4-6: Summary of management interventions

BOWEL SYMPTOMS	
Self-management/Lifestyle modifications	• Dietary modifications • Access to toilets • Pelvic floor exercises
Information provision	• MacMillan advice on dietary modifications and pelvic floor exercises
Medical interventions	• Loperamide (diarrhoea/frequency/incontinence) • Laxatives (constipation)
Surgical interventions	• Sacral nerve stimulation • Defunctioning stoma (very rare post treatment)
Screening and referral	• Coeliac, faecal elastase, B12, folate, thyroid, small bowel breath test before referral to gastroenterologist with a specialist interest
BLADDER SYMPTOMS	
Self-management/Lifestyle modifications	• Fluids; cranberry juice (acute radiation cystitis) • Pelvic floor exercises
Information provision	• MacMillan advice on pelvic floor exercises
Medical interventions	• Oxybutanin
Surgical referral	• Referral to urogynaecologist or urologist for consideration of self-catheterisation
MALE SEXUAL DYSFUNCTION: IMPOTENCE	
Self-management/Lifestyle modifications	• Penile pumps
Medical interventions	• Phosphodiesterase-5 inhibitors (e.g. Viagra)
Surgical referral	• Referral to urology (specialist nurse/ doctor)
FEMALE SEXUAL DYSFUNCTION AND MENOPAUSE	
Self-management/Lifestyle modifications	• Vaginal dilation – using dilators (of increasing sizes) or vibrator
Information provision	• Website 'Menopause matters' • DVD on vaginal dilator use
Medical interventions	• Topical treatments: Lubricants/moisturisers/steroid cream/hormonal pessaries or cream (not in hormone-dependent endometrial cancer patients) • Medications: HRT/COCP (<40years old)/testosterone (rarely)
Surgical interventions	• Surgical vaginal dilation • Procedure for fibrosis of hymen ring (anal cancer)
Counselling and referral	• CNS counselling • Referral to psycho-oncology for level 4 support
RADIATION SKIN REACTION	
Self-management/Lifestyle modifications	• SKIN: Analgesia; aqueous/cavalon cream; daily-weekly skin checks (also post completion of treatment if necessary); dressings • IMPACT ON DEFAECATION: Stool consistency; wet gauze to wipe with aqueous cream; proctosedyl ointment and instillagel for pain; actiform cool sheets between buttocks for comfort • IMPACT ON MICTURITION: Pouring water as pass urine • INTERNAL VAGINAL IRRITATION: Cooling gel sheets for outside; no internal treatments currently
Medical interventions	• Analgesia • Medications to manage stool consistency
PELVIC INSUFFICIENCY FRACTURES	
Medical interventions	• Analgesia; vitamin D supplements

Key: B12 – to assess for vitamin B12 deficiency; HRT – hormone replacement therapy; COCP – combined oral contraceptive pill; CNS – cancer nurse specialist

Symptom management in the acute setting was described as a triage process:

'…to me this whole triaging business, whether it is formalised or not is a different matter, and different centres do different things, so in some senses radiographers are entirely leading on everything in this respect. So they are the ones who see the patients every day without fail, assuming the patient turns up, they actually then triage, because they are going to say to patients how are you doing today, they are going to actually see the treatment field every day, going to pick up if the skin is looking any different, if the patient says, oh I had trouble whatever last night, if they are not able to deal with that, then in our setting, they then triage to us [nurse] usually, then if it is definitely a medical problem we will triage to a medic, but generally it is through us and then that might be to a medic, but it may be to a divisional health professional if it is something that needs referring on, but that depends, in different centres on what groups of health professionals you've got as a part of that big team.' (HP4.)

A similar pattern of triaging is present for late effects with the majority of symptoms managed through the clinical oncology or surgical doctors and the CNS team during outpatient visits. Further management support is then requested at this stage from the patients' general practitioner or through referral to specialist medical (gastroenterologist or endocrinologist) or surgical (urology or urogynaecology) teams. Clinicians receive different training in symptom management and this expertise along with patient expectations led to defined roles within the multi-disciplinary team:

'I think the doctors are medical professionals that are delivering a treatment programme, they have such expert knowledge and the patients recognise that, where as I think they recognise the CNS does more of the practical day to day things with them and I think that's perhaps where it comes in as well...I am not sure that the patients would ever talk to doctors about their sexual function or their sex life, whereas I think that history dictates that they can talk to the nurse about it.' (HP3.)

Provision of psychological support was more often described by nursing or other allied health professionals as part of their role whereas doctors expertise was described as focused on medical or surgical management of symptoms, particularly in relation to sexual dysfunction: *'but the psychological aspect is beyond my training and we don't have any psychosexual counsellors as far as I'm aware of or any psychosexual specialists.' (HP1.)*

The lack of discussion of sexual issues was highlighted in one comment:

'…sexual dysfunction is the least common but we do see it, but interestingly I have never had in women, but that's probably because I haven't asked the question.' (HP7.)

Both quotes on sexual dysfunction highlight the limits of knowledge and role expectations of different health professionals in their provision of care. This may limit

patient support and referral if clinicians are not fully aware of all symptoms and support services available.

4.4.2.6 Improving the service

Many of the discussions around improving the service provided to patients involved focusing on better information and support for long-term conditions. The clinicians interviewed could see a role for the use of PROs integrated within in their clinical practice to help establish the prevalence of adverse events, to focus the consultation and to highlight areas for further improvement: *'So this is my problem with all the toxicity stuff, it's great measuring it and I think it's right that we are measuring it but this sort of thing [this project] is a step beyond measuring it… But also you'd be able to home in, instead of having to go through the list of everything like you do each time, you'd be able to home in on, you could almost say – "I've looked through your questionnaire and I can see that there are a number of issues but perhaps your main issue are your bowels and perhaps we should concentrate on sorting your bowels out" and bearing in mind that there are other issues there.' (HP1.)*

Clinicians highlighted that during treatment patients were not able or chose not to discuss issues around long-term side effects. A suggestion about how to improve the service was a nurse-led survivorship clinic 6-8 weeks following completion of treatment to cover the transition from treatment to home life:

> *'To look at the things that they have never given a thought to and quite rightly so like returning to work, like their sexuality, going over signs and symptoms of recurrence. I know it's a bit early but going over possible long term side effects, I think that would be the ideal because I often think they don't raise these issues not because they are not informed but because they have not been able to take it all on board...' (HP3.)*

Improving support and discussion of issues around sex was a recurrent theme. Suggestions ranged from working with a psychosexual counsellor to produce an information booklet outlining recommendations and interventions to improve sexual desire to setting up patient support groups to discuss relationships. For patients with cervical cancer a couple of specific sexual concerns were highlighted where patients may benefit from further support: (1) issues of guilt due to the sexually transmitted nature of HPV; and (2) patients describing feeling 'violated' by the brachytherapy.

4.4.3 Expert review panel discussion

I provided a summary of the results of the inductive content analysis and health professional interviews to the five expert clinicians. During the discussion selecting the PRO with the most extensive coverage of relevant toxicity items emerged as the dominant attribute required for the purposes of this project. This was to minimise the development of new (non-validated) items for the clinical studies.

The results of the inductive content analysis, confirmed by the thematic analysis of the health professional interviews, found the EORTC-QLQ system to have least missing symptomatic adverse event items for use in clinical practice to evaluate the relationship between toxicity severity and dose delivered to the organs at risk. Many clinicians were also familiar with the system from clinical trials, which may improve implementation.

4.5 Discussion

For the aims of this project no one PRO, or group of PROs, covered all toxicity items expected in these cancer sites. Overall however, the EORTC-QLQ-C30 and disease-specific modules have the fewest missing items relevant to pelvic radiotherapy adverse events. This questionnaire system was selected for use within the clinical studies of this project. The EORTC-QLQ system does not have a cancer specific module for anal cancer, however the majority of missing items from the validated disease-specific modules may be supplemented from the EORTC-QLQ item bank. Any other missing items will be developed in the next phase of the project through cognitive interviews with patients and the pilot study using the EORTC-QLQ format (Chapters 5 and 6). The analysis found the NCI-PROCTCAE to have many missing items in relation to pelvic radiotherapy adverse events and whilst the PSQs focuses on the most common side effects (bowel, bladder an sexual dysfunction) for the purposes of dosimetric evaluation required within this study, the EORTC-QLQ system provided more extensive coverage.

This evaluation used an innovative mixed methods approach to evaluating the content of existing validated PROs for use within this project. Previous research on how to select a questionnaire for using in clinical practice has described the decision-making required to choose a questionnaire but without elaborating on which methodological approaches to use(102). The use of an inductive content analysis technique comparing multiple questionnaires with the CTCAE as the gold standard proved an effective method to highlight missing items in each of the PROs evaluated. This rigorous qualitative process (involving two independent coders) followed by application of the

domains and codes discussed in the health professional interviews into the coding framework provided a clear and transparent process through which to select the PRO with the best coverage of adverse event items in patients treated with pelvic radiotherapy. This collaborative work piloted the use of the inductive content analysis technique to evaluate item content between different PROs. This work will be developed further through international collaboration with the NCI-PROCTCAE team to ensure full coverage of all toxicity items relating to pelvic radiotherapy within the questionnaire system.

The use of different methodological approaches to the development of PRO and clinician reported toxicity systems may lead to some of the differences found in the content of the questionnaires. Bowel urgency, for example, is one of the most common adverse events reported by patients and health professionals following pelvic radiotherapy and is not included as an item in the CTCAE (v.4) or by the NCI-PROCTCAE developed from the CTCAE(252) . The CTCAE is developed and updated based on clinician feedback and standardised by the NCI review committee as compared to the EORTC-QLQ system, for example, which is developed with patient involvement. This finding highlights the potential benefits of a patient-reported approach to reporting toxicity and also the challenges to matching the PROs to clinician grading. The relationship between the EORTC-QLQ grading and the CTCAE will be evaluated in more detail in the following chapter through cognitive interviews with patients. The number of missing items relating to the late effects of pelvic radiotherapy within the NCI-PROCTCAE may also reflect the sample of patients used in the cognitive interviews to develop the PRO items(242). Patients were included if they were undergoing active treatment with chemotherapy and/or radiotherapy or had completed treatment within the past month. This led to effective coverage of items for patients during cancer treatment but will be unlikely to draw attention to late effects.

All three PRO systems broadly covered the three most commonly reported side effects following pelvic radiotherapy described by the health professionals: bowel, urinary and sexual dysfunction. These adverse events are repeatedly highlighted in studies using different methodological approaches ranging from RCTs to qualitative research(11, 127, 253). However, the use of qualitative interview analysis allowed the views of multiple health professionals from diverse clinical roles to highlight the impact of the adverse events on patients' daily lives and their professional roles in alleviating and managing symptoms in both an acute and chronic setting. This additional analysis highlighted potential differences in patient's expectations of symptoms and outcomes following treatment that may be age, disease and treatment related; the huge

psychological impact of on-going toxicity; and limitations of different clinicians in the support and interventions they are able to provide patients.

The analysis of the health professional interviews revealed that the integration of PRO results electronically into patients' health records within the local organisation would be an acceptable intervention and could be an effective means to improve an aspect of local service provision. The health professional interviews also provided an opportunity to strategically engage the clinicians who will be involved in recruiting the patients involved in the clinical studies. This interaction aimed to ensure that the outcomes of the intervention fulfil not only the research aims of the project but also complement the existing clinical pathways. Information on how clinicians may imagine using the PRO results in their consultation provided guidance on what adverse event information is useful, the timings of when to present the data and how to present the data. The findings from these interviews informed the decisions made regarding the format and timings of the presentation of PRO data described in Chapter 6.

4.6 Strengths and limitations

This study has a number of strengths. Using multiple qualitative methods may guard against unreliable results(254). The inductive content analysis enabled rigorous coding of all items in the selected questionnaires and the interview analysis enabled the selection of items relevant to the patient groups to be included in the clinical studies. The qualitative analysis of the interviews also allowed inductive exploration of the broader issues involved with the treatment and follow up of patients treated with radiotherapy within the local organisation. However, the interview study was time limited rather than related to saturation of the data. Purposive sampling of health professionals with different backgrounds was implemented to account in part for this limitation. The inductive content analysis was also limited to the questionnaires used most frequently, in the case of the PSQs and the EORTC-QLQ system, and by the PRO version of the CTCAE as the gold standard for adverse event reporting. Other questionnaires are in common use within clinical trials, for example the FACT-system(104), however to pilot this analysis technique these constraints were employed.

4.7 Conclusions

In summary, this chapter has explored the content and clinical relevance of three commonly used PROs for use in this project using multiple qualitative research

methods. There are gaps in the questionnaires commonly used to report on adverse events, however, for use in the longitudinal follow up of patients with anal, cervical, endometrial and rectal cancer treated with (chemo)radiation currently the EORTC-QLQ system has the fewest missing symptom items for use as a validated PRO in clinical practice and research. Expert opinion was valuable in highlighting relevant missing items and envisioning the application of the PRO intervention in practice but provided no consensus on design and wording preferences. Future work will involve international collaboration in the development of PROs to cover all adverse events for patients treated with radiotherapy for anal cancer with the EORTC-QLQ group and pelvic radiotherapy with the NCI-PROCTCAE team.

Chapter 5 Cognitive interviews with patients: A comparison between patient and clinician ratings

5.1 Introduction

Following on from the selection of the EORTC-QLQ system for use within this project, this chapter seeks to evaluate the relevance of the items within the questionnaires for the pelvic radiotherapy patient population within St James' University Hospital and to establish the views of patients on the methods of application (electronic and paper methods) that will be used within this project. In addition, this chapter aims to qualitatively analyse the level of agreement between clinician and patient reporting of symptoms using the cognitive interviewing method of verbal probing to explore the questionnaire item responses in more detail(107).

Many research articles have demonstrated the weak associations between clinician reported toxicity and patient reporting of symptoms using quantitative methodology both in a clinical trial settings and within clinical practice(56, 57, 71, 137, 255-259). The findings have highlighted significant variability between clinician and patient rating of symptoms, principally with more subjective symptoms such as fatigue and pain, and functional issues, such as the impact on a patients' role or social functioning(56, 257, 258). One study, analysing data from a multicentre clinical trial, also highlighted large differences in patient and clinician ratings between institutions with discrepancies between clinician and patient ratings ranging from 4% in one institution to 71% in another(57). Other research has focused on inter-rater variability using clinician-reporting systems, finding lower associations with more subjective items, such as fatigue compared to objective, laboratory-based severity ratings, such as febrile neutropenia(260, 261). The evidence that the integration of patient reported outcomes (PROs) can improve the accuracy, quality and efficiency of adverse event data collection has led to the recommendations to include PRO data collection alongside clinician reporting in cancer clinical trials(137).

However, studies comparing the severity ratings for adverse event (AE) items from patient and clinician instruments have used different methods to evaluate the comparisons. In two studies comparing the EORTC-QLQ and CTCAE, one study used a generic rule for agreement between the items of the EORTC-QLQ-C30 and CTCAE(71). An EORTC-QLQ-C30 score 1 ('not at all') was equivalent to a CTCAE score 0; EORTC-QLQ-C30 score 2 ('a little') to a CTCAE score 1; EORTC-QLQ-C30

score 3 (‘quite a bit’) as CTCAE score 2; EORTC-QLQ-C30 score 4 (‘very much’) as CTCAE scores 3 and 4 combined(71). In the second study, discrepancies in severity ratings were recorded if a CTCAE was graded as 0 and a patient-rated EORTC-QLQ item was rated as 3 (‘quite a bit’) or 4 (‘very much’)(57).

Potential flaws in the CTCAE development were critiqued in detail in a Journal of Clinical Oncology paper by Deborah Bruner, one of the members of the development committee for CTCAE versions 2 and 3(245). Bruner commented on not only the lack of psychometric testing of the CTCAE, a methodological process insisted on by the US Food and Drug administration for all PRO measures before use in clinical trials(45), but also the reliance primarily on expert consensus to decide on the severity ratings of the scale rather than through rigorous analysis of the evidence. Whilst this was a pragmatic decision, this limits our understanding of what separates a grade 1 CTCAE toxicity from a grade 2 or 3 toxicity and provides no information on whether these differences are clinically significant or important to patients(245).

This chapter uses cognitive interviews with patients treated with pelvic radiotherapy, analysed using a thematic framework methodology, to investigate the relevance of the items in the EORTC-QLQ system for the pelvic radiotherapy patient population and evaluate the severity ratings of the toxicity items in EORTC-QLQ and CTCAE grading systems. Cognitive interviewing has developed as a tool to pre-test questionnaire items to enable modifications to be made prior to administration(262). Verbal probing aims to reveal the cognitive processes involved in answering the survey questions and evaluate the validity of the item content(262). Cognitive interviews have been used for questionnaire development in many areas of health and clinical research (263-265) including in the recent development work by the NCI to adapt their CTCAE items for patient self-reporting(242).

Chapter 4 in part comments on the ambiguity of some of the item wording for the different PRO measures from the point of view of the health professionals. This chapter aims to explore the presence of wording ambiguities within the EORTC-QLQ system further with a patient sample, investigate comprehension of the questions, and evaluate the extent to which the items accurately reflect their experiences. Verbal probing was used to explore the patient’s experience and interpretation of the items and understand their reasons for selecting a particular response category on the PRO measure. The discussion between researcher (clinician) and patient was used to retrospectively establish the equivalent grading of the same AE using the CTCAE, as might be done in clinical practice(245). A reflexive process of qualitative analysis critiques the decision-

making process involved in the interpretation of a patient's toxicity by a clinician(266). Using qualitative methodology to evaluate the discrepancies between clinician and patient reported outcomes aims to enable an exploration of the content validity of the different grading systems used in the EORTC QLQ and CTCAE, which is not possible using quantitative methodologies(45, 267), and ask the question: are we *able* to report the same levels of adverse event severity using patient reported and clinician reported measures?

In summary, this chapter aims to evaluate the relevance of the EORTC-QLQ system items for the pelvic radiotherapy patient population within our organisation and to establish patient views on the study methodology for PRO implementation using electronic and paper methods. Finally, a retrospective qualitative analysis of the level of agreement between patient severity grading using the EORTC-QLQ system and clinician grading using the CTCAE will be evaluated from the cognitive interview transcript.

5.2 Methods

5.2.1 Participants and Setting

Participants represented a purposive sample of patients currently receiving or previously treated with radical (curative) pelvic radiotherapy for anal, rectal, cervical or endometrial cancer at a single institution: Institute of Oncology, St James's University Hospital, Leeds, UK (see table 5.1 for sampling table). NHS Research Ethics Service Leeds East Committee approved the study following ethical review (13-YH-0156). Patients were eligible for the study if they were 18 years or older, able to read and understand English and not exhibiting overt psychopathology or serious cognitive dysfunction. All participants provided written informed consent. A purposive sampling strategy was adopted to balance age, gender, tumour site and timing of completing the interview in relation to start of radiotherapy treatment. As there is no consensus on optimum sample size for cognitive interview studies, a pragmatic decision to interview between 16-24 patients was made, based on expert advice and the time available, with the decision to stop recruitment when emerging themes became saturated(105).

Table 5-1: Purposive sampling strategy

Cancer site	Men				Women			
	< 50 years	> 50 years	Acute Timing*	Late Timing**	< 50 years	> 50 years	Acute Timing	Late Timing
Cervical					1 or 2	1 or 2	1 or 2	1 or 2
Uterine								
Rectal	1 or 2	1 or 2	1 or 2	1 or 2	1 or 2	1 or 2	1 or 2	1 or 2
Anal								

*Acute timing – during treatment or less than 3 months post end of radiotherapy; **Late timing – greater than 3 months post end of radiotherapy

Eligible patients receiving radiotherapy treatment attend the hospital daily and were approached by a member of the clinical team who sought permission for the researcher to speak them about the study. Eligible patients on long-term follow up were identified by the clinical staff by screening the clinic appointment lists in advance and contacted by a letter from their named consultant inviting them to take part in the study in advance of their appointment. This approach was required to allow patients the opportunity to consider taking part in the interview prior to their appointment, as patients on long term follow up have infrequent hospital visits (typically every 6-12 months).

5.2.2 Cognitive interview goals and procedure

Two researchers completed the interviews. I (AG) completed the majority of the interviews (n=15) and a research assistant with experience in cognitive interviewing (Simon Pini, SP) completed two of the interviews.

Semi-structured interviews were carried out face-to-face using an interview guide. Participants received an invitation to take part in the study along with a participant information sheet. Interviews were arranged at a mutually convenient time and place. At the beginning of each interview participants were reminded about the rationale for the research and given the opportunity to ask any questions before signing a consent form. All interviews were audio-recorded and detailed notes were made alongside each item to guide analysis.

Patients initially completed a paper version of the EORTC-QLQ C30 (symptom items only) and related tumour module (CR29, CX24 and EN24 with additional relevant items added following the work from chapter 4). Verbal probes were used to investigate three key areas: (1) patient comprehension of the questions; (2) whether the items accurately

reflected their experience; and (3) what the EORTC-QLQ severity grading ('not at all, a little, quite a bit, very much') meant in relation to the patient's symptomatic experience. In addition, patients were asked about the methods of PRO presentation (electronic and paper methods) that will be implemented in this project. Patients had the opportunity to use a 'think aloud' technique during completion of the questionnaire items as well as the researcher using retrospective verbal probing to explore the answers in further detail after completion of the items(105). Verbal probing focused on exploration of items where patients indicated symptomatology or difficulty in answering the items as well as selecting a few items where the participant denied symptoms to investigate potential false negatives. The interviewers also observed and responded to patients' body language and other non-verbal cues such as facial expression that may indicate difficulties with understanding or language during the interview(262).

Verbal probing on the severity grading was carried out to the extent that one might as a clinician in a consultation in routine practice exploring patient symptoms. Symptom severity was then retrospectively graded using the CTCAE version 4(34) from the transcript to reflect the way in which a clinician might complete a form regarding CTCAE adverse events within a clinical trial following a consultation(245).

5.2.3 Analytic approach

The cognitive interview process aims to provide insight into the participants understanding, knowledge, memory and judgments used in the process of answering questions. Willis(262) describes the cognitive interview process as analogous to clinical interviews in which the content and trajectory of the interview is guided by the interviewer making decisions about content and potential themes of the analysis *during* the data collection rather than retrospectively at the point of analysis. This allows the interviewer to engage in a more exploratory approach to interviewing. The themes within the cognitive interviews were not dissimilar from a standard clinical consultation in which the severity of patients' symptoms are ascertained to determine the appropriate management. These interviews differed in that the responses to the EORTC-QLQ items were the prompts used to guide the emerging probes rather than clinical history taking.

All interviews were transcribed verbatim. Microsoft Excel was used to manage the data, using pivot tables to explore differences in content. A thematic framework approach was applied. Following a period of familiarisation the data was coded using both open and deductive coding techniques(108). The pre-defined (deductive) broad areas of interest were:

(1) Views on the completion method – Internet or paper;

(2) Views on completing questionnaires – overall format and difficulties with specific items

(3) Probed responses on specific questions of interest (ease of using the scale, recall, etc.); and

(4) Other notes that will be helpful in making changes.

Open coding within and around these categories was explored and the interpretations compared to the verbatim transcript data. Inductive themes emerging during the interviews were explored.

The relevant sections from the transcript, relating to the probed discussion of a particular questionnaire item, were associated in the analysis template with the patient severity rating for the item (e.g. not at all – very much). The content of the interview discussion was then used to independently decide on the appropriate CTCAE grade for that item. For example: EORTC-QLQ C30 item 17 asks ‘Have you had diarrhea?’ If a patient reported symptoms, their interpretation and comprehension of the item were further tested by asking questions such as ‘what does the word ‘diarrhoea’ mean to you?’ and through exploring how the patient’s EORTC-QLQ rating (not at all – very much) related to their daily experience with the symptom; such as frequency or impact on activities of daily living (ADL). A number of items in which patients did not report symptoms were also probed.

I independently analysed all 17 transcripts and Beverly Clayton (BC) independently analysed 8 transcripts. To enhance the validity of the analysis, CTCAE severity ratings were independently coded by the two clinical researchers - AG (clinical oncology trainee doctor) and BC (research nurse) - using a reference spreadsheet including all EORTC-QLQ items matched to the CTCAE items (taken from Chapter 4) with their descriptions for each severity grade. See table 5.2 for an example. Both clinical researchers took part in the process of reflexive analysis of the clinical interpretation of symptoms.

Table 5-2: Example of the coding spreadsheet

EORTC-QLQ CR29 ITEM	PATIENT RESPONSE	EXTRACT	CTCAE DESCRIPTION	CTCAE GRADE AND DESCRIPTION	
				CLINICIAN 1	CLINICIAN 2
Did frequent bowel movements occur during the day?	Quite a bit	AG1. You are saying that you are opening your bowels about 5/6 times a day, did you say, before you had any problems what was normal? CI14. Maybe about 2 AG1.So it has doubled? CI14. Maybe even tripled…	Diarrhoea	**GRADED 2:** Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	**GRADED 1:** Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline

Reflexive analysis was applied throughout the process of retrospective grading of the discussions into CTCAE item severity(266). Reflexive analysis allows the researcher to analyse how subjective and intersubjective aspects of their role in the research process impact on the research outcomes. It is defined as a more dynamic process than the more passive process of reflection(266). The analytic process recognises that the researcher as well as the participants influence the collection and interpretation of the data and enables the researcher to actively analyse the impact of their role on the decision-making processes(268). In the example seen in table 2, for example it is possible to see that clinician 1 coded the CTCAE grade based on the worst case scenario (from 2 to 6 times a day) and clinician 2 based the severity grading on the best case scenario (from 2 to 5 times a day). There is no guidance in the CTCAE as to how to manage this situation and the decision is left to clinical interpretation.

5.3 Results

5.3.1 Patient sample

17 patients took part in the cognitive interviews with a mean age of 56 (range 31-77 years) recruited between October and December 2013. Five of the participants were under 50 years old; four were women and one man (see Table 5.3). 53% were recruited with minimum school leaving age education level and 60% did not have a professional degree or qualification. 44% (n=7) of patients were retired, 38% (n=6) were not working during radiotherapy treatment and 19% were working full time (n=3). Recruitment stopped when emerging themes were saturated. The mean duration of the interviews was 31 minutes (range 12-58 minutes). Overall there were minimal differences between the transcript-coding between the two researchers (AG and BC). This is in likelihood due to the framework provided by the questionnaire and the method of verbal probing used. However, any discrepancies were discussed and resolved.

Table 5-3: Sample characteristics

Cancer site	Men		Women		Total
	Acute timing*	Late timing**	Acute timing	Late timing	
Cervical			1 (n=1 <50 years)	2 (n=1 <50 years)	**3**
Uterine			2	0	**2**
Rectal	3	0	1 (n=1 <50 years)	0	**4**
Anal	2 (n=1 <50 years)	1	3	2 (n=1 <50 years)	**8**
TOTAL	**5**	**1**	**7**	**4**	**17**

*Acute timing – during treatment or less than 3 months post end of radiotherapy; **Late timing – greater than 3 months post end of radiotherapy

5.3.2 Themes

The original deductive themes evaluating views on the completion method and views on completing the questionnaire and individual items led to emerging themes around views on the overall project aims and the potential application within their treatment pathway. Missing items also emerged as a new theme. The probed responses to the items led to the detailed analysis of the content validity of the EORTC-QLQ system

grading and the CTCAE adverse event severity rating, evaluating both the coding discrepancies between researchers using the CTCAE and between patient and researcher (PRO and CTCAE mismatches).

5.3.2.1 Views on the completion method

All patients completed a paper version of the EORTC-QLQ for this study however, of the 13 patients specifically asked about their preference for completion method, eight participants stated they would prefer electronic methods over paper-based ones; often stating ease of use for the choice of electronic methods over paper-based ones:

> *AG1. Do you have Internet at home?*
>
> *CI5. I do yes, and that would be quite useful to go online and do it to be honest. Sort of minimise the length of the visit here.*

Patients who stated that they would prefer paper-based methods were mixed in their reasons for this preference. Some patients preferred the perceived ease and reliability of using paper, or did not feel confident using the Internet for this use:

> *CI9. I just don't like using the Internet for information for things like that. I'm probably more old-fashioned that you revert to sort of the paper formats and things like that … and I've got that in front of me and your holding it and ticking it off and you're seeing … to me that's easier for me personally to do that than the Internet.*

However, the same participant agreed that she would be more confident completing the questionnaires using touch-screen computers within the hospital:

> *AG1. Have you ever tried anything like … I don't know if your GP surgery whether they have the [touch screen] log-in?*
> *CI9. Yes, the log-in.*
> *AG1. Have you found that relatively easy?*
> *CI9. Yes, that's easy…*
> *AG1. Yeah, you probably would find it okay if you … is it … are you worried about people accessing your information?*
> *CI9. I think probably.*

Only one participant had no access to the Internet and so paper was their only option. One participant felt that during their treatment when they were very unwell that they would not have wanted to use the online version of the questionnaire, particularly during their inpatient admission.

5.3.2.2 Overall views on the project aims

In general the participants viewed the intervention positively and could see the potential benefits of completing the PRO in advance of their hospital visits:

> *CI11. It is a good idea because, like you say, you do come away and think of I forgot to say that. Then tomorrow it might be a big worry that you think I mentioned it and someone's gonna pick up on it. Because you do forget to ask things…*

Some participants mentioned how they felt guided by the questionnaire items to reflect on symptoms and experiences that they had not considered previously or thought of as potential side effects.

> *CI3. The whole thing, I think, there are questions in there that you don't think about, until you actually read them and you think, yeah I had that and that and you don't realise what is going on in yourself at all.*

However, two of the participants had some concerns about how they might have felt completing the questionnaires during treatment, raising some important points to consider for the consent of patients for the prospective study:

> *AG1. And do you think it would be all right to fill this in during your treatment. Would you have found it useful, do you think, if you filled it in during treatment and also afterwards?*
>
> *CI4. I think for me now, it's my last day tomorrow, so coming at this time, yes, it's all right but at the beginning I think I'd have just refused because I don't think I could have been bothered, you know.*

This example highlights the importance of the use of PRO interventions to supplement and support patient care in clinical practice and not to feel burdensome to patients during an already potentially emotionally overwhelming time.

5.3.2.3 Overview of completing the questionnaire items

No patient complained of difficulties with the length or complexity of completing the questionnaire, in fact many described the process as 'easy'. No specific or more general wording difficulties were described and only one item - Have you been dissatisfied with your body? – was described as ambiguous in it's meaning by a couple of patients, as was also discussed in the health professional interviews.

> *SP1. Were there any questions that weren't clear or anything that you weren't sure about?*
> *CI7.No, they were all fine.*

Patient's appeared content with completing items on sexual function during the interview, both patients who were sexually active and not, and understood the rationale for asking the questions:

> *CI1. [On the sexual function questions] It's to the point but it's not too intrusive. I wouldn't mind answering that I'd think 'oh well I might as well'.*

Those who were sexually active were open about discussing their symptoms, even if some of the patients felt a little awkward initially:

> *AG1. Did it feel strange to be talking about it then?*
> *CI17. A little bit, but once you get over that first initial cringe, so no not too bad, no.*

Many of the participants were currently receiving (chemo)radiotherapy treatment and so were not sexually active at the time of the interview with some referring to sex as being the *'last thing on my mind'* (CI6). One patient highlighted the impact of receiving multiple treatments. He discussed his feelings towards sexual activity following an operation to form a stoma with the additional impact of receiving pelvic radiotherapy at the time of the interview:

> *AG1. You said have said sex has been a little enjoyable and you said you have felt a little bit uncomfortable about being intimate. Now, do you think those are linked together?*
> *CI13. Yes, because of the stoma bag as well, yes.*
> *AG1. And partly do you think because it's a bit sore? With the skin?*
> *CI13. Yes.*
> *AG1. So probably a combination of those?*
> *CI13. Yes definitely.*
> *AG1. Ok. And would that be different from normal?*
> *CI13. Yes definitely.*
> *AG1. And would it be different do you think even now being on the radiotherapy on top of having the stoma bag do you think that you feel, it feels more uncomfortable or less enjoyable perhaps because of having radiotherapy at the moment? Or about the same?*
> *CI13. No. It's obviously a bit different.*

Another patient considered her sexual experience following a hysterectomy:

> *CI15.That was a full hysterectomy, I think the top of the vagina as well but they'd always said it's still the same length and stuff but you never know …*

Interviewing patients during treatment, particularly involving multiple treatment modalities, highlights the dramatic changes that patients are experiencing at this time, both in terms of their physical function but also in relation to their experience of 'self'. This becomes particularly apparent in the discussion around sex and sexuality.

5.3.2.4 Missing items and additional item content validity

Following the discussions in the health professional interviews a number of additional items were added to the questionnaires. Many were from the EORTC-QLQ item bank (see Appendix B for questionnaires). However two items were developed in the style of the EORTC-QLQ items to cover missing items on radiation skin reaction and vaginal function whilst using vaginal dilators. The item wording was discussed with clinical experts and face validity evaluated further through the cognitive interview process. The skin reaction question was worded: 'Have you had any changes to your skin treated with radiotherapy?' The vaginal function items followed the wording of the items from EORTC-QLQ EN24 enabling patients who are not sexually active, but have been using vaginal dilators in the past four weeks to answer questions on vaginal symptoms: 'Has your vagina felt dry when using vaginal dilators?' 'Has you vagina felt short/tight when using vaginal dilators? 'Have you had pain when using vaginal dilators?' These questions may then function in two ways to ascertain the numbers of patients using vaginal dilators in a population as well as evaluate vaginal function questions in non-sexually active patients. The new items were well understood by patients when questioned on the meaning and relevance:

> *CI15 Yeah. I knew what you were talking about…[in reference to the questions on vaginal function using dilators]*
> *AG1. I just think that some people, particularly post-treatment … but particularly straight after treatment, lots of people do start using dilators first before they move to having sex. I think they kind of don't know what it's going to be like so it's more like a practice.*
> *CI15 Yeah, I'd agree with that.*

> *AG1. I just wanted to check this one here, have you had changes to your skin treated with radiotherapy?*
> *CI3. Yeah, very much.*
> *AG1. And so, what do you understand by that question?*
> *CI3. Soreness, skin breaking, burning and I have all that going on…*

An additional item from the EORTC-QLQ item bank was added to the cervical cancer questionnaire following a discussion about rectal pain and inflammation during treatment: *Did you have pain in your buttocks/anal area/rectum?*'

5.3.2.5 Coding discrepancies between clinician grading of interview content using CTCAE v.4

630 coded extracts were independently graded using the CTCAEv.4 (330 by AG and 300 by BC). Of the 300 extracts that both researchers graded using the CTCAE definitions, consensus was reached for 80% of items (n=239). On 61 occasions the two

researchers disagreed by a maximum of one or more CTCAE grade. Discrepancies were coded when the researchers selected a numerical grade that differed or selected multiple options (for example coding the extract as a CTCAE ‘grade 1 or 2’) of which one of the grades was different from the other researcher; i.e. the most discrepant outcome was selected. Table 5.4 reports the findings.

A number of themes were evident when considering the mismatches in more detail. Many of the more subjective symptoms, such as those surrounding the CTCAE items of fatigue (rest, tired, weak), changes in appetite, nausea and pain showed mismatches in scoring as well as items on sexual interest (libido) and function (impotence and vaginal stenosis). A number of items related to bowel function showed a higher frequency of mismatches – diarrhoea and faecal incontinence. Urinary frequency and skin reaction also had a higher frequency of mismatches.

Table 5-4: Frequency of mismatches between clinician grading by symptom

SYMPTOM	FREQUENCY OF MISMATCH BETWEEN CLINICIANS	RANGE OF DISCREPANCY IN CTCAE GRADE				
		0-1	1-2	2-3	0-2	1-3
Anal pain	1			1		
Appetite	3		2	1		
Back pain	1			1		
Bowel frequency	2	1	1			
Cystitis	1		1			
Diarrhoea	8	3	5			
Dry mouth	1		1			
Faecal incontinence	2	2				
Flatulence stoma	1		1			
Hair loss	1	1				
Health worry	1		1			
Impotence	2	1			1	
Mucous discharge	1		1			
Nausea	3	2	1			
Pain	2		1	1		
Pain ADLs	2	2				
Per rectal bleeding	1		1			
Rest	2	1	1			
Sexual interest	3	2	1			
Skin reaction	3		1	2		
Sleeping	1		1			
Stoma frequency	2		2			
Strenuous ADLs	1		1			
Taste change	1		1			
Tense	1		1			
Tired	3	2	1			
Urinary frequency	3	1	2			
Urinary incontinence	1		1			
Urinary urgency	1		1			
Vagina short	1					1
Vagina tight	1		1			
Vomiting	1	1				
Weak	3	1	2			
Worry	1		1			
Total	**61**	**20**	**33**	**6**	**1**	**1**

Key: ADLs – activities of daily living

Some of the differences in coding may relate to the multiple options within the grading descriptions in the CTCAE. For the pain items, grade 2 is described as ‘Moderate pain; limiting instrumental ADLs’ (activities of daily living) and grade 3 as ‘Severe pain; limiting self care ADLs’, where the semi-colon indicates ‘or’ in the description. The severity rating requires a judgement on the behalf of the clinician/researcher to decide on how severe the description of the patient’s symptoms appears. Inherent in the decision-making process is the patient’s description of the impact the problem has had

on their daily lives. The availability of the patient's rating on the PRO during this analysis added another layer of complexity as the clinician rating could be influenced by the patient's PRO response. For example, one researcher interpreted this quote regarding back pain as a grade 2 and the other researcher a grade 2 or 3. The patient rated her back pain as 'quite a bit'.

> *CI16. Yes, there are certain things that I want to do, like dancing, gardening for any length of time, and in actual fact bending is a problem, if I am weeding and bending down….*

The CTCAE provides guidance to select either description, to do with perceived severity or impact on ADLs, to score the item but this flexibility in the scoring system can bring in an increased potential for discrepancies to occur. In this example, one researcher opted to base the grading decision on the information that only instrumental ADLs were affected (grade 2) whereas the other researcher based the grading on the patient's severity rating as well as the description (grade 2 or 3). This finding is important when considering the implementation of viewing and using PRO results in clinical practice.

For the fatigue items, the CTCAE describes grade 1 as 'Fatigue relieved by rest' and grade 2 as 'Fatigue not relieved by rest; limiting instrumental ADL'. In the discussions it was difficult to ascertain how much relief patients received from resting and the clinician scoring was influenced by patients who had rated themselves as having some fatigue ('a little') but then went on to describe that state as normal for them, leading to ratings of grade 0 from one researcher and grade 1 from the other researcher for this extract: *CI4. I don't think it's with the treatment I think … I can't really say it's the treatment. I think it's just me.*

The clinician judgements were also influenced by patient expectations about what they were able to do normally. In the following example one researcher graded the patient's fatigue a grade 2 and the other either a grade 1,2, or 3:

> *AG1. What would be the difference between filling out a 4 and saying very much that something is really bothering you? In terms of tiredness…*
>
> *CI17. Well probably like I didn't feel like doing anything at all like yesterday, I just sat and laid on sofa most of the afternoon and by 6 o'clock I felt a bit bored and I thought I need to do something now, so I went out to Sainsburys for half an hour, so probably, very much I probably wouldn't have felt like doing that really. When I get up on a morning I feel alright, it's sort of as day goes on and I try to do too much, you feel like your batteries are running out...*

In this particular case, one researcher concluded that the patient's normal instrumental ADLs were affected as they might usually expect to do more (grade 2); the other researcher was unable to decide on a grade, deciding that this scenario could be graded as a severe problem (grade 3) as the patient was describing a significant change from her baseline capabilities, or a grade 2 as she was still able to do some instrumental ADLs but not all or grade 1, as the patient insinuates her fatigue may be relieved by rest.

The symptom that provided the most challenges for grading between clinicians was diarrhoea with eight mismatches. The CTCAE item ratings for diarrhoea are all based on bowel frequency (e.g. Grade 1: Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline) and indeed the EORTC-QLQ items on diarrhoea (EORTC-QLQ-C30) and bowel frequency (disease-specific modules) are coded using the same CTCAE grade. When probed about what the meaning of diarrhoea and their ratings meant to patients the majority would discuss consistency of stools and it was rare that a patient discussed bowel frequency at this point:

AG1. ...but you have said you had a little bit of diarrhoea…
CI17. Just a bit loose but not like liquid….
AG1. So with you going lots of, opening your bowels quite a bit on a morning, would you not class that as diarrhoea because the poo is not loose?
CI17.No, because it is not watery.
AG1. So diarrhoea to you means watery?
CI17. Yeah, because everyone has their own take on things.

When using the EORTC-QLQ C30 in combination with a disease-specific module this problem will be alleviated as all of the modules used in this study include an item on bowel frequency providing a more accurate coding match to the CTCAE. However, this raises some concern for studies only using the EORTC-QLQ C30 diarrhoea item in a comparison of patient and clinician grading as clearly patients are grading their response based not only on stool frequency but also on consistency of stools and urgency in some cases. Whilst not explicitly assessed in this analysis, another challenge, which might arise when using the CTCAE longitudinally for the diarrhoea item, is the reference to baseline symptoms. If the baseline bowel frequency was not recorded accurately then this item may be variably assessed over time.

Faecal incontinence also provided some difficulties for scoring. Whilst the discussion was sufficient to assess symptom frequency and impact on ADLs, the grading in the CTCAE specifically relates to the use of pads and makes no mention of frequency or impact on ADLs. Some patients may wear pads as a precaution and have no restriction on ADLs and others may not wear pads but restrict their activities for fear of

incontinence making it challenging to assess severity based only on the use of incontinence pads. Whilst the flexibility of the scoring systems may add complexity as previously discussed, the lack of multiple options in a number of symptoms also created challenges when retrospectively scoring the discussions. The medical need for the use of medications to treat a particular symptom was particularly helpful in the grading on constipation (e.g. Grade 1: Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema) and this addition would be potentially helpful for clinicians grading severity in other symptoms where medications are frequently indicated in cancer patients; for example, diarrhoea (loperamide), pain (analgesia) and nausea (antiemetics). This may help provide a more accurate view of 'true' toxicity and potentially make the scoring more accurate as this is an objective measure of severity for subjective symptoms.

The item on skin reaction also provided some differences in clinician ratings, which was not unexpected as the CTCAE scores relate to the visually inspected appearance rather than patient descriptions of pain and impact on ADLs. This new item will be further evaluated during this project. Similarly, including the need for topical and medication interventions to support skin reaction symptoms into the CTCAE rating scale could be beneficial.

The sexual function items on impotence and vaginal stenosis provided the greatest differences between clinician severity ratings. These items will be discussed in more detail in the following section as the reasons for the discrepancies between clinician ratings also led to mismatches between patient and clinician grading.

5.3.2.6 PRO and CTCAE mismatches

For the comparison analysis between PRO and clinician mismatches only the responses of one researcher (AG) were used. Each extract was independently graded using the CTCAE grading and compared to the EORTC-QLQ patient response. It was not possible to be blinded to the patient responses as the verbal probing technique used within the discussion made reference to the patient score. 60% of patient 'Not at all' responses corresponded to a CTCAE Grade 0 and 68% of 'A little' responses corresponded to a CTCAE grade 1, following the pattern described by Quinten and colleagues(71) - see table 3 green selections. Quinten and colleagues also proposed that the EORTC-QLQ response for 'quite a bit' corresponds to the CTCAE grade 2 and 'very much' to CTCAE grades 3 or 4(71). However, for EORTC-QLQ scores 'quite a bit' and 'very much', the clinician grading was lower in all instances in the 'very much' category and mainly split between grades 1 and 2 for the PRO response 'quite a bit'.

The instances where differences of two or more points were seen are highlighted in Table 5.5 in orange; accounting for 3% of the clinician grades recorded.

Table 5-5: Comparison between CTCAE clinician grading and EORTC-QLQ patient response

CTCAE v4 Clinician Grading	EORTC-QLQ response				Total
	Not at all	A little	Quite a bit	Very much	
0	38	1	1	0	40
1	6	102	28	3	139
2	2	14	29	14	59
3	0	2	1	0	3
Total	64	151	76	25	

50% of the instances (14/28) in which a patient response of 'quite a bit' was graded as a CTCAE grade 1 and 11/17 of the instances where 'very much' was graded 1 or 2 were due to a lack of impact of the symptom on a patient's instrumental activities of daily living (ADLs). The items where this was evident were: fatigue, pain, anxiety, urinary frequency and urgency and hot flushes. Although the grading of these items may refer to perceived severity (e.g. moderate pain), many clinicians will look to a potentially more objective measure of severity, such as impact of a symptom on daily life, to ascertain the severity level. There is perhaps a perception that using impact on ADLs as a measure of severity would be more consistent across multiple patients, timeframes and situations.

The two instances in which the patient response was 'a little' and the clinician CTCAE was grade 2 related to the items on vaginal stenosis. One of the items when the patient responded 'not at all' corresponding to a clinician grade 2 related to an item on erectile dysfunction. The mismatches associated with the sexual dysfunction items are discussed later in this section. The other item with a mismatch between 'not at all' and a clinician grade 2 related the EORTC-QLQ C30 item 'Have you felt weak?'

> *AG1. "…were you tired", you said "very much".*
>
> *CI15 Yeah.*
>
> *AG1. And you've talked a bit about how, you know, that's had an impact on you and all sorts of things but it's interesting you haven't felt that weak particularly.*
>
> *CI15 Well during the past week, after I had my treatment, it was like the week … normally I've been okay. I've not been great but the last time I was really bad that week and I felt really weak but … And when you're in the shower, you just have to go and lie down and stuff like that so that's how I class it as "weak". But since then, I have been a lot more tired than*

previous times so I've been going to bed at like half eight, nine every night so …

This item corresponded to the CTCAE fatigue item. The extract was coded as a CTCAE grade 2 due to the impact of fatigue on the patients instrumental ADLs. Within the scoring of the EORTC-QLQ C30 the 'weakness' item is included in a scale with two other items relating to fatigue ('Were you tired?'/'Did you need to rest?'). For these two items the patient responded with 'very much'. If the three items were scaled (grouped together) the differences between clinician and patient rating for the 'weakness' item would no longer present as a mismatch.

A further reason for patient and clinician scoring differences was in relation to the timing of symptoms. Although patients completed the questionnaire at the same time as having the interview the stipulated time frame of 'During the past week' for the EORTC-QLQ items differed from the lack of defined timeframe for the CTCAE. The lack of a clear time window for the CTCAE may led to ambiguity between different clinical raters and between patient and clinician:

AG1. And so here you have written that you have had some diarrhoea as well?
CI6. Yes.
AG1. And that's what you are saying about your tablets.
CI6. Yes, it is getting the balance. I find if I take 2, 3 times a day, I don't go to the toilet at all, if I stop taking them altogether, then I am never off the toilet, I am on the toilet all weekend.
AG1. It's trying to get that balance…
CI6. So now I am taking 1 and just trying that, and touch wood, it appears to be working, it has stopped the diarrhoea, but will I ever go again.

In this scenario the patient rated her diarrhoea as 'quite a bit', one rater graded as 0, as the diarrhoea symptoms had resolved at the time of the interview and the other rater scored as 2 due to the symptoms experienced over the past week and the use of medications. In this situation, the inclusion of medication use in symptom management may have alleviated this ambiguity as well as some description around what time-point or timeframe to use when completing the CTCAE.

The sexual function items provided a further area where both clinician-rated and patient rated mismatches occurred. On the impotence item, two patients described their use of a phosphodiesterase type 5 (PDE5) inhibitor ('Viagra') to improve their erectile function. However they differed in how they graded their symptom, with one patient responding 'not at all' to the question 'Did you have difficulty getting or maintaining an erection?' and the other responding 'very much', knowing that without the treatment his erections

are reduced. In this instance the grading system of the CTCAE was helpful as both patients discussions were graded 2 as the scoring description indicates the use of medication.

For vaginal function items, the CTCAE scoring of vaginal stricture is challenging to relate to patient experience. This item matches to the EORTC-QLQ items 'Has your vagina felt short?' and 'Has your vagina felt tight?'. The CTCAE description for grade 1 is 'Asymptomatic; mild vaginal shortening or narrowing'; grade 2 'Vaginal narrowing and/or shortening not interfering with physical examination' and grade 3 'Vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity or physical examination'. For the EORTC-QLQ items the discussion of symptoms surrounded the impact of this symptom on sexual activity or the use of dilators:

> *AG1. So here you have said that you have had a little bit of vagina dryness, and you have felt a little bit short or tight, and a little bit of pain here and it was a little enjoyable for you. Is that just because everything feels a little bit tighter and more uncomfortable, so do you feel all of those things are linked together?*
> *CI17.Yes, I think so and also I think you are a little bit wary and expecting it to feel different, I think some of it is probably psychological to be fair, then it is hard to know really.*
> *AG1. Does it feel different to starting radiotherapy treatment to how it did to just after having the operation?*
> *CI17.Yeah, just a little bit more tight and a little bit more dry.*

The CTCAE description of severity for this item raises a number of issues. It may be important to consider how one might differentiate between a patient with a grade 1 and a grade 2 vaginal stricture if physical examination was not impaired. It may also be worth considering if there may in fact be some differences in severity with a vaginal stricture interfering with the use of tampons compared to a stricture impairing sexual intercourse, dilator use or physical examination and to what extent the activity is impaired. In this instance the patient experience seems better described by the EORTC-QLQ grading system in which patients who are able with some modifications (such as the use of lubrication or HRT) to have intercourse or use dilators may rate themselves differently to patients who are unable to have penetrative sex at all and may benefit from surgical interventions.

5.3.3 Reflexive analysis

Whilst the use of cognitive interviews and verbal probing aimed to bring transparency to the process of decision-making for patients, so the reflexive analysis strived to bring transparency to the process of decision-making for clinical judgements, creating a dialogue between experience and awareness. This technique also locates the

researcher within the qualitative analysis process and acknowledges the bias that that will bring, particularly in the case of my role as a doctor and interviewer. In the interviews it was noticeable that I switched between my role as an interviewer and as a doctor to proffer advice when patients could be distressed by symptoms. This is perhaps not surprising as my overarching role within a hospital setting is as a doctor and as I introduced myself as a doctor to patients in the interviews it is perhaps my professional responsibility to contribute to the discussion as both a researcher and a doctor.

The cognitive interview method allowed flexibility in the approach taken to probe patients on items. However in a number of cases it was evident that in the moment I had decided that I had discussed the item sufficiently with a patient, relying on my heuristic judgements and aware of the pragmatic balance struck between time and amount of information gathered. In other cases I had responded to patient non-verbal and verbal indications that whilst significant symptoms were apparent these were not an issue at the current time. It was only on reviewing these discussions retrospectively that it became clear the short-hand heuristic decision-making during the interview had led to insufficient detail to make a clinical grading.

The cognitive interviews were not designed with the purpose of looking at thresholds between EORTC-QLQ responses and CTCAE grades and therefore I may not have asked the specific questions needed for such comparisons. To develop more robust thresholds in future research it would be worth discussing the CTCAE grading descriptions with patients to decide collaboratively on a severity rating and assess how the descriptions might be developed to more accurately reflect patient experience.

5.4 Discussion

This qualitative study established that the EORTC-QLQ items are acceptable and clearly understandable for reporting symptoms related to pelvic radiotherapy in our organisation. The analysis found the EORTC-QLQ to be easy to administrate within our practice and patients in general were positive about the aims of the wider project and the methods of completion. The qualitative analysis found that the discrepancies between patient and clinician using the two different scoring systems are often inherent in the content of the CTCAE description and will therefore commonly lead to differences between patient and clinician scoring using the CTCAE and EORTC-QLQ. It is not that the clinician is under-reporting symptoms per se but may in some cases be unable to score a patient’s symptoms more severely due to the restrictions implicit in

the CTCAE description or in other instances may choose to score the symptom using one of the more objective definitions rather than a seemingly more subjective one. For example, grading severity based on the impact a symptom has on a patient's ADLs over a severity rating of mild, moderate or severe. This has implications in the development of clinical thresholds for symptom severity grading as to develop a robust instrument for clinicians the descriptions of the severity ratings need to reflect patient experience. It is only through discussion with patients that clinicians are able to ascertain the severity of subjective symptoms and therefore to improve the accuracy of reporting thresholds, future studies should explore involving patients in their development alongside clinicians.

This is the first study to use qualitative methods to evaluate the differences between clinician and patient grading of adverse events and consider content validity as an explanation for the differences between patient and clinician scoring of symptoms found in quantitative studies. In comparison to quantitative methods using qualitative methodology provided clarity and potential reasons for scoring differences through exploring transparently the process of decision-making behind patient and clinician grading. A further strength of the study is the independent coding of the interviews by two researchers with different clinical backgrounds (doctor and nurse). This comparison allowed differences in inter-rater scoring to be evaluated.

Whilst it is commonplace in qualitative studies to have smaller sample sizes, the generalisability of some of the findings may be limited as only patients with pelvic malignancies were interviewed. However, the interviews continued until saturation of themes had been achieved within this sample and the 17 interviews generated 630 different grading codes between the two researchers including many items experienced by cancer patients with different diagnoses. The retrospective clinician grading using the CTCAE was not blind to patient's PRO responses using the EORTC-QLQ. As discussed, patient's grading did influence the clinician ratings. However, as the PRO response was used to probe the severity of the symptom in the discussion it was not possible to blind the transcript without losing the coherence of the conversation.

The findings from this analysis support the proposition that associations between the scores in the CTCAE and EORTC-QLQ systems are non-linear, although it is commonplace for both systems to be included in quantitative analyses using a linear model(57)This finding conflicts with the pragmatic decision to use uniform matching of scoring used in the paper by Quinten and colleagues(71). Our results show that whilst for the lower grade severity symptoms their model holds up, for the more severe

adverse event items the CTCAE description for many of the more subjective items make it challenging for a clinician to score a symptom more highly. In particular if a patient does not describe the symptom impacting on their ADL. However, our findings agreed with the poor agreement for diarrhea and nausea symptoms found in the study by Quinten et al.(71) Using the EORTC-QLQ CR29 items for bowel frequency may provide a better match to the CTCAE description of diarrhoea and including medication use in the CTCAE description may improve the consistency for both of these items. In support of this recommendation, the study using PRO developed from the CTCAE scoring found better agreement between patients and clinicians on the diarrhea item(56). In comparison to quantitative studies evaluating patient and clinician reporting differences, our study found similarly high rates of mismatches in fatigue, pain, urinary symptoms and vaginal stenosis(56, 57, 259). One study involving different European countries found significant institutional differences(57). The author suggested that these differences may be explained by sociocultural variation, however, the findings from this study may suggest that differences in clinical history-taking and understanding of the CTCAE (as the document is only available in English) could also play a role.

As the CTCAE is not used, or designed to be used, as a direct assessment tool (i.e. completed whilst in face-to-face contact with the patient) to evaluate adverse events any ambiguity in the wording of the grading descriptions may lead to greater inter-rater discrepancies than measures applied through direct evaluation. The use of the words ‘mild, moderate and severe’ have been criticised for showing wide variability in clinical interpretation, however, the ambiguity in the wording is wider than this(245). The use of a semi colon to denote ‘or’ throughout the document is only referenced at the beginning of the document. When CTCAE items are often included in documents outside of the CTCAE itself, this may not be clearly signposted and could lead to differences in interpretation. It may also be beneficial to encourage more emphasis on descriptions including more objective measures of severity, such as medication use and the impact of symptoms on ADLs to ease completion and interpretation of patient’s symptoms.

The EORTC-QLQ system remains the most widely used PRO measurement system in cancer clinical trials due in part to its excellent content coverage of symptoms(127). Whilst the EORTC-QLQ system was designed to report on health related quality of life in clinical trials rather than as a toxicity reporting tool the results are used as a surrogate for symptomatic toxicity and have influenced clinical decision making. However, this analysis raises questions about how future trials should interpret the EORTC-QLQ PRO results in relation to clinician toxicity reporting. The National Cancer Institute have developed the PRO version of the CTCAE specifically as a toxicity

reporting tool to resolve many of the issues found between clinician and patient grading(269). For the EORTC-QLQ to remain a contender for use within future clinical trials it will be important to develop a rigorous process of response matching between the symptom items and the CTCAE to enable clearer conclusions to be made in future trials. More specifically, this analysis raises concerns about the content validity of the diarrhoea item on the EORTC-C30 in an English clinical setting in relation to the CTCAE item. The discussions around the EORTC-QLQ items on bowel frequency were much more closely aligned to the CTCAE. Future work will need to explore these findings in different cancer sites, with clinicians and researchers from different clinical backgrounds and experience levels and in international organisations to evaluate the generalisability of the results.

Chapter 6 Setting up the clinical studies and Pilot study

6.1 Introduction

This chapter reports on the methods used to ensure effective integration of the electronic PRO assessment using the EORTC-QLQ system within clinical practice for the two clinical studies (cross sectional – Chapter 8 and prospective – Chapter 9). The chapter is divided into several sections:

1. Development of the presentation of PRO data in electronic formats for clinicians and patients:
    i. Review of the Internet-based technology - QTool
    ii. Development of the scoring procedures and the graphical display of the EORTC-QLQ items for the clinician view
    iii. Development of the online patient experience including online consent form and visual display of the questionnaire items

2. Methods employed for the cross sectional and prospective studies
    i. The approach methods for the cross sectional study
    ii. The approach methods for the prospective study
    iii. The software development for tracking patients and sending out email and letter reminders for participants in the prospective study

3. Managing the data: eCRF system - The data management system is described and the processes developed to export and validate existing clinical data including demographic, treatment and histology data from the electronic health records (EHR) system Patient Pathway Manager (PPM) for use within the analysis.

4. Evaluation of the approach methods and integration process through a pilot study.

6.2 Development of PRO data presentation in electronic formats for clinicians and patients

6.2.1 Review of the Internet based technology - QTool

The Internet-based questionnaire technology used within this project, QTool, was developed through numerous iterations of projects (funded by National Institute for

Health Research (NIHR), Cancer Research UK and MacMillan Cancer Support) within the research group and has been used successfully in a previous study linking PRO survivorship data with cancer registry data(135). QTool provides the technical platform to collect online PRO data at multiple time-points and was designed and built by X-Lab (using jQuery, MS ASP.NET and SQL Server). Usability testing took place during previous projects(94) but further usability testing took place during the set up within this project. Rob Carter and I performed extensive testing prior to the pilot study with further testing carried out with patients during the pilot study. Bug-fixes and modifications were discussed directly with X-Lab.

The technology to support the successful integration of QTool responses into PPM, QStore, was developed through the NIHR funded programme development grant for the eRAPID project (Electronic patient self-Reporting of Adverse-events: Patient Information and aDvice)(111). eRAPID provides self-management advice to patients reporting mild to moderate side effects and alerts the clinical team regarding patients reporting serious side effects. However, the integration of QTool responses into PPM via QStore was first piloted, modified and used in clinical practice within the pilot, cross sectional and prospective studies in this project (see Figure 6.1 below).

6.2.2 Development of the scoring procedures and the graphical display of the EORTC-QLQ items for the clinician view

Electronic versions of the EORTC-QLQ and disease specific modules (EN24, CX24, and CR29) were created including the additional items assigned to each module following the development work in this project. Different studies were set up in QTool for each of the three trials – pilot, cross sectional and prospective studies. Four study arms were set up for the pilot and cross sectional studies, grouping together participants who received the same questionnaire: cervical, endometrial, lower gastrointestinal (GI) female and lower GI male. Ten different study arms for the prospective study were set up due to differences in the follow up schedule of patients (see more detail on these groups in Chapter 9): cervical, endometrial, anal cancer female, anal cancer male, long course rectal cancer female, long course rectal cancer male, short course rectal cancer female, short course rectal cancer male, short course and delay rectal cancer female, and short course and delay rectal cancer male. Corresponding trials were set up on PPM to enable integration. Patients were added to the trial on PPM and a unique username and password generated through QStore for use within the trial. Participants were then able to use their username and password to log in via the QTool website to complete questionnaires with their responses recorded for viewing within PPM. I set up the questionnaires and studies on QTool and PPM with

support from the research group's data manager (Rob Carter) and IT manager (Leon Bamforth). Figure 6.1 shows this process diagrammatically.

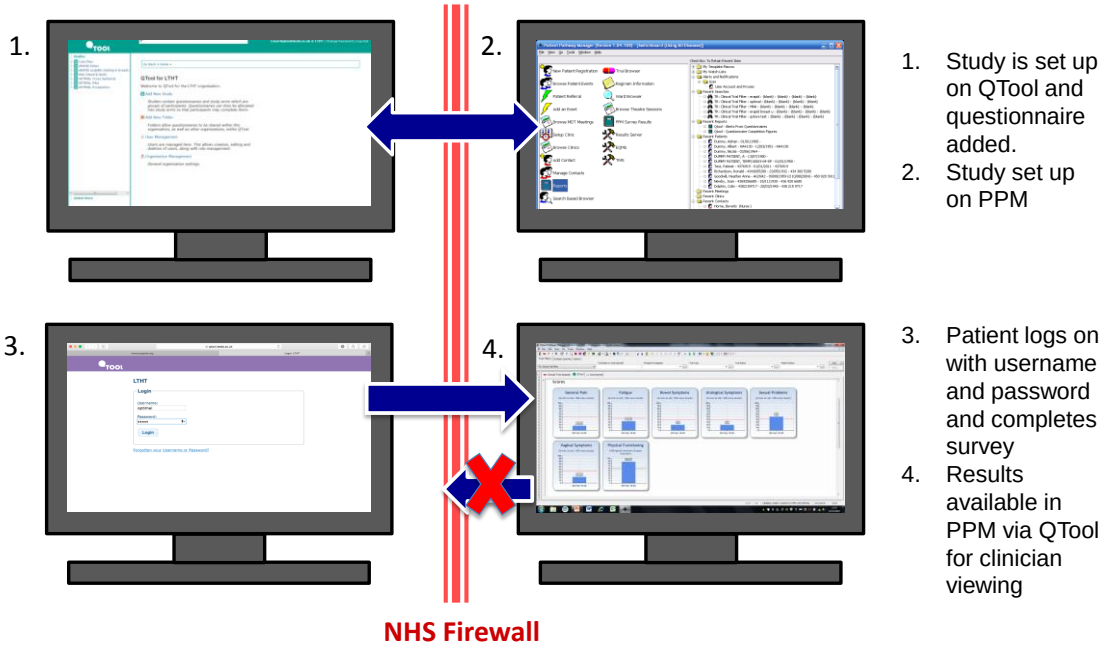


Figure 6-1: Using QTool in clinical practice

The EORTC-QLQ C30 and cancer specific modules have scoring manuals providing guidance on how to calculate the scoring for individual items and scale scores for grouped items(129). Patients respond to the EORTC-QLQ system with responses of 'not at all' (score 1), 'a little' (=2), 'quite a bit' (=3), and 'very much (=4). The wording for the majority of items is phrased in the negative so that a response of 'not at all' responds to no symptoms or functional problems i.e. a positive state: For example – 'Have you had pain?' However there are a number of items in the cancer specific modules in which the items are phrased in the positive with a response of 'not at all' responding to a negative state: for example 'Was sexual activity enjoyable for you?' In the score calculations the scoring is reversed to reflect this difference.

The four-point Likert-type scale, used for the majority of items, is converted through a linear transformation for both individual and scaled items onto a 0-100 scale. For grouped scales and individual items the scores range from 0 to 100 with a high score for a functional scale and global health status representing a high/healthy level of functioning/QOL and a high score for a symptom scale representing a high level of symptoms. Scaled items are summed and averaged once transformed using the process of imputing to account for missing items as recommended in the EORTC scoring guidelines(129). Provided over half of the items in the subscale have been

reported the mean value of these items may be substituted for the missing item. For the statistical analysis performed within the clinical studies the scoring manual for the EORTC-QLQ was used(129). However, for the purposes of presentation to clinicians in routine practice via the electronic integration into PPM it was decided that a more pragmatic approach to scoring was appropriate. This followed the discussions with health professionals in the interviews (Chapter 4) and with my clinical supervisors. All individual items were scored and transformed as per the scoring manual along with the scaled items resulting from the EORTC-QLQ C30 and EN24. However, for the disease specific modules, CX24 and CR29 additional items from the item bank were incorporated into the questionnaire. For example, the bowel urgency item from EN24, which was included in all questionnaires. Rather than present these items separately, they were summed and averaged along with all items relating to a particular group of symptoms, in this case 'bowel symptoms'. These scaled items were then presented as summary results in both graphical and tabular format for simplicity of viewing. The individual item scores were also presented in tabular format in order that the individual item responses could be evaluated further. I designed the scoring criteria and the scoring syntax was created and implemented in QTool by Rob Carter. We both carried out multiple testing of the system to ensure the accuracy of the scoring and questionnaire set up.

6.2.3 Designing the presentation of results in QStore

Once the clinical trials were set up in QTool and PPM it was then possible to develop and modify the presentation of questionnaire results for clinical practice using QStore. The PRO data collected needs to make sense to the clinician looking at it and therefore the formatting of the results must be considered as it has in previous clinical trials(117). As a practicing clinician I was keen to reflect the visual presentation of results used in PPM for clinical data with the PRO results in QStore. 'Abnormal' results were highlighted in the results table in red, as used in the presentation of blood results out of normal range. Evidence regarding what patients and clinicians consider to be a clinically serious response on data collected at a single time-point (either in a clinical trial or in clinical practice) using the EORTC-QLQ system is not available. Therefore a pragmatic decision was made to highlight in red individual item responses where patients responded 'quite a bit' or greater and in scaled items where patient reported 'quite a bit' for one item and 'a little' for the remaining items (or greater). Line graphs were used to see significant changes over time within the prospective study and data is shown as a single bar chart for patients on the cross sectional study. Graphical styles have been found to be helpful for interpretation of questionnaire data and may be delivered with electronic collection and computer scoring of patient responses(102, 270). Combining both tabular and graphical formats also enable changes over time to

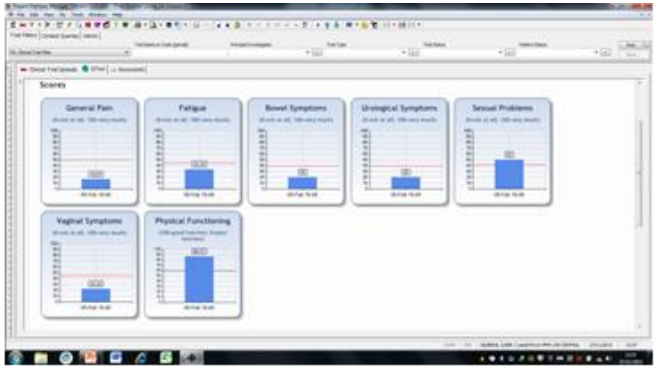
be clearly seen in relation to the completion date of the questionnaire. Figure 6.2 shows a worked example.

As this was the first clinical use of the QTool/QStore integration, it was possible to request a number of modifications to QStore to improve the presentation of results. Leon Bamforth implemented these changes. In particular the inclusion of a ‘tooltip’ function where the user is able to hover the cursor over both the item title and view the full wording of the question and view the response category, for example ‘not at all’ (see examples in figure 6.3).

Figure 6-2: Worked example.

a) Graphical summary; b) tabular results

a)



Worked example:

52 year old treated with chemoradiotherapy followed by brachytherapy for cervical cancer presenting with sexual dysfunction. She self reported 'a little' (score of 33.33) for vaginal dryness and stenosis and 'quite a bit' (score of 66.66) for vaginal shortening and dyspareunia.

Overall Sexual problems reported scored as 50:

$$\text{Sexual problems} = \frac{(33.33 \times 2) + (66.66 \times 2)}{4}$$

Individual items are highlighted in red if patients report the item as 'quite a bit' (score 66.66)

Grouped items are highlighted in red when patients report at least one item as 'quite a bit' (score 66.66) and all other items as 'a little' (score 33.33).

For sexual problems scores greater than 41.6 are highlighted: $\frac{(3 \times 33.33) + 66.66}{4}$

b)

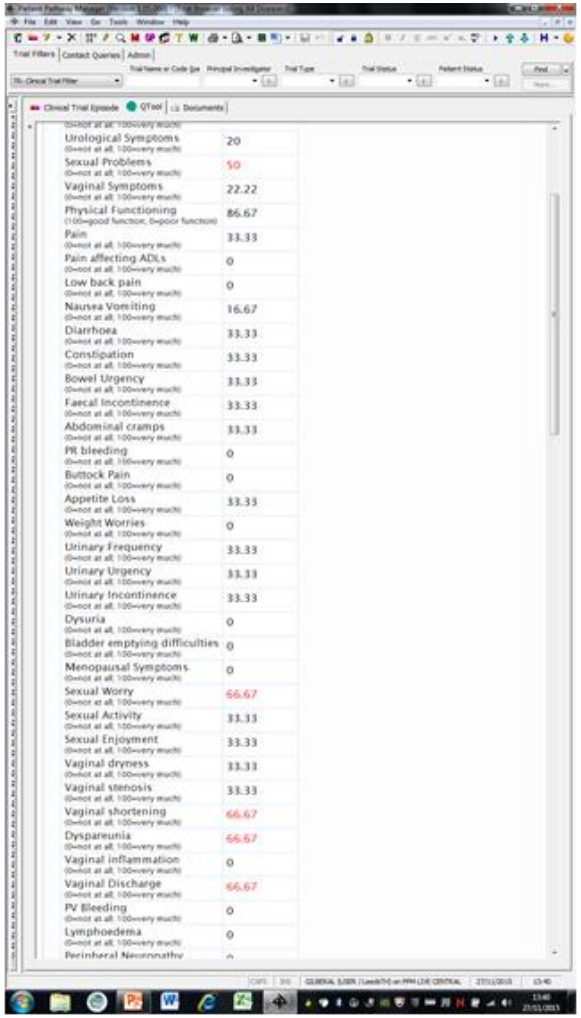
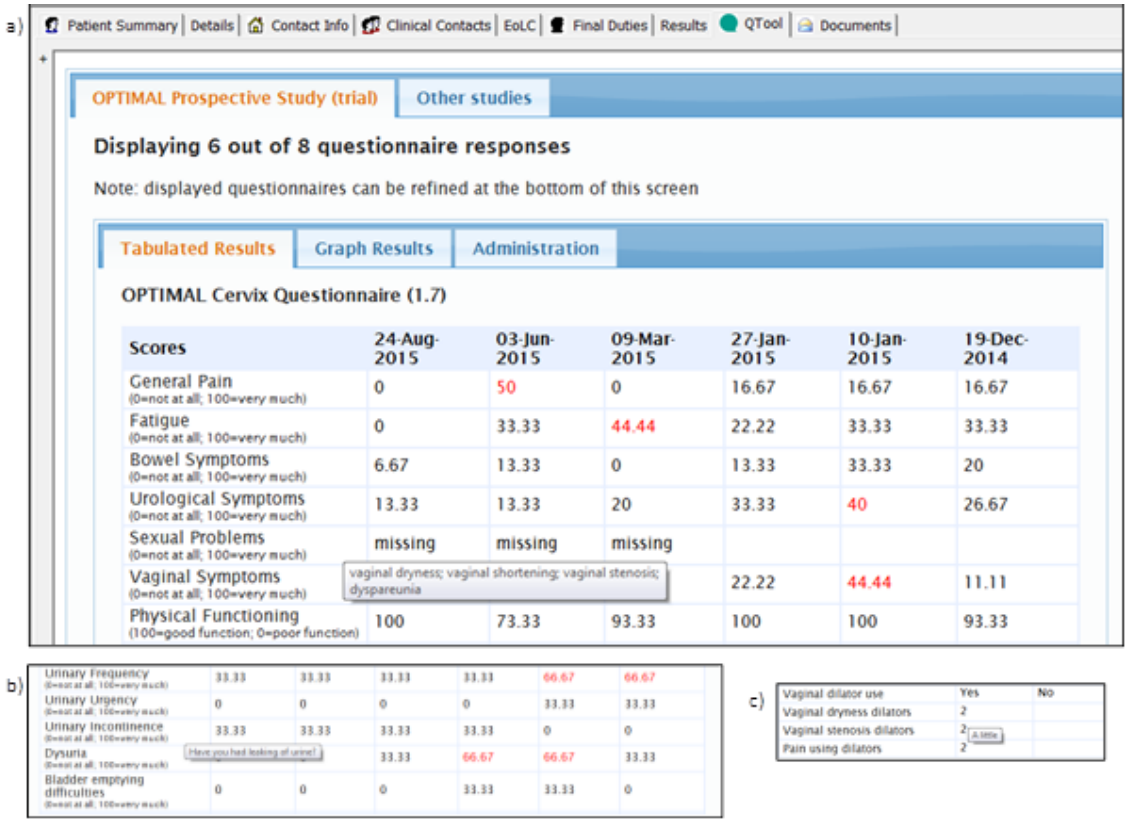


Figure 6-3: Examples of the tooltip function



6.2.4 Development of the online patient experience including online consent form and visual display of the questionnaire items

Guidance on ethical considerations and informed consent using online research methods was taken from the research resource - TRI-ORM: exploring online research methods - compiled by researchers at University of Leicester and University of Nottingham (271). An online consent form process was developed using this web resource as a guide to allow patients to provide fully informed consent prior to completion of the questionnaire without a face-to-face discussion with a researcher – see figure 6.4 and Appendix C. This process was developed to enable patients on long term follow up to be approached by letter prior to their hospital appointment, to go online and complete the questionnaire, providing online consent, so their results could be reviewed at their clinic appointment (where they would be seen by the research team and written consent provided). This study design for the cross sectional study allowed the most efficient method to enable the maximum number of patients to complete the questionnaire in advance of their appointment so their results would be available for viewing during their hospital visit. This study was the first pilot of this recruitment approach within our research group.

Patients were guided to log on to QTool via the research group website: www.pogweb.org. This was based on previous study experiences where participants had struggled to type in a particular web address into their Internet browser. However, the research group website is easily searchable through a search engine using the term ‘pogweb’ and comes up as the first hit allowing patients to then click on the link. Participants then log in to QTool and following completion of the consent forms will be guided through to the questionnaire pages. See figure 6.4. The consent form (Appendix C for detail) highlighted the questionnaire was developed for research purposes and the patients’ individual clinician may or may not use the questionnaire responses in the consultation. An option to opt out after logging on to the questionnaire if patients decide to withdraw consent was provided including after completion of all or part of the survey. In addition, patients were reminded that they could skip questions they did not want to answer at any stage.

One of the research advisory group members has advised me throughout the whole development, design and write up process of this project and he was able to provide advice and feedback on the layout and design of the questionnaire items in the patients view within the constraints of the QTool template.

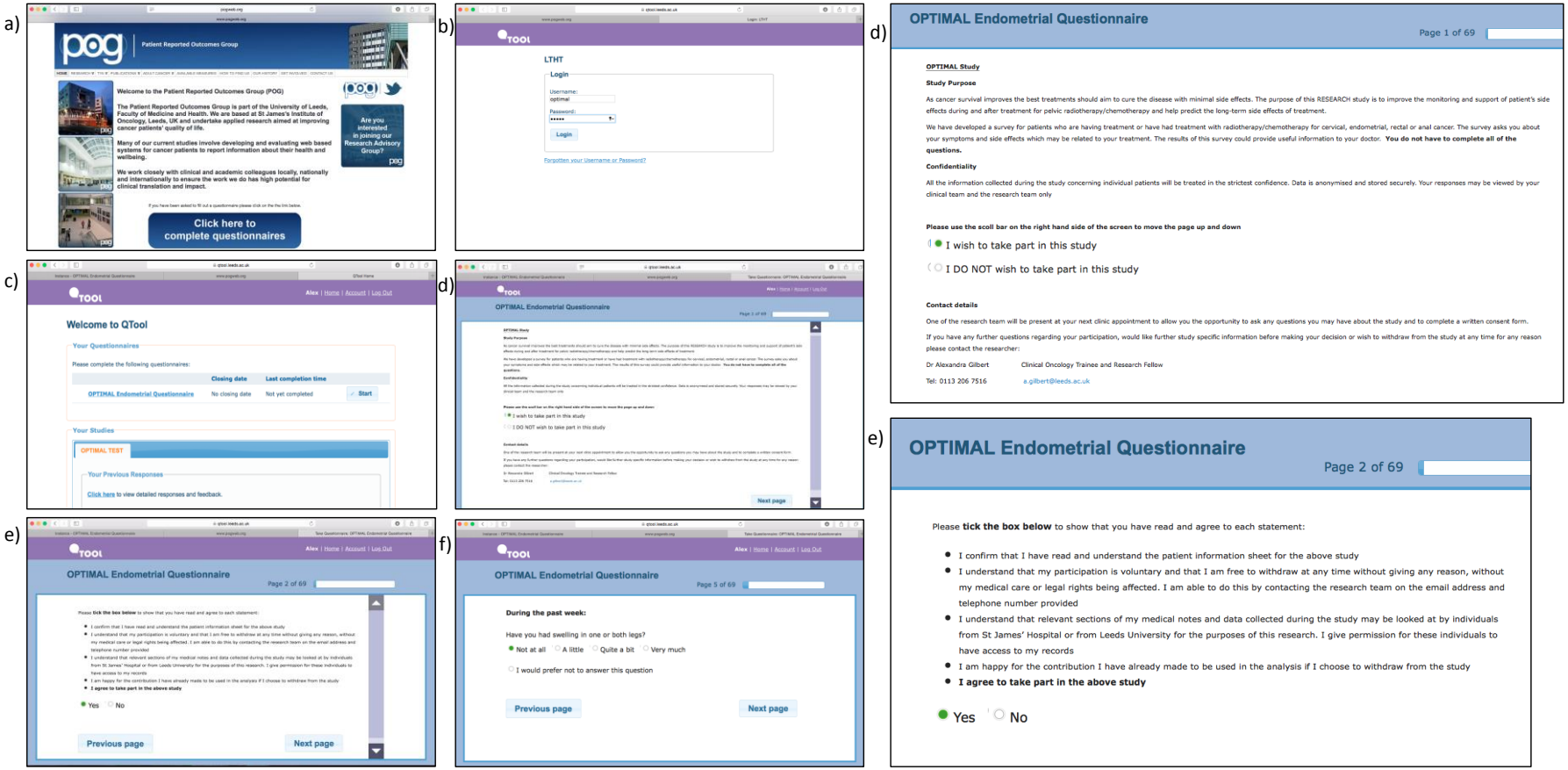


Figure 6-4: Screenshots of the patient process for QTool completion:

a) Research group website; b) QTool login page; c) Welcome page; d) Initial consent process (also shown in detail); e) Consent form (also shown in detail); f) Example of a question page

6.3 Methods employed for the cross sectional and prospective studies

I completed approximately half of the face-to-face recruitment for all three studies. Andrea Gibson (research nurse) and Marie Holmes (research assistant) recruited the remaining patients. Support for recruitment was funded through NIHR Clinical Research Network. I provided regular updates to the colorectal and gynaecological cancer and psychosocial sub-groups and uploaded monthly recruitment information.

6.3.1 Cross sectional study

This study used a cross-sectional design to administer the PRO measure (electronically or using paper-based methods) to describe the frequency and severity of late adverse events up to five years post treatment and to examine associations between patient-reported toxicity, clinical and radiotherapy dosimetric data to explore predictive models linking radiotherapy to toxicity severity.

6.3.1.1 Patients on follow up in Leeds Cancer Centre

Patients treated with radical (curative) external beam radiotherapy (EBRT) for anal, cervical, rectal and endometrial cancer 1-5 years post treatment completion within Leeds Cancer Centre were eligible. Patients are followed up routinely and are commonly seen in clinic every three months following treatment for the first six months to a year before the frequency of visits is reduced, with later appointments six monthly or yearly. In order for patients to complete the single electronic questionnaire prior to being seen in clinic by the clinical team, patients were contacted by letter two weeks prior to their appointment to invite them to take part in the study. This approach aimed to enable the clinician and patient to benefit from potentially incorporating the patient's responses to the questionnaire in their consultation. Clinic lists were screened in advance using a patient screening tool developed for this project (and described in the following section) to allow adequate time to send out the letter and for patients to have time to respond. The clinical research teams for each cancer site (gynaecology, GI and colorectal) carried out this process and evaluated patient eligibility prior to sending out the letters. In addition to the invitation letter a patient information sheet about the study and a consent form were also included. In the letter patients were invited to complete the electronic toxicity questionnaire either online prior to their visit, prior to their clinic appointment on touch screens available in the clinic areas or after their clinic visit either online, on touch screens or on paper (on request). The individual login details for the

online questionnaire were included in the letter. Figure 6.5 described the potential pathways through the process.

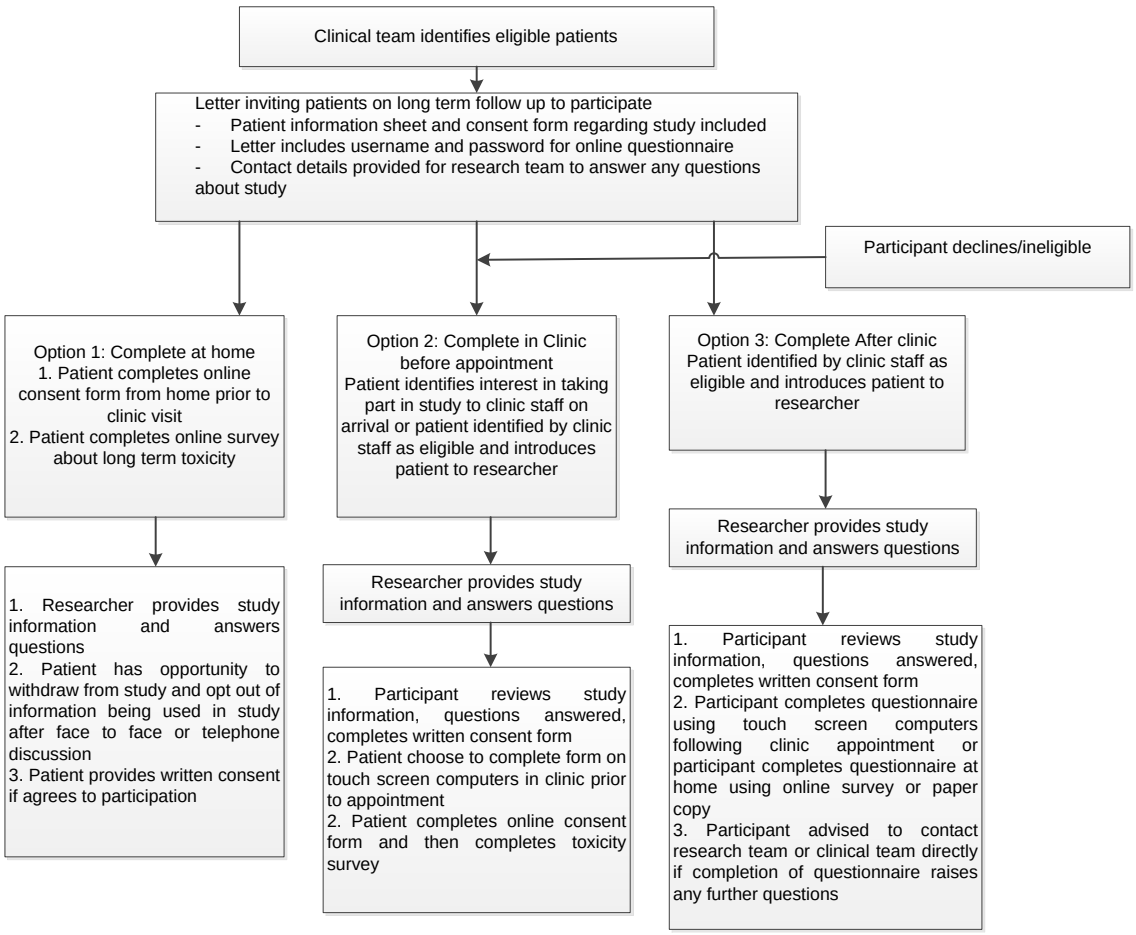


Figure 6-5: Cross sectional study recruitment process for patients seen at Leeds Cancer Centre

All patients were advised that in addition to the written information sent out that all participants would have a face-to-face discussion with the research team when they arrived for their clinic appointment and at this point would be invited to complete a written consent form. The patient was able to choose at this point to withdraw or opt out of the study and any questionnaire information already completed by the patient would be destroyed at the patient's request. Patients who were missed in clinic and had completed the online questionnaire could also return their written consent along with the relevant socio-demographic and clinical forms (in a stamped address envelope provided) following a telephone or email discussion with the research team. This approach was included as many patients would not been seen back in the hospital for many months or even years.

6.3.1.2 Patients followed up in satellite units (rectal and endometrial patients only)

Patients treated with pelvic radiotherapy for rectal and endometrial cancers have long term follow up under the surgical teams who treated them, which means once they have completed their radiotherapy they attend follow up appointments in local surrounding cancer units. Consequently many of the patients eligible to participate in the cross-sectional study did not attend the clinics at St James' University Hospital for follow up appointments. The slower recruitment in these cancer sites highlighted this issue and a substantial amendment was approved by the research ethics committee to allow recruitment outside of Leeds Cancer Centre. In order to access this cohort, patients were invited to participate by letter with the option of taking part from home, either online or by completing a paper copy of the questionnaire and returning it in an enclosed stamped addressed envelope (Figure 6.6). All documentation was included in the envelope including the individual login details for the online questionnaire, a paper copy of the questionnaire, all socio-demographic and clinical forms for completion and a stamped addressed envelope for returning the questionnaires. Participants were advised that the questionnaire data reported would not be available to their clinicians.

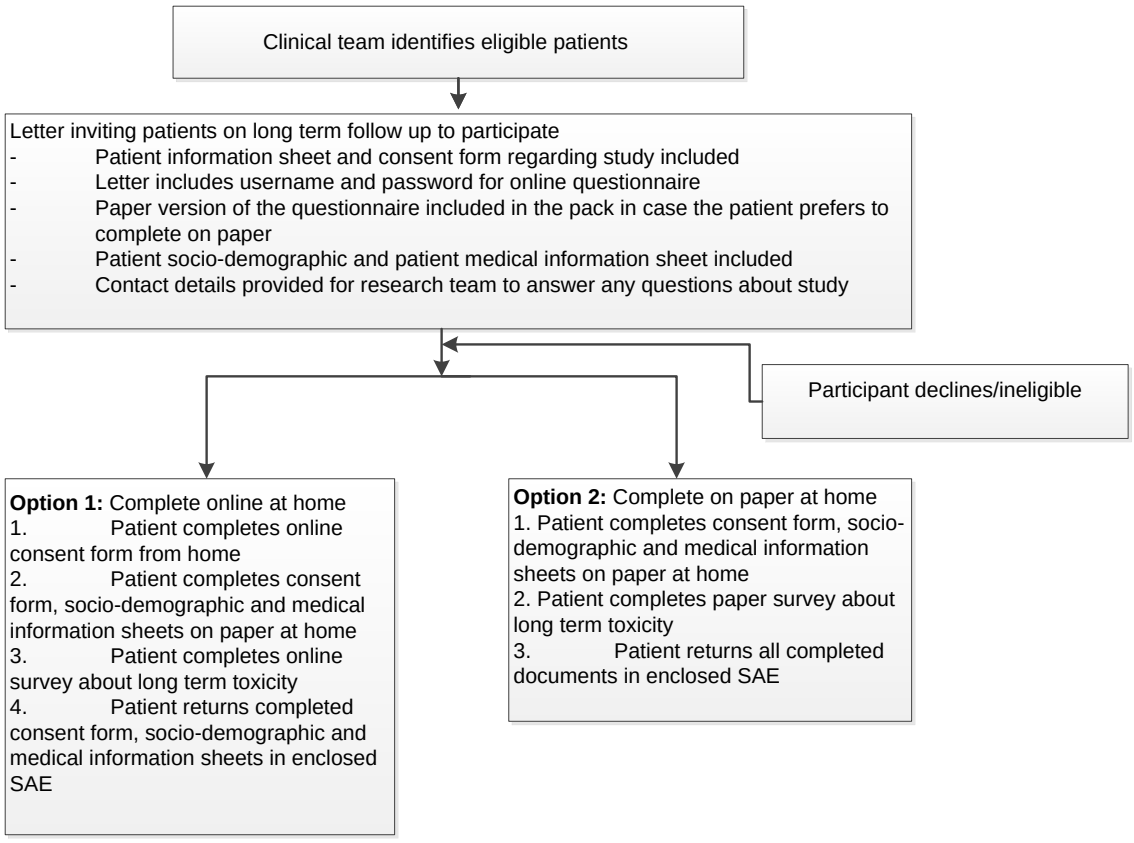


Figure 6-6: Cross sectional study recruitment process for patients followed up outside Leeds Cancer Centre

6.3.1.3 Patient Screening Tool for Cross sectional and Pilot studies

The primary report was developed to generate a cohort of patients who had received radiotherapy over the past 1-5 years. These patients were selected under five cancer categories: Anal *(ICD10 code C21*)*, Cervical *(ICD10 code C53*)*, Rectal *(ICD10 code C19* and C20*)*, Endometrial *(ICD10 code C54*, C55*, C57*)* and Other. The method of selection began with searching for any variant of these categories across the architecture of the PPM system, which involved looking at pre-diagnosis definitions, various radiotherapy coding fields and definitive diagnosis coding. The cohort was then narrowed to focus on patients with any Leeds Teaching Hospitals interaction, over the age of 18, who were still alive, with a confirmed primary cancer, having had either adjuvant or radical radiotherapy in the last five years and who were not currently on the trial. I designed the screening report initially in collaboration with Alexander Newsham (Leeds Cancer Centre Senior Data Manager) and then Ed Bolton (Assistant Information Manager), who implemented the code, generated the report and provided the technical detail for this section of the thesis. The reports used SQL Management Studio 2013 to build the code and host the database.

The final output consisted of information on date and time of outpatient clinic, and diagnostic and demographic information presented using Visual Studio 2013 and uploaded to the Reporting Services 2012 server within PPM. The report was also emailed securely to the clinical research team to validate patient eligibility before patients were enrolled on the pilot and cross sectional study using the methods described previously and an invitation letter sent out.

A second report was developed that would look for patients followed up outside of Leeds Teaching Hospitals who were otherwise eligible for the study and would also capture additional patients missed by the first report due to patient data inaccuracies, focussing on the rectal and endometrial cancer groups where recruitment was slower. Using the same core structure as the first, this second report looked into cancer tracking and responsible tracking organisations, outside of Leeds Cancer Centre. It then generated a randomised patient list, returning eight random records per external organisation, per gender. This enabled patients followed up outside of Leeds Cancer Centre to take part in the cross sectional trial. Recruitment was then targeted on hospital sites where PPM is used to record clinical interactions to improve the quality of clinical information available for analysis.

6.3.2 Prospective Study

This study aimed to prospectively measure acute and long term toxicities over a one year period in patient treated with pelvic EBRT for anal, rectal, endometrial or cervical cancer using the PRO instrument (EORTC-QLQ system) to establish the feasibility of the study methodology and record the trajectory, frequency and severity of PRO toxicity using either electronic or paper based methods.

Newly diagnosed patients with anal, rectal, endometrial or cervical cancer requiring radical pelvic EBRT treatment as part of their care were eligible. Clinic lists were screened in advance using the PPM ‘watch list’ facility by the clinical research team to identify new patients who fit the eligibility criteria. Following an introduction from clinical staff patients were approached by the research team at one of their initial hospital visits. Commonly patients who have been newly referred for radiotherapy treatment will have an initial consultation appointment to discuss the planned treatment and then return at a later appointment to consent to treatment. Ideally patients were invited to take part in the study at their initial consultation appointment and then interested patients consented at their next appointment or at the start of radiotherapy treatment, completing socio-demographic and clinical forms along with a baseline questionnaire. Figure 6.7 shows the overview of the recruitment process.

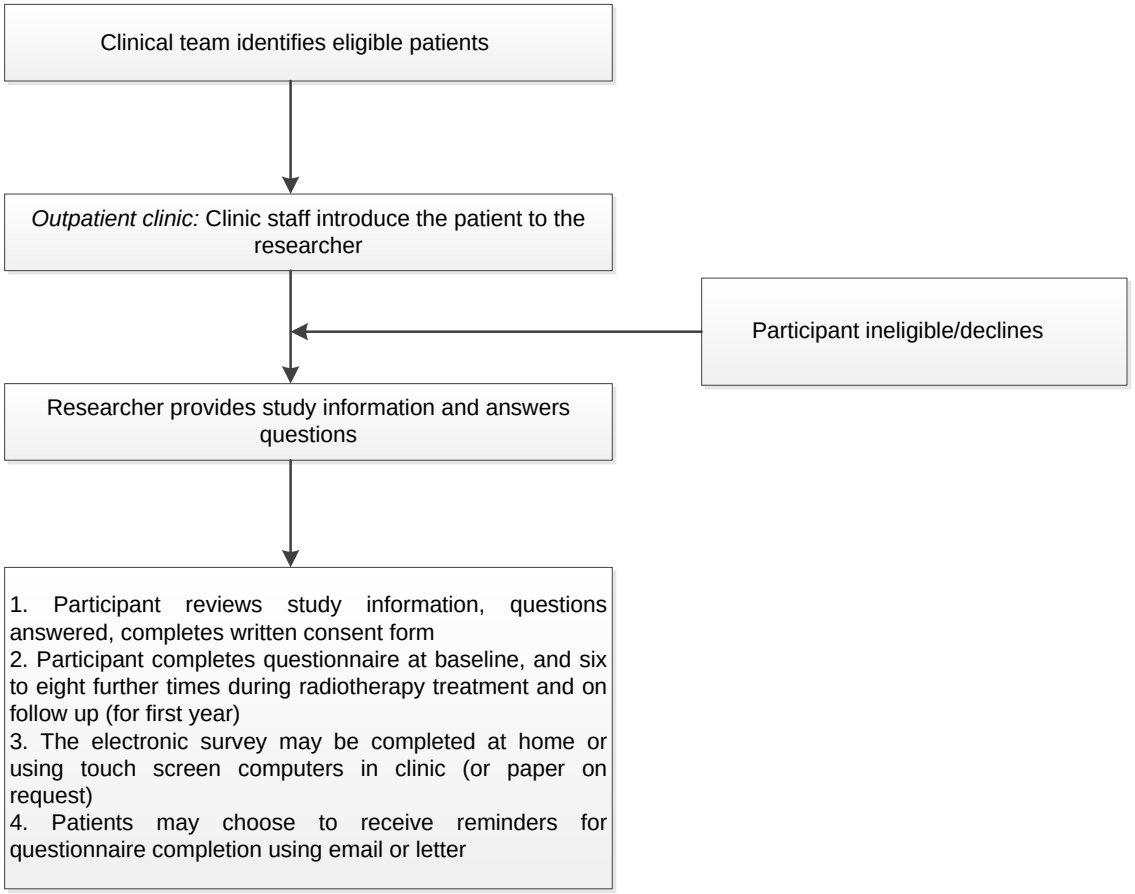


Figure 6-7: Prospective study recruitment process

Depending on treatment schedule, patients were allocated to one of 10 study arms determining their follow up schedule. Specific timing of assessments was based on patient and clinician feedback during the interviews and was in line with routine clinic follow up schedules already in place within Leeds Cancer Centre. Patients were invited to complete the EORTC-QLQ C30 and cancer specific module at baseline and then between 7-9 times in follow up depending on the cancer site treated (see table 9.1 in chapter 9). Patients could choose to complete questionnaires online, receiving email correspondence, or on paper.

6.3.2.1 Software development for tracking patients

The tracker was originally developed for a previous study carried out within the research group(94) but was modified for use within this study. The tracker is a Microsoft Access based application aiding the management of patient communication through a study or treatment pathway (see figure 6.8). The application allows the entry of multiple follow up schedules (pathways) and has the functionality to set pathway specific follow up periods and communication information, as required in the prospective study. Patient information is set up in the tracker and the start date of radiotherapy treatment set as day one, providing the start date for their pathway. The tracker automatically generates either an email, using a system-specific NHS email account, or letter communication at the correct invite point for the patient. The automated generation of patient communication is restricted and therefore the tracker requires administrative intervention to make the final decision to create the communication.

The tracker also incorporates information from QTool and informs the tracker logic as to whether the participant has completed the questionnaire within the time window. The tracker then either generates a ‘reminder’ or ‘thank you’ communication at a set period after the initial invite. A reporting system outlining completion status for each patient allowed manual chase up if required. For the prospective study additional functionality was developed to allow pathway follow up to be paused allowing flexibility to create communications at a clinically relevant time-points. James Thomas (database manager, NHS England) built the tracker and provided the technical details for this section of the thesis. I designed the modifications necessary to fit with this study design in collaboration with James. Administrative support for the tracker was provided by me, Andrea Gibson, Marie Holmes and Sarah Dickenson (research group administrator) throughout the project.

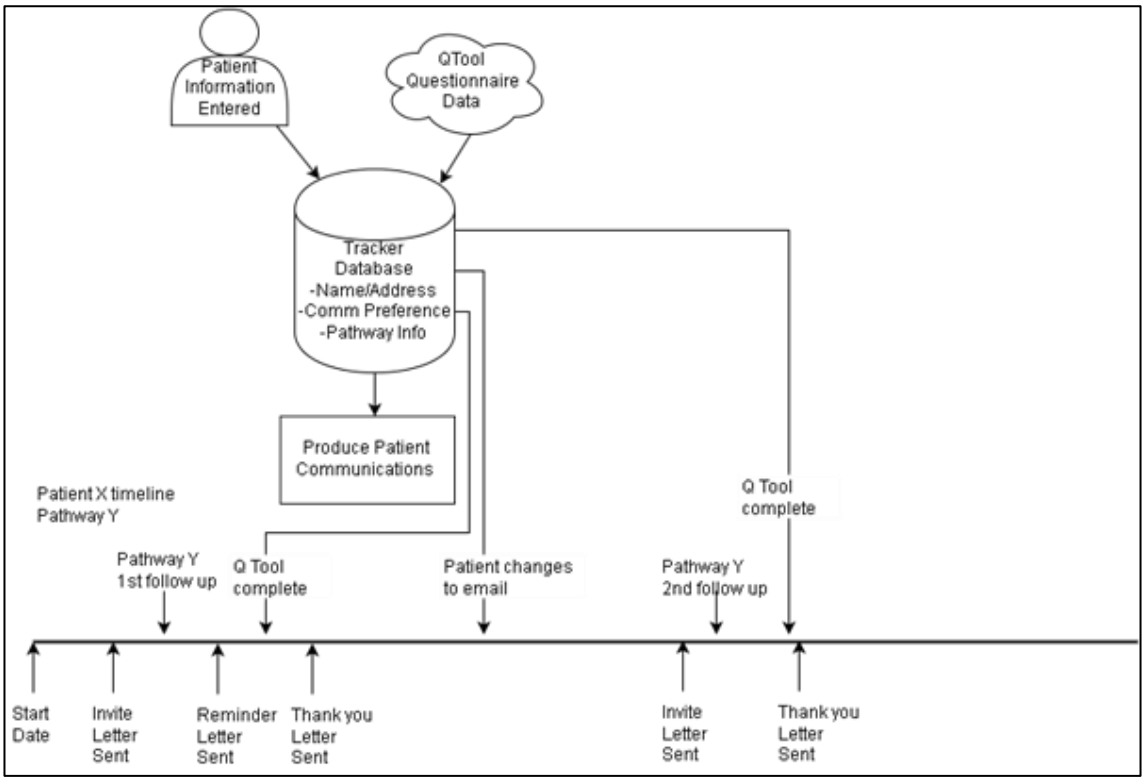


Figure 6-8: Schematic of the data/communication flows for the tracker

6.4 Managing the data: eCRF system

The electronic case report form (eCRF) system was developed for the research group by Rob Carter who provided the technical detail for this section. The purpose of the software is to provide the research team with a means of accurately capturing anonymised trial information for analysis in clinical trials.

The software has the following features used and developed within this study:

- Secure database with scheduled daily and weekly data backup to a secure server
- Windows based data entry screen with inbuilt data validation
- Data auditing capability
- Ability to quickly design CRF (Case Report Form) templates for data entry
- Create CRF's for each anonymised patient on a study
- Track and report on CRF statuses such as data completion & validation
- An import function allowing electronic data (in excel format) to be directly imported into the eCRF system (e.g. for data exported from EPR systems)
- Export function to output CRF data into IBM SPSS Statistics 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) data format for statistical analysis

The software also has further features not required for this project:

- Schedule CRF's to be completed at predefined time points
- Send out automatic reminders to clinical staff or patients to complete questionnaires or CRF data entry on an individual scheduled basis

The eCRF System was developed using Microsoft .NET technology and written in the C# language as a Windows application. The CRF data collected is stored anonymously in a backend SQL Server on a secure dedicated server hosted by the University of Leeds. There is a dedicated SQL backup service running which performs full database backups on a weekly schedule.

Following the collaboration with Alex Newsham and Ed Bolton to set up the screening tools from PPM the capacity to export clinical data from PPM was highlighted. Using the initial eCRF manager template, I designed, along with Rob Carter and Ed Bolton who carried out the coding, the criteria for clinical data to be exported directly from PPM into the eCRF for use within a clinical study. This functionality allows high quality data on weight and height, ethnicity, gender, histology, radiotherapy, surgery and chemotherapy treatment to be exported from a clinically based EHR system before manual validation. The data within the EHR is used in clinical decision-making and in the case of chemotherapy and radiotherapy treatment data is recorded directly from the treatment software. This data export process enables a reduction in the data entry errors common in recording data of this kind, particularly where dates and numbers are involved. A validation protocol (Appendix D) was designed to allow all exported data to be validated prior to analysis. Andrea Gibson, Marie Holmes and I validated all clinical data for the studies. Any technical clinical queries that Andrea or Marie had were systematically recorded in a spreadsheet. I resolved these issues using the medical information available from PPM or data was reported as missing.

The data which most commonly required modification was tumour staging. This is due to the clinical complexity and multiple stages to this process. Patient's initial staging is recorded within the EHR system but this may change following the outcomes from later investigations. Often this later, more accurate staging was not recorded at the multi-disciplinary team (MDT) meeting in a data format that may be exported. In the case of patients treated with neoadjuvant chemoradiotherapy for rectal cancer their tumour is staged prior to any treatment. Further staging post chemoradiotherapy on their post treatment MRI scan is noted, followed by post operative staging following surgery. For this project, patient's final pre-radiotherapy staging was reported as recorded by the clinical oncology team within their letters.

6.5 Pilot study

The pilot study aimed to examine the feasibility of integrating electronic PRO completion within Leeds Cancer Centre to test the study design, approach methods, content of the PRO measures and technical set up of the project in a small purposive sample.

6.5.1 Methods

6.5.1.1 Patient sample

A purposive sample by diagnosis of newly diagnosed patients receiving EBRT treatment and patients on long term follow up were recruited for the pilot study. Eligible patients were currently receiving or had received radical EBRT for anal, rectal, cervical and endometrial cancer in Leeds Cancer Centre. The approach methods used combined the methods set out for the cross sectional study and prospective studies above (see figure 6.9). The National Research Ethics Service Leeds East Committee approved the study following ethical review (13-YH-0156). Patients were eligible for the study if they were 18 years or older, able to read and understand English and were not exhibiting overt psychopathology or serious cognitive dysfunction. All participants provided written informed consent.

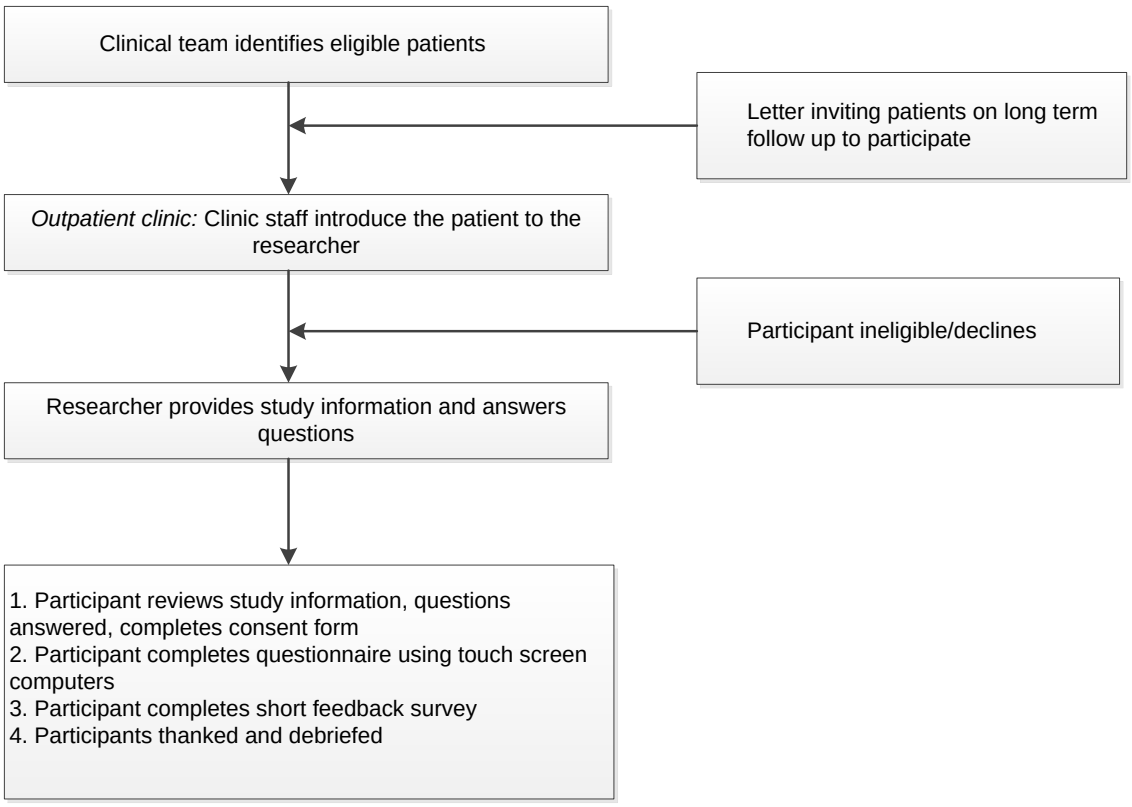


Figure 6-9: Pilot study recruitment process

6.5.1.2 Assessment

Patients were invited to complete a single PRO assessment either online at home or using the touch-screen computers within the hospital or using paper methods. Each patient was then asked to complete a feedback questionnaire (on paper) evaluating the process. Patient results were available to clinicians immediately on PPM for those patients who completed the questionnaire online. The recruiting researchers provided informal training of clinicians in clinic during the pilot study and throughout the prospective and cross sectional study recruitment process. Informal feedback on the process from the clinical staff was sought and recorded.

6.5.1.3 Outcomes measures and statistical analysis

The study design process was evaluated through the feedback questionnaire and through informal feedback from clinicians using the PRO results in PPM. Socio-demographic, clinical information and feedback questionnaires were analysed using descriptive statistics. Data was analysed using Stata/SE 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13.1. College Station, TX: StataCorp LP).

6.5.2 Results

6.5.2.1 Patient characteristics, questionnaire completion method and oncological treatment

Patients were recruited between 27 January 2014 and 27 February 2014. 80 patients in total were approached. 31 patients completed the pilot study and only nine patients (11%) declined (figure X). A further 9 patients consented to take part but either did not complete the feedback questionnaire or other forms correctly. The remaining 31 patients were either not eligible to join the study (n=1 was too unwell to approach at their appointment; n=1 had insufficient English to take part) or were not true decliners as recruitment was complete (n=29). These 29 patients were invited instead to take part in the cross sectional study if eligible. 22 participants were female and nine male with a mean age of 61 years (SD14.8; range 28-88 years). Table 6.2 shows the diagnosis and treatment characteristics and table 6.3 the socio-demographics of the sample. The majority of the patients were cervical cancer patients (55%), which reflects the numbers of patients treated and then followed up within our institution. In comparison, the rectal and endometrial patients are often followed up at satellite units. Whilst the anal cancer patients are followed up at Leeds Cancer Centre it is a rare cancer. The socio-demographics table shows the majority of patients taking part are White British (84%), married (58%), retired (48%) and have not continued education after leaving school (58%).

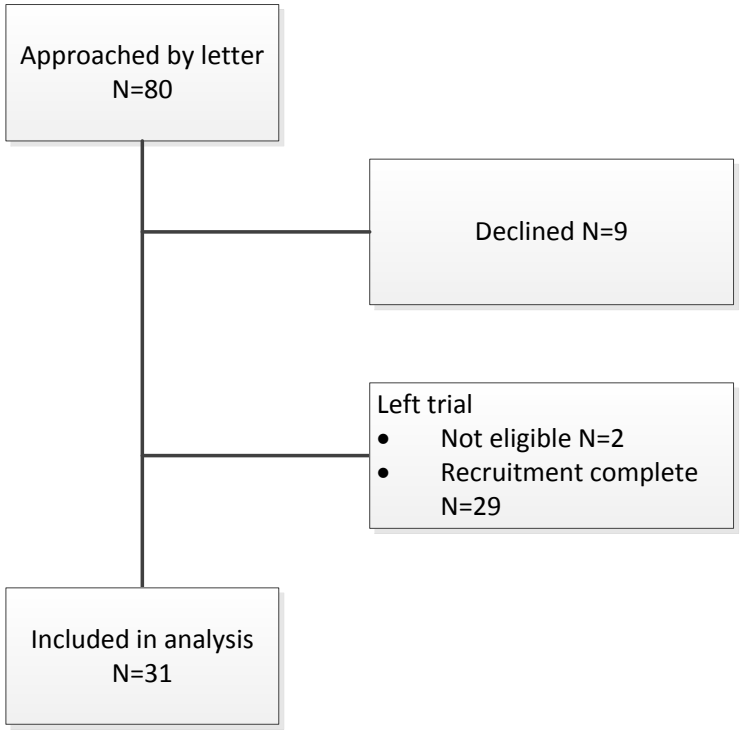


Figure 6-10: CONSORT diagram for pilot study

Table 6-1: Participants by diagnosis and treatment

	Gender				Total	
Diagnosis	**Female**		**Male**			
	Number of patients	**Percent**	**Number of patients**	**Percent**	**Number of patients**	**Percent**
Anal	3	13.6%	3	33.3%	6	19.4%
Short course rectal	0	0.0%	2	22.2%	2	6.5%
Long course rectal	3	13.6%	4	44.4%	7	22.6%
Endometrial	4	18.2%			4	12.9%
Cervix	12	54.5%			12	38.7%
Total	22	100.0%	9	100.0%	31	100.0%

Table 6-2: Socio-demographic information

Marital status	**Number of patients**	**Percent**
Married/ Civil Partnership	18	58.1%
Cohabiting	4	12.9%
Separated/Divorced	1	3.2%
Widowed	3	9.7%
Single	5	16.1%
Total	31	100.0%
Employment status	**Number of patients**	**Percent**
Working full time (30+ hours/week)	5	16.1%
Working part time (<30 hours/week)	6	19.4%
Unable to work (through disability or illness)	5	16.1%
Retired	15	48.4%
Total	31	100.0%
Continued education after school	**Number of patients**	**Percent**
No	18	58.1%
Yes	13	41.9%
Total	31	100.0%
Degree or professional qualification	**Number of patients**	**Percent**
No	22	71.0%
Yes	9	29.0%
Total	31	100.0%
Ethnicity	**Number of patients**	**Percent**
White British	26	83.9%
Not stated	4	12.9%
Black African/Black Caribbean White	1	3.2%
Total	31	100.0%

6.5.2.2 Feedback questionnaire results

The majority of patients completed the questionnaire using online methods, either at home or in the hospital, with only seven patients (23%) completing the questionnaire on paper. In general patients reported they found completing the questionnaire useful

(42%) (table 6.4). The reasons given were improved communication (n=5; 16%); allowed them time to think about their problems in advance (n=12; 39%); the survey provided different words to use (n=2; 6%); gave patients more confidence (n=2; 6%); and helped patients to remember their concerns (n=8; 26%). Patients who did not find completing the questionnaire useful gave the following reasons: no problems to report (n=2; 6%); the questions were not relevant (n=1; 3%) and free text responses: '*I didn't directly relate the questionnaire with my clinic appointment*' and '*It would have been useful to know I was getting the questionnaire in advance*'.

97% of patients reported that they found the questionnaire easy to understand (n=30) and 81% (n=25) felt the questions included questions that reflected their experience with the remaining patients reporting that the survey reflected their experience 'sometimes' (n=5; 16%). 28 patients felt the number of questions asked was acceptable (90%) and only two patients reported they did not complete the full questionnaire (7%). The majority of patients did not consider the questionnaire completion changed their interaction with their clinical teams (n=17; 55%).

Table 6-3: Summary of feedback responses

QUESTIONNAIRE ITEM		
Where did you complete or try to complete the questionnaires?	**Number of patients**	**Percent**
Computer/laptop at home	12	38.7%
Computer at the hospital	7	22.6%
On a mobile device (e.g. tablet, phone)	4	12.9%
On paper	7	22.6%
Other: Computer at work	1	3.2%
Total	31	100.0%
When did you usually complete the questionnaires?	**Number of patients**	**Percent**
Before being seen by a member of the clinical team	14	45.2%
After seeing a member of the clinical team	16	51.6%
Not stated	1	3.2%
Total	31	100.0%
If you did complete the questionnaire on any occasion before seeing your hospital team did you find it useful?	**Number of patients**	**Percent**
Yes	13	41.9%
No	2	6.5%
Sometimes	2	6.5%
N/A or not stated	14	45.2%
Total	31	100.0%
Did you find the survey easy to read and understand?	**Number of patients**	**Percent**
Yes	30	96.8%
Sometimes	1	3.2%
Total	31	100.0%
Did the survey include questions that reflected your experience?	**Number of patients**	**Percent**
Yes	25	80.6%
Sometimes	5	16.1%
Not stated	1	3.2%
Total	31	100.0%
What did you think about the number of questions in the survey?	**Number of patients**	**Percent**
About right	21	67.7%
I would have answered more	7	22.6%
I did not complete the whole questionnaire	2	6.5%
Not stated	1	3.2%
Total	31	100.0%
Do you think completing the questionnaires changed your interactions with your hospital teams?	**Number of patients**	**Percent**
Yes	6	19.4%
No	17	54.8%
I'm not sure	5	16.1%
Not stated	3	9.7%
Total	31	100.0%
RESPONSES OF PATIENTS COMPLETING THE QUESTIONNAIRE USING INTERNET METHODS		
How easy or difficult did you find it to get onto the study website?	**Number of patients**	**Percent**
Very easy	18	58.1%
Easy	5	16.1%
I did not log in	2	6.5%
N/A	6	19.4%
Total	31	100.0%
How easy or difficult did you find it to log in with your username and password?	**Number of patients**	**Percent**
Very easy	18	58.1%
Easy	3	9.7%
I did not log in	3	9.7%
N/A	7	22.6%
Total	31	100.0%
Did you have to contact the research team to ask for help at any point	**Number of patients**	**Percent**
No	22	71.0%
Yes	3	9.7%
N/A	6	19.4%
Total	31	100.0%
If you were asked, would you continue to answer similar questionnaires using this Internet system (for example, before future hospital appointments)?	**Number of patients**	**Percent**
Definitely	18	58.1%
Very likely	3	9.7%
Unsure	2	6.5%
N/A	7	25.8%
Total	31	100.0%

For the patients who completed the questionnaire online, the majority of patients found using the website and login process ‘very easy’ (58%). The majority of patients did not require support from the research team to complete the questionnaire online (n=22; 71%) and most patients reported they would be happy to continue to use a similar system in the future (n=21; 68%).

Home Internet access was not available for seven patients (23%). Reasons for choosing paper methods were provided with the majority of patients considering paper methods to be easier (n=4; 13%). Other reasons were a lack of confidence with computers (n=3; 10%); preference for paper-based methods (n=3; 10%); and data safety concerns (n=2; 6%).

6.5.2.3 Modifications made following patient and clinician feedback

Following the pilot study an additional questionnaire item ‘Have you had tingling or numbness in your hands or feet?’ taken from CX24 was added to the lower GI questionnaires following feedback from a consultant medical oncologist. Rectal patients are commonly treated with oxaliplatin chemotherapy and this item is not covered in the CR29 module. In QTool/QStore, the tooltip function was added to the question part of the results table (as previously described) and the scoring for the emotional functioning scale and financial item was added to include these items in the results table. This was based on feedback from two clinical nurse specialists who reported they would find this information useful; as it is included in the patient’s holistic needs assessment. Finally a weekly report (with support from Alexander Newsham) was developed reporting on patients who had been approached and were attending clinic the following week to enable planning and management of recruitment resources.

6.5.3 Discussion

This chapter has outlined the set up and management of the clinical studies including discussion of the technical aspects of the study design along with the practical approach and follow up methods used. These clinical studies have piloted the integration of electronically collected PRO data into EHR within Leeds Cancer Centre following on from the development work of the eRAPID programme. This chapter describes the procedures involved in implementing a complex intervention into clinical practice and managing the process over a period of time. In addition, this chapter describes an innovative use of the data from PPM by creating a method to export the data from PPM, convert it into a modifiable format (the CRF manager) to allow

validation and then export the data in a format that may be analysed in a statistical package.

The pilot study is the first study to the link the existing technology into one coherent system. The pilot study confirmed that the systems developed worked well, demonstrated the questionnaire is relevant and acceptable to the sample population and provides a platform for further evaluation within the cross sectional and prospective studies. No particular concerns were highlighted with the length or content of the questionnaire. The level of true decliners for the study was low and patients were in general very positive about the experience of completing a single PRO assessment. The modifications suggested following the pilot study were implemented before the start of the cross sectional and prospective studies. Any conclusions are limited due to the small sample size, however the findings of the pilot study are encouraging and useful for planning the larger studies.

The following chapter describes the decision-making and protocol development for the contouring of the organs at risk in the radiotherapy plans and the process used for exporting the treatment planning data.

Chapter 7 Protocol development for organ at risk (OAR) contouring and methods used for dose-volume histogram (DVH) export

7.1 Introduction

Precision radiotherapy techniques, such as intensity modulated radiotherapy (IMRT) facilitate the ability to reduce dose to surrounding normal tissue, or organs at risk (OAR) and has therefore led to a need to delineate all relevant OARs. The introduction of IMRT has led to more extensive research evaluating the quantitative relationship between the dose and volume of normal tissue irradiated during external beam radiotherapy (EBRT) and reported toxicity to establish dose-volume constraints for OARs. Predicting toxicity following radiotherapy is complex and related to dosimetric and clinical factors, such as comorbidities and age, as well as genetic risk factors. This project focuses on developing models incorporating dosimetric and clinical risk factors only, as robust research models including genetic risk factors associated with radiation toxicity require large pooled data sets from multiple organisations.

Some OAR, such as the spinal cord, and the oesophagus in lung cancer patients have been routinely contoured and the dose minimised for patients treated with three-dimensional (3D) conformal radiotherapy. However, within the pelvis the OAR contouring has been limited until recently. This means that eligible patients in the cross sectional study did not have their OAR contoured. Therefore the treatment plans for all patients recruited into this study had their OAR retrospectively contoured.

The initial development work for this project has focused on selecting a PRO instrument that will provide a robust measure of both acute and late patient-reported toxicity, which is relevant for the pelvic radiotherapy population. This chapter has three objectives:

1. Developing rigorous and reproducible contouring methods for OAR using the best available evidence suitable for use in clinical practice. This section includes an evaluation of the use of image registration using the simulation computed tomography (CT) scan and diagnostic magnetic resonance imaging (MRI) scan to aid OAR contouring.
2. Describing the method and technology developed to combine doses for patients treated with two different treatment phases.

3. Describing the technical process of exporting DVH data from the treatment planning system (TPS) - where DVH describes the two-dimensional (2D) graphical display of the relationship between the dose delivered to each incremental volume of a particular tissue treated.

7.2 Protocol development for OAR contouring

7.2.1 Background

The Radiation Therapy Oncology Group (RTOG) recently published consensus guidelines for contouring normal pelvic tissues along with a CT image atlas(122). The publication aimed to improve the anatomical definitions of normal structures in the pelvis to allow more robust comparisons between complication rates and dosimetric information for OAR. The consensus panel comprised of 16 radiation oncologists with expertise in treating different cancer sites (gastrointestinal (GI); gynaecologic; and genitourinary (GU). On reviewing previous RTOG trials, the panel observed significant variability in the contouring of OAR in the pelvis leading to time-consuming and costly re-contouring to enable dosimetric evaluation. The document produced provided a good reference point to build on within this project.

However, there are a number of limitations to the practical use of this protocol. A number of definitions are missing from this document for potential OAR which may be related to commonly reported toxicity, namely definitions for sexual function organs – vagina, and female and male external genitalia – and some bony anatomy (sacrum and iliac crests). To some extent recent contouring guidelines by the Australasian GI trials group (AGITG) for anal cancer IMRT have addressed this deficiency by creating OAR definitions for male and female external genitalia(123). The AGITG guidelines were developed and refined through workshops with GI radiation oncologists with the aim of producing a contouring atlas describing outlining of gross disease and OAR for use in anal cancer IMRT. This protocol followed on from an initial quality assurance evaluation of the target volume contouring within the Phase II RTOG 0529 anal cancer IMRT clinical trial(33). This early assessment found discrepancies in the contouring of the mesorectum in the first five cases and an atlas was produced outlining the elective nodal volume definition for the remainder of the trial.

However, the major methodological limitation with many of the definitions provided in the OAR contouring protocols is the creation of the protocols by radiation oncologists alone. Physicians are trained to make well-reasoned decisions as part of their clinical

practice; however, this leads to problems when protocols are developed solely by doctors. Much of the technical anatomical detail is left out of the definitions provided in the protocols leaving the clinician to use their heuristic decision-making skills to 'fill in the gaps' with their knowledge. For example the definition of BowelBag (intestinal cavity contents) described by Gay and colleagues(122) states:

> *"Inferiorly from the most inferior small or large bowel loop or above the Rectum (GU) or AnoRectum (GYN), whichever is most inferior.* If, when following the bowel loop rule, the Rectum or AnoRectum is present in that axial slice, it should be included as part of the bag; otherwise, it should be excluded.*
>
> *Tips: Contour the abdominal contents excluding muscle and bones. Contour every other slice when the contour is not changing rapidly, and interpolate and edit as necessary. Finally, subtract any overlapping non-GI normal structures. If the TPS does not allow subtraction, leave as is."(e355)*

This description is limited as there is no discussion of how to manage vascular structures within the intestinal cavity, patients with a stoma, or retroperitoneal structures such as the kidneys should the treatment extend more superiorly. Unfortunately this lack of detail leads to multiple different decisions being made and thus inconsistencies and variation between the OAR contours produced. To address this issue the protocol for this study was developed with consideration of the practical implementation of its use within clinical practice employing a multi-disciplinary team of experts.

The use of MRI fusion with the simulation CT is recommended to improve the contouring for a number of OAR within the RTOG guidance(122). Radiotherapy is planned using the simulation CT scan in the treatment position. CT has high spatial resolution (i.e. a greater number of pixels) and provides information on the electron densities of tissues used for dose calculation in radiotherapy. However, CT lacks contrast resolution to differentiate between normal soft tissues structures. This is a particular problem within the pelvis as many soft tissues are close to each other leading to potential errors in delineation of OAR and tumour. Therefore information from other imaging modalities is frequently combined to improve tumour and OAR delineation. MRI in particular provides better soft tissue resolution but currently the images alone are not suitable for EBRT planning. The majority of patients will have a MRI scan prior to radiotherapy treatment to improve diagnostic information and this may be reviewed in parallel with the CT to aid contouring. However, more recently software (Mirada) allowing CT and MRI scans to be image registered has been introduced into clinical practice. CT/MRI fusion is routinely used for patients with brain

tumours and has more recently been introduced within Leeds Cancer Centre for patients treated with head and neck cancers following evidence of improved delineation for target volumes leading to a reduction in dose to normal tissues(272). As yet the use has not been evaluated in patients treated with pelvic malignancies within our organisation. However, the process of image registration is likely to be more challenging because in contrast to brain and head and neck treatment the accuracy of rigid immobilisation is not achieved, the organs within the pelvis are hollow and deform with filling and are thus more mobile, and in the past it was common for the diagnostic MRI and planning CT scans to be acquired with different patient positions (as patients were often treated in a prone position to reduce the irradiation to the small bowel). However, research within prostate cancer supports the use of CT/MRI rigid image registration for improving target organ delineation(273) and MRI alone has been used to improve brachytherapy placement in cervical cancer treatment(274).

This chapter will qualitatively evaluate the process of incorporating CT/MRI fusion for OAR contouring within the pelvis. One of the limitations of CT/MRI fusion has been the challenge of the planning CT and MRI being acquired in different positions. Recent studies in the head and neck have found however that effective alignment may be found using deformable image registration(275, 276). As patients within Leeds Cancer Centre are not routinely scanned in the treatment position for the diagnostic MRI scan, this study will evaluate the use of deformable registration as a means of improving co-registration for OAR contouring.

7.2.2 Methods and materials

7.2.2.1 OAR protocol development

I led the OAR protocol development with consultation from a multi-disciplinary team of experts from Leeds Cancer Centre: consultants in medical (GV) and clinical (radiation) oncology (DSM, SD and Rachel Cooper (RC)) with an interest in linking pathophysiological processes to toxicity outcomes; consultant radiologists with specialist expertise in radiation oncology, and target volume and OAR contouring (GU – Brendan Carey (BC) and gynaecological cancers – Sarah Swift (SS)); a medical physicist with a research interest in image registration (Richard Speight); and a team of four dosimetrists (Lynn Aspin (LA), Simon Beanland (SB), Laura Garratt (LG) and Stuart Wilson (SW)).

Following my evaluation of the literature describing pelvic organ normal tissue contouring, I developed an initial draft protocol using OAR descriptions taken from the

RTOG consensus guidelines(122) and included three definitions taken from the AGITG anal IMRT guidelines (male and female external genitalia and Iliac crests)(123) using standardised definitions (in parentheses) as defined by Santanam and colleagues if available(277). The definitions included:

- Anus and rectum (AnoRectum)
- Intestinal cavity (BowelBag)
- Colon (Colon)
- Small bowel (SmallBowel)
- Bladder (Bladder)
- Prostate (Prostate)
- Seminal vesicles (SeminalVesc)
- Penile bulb (PenileBulb)
- Uterus and cervix (UteroCervix)
- Ovaries and fallopian tubes (Adnexa_R/Adenexa_L)
- Proximal femurs (Femur_R/Femur_L)

These OAR were included in the initial draft alongside additional OAR definitions for the sacrum (Sacrum) and vagina (Vagina) and the inclusion of segmentation to the rectum. These definitions provided the baseline definitions, which were then modified and expanded during the development process. The rectal contour was segmented into three sections as defined by Stenmark and colleagues in a previous dosimetric study(15). This segmentation of a whole structure aimed to retain an element of spatial information lost in dosimetric analysis where 3D treatment data is reduced to 2D within the DVH exported.

CT simulation plans for all participants in the cross sectional study were anonymised. I contoured a purposive sample of 10 patients including all OAR as described in the initial draft protocol. Training and feedback was provided for all OAR contouring for the initial five male and five female patients from two consultant radiologists (SS and BC) as well as for challenging cases throughout the study, recognising the need for expert radiological input in the study process. Particular support and advice for the contouring of sexual organs was provided due to the lack of clear standardised guidelines. It was decided that because contouring of the sexual organs required the evaluation of the CT simulation in association with the diagnostic MRI scan that these OAR should only be contoured by a clinician. I therefore carried out all sexual organ contouring for the cross sectional study. Following an informal evaluation of this process with two consultant clinical oncologists (DSM and SD) and the consultant radiologists (BC and SS) the OAR list was modified to only include OAR that may be clearly related to end organ toxicity and simplified to enable the contouring to be easily reproducible by a multi-disciplinary team.

A further pilot evaluation with 12 consecutive patients was carried out following these changes. Three dosimetrists (SB, LA and LG) and I completed contouring on three patients each using this protocol. This group reviewed the contours with additional support from a senior dosimetrist (SW) and medical physicist advisor (John Lilley) and modified the protocol. The protocol was modified further following feedback from an independent clinical oncology consultant with expertise in both GI and gynaecological cancer treatment (RC) before the retrospective contouring process was extended to include a further six dosimetrists to support the work (Paul Junni, Joanna Davies, Christopher Stones, Charlotte Telfer and Hilary Robinson).

7.2.2.2 Mirada: CT/MRI fusion

An exploratory pilot evaluation of image registration using Mirada RTx v1.4 (Mirada Medical, Oxford UK) to combine the CT simulation scan with the diagnostic MRI was carried out on a purposive sample of 20 patients from the cross sectional study (Chapter 8) to evaluate its potential use in improving the contouring of sexual organs as recommended in the RTOG guidelines(122). I contoured all patients following training on Mirade by Richard Speight. The first 10 of these patients were also included in the initial evaluation of the protocol. The automatic rigid fast algorithm (Automatic rigid), requiring no manual input was used for the initial image registration and as the starting point for any further manual or deformable manipulation. If the automatic registration was insufficient to co-register the images effectively, a manual rigid registration was carried out, either by co-registering the whole MRI to the planning CT with a rigid registration, optimised by rotation and manual placement, or by optimising the rigid registration over a region of interest (Manual rigid). Finally, if the images were still poorly aligned the deformable registration was applied over the whole image (Deformable). The deformable registration process uses the software's registration algorithms with the aim of improving the alignment between the two images by distorting the MRI to map onto the CT. The findings from this small sample were evaluated qualitatively.

7.2.3 Results

315 patients were contoured retrospectively using the protocol developed. I quality assured all OAR contours for each patient at the point of sexual organ contouring. On average, including all operators it took approximately 75 minutes to complete the contours for a single patient after the initial training period. Overall, I contoured 42

(13%) patients in their entirety, contoured every patient's sexual organs (n=315) and provided quality assurance on every patient, modifying contours as required. The steps involved in the contouring process were as follows:

- Patient entered into trial
- Relevant data extracted to database
- Set up anonymisation
- Retrieve patient from archive
- Contouring on CT on treatment planning system (TPS)
- Anonymisation of CT
- Anonymisation of MRI
- Import into Mirada
- Fusion
- Contouring in Mirada
- Export to TPS
- Recreate treatment plan
- Export to DVH analysis
- Archive anonymised patient

7.2.3.1 Mirada: CT/MRI fusion

A total of 20 patients were included in this evaluation as a purposive sample of the overall cohort taken from the first consecutive 56 patients. Three patients included only had CT scans available and therefore were contoured using CT alone (15%). The sample included 13 female patients and seven male.10 patients had an anal cancer diagnosis (females n=7; males n=3); three patients with cervical cancer; three patients with endometrial cancer; and four male patients with rectal cancer.

The process was evaluated qualitatively. There were three stages of registration available: automatic rigid, manual rigid and deformable registration as previously described. In general the registration was only useable if the images from each modality were taken with the patient in the treatment position due to the distortion of anatomy observed. Five patients (four patients with anal cancer and one cervical cancer) were treated in a prone position and their MRI scans were taken, as is common practice, in a supine position (25%). Another patient had MRI images only available in the oblique plane with no axial images provided, which proved challenging for image registration, as did an area of distortion in the MRI images of a different patient. The three patients with endometrial cancer had their diagnostic MRI taken pre-operatively and the planning CT for their radiotherapy taken post-operatively following

total hysterectomy. This distorted the pelvic anatomy sufficiently to make all stages of image registration unhelpful.

Overall, the co-registration was useful in aiding penile bulb contouring in four out of the seven patients. Automatic rigid registration was used in two patients, manual rigid in one patient and deformable registration in one (figure 7.1). The three patients where CT/MRI fusion was limited was due to (1) no MRI; (2) distension in the bladder and rectum on the MRI compared to the CT and (3) scans taken in different positions. Vaginal contouring was aided in four out of thirteen female patients, using deformable registration in three patients and automatic rigid registration in one (figure 7.2). For the patients where image registration was unhelpful, three patients were post-operative endometrial cancer patients; two patients had no MRI scans; two patients had poor quality MRI scans; and two patients had their scans in different positions. Deformable registration was unhelpful for contouring the uterocervix and adenexa (in one pre-menopausal GI patient) as the coregistration stretched the anatomy so that the original tissue shapes were no longer recognisable. In addition, if bladder size or rectal distension varied significantly between the planning CT and the diagnostic MRI the deformable registration was less effective and distorted the normal tissue architecture making delineation challenging.

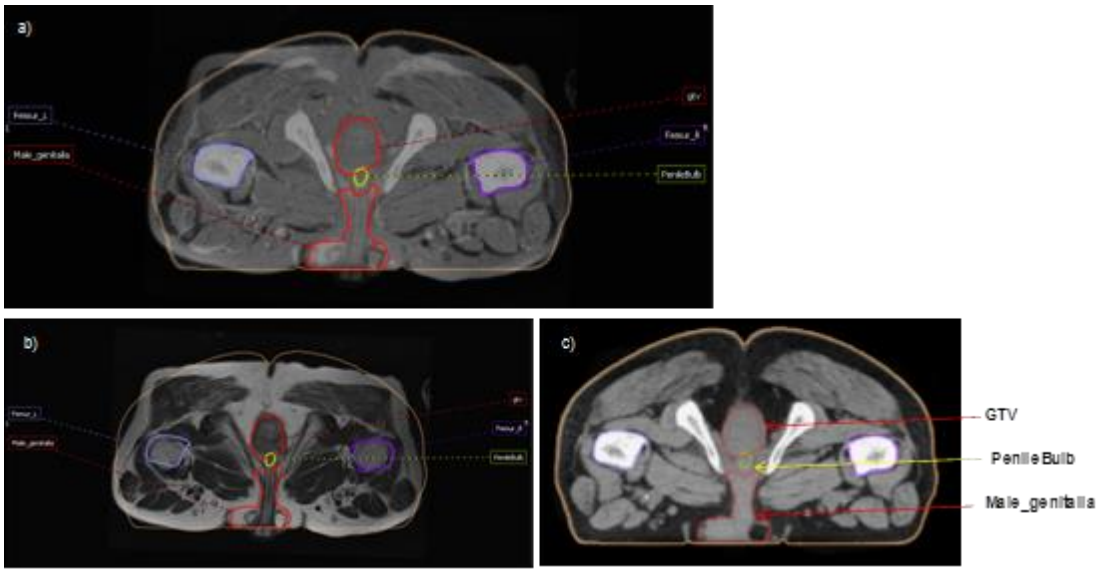


Figure 7-1: PenileBulb contouring using Mirada

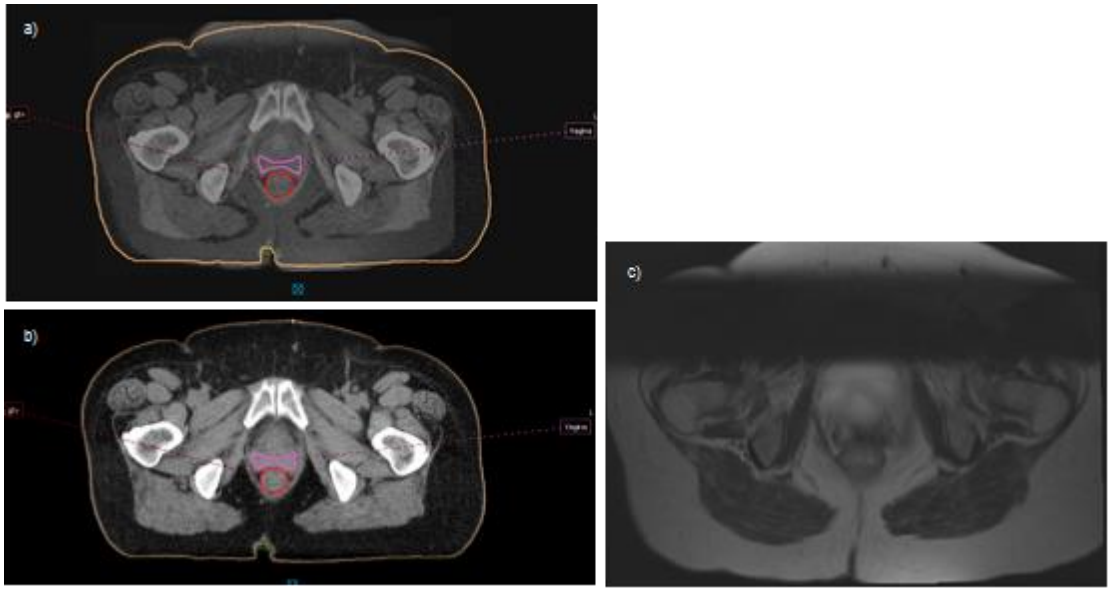
(a) CT/MRI fusion image (b) MRI image (c) CT image. Images all taken from the same axial slice. Note MRI imaging in supine position and CT in prone position - despite this good registration achieved using Automatic rigid registration.

The additional time and processes involved in incorporating image registration were also considered in comparison to using the diagnostic MRI in parallel when contouring

OARs. Overall the practical problems with differences in treatment position, organ distortion due to bladder and rectal filling and quality of the diagnostic MRIs were found to outweigh the potential benefits of image registration. This is no reflection on the potential usefulness for image registration in target volume definition, as this was not evaluated within this project. In general, the more experienced I became in contouring the male and female sexual organ anatomy the less important the MRI was in aiding the delineation process. However, image registration is most useful when diagnostic MRI and planning CT are performed in the same position as treatment on a flat bed couch, ideally on the same day at a specialist radiation oncology centre to ensure high quality imaging. For patients treated with post-operative radiotherapy repeat MRI imaging would improve image registration quality. Management of pelvic organ motion is a more complex challenge and is outside of the remit of this evaluation; however, should the set up and quality issues with image registration be resolved deformable registration may provide some support to manage the problems with internal organ movement.

Figure 7-2: Vagina contouring using Mirada

(a) CT/MRI fusion image (b) CT image (c)MRI image. Taken from same axial slice following image registration. Due to the distortion of the MRI image registration did not improve contouring of the vagina.



7.2.3.2 Protocol evaluation

7.2.3.2.1 AnoRectal and segmented rectum

The RTOG pelvic normal tissue contouring guidelines aimed to standardise the OAR contouring for the Rectum and AnoRectum(122). Whilst the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) report on the rectum reviewed the evidence to provide normal tissue dose constraints, the studies included in the review

defined the extent of the rectum in multiple ways(122, 278). In the RTOG contouring guidelines the Rectum is defined inferiorly from the lowest level of the ischial tuberosities (right or left)(122). Whilst this provides a good bony landmark making the structure easily reproducible in some patients this meant the structure of the AnoRectum did not differ from the Rectum as the ischial tuberosities were present at the most inferior aspect of anal tissue on the axial CT scan due to the tilt of the pelvis. This note would be a useful inclusion to the protocol and important to consider how to manage this overlap for future work separating the anus from the rectum to evaluate differences in their dose constraints. Very few patients had an anal marker present which is suboptimal but reflects the lack of inclusion of the anus and rectum as OAR within the retrospective CT data set. The inferior aspect of the anal tissue when a marker was not present was defined as the point at which the oval shape of the anus is present in the axial plane.

The Rectum ends superiorly on the axial slice before the structure loses its round shape in the axial plane and become elongated forming the sigmoid. The additional note of using the sagittal view to visualize the anterior movement of the rectum at this point may improve the decision-making process and protocol definition. Defining this point was challenging at times and use of the sagittal view improved decision-making.

Another challenge observed during the training period was the inclusion of vaginal tissue within the inferior part of the rectal contour. The dosimetrists supporting this work were experienced in contouring the rectum as an OAR in male patients treated for prostate cancer, however this study also included female patients. Training and feedback was provided for all dosimetrists to reduce this problem and all plans were quality assured prior to analysis.

Use of segmentation for the rectal structure was included in this study as recommended by the outcomes of a dosimetric study evaluating the impact of the inferior, mid and superior aspects of the rectum on toxicity following EBRT for prostate cancer(15). One of the problems with reducing 3D data into 2D DVH information is the loss of spatial information. To some extent segmenting an OAR can provide spatial information by dividing the organ into different sections. This provides useful information when analysing the dosimetric data about the anatomical position of each section in relation to the target volume. In the study by Stenmark and colleagues, the rectum was segmented into inferior: ischial tuberosities to 3cm superior; mid (next 3cm) and superior rectum (from the superior aspect of the mid rectum to the sigmoid colon)(15). The dosimetric evaluation found the different segments of the rectum were

associated with different symptom outcomes and therefore this approach was further evaluated in this study.

Table 7.1 below outlines the original RTOG definitions followed by the definitions developed through this study in italics. Note that these structures were only included as OAR for the gynaecological cancer patients in this study as the rectum and anus are target organs for the GI patients.

Table 7-1: Comparison of definitions for Rectum and AnoRectum

Organ	Standardised TPS name	Tumour category	Definition
RTOG Male and female pelvis normal tissue consensus definitions(122)			
Rectum	Rectum	GU	Inferiorly from the lowest level of the ischial tuberosities (right or left). Contouring ends superiorly before the rectum loses its round shape in the axial plane and connects anteriorly with the sigmoid. The Rectum is used with the BowelBag.
Anus + rectum	AnoRectum	GYN	Inferiorly from the anal verge as marked with a radiopaque marker at the time of simulation. Contouring ends superiorly before the rectum loses its round shape in the axial plane and connects anteriorly with the sigmoid. The AnoRectum is used with the Sigmoid and BowelBag.
Multi-disciplinary definition from this study			
AnoRectum	*AnoRectum*	*GYN*	*Anus starts inferiorly from the anal verge as marked with radiopaque marker at the time of simulation. Rectum starts at the lowest level of the ischial tuberosities (right or left). Contouring ends superiorly before the rectum loses its round shape in the axial plane and connects anteriorly with the sigmoid. Use of the sagittal view may improve visualisation of the superior border.*
Anus	*Anus*	*GYN*	*Anus starts inferiorly from the anal verge as marked with radiopaque marker at the time of simulation. When an anal marker is not present, contouring starts inferiorly where the oval shape of anal tissue in the axial plane may be viewed. Rectum starts at the lowest level of the ischial tuberosities (right or left). This may mean in some cases that it is not possible to draw the anus as the ischial tuberosities start at the anal verge.*
Segmented rectum	*RectumInferior* *RectumMid* *RectumSuperior*	*GYN*	*Rectum segmented into three parts: inferior (ischial tuberosities to 3 cm superior), mid (next 3 cm), and superior rectum (superior aspect of mid rectum to sigmoid colon)(15).*

7.2.3.2.2 BowelBag

RTOG guidelines presented the small bowel and colon for OAR contours for GI cases and the BowelBag for use in gynaecological and GU patients as the panellist were unable to reach consensus on the optimal contouring strategy(122). The panellists were unable to agree on which of these strategies was best given a particular clinical situation.

Outside of the RTOG guidelines authors have disagreed on how best to contour the bowel for dosimetric evaluation. The bowel is a mobile structure and studies evaluating the position of the bowel over the course of treatment have found that the bowel only occupies the same position approximately 20% of the time(279, 280). This temporal variation in position and shape of the bowel leads to uncertainty when considering the development of normal tissue complication probability models from DVH information. The whole peritoneal cavity has been suggested as an alternative to individual bowel loops to fully account for bowel mobility during treatment(280).

In a study evaluating the differences between three different bowel contouring techniques and acute GI toxicity in patients treated with IMRT for endometrial cancer, the small bowel was contoured as separate loops; as a limited bowel space encompassing the outermost extent of the visible small bowel loops; and including the whole intestinal cavity(121). All contours began from the most inferior extent of small bowel in the pelvis to 2cm above the PTV. Although the absolute volume of the intestinal cavity contour was much greater than the other methods, overall the percentage volume treated at each dose level was very similar with less variability seen between patients when using the intestinal cavity contour. The regression analysis results also found the volume treated to 45Gy when contoured as the intestinal cavity was associated with changes in acute GI toxicity where as the alternative methods were not associated with any dosimetric outcomes.

The literature supports the use of the intestinal cavity contour to provide a robust and reliable method to contour the bowel for use in dosimetric evaluation of normal tissues(121, 280, 281). In addition this approach eliminates the need for patients to have high-density oral contrast to improve the visualisation of the small bowel(282). However, in an attempt to recreate the RTOG guidelines initial contouring was carried out using a combination of different approaches to explore the two techniques. An obvious advantage not discussed in the guidelines or research is the differences in speed and reproducibility of the two methods. Once the protocol had clearly defined criteria for (1) the inclusion and exclusion of different major vessels within the pelvis; (2) how to contour patients with a stoma and (3) inclusion and exclusion criteria for retroperitoneal structures, the contouring of the intestinal cavity was significantly faster than contouring individual bowel loops or a limited bowel space. This is mainly because it is possible to interpolate and modify between axial CT slices on the treatment planning system (TPS) when the intestinal cavity anatomy is not changing rapidly(122). In comparison, it was significantly more challenging to contour individual small bowel and colon anatomy. Interpolation was rarely achievable, distinguishing between the two

small and large bowel organs was often challenging and made more difficult in patients who did not have oral and/or intravenous contrast for their planning scans. The duration of time taken to create the small bowel and colon contours was appreciably longer than the time taken to contour the intestinal cavity. For contouring OARs in a clinical practice setting time is an important factor to consider.

An additional issue is the reproducibility of contouring the small bowel and colon with multiple practitioners who are not trained radiologists or clinical oncologists. As the benefits of contouring these organs separately is not clear from the literature, following the challenges observed in my own practice with contouring these organs separately the additional training and quality assurance required to teach the dosimetry team supporting this project did not appear to outweigh the benefits of using the intestinal cavity contour.

Table 7.2 outlines the original RTOG guidelines followed by the modifications suggested for improvement in italics and figure 7.3 provides an image atlas for the BowelBag contour. The superior border of the contour in the RTOG guidelines is 1cm above the planning target volume. As this volume is variable when comparing treatments from multiple cancer sites a description for the whole cavity was developed as well as creating BowelBagL3. The superior border of BowelBagL3 was defined as the cranial aspect of L3 lumbar spine creating a fixed, anatomically definable contour to standardise the volume when analysing the data across multiple treatment regimes. L3 was chosen as the in the gynaecological cancer patients this is the superior most border of PTV. .

Figure 7-3: BowelBag contour:

(a-f) Axial views from most inferior extent (a) to (f) superior extent

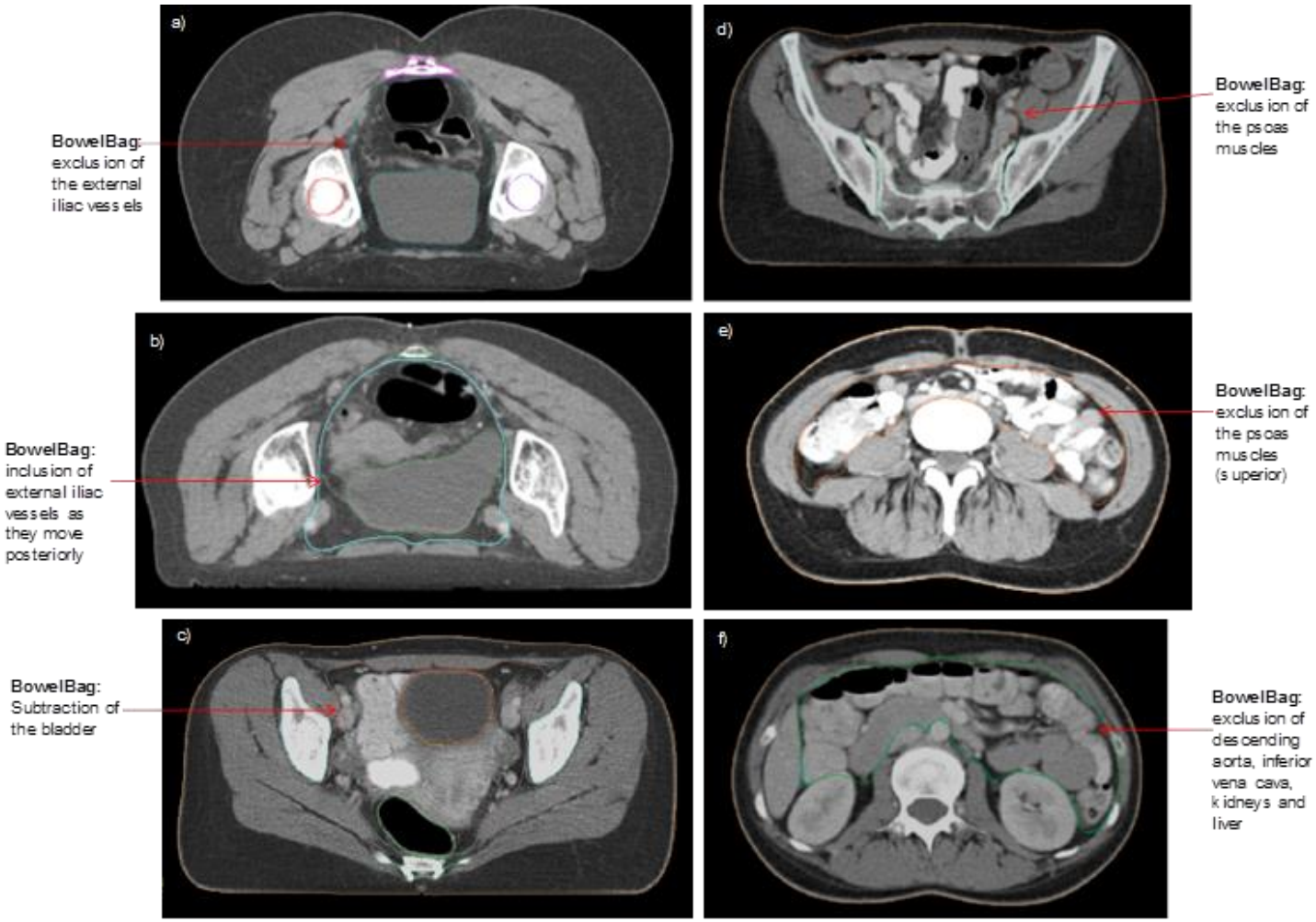


Table 7-2: Comparison of definitions for BowelBag and SmallBowel and Colon

Organ	Standardised TPS name	Tumour category	Definition
RTOG Male and female pelvis normal tissue consensus definitions(122)			
Bowel bag	BowelBag	GU, GYN	Inferiorly from the most inferior small or large bowel loop or above the Rectum (GU) or AnoRectum (GYN), whichever is most inferior.* If, when following the bowel loop rule, the Rectum or AnoRectum is present in that axial slice, it should be included as part of the bag; otherwise, it should be excluded.
			Tips: Contour the abdominal contents excluding muscle and bones. Contour every other slice when the contour is not changing rapidly, and interpolate and edit as necessary. Finally, subtract any overlapping non-GI normal structures. If the TPS does not allow subtraction, leave as is.
Small bowel	SmallBowel	GI	To distinguish from large bowel, the use of oral contrast is encouraged.* After administration of contrast (*e.g.*, 3 oz of Gastrografin (Bracco Diagnostics Inc., Princeton, NJ) and 3 oz of water–barium mixture) 30 minutes before scanning, the small bowel can be outlined as loops containing contrast.
Colon	Colon	GI	Large bowel continuing where the AnoRectumSig contour ended.* Depending on the volume treated, this will include portions or all of the ascending, transverse, descending, and sigmoid colon.
* One should stop contouring the BowelBag, SmallBowel, and Colon 1 cm above the PTV for most coplanar beam plans, but the choice will depend on the treatment technique. One should stop these PTVs at distances much greater than 1 cm for non-coplanar beam plans depending on the beam angle and path. TomoTherapy plans will require stopping from 1 to 5 cm above the PTV, depending on the selected field size, which is often 2.5 cm.			
Multi-disciplinary definition from this study			
Intestinal cavity	*BowelBag*	*GI/GYN*	*Inferiorly from the most inferior small or large bowel loop or AnoRectum (GYN), whichever is most inferior. If, when following the bowel loop rule, the AnoRectum is present in that axial slice, it should be included as part of the bag; otherwise, it should be excluded. Use bone and muscle as the edges of the structure.* *At the anterior inferior part of the Bowelbag exclude the external iliac vein/artery but when the vessels move posteriorly include in the bowel bag contour (See screenshots). Superiorly exclude the descending aorta and IVC along with the psoas muscle. Include the common iliac arteries within the BowelBag and then exclude when forms descending aorta. Retroperitoneal structures (kidney) should be excluded using the lateral and posterior borders of the kidney as the BowelBag borders. Superiorly exclude liver and spleen and extend contour to most superior aspect of small/large bowel.* *Subtract bladder from Bowel bag structure (ONLY).* *STOMA - include the stoma opening and the stoma tissue at the skin surface within the BowelBag structure but exclude the actual bag.*
Intestinal cavity up to L3	*BowelBagL3*	*GI/GYN*	*Contour intestinal cavity as above but remove the contours above the cranial border of L3 (in some instances this will be the same volume as the intestinal cavity). If the scan does not go up as high as L3 still produce an OAR for BowelBagL3*

7.2.3.2.3 Bladder

In comparison to the bowel OARs the bladder contouring is relatively simple. The most inferior and superior extent on some patients may be challenging to visualise but in general the axial slice on which the bladder may first be visualised, containing urine, may easily be viewed due to the differences in electron density of the two substances

(bladder wall and urine). The QUANTEC report highlighted the trigone region of the bladder (inferior region) as potentially more important functionally than the superior dome of the bladder, but admitted that visualising this area of the bladder on the CT was challenging and therefore segmentation of this organ was not evaluated(283).

Dosimetric studies have differed in their approaches to including the whole bladder (including urine) where DVH-based information is extracted and studies where the bladder wall alone (excluding urine) is defined and dose-surface histogram information is derived. A high degree of correlation between these two metrics has been found, with QUANTEC concluding that further evaluation of these two approaches in their association with late toxicity was required(283, 284). The dose constraints listed for the bladder in QUANTEC take the bladder as a solid organ (i.e. using a DVH approach)(283). A further challenge is the extent of organ motion due to differences in bladder volumes throughout treatment. The extent of this problem was visualised during the initial contouring process using MIRADA. The differences in bladder size between the diagnostic MRI (where typically patients will start with an empty bladder) as compared to the CT planning scan where patients are typically treated in Leeds Cancer Centre with a full bladder made registration between the two scan challenging and in some cases impossible. The current literature does not suggest a clear approach to managing this problem. As such for this protocol the RTOG guidelines and recommendations from QUANTEC to approach the bladder as a solid structure were adhered to with no modifications required(122, 283).

7.2.3.2.4 UteroCervix and Adnexa

A pragmatic decision was made to only contour the reproductive female sexual organs in patients treated for a GI cancer who were pre-menopausal at the start of treatment. These structures are part of the target organs for patients treated for cervical cancer and infertility following treatment is unavoidable. However, it was felt that for pre-menopausal women, it might be preferable to limit dose to these organs to potentially preserve fertility. A cut off age of 45 years was used as a surrogate for pre-menopausal status as this information was not available for a retrospective sample.

The contouring of these organs is described as ‘challenging ‘ in the RTOG guidelines(122). The RTOG guidelines were followed and as recommended MRI fusion was trialled. However, as discussed previously, using the Mirada software for deformable registration of the MRI and CT images was not helpful as the anatomy became distorted for the reasons previously covered. The UteroCervix contour was

more easily defined, however defining the ovaries and fallopian tubes (as Adnexa_R and Adnexa_L) was challenging and support from a consultant radiologist (SS) was required to verify the adnexa structures.

Within the cross sectional sample only five patients were eligible for contouring their reproductive sexual organs. The RTOG definitions were used and no modifications were required. The data from these OARs are not included in the cross sectional study analysis however the contouring experiences will form the basis to explore this research area further.

7.2.3.2.5 External genitalia – female: Female_genitalia

Whilst the RTOG guidelines do not include the external genitalia as an OAR there is recognition that this area, in both male and female patients, receives a high dose in patients treated with EBRT or IMRT for anal cancer(33, 123). The AGITG guidelines for external genitalia for both women and men include in the definition the ‘area including skin and fat anterior to pubic symphysis’ with the caudal edge of the pubic symphysis as the superior extent of the contour(123). In practice it was unclear where the lateral borders of this structure could be defined and the experts within this panel raised concern as to the reproducibility of this contour because of this issue. In addition it was not clear how the subcutaneous fat might be related to a late toxicity outcome as opposed to the more clearly definable areas of the crus of the clitoris and labia minora, which may easily be viewed on CT (see images) and potentially related to sexual enjoyment and dyspareunia.

The inferior border was defined as the inferior most CT slice where the muscular structure of the labia minora may be viewed and the superior border the caudal edge of the pubic symphysis (taken from the AGITG guidelines). The inferior border of the vaginal contour was also taken as the caudal edge of the pubic symphysis (See figure 7.4a). Any part of the structure not included in the GTV was included as the OAR. The area of fat and skin included in the AGITG definition was excluded from the definition used in this study. Over and above improvement in reproducibility, reducing the size of the OAR has the additional benefit of improving the chances of avoiding this structure in the process of treatment planning. However, as this definition excludes skin and subcutaneous tissue this may limit the application of this OAR contour for dosimetric

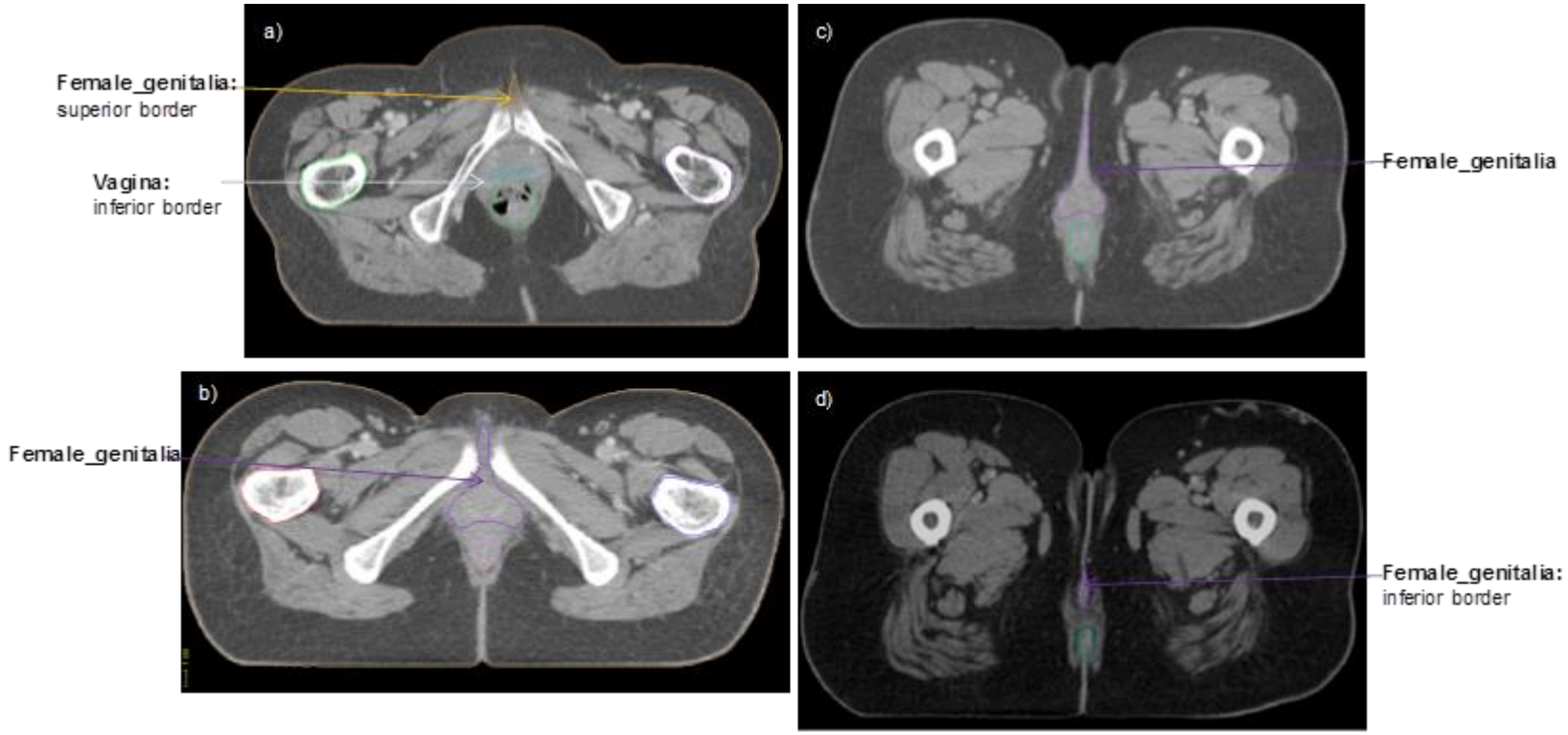
evaluation of acute skin related toxicity in the genitalia region seen in anal cancer patients. Table 7.3 describes the modifications and figure 7.4 provides atlas images:

Table 7-3: Comparison of definitions for female external genitalia

Organ	Standardised TPS name	Tumour category	Definition
AGITG guidelines and atlas for IMRT in anal cancer(123)			
External genitalia and perineum - female	Not available	GI	In females, this volume will include the clitoris, labia majora and minora, and area including skin and fat anterior to pubic symphysis. The cranial extent of this volume is the caudal edge of the pubic symphysis.
Multi-disciplinary definition from this study			
External genitalia and perineum - female	*(Female_genitalia)*	***GI/GYN***	*In females, this volume will include the clitoris and labia minora. Inferior extent is where the muscular structure of the labia minora is present. The cranial extent of this volume is the caudal edge of the pubic symphysis. Exclude if all of the external genitalia is included in the GTV otherwise include part of the structure not included in the GTV.*

Figure 7-4: Female_genitalia contour:

(a-d) Axial images. (a) Superior extent of Female_genitalia and inferior border of Vagina OAR to (d) Inferior border of Female_genitalia OAR



7.2.3.2.6 Vagina

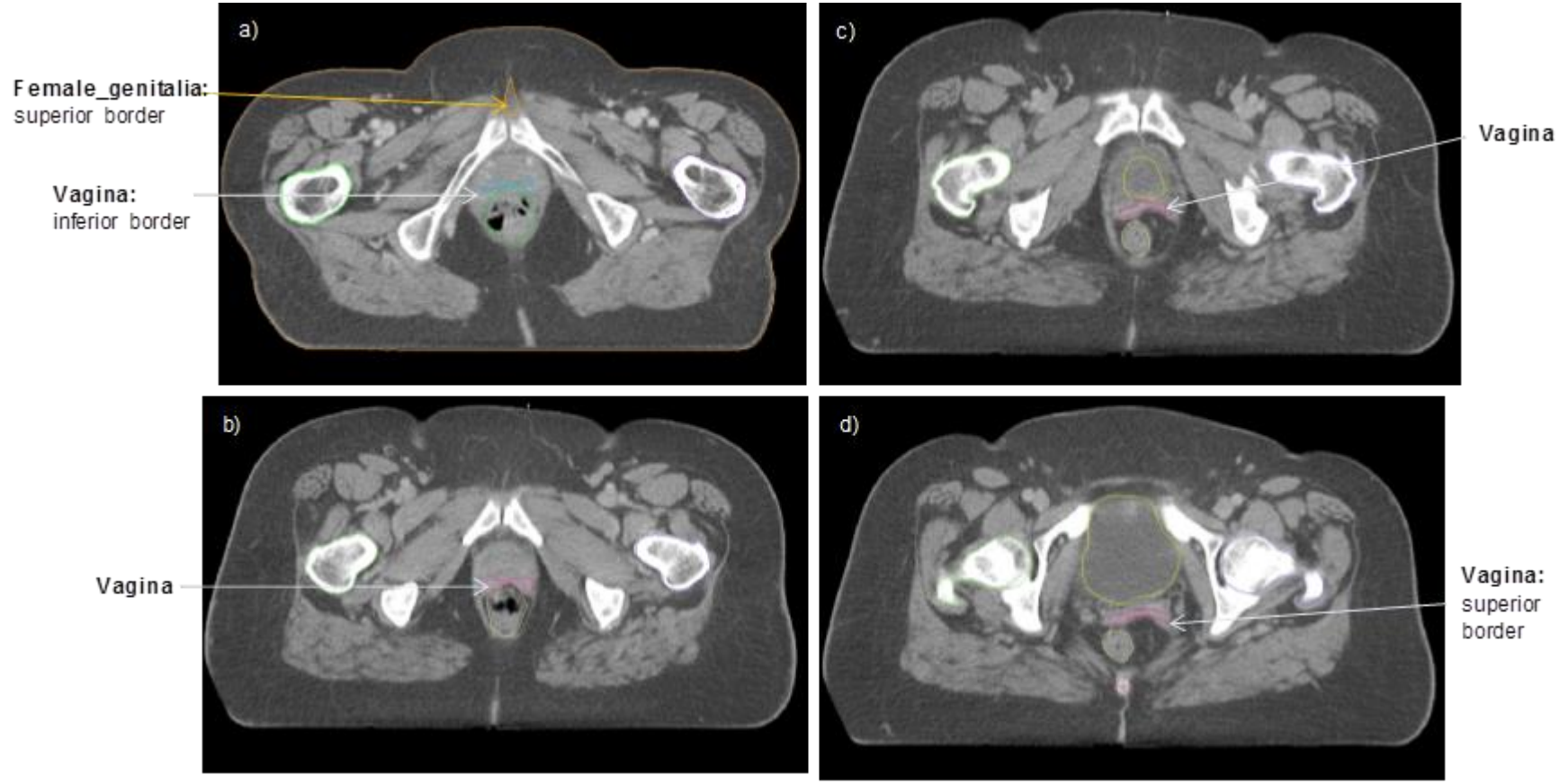
The RTOG contouring guidelines do not include the vagina as an OAR. However, a number of studies have evaluated the dose and volume of the vagina treated in relation to toxicity(285, 286). The inferior border in the definitions used in these studies is unclear with one study not providing a definition for the vaginal contour(285) and the other describing the contour as 'extending from the vaginal meatus'(286). These studies were published in 2014/2015 after the contouring for this project was complete. The RTOG contouring guidelines to define the clinical target volume (CTV) for postoperative IMRT for endometrial and cervical cancer discuss the use of a vaginal marker to delineate the superior extent(124). The marker is also used delineate the inferior border of the vagina CTV as 3cm below or 1cm above the caudal edge of the obturator foramen, using the most inferior structure. The use of markers is not standard practice in Leeds Cancer Centre and therefore the superior extent was defined as the caudal edge of the cervix. To ensure the transition from female external genitalia to vagina was reproducible the caudal edge of the pubic symphysis was taken as the inferior extent of the vaginal contour. This anatomical point is very similar to the inferior border using 1cm above the obturator foramen but the alternative terminology was used to reflect the female external genitalia contour. Table 7.4 outlines the definition and figure 7.5 illustrates with an image atlas.

Table 7-4: Definition of Vagina OAR developed

Organ	Standardised TPS name	Tumour category	Definition
Multi-disciplinary definition from this study			
Vagina	*Vagina*	*GI/GYN*	*Inferior extent caudal edge of public symphysis to cervix. Fuse or review MRI if possible. Exclude if **all** of the vagina structure is included in the GTV otherwise include part of structure not included in GTV.*

Figure 7-5: Vagina contour:

(a-d) Axial images (a) Inferior border of Vagina and superior extent of Female_genitalia OAR to (d) Superior extent.



7.2.3.2.7 Prostate, SeminalVesc and PenileBulb

Although the seminal vesicles and prostate are defined as potential OAR in the RTOG contouring guidelines, after discussion with the expert team for this study it was unclear how the patient reported toxicities from the questionnaires could be related to pathophysiological damage to these tissues. Based on this discussion, only the penile bulb was included as a surrogate organ for erectile function(287). MRI fusion with the CT was more beneficial for penile bulb definition than for the female sexual organ contouring however, due to the practical problems found with the MRI fusion process viewing the MRI in parallel to CT contouring was found to be a good substitute.

Following a period of training and feedback from an expert consultant radiologist (BC) the only modification suggested to the RTOG protocol was to highlight that on 0.5cm axial CT slices the penile bulb is often only present on one or two slices of the CT. Table 7.5 below describes this addition to the original definition:

Table 7-5: Comparison of definitions for PenileBulb

Organ	Standardised TPS name	Tumour category	Definition
RTOG Male and female pelvis normal tissue consensus definitions(122)			
Penile bulb	PenileBulb	GU	That portion of the bulbous spongiosum of the penis immediately inferior to the GU diaphragm. Do not extend this structure anteriorly into the shaft or pendulous portion of the penis.
			Tips: The penile bulb is best identified with MRI (bright on T2) or CT scan when there is contrast in the urethra. On CT scan, the penile bulb will be posterior to the urethra and has a round shape. Refer to the article by Wallner *et al*.
Multi-disciplinary definition from this study			
Penile bulb	*PenileBulb*	***GI***	*That portion of the bulbous spongiosum of the penis immediately inferior to the GU diaphragm. Do not extend this structure anteriorly into the shaft or pendulous portion of the penis.* ***Note the structure is often only present on one or two slices of the CT (0.5cm).*** *Tips: The penile bulb is best identified with MRI (bright on T2) or CT scan when there is contrast in the urethra. On CT scan, the penile bulb will be posterior to the urethra and has a round shape. Refer to the article by Wallner et al.*

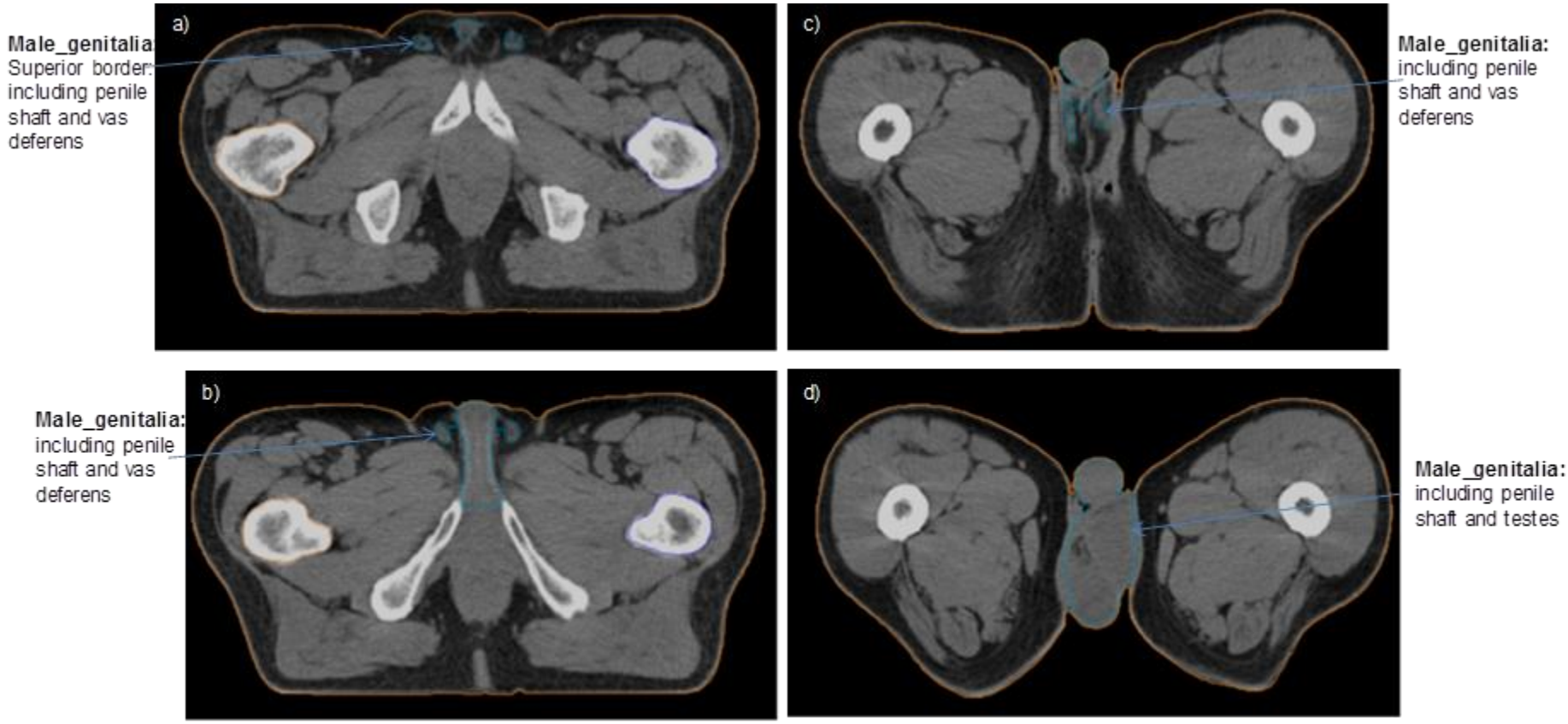
7.2.3.2.8 External genitalia – male: Male_genitalia

As previously discussed the AGITG guidelines for external genitalia include within the contour an area of skin and fat anterior to the pubic symphysis. As for the female patient, the lateral borders of this area are not defined and it is challenging to see how clear, anatomically reproducible boundaries could be imposed(123). As for the female patients it is unclear how this area may relate to late toxicity outcomes. The other structures included in the AGITG defined OAR include the penis and scrotum. There is some evidence of a dose-volume relationship between testicle dose and testosterone reduction although no reliable dose constraints exist(281). The dose to penile tissues has been evaluated in the past but recent studies evaluating the relationship between impotence and irradiation have focused on the penile bulb(281, 287, 288). Overall it

appears there is no one single organ responsible for erectile function and the work in this area continues to be exploratory(289).

Figure 7-6: Male_genitalia contour:

(a-d) Axial images. (a) Superior border to (d) Inferior image. The contour extends inferiorly to include all of the penile shaft and scrotal cavity.



For the OAR contour, as with the female genitalia contour we excluded the area of skin and fat from this contour. The contour included the penile tissue excluding the penile bulb (contoured as a separate structure), the scrotal sac and vas deferens. The vas deferens was included due to its role in ejaculation function. See table 7.8 for a description and figure 7.8 for atlas images.

Table 7-6: Comparison of definitions for male external genitalia

Organ	Standardised TPS name	Tumour category	Definition
AGITG guidelines and atlas for IMRT in anal cancer(123)			
External genitalia and perineum - male	Not available	GI	In males, this volume will include the penis, scrotum and area including skin and fat anterior to pubic symphysis. The cranial extent of this volume is the caudal edge of the pubic symphysis.
Multi-disciplinary definition from this study			
External genitalia and perineum - male	*(Male_genitalia)*	***GI***	*In males, this volume will include the penis (excluding the penile bulb), scrotal cavity (excluding skin and fascia) and vas deferens. The cranial extent of this volume is the caudal edge of the pubic symphysis.*

7.2.3.2.9 Pelvic bones

The dose-volume relationship between pelvic bones and haematological acute toxicity is established with a reduction in haematological toxicity seen in patients treated with IMRT for gynaecological malignancy where the volume of pelvic bones irradiated was reduced in comparison to a standard four-field technique(290). In this study by Brixey and colleagues, the sacrum, iliac crests and lumbar spine were contoured. Only the inferior border of the iliac crest contour was defined as the ‘top of the acetabulum’ and all bones were grouped together in the analysis(290). Other studies have considered the volumes treated in the pelvis separately, with one study finding the dose to the lumbosacral spine and lower pelvis having a greater relationship to haematological toxicity than the iliac crests(291).

The dose-volume relationship between bony structures and long-term outcomes such as pain and fractures is not clear. The use of IMRT increases the low dose to a greater volume of bony structures but reduces the high dose region. Whilst this reduces the acute haematological toxicity the impact on late toxicity outcomes is unknown. A number of studies of 3D conformal radiotherapy have highlighted the associations between radiation to the pelvis and pelvic insufficiency fractures with rates between 9-25% reported in more recent publications of patients treated for gynaecological

malignancies(292-295). In rectal cancer the rates may be lower with one study reporting rates of 3%(296). A large retrospective cohort of 6428 women over the age of 65 years with pelvic malignancies found patients who received pelvic irradiation had a higher incidence of fracture than those who received no radiotherapy and patients treated for anal cancer had higher rates of fracture (14%) than cervical (8%) or rectal cancer (11%)(297).

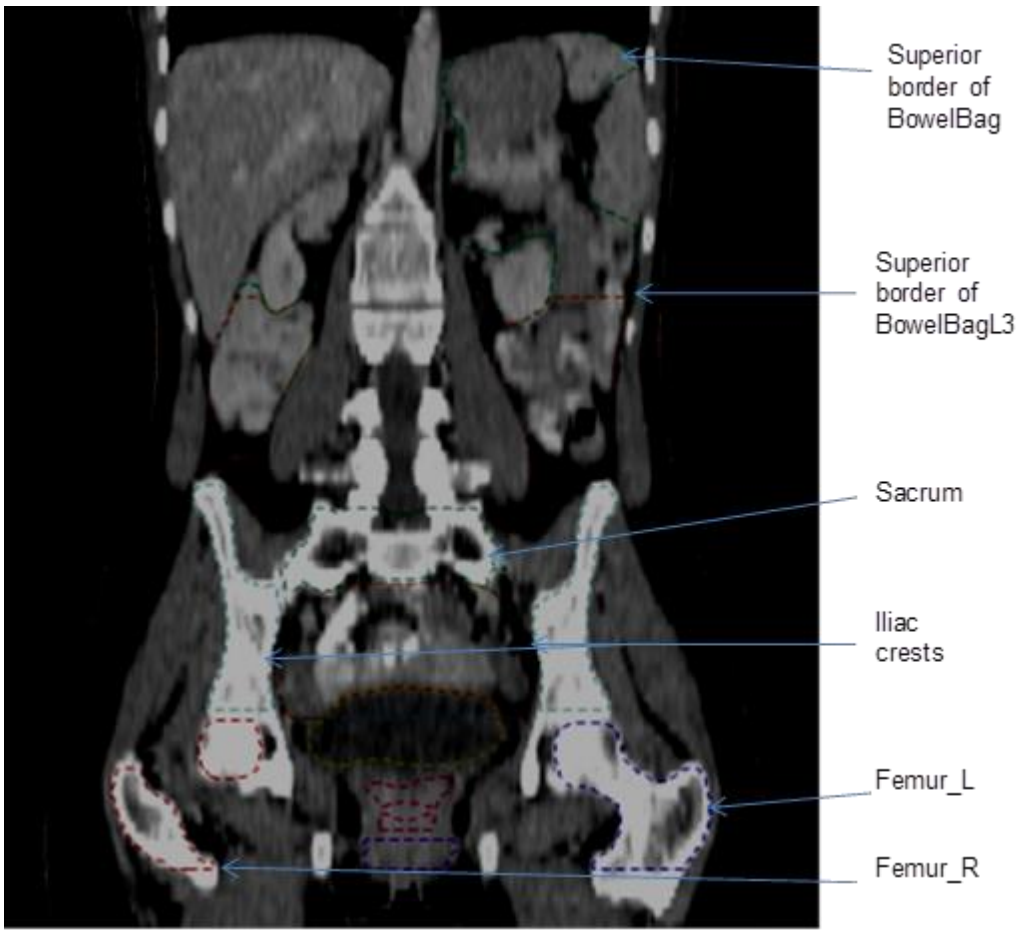
The commonest presenting symptom was pain and the most frequent site for insufficiency fractures was the sacrum (292, 294, 296). Factors associated with an increased risk of fractures are female gender, increasing age, lower BMI, postmenopausal status and lower density of bone and bone marrow on CT(292-296). Radiation dose greater than 50.4Gy was noted as a risk factor in one study evaluating EBRT in cervical cancer patients(292). The AGITG contouring guidelines for the iliac crests and the RTOG guidelines for the femurs were used in this study(122, 123). The RTOG states clear recommendations to include not only the femoral heads but to extend the contour inferiorly to the lowest level of the ischial tuberosities. Although not stated in the text this is to include the neck of femur as a common site for fractures. The sacrum was outlined to include the whole structure including the coccyx inferiorly as an extension of the sacrum. The definition is provided in table 7.7 and a coronal image (figure 7.7) shows all bony structures.

Table 7-7: Definition of Sacrum OAR developed

Organ	Standardised TPS name	Tumour category	Definition
Multi-disciplinary definition from this study			
Sacrum	*Sacrum*	***GI/GYN***	*Delineation will extend cranially from the top of the sacrum to the caudal extent of the coccyx.* *TIP: use sagittal view to aid contouring at superior border.*

Figure 7-7: Coronal image showing all bony structures.

The superior borders of BowelBag and BowelBagL3 are shown.



7.3 Combining doses from two treatment plans

The cross sectional study involved a retrospective cohort of patients treated with pelvic radiotherapy prior to more extensive implementation of precision EBRT techniques such as IMRT within Leeds Cancer Centre. This means that a significant number of patients included in the study have been treated with radiotherapy delivered in two or more phases. In the anal cancer patients, standard treatment for patients (excluding patients with T1N0 disease) involves a parallel-opposed pair of beams to the whole pelvis for the first phase of treatment (Phase 1: 30Gy in 15 fractions) followed by Phase 2 (20Gy in 10 fractions) to the gross tumour and nodal volumes (GTV) with a 3cm margin, using a 3 or 4 field technique. Some gynaecological cancer patients received an EBRT boost to nodal areas. Other patients required re-planning during the process of treatment and therefore had more than one treatment plan. In these cases, the most clinically appropriate CT planning scan was selected and the other treatment plan approximated to the selected CT scan in order that all patients would have their treatments combined onto a single CT scan with a single set of targets and OAR.

For patients treated in two or more phases the physical doses for each treatment phase were scaled and combined to generate the total equivalent dose in 2Gy fractions

(EQD2) using an α/β=3Gy(126). I designed the process for this work alongside medical physicists John Lilley, John Fenwick, and Stephen Gregory who wrote the code using Python and provided the technical detail for this section of the thesis. Python computer software (version 2.7.10) was used as part of the open-source and freely available Anaconda suite of tools, including use of the NumPy and Pydicom libraries, on Windows 7(298-300). An overview of the process is shown in Figure 7.8.

Each patient was processed in turn. Prior to export from Oncentra Masterplan (OMP; the TPS), the dose grids for each plan were manually checked to ensure their coordinates were aligned and set to a voxel size of 0.3 x 0.3 x 0.2cm. The clinical dose distributions were then exported to DICOM files on the network. The code sorts through these files and groups them together by patient identifier (ID) and plan unique identifier (UID). If not already summed, the dose from each beam in a plan was added together to give a plan dose distribution.

The EQD2 using α/β=3 was then calculated for each plan, using the number of fractions (n) for that plan in the equation:

$$EQD2 = voxel\ dose * [(voxel\ dose / n) + \alpha/\beta] / (2.0 + \alpha/\beta)$$

The EQD2 for each plan are then summed together (voxel by voxel) to give a combined EQD2 total dose distribution for each patient, representing the total radiation dose they received.

This total dose distribution was then reformatted into a 16-bit integer array, with a corresponding dose scaling factor, mirroring the output of OMP. Two new valid DICOM files created, holding the new combined dose distribution (Dose) and a dummy beam (Plan). Once the data is reimported into the TPS, the plan should not be re-calculated as this overwrites the combined dose distribution. The code performs a number of checks to ensure the data exported is accurate and suitable for combination. These checks are outlined in figure 7.8. The code quarantines failing files for further inspection.

A similar process was used to transform the patients treated on a single plan with 5Gy per fraction (short course rectal cancer patients) into EQD2 dose distributions for use in

the analysis, with the only difference being that only one EQD2 distribution is created in the process.

Once successfully re-imported into OMP, a new DVH can be calculated based on the combined total EQD2 dose distributions and original targets / OAR.

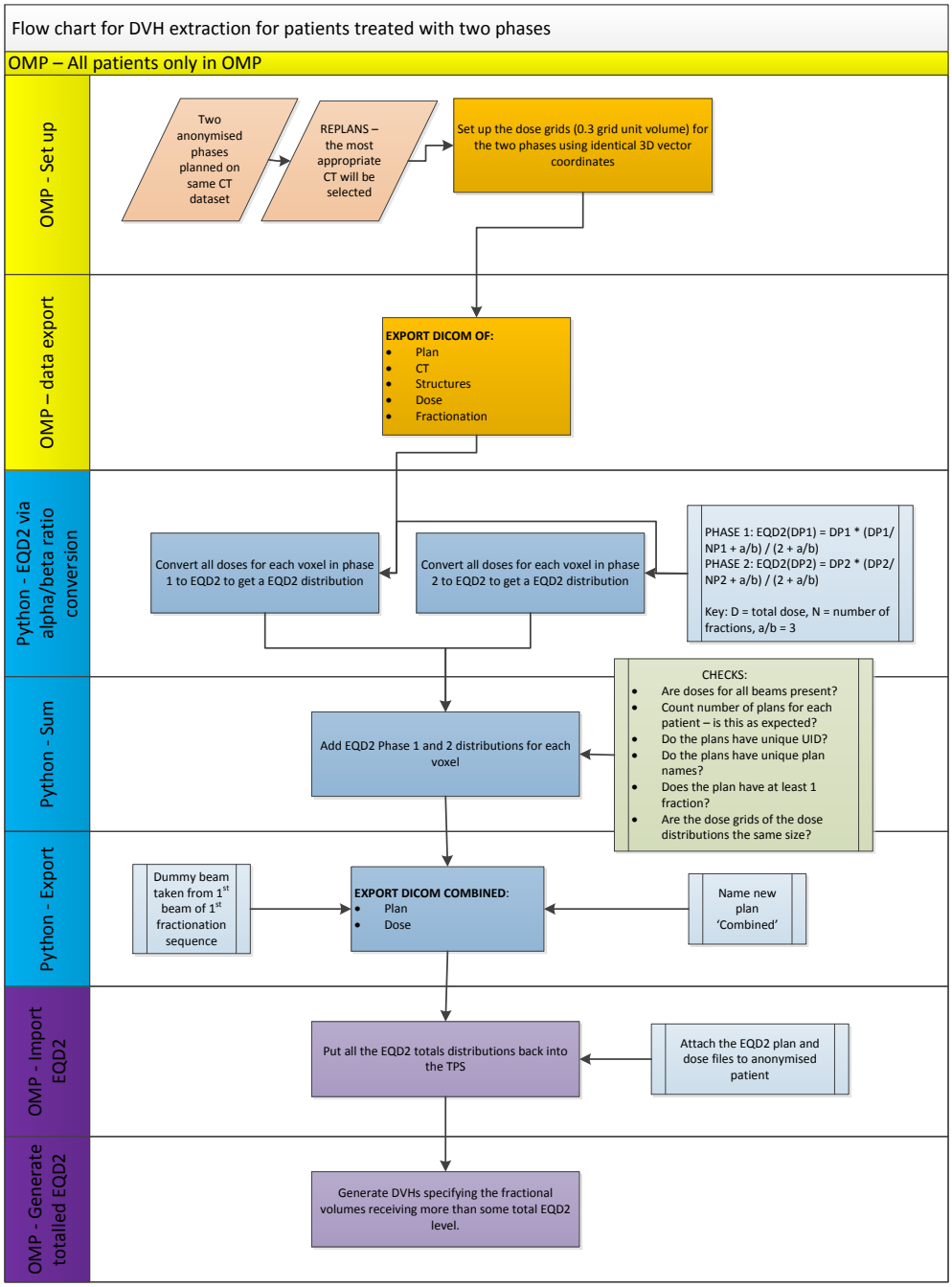


Figure 7-8: Flow diagram of EQD2 transformation

7.4 DVH export

Once all OAR contours had been completed for each patient and patients treated in more than a single phase had their dose distributions combined the data was exported from the TPS for analysis. Mitchell Naisbit (medical physicist) developed an application for this process for clinical use, using Matlab version 2013b to compile the code, and provided the technical detail for this section. A number of manual checks ensured that all patients had their OAR labelled correctly using standardized names as set out in the protocol and that all patients had the correct OAR contoured. The TPS was set up to export absolute cumulative DVH.

Figure 7.9 shows the process applied. The DVH data is exported as text files, using the anonymisation name to identify the data. The file names (patient ID) are used to create a list of patients to import within Microsoft Excel. During import the application extracts the data for each structure and labels it accordingly. The absolute and cumulative DVH data for each structure is extracted. The cumulative DVH data is reformatted into uniform dose bins of 0.1Gy. Each patient has a separate excel spreadsheet produced including the absolute volume data and the cumulative DVH for each OAR.

The code checks that the data is in the correct format (absolute cumulative) and the correct file has been selected by comparing ID within the data file to the expected ID read from the patient list in the Excel spreadsheet.

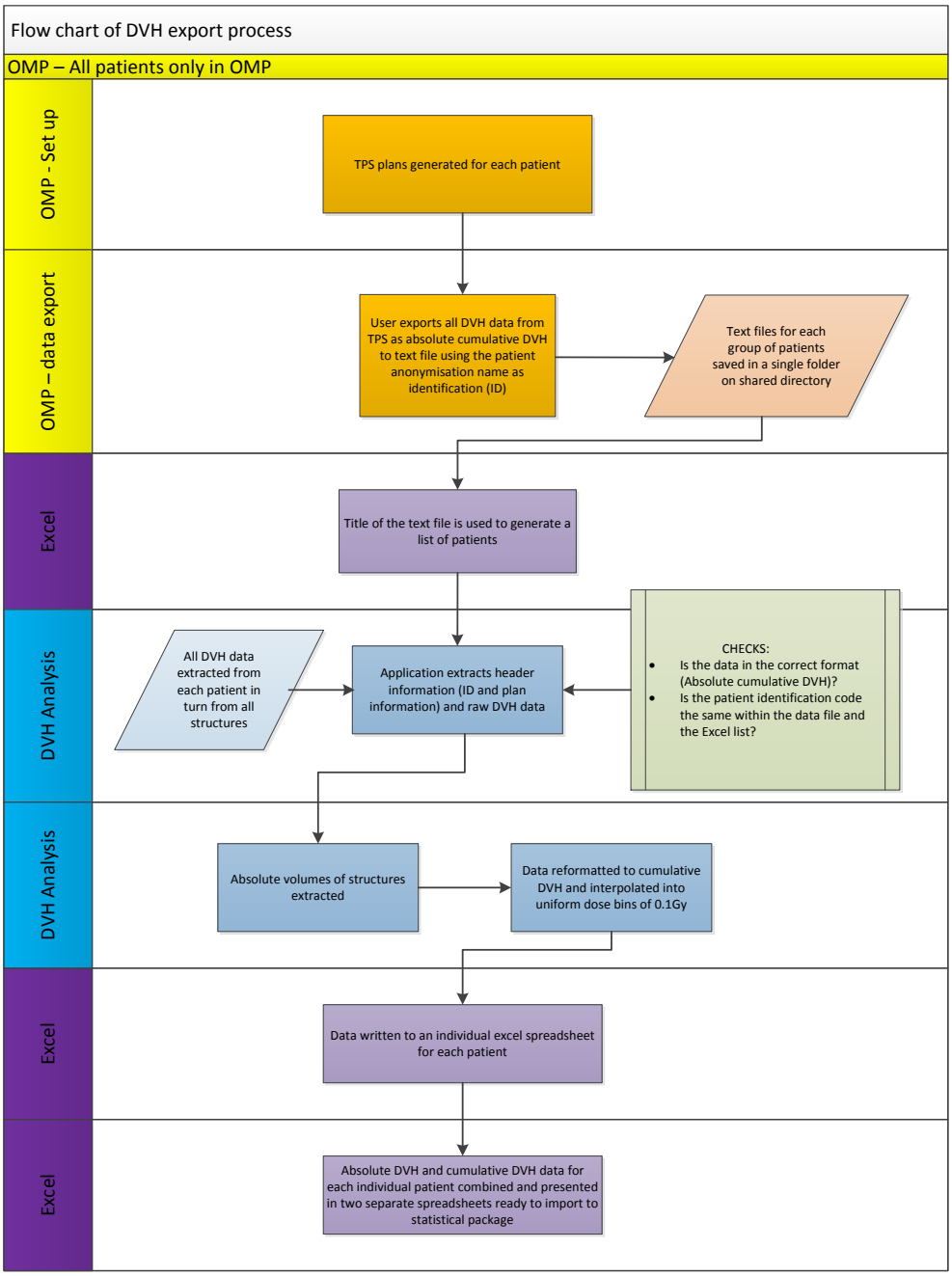


Figure 7-9: Flow diagram of the DVH export process

The DVH data for each individual patient was then combined with other patients in Excel using a macro developed specifically for this purpose. I designed the requirements for the code along with support from Gill Santorelli (statistician for the project) and Rob Carter (data manager for the research team) wrote the code.

7.5 Discussion

This chapter has described the development of precisely defined and reproducible OAR contouring definitions suitable for use with a multi-professional team in clinical practice. In addition, this chapter describes the challenges with the use of CT/MRI fusion software in the pelvis. Finally, the technical solutions developed to both combine patients treated in two or more treatment phases and export DVH data were outlined.

The practical evaluation of existing OAR contouring guidelines with a multi-professional team found a lack of precision in the OAR definitions and the improvements made have improved the reproducibility between different practitioners from different clinical backgrounds. Dosimetrists were unwilling to contour OAR using a protocol, which did not specifically define in detail the anatomical boundaries of the contour. This led to the development of a protocol that defined the contours unambiguously. Further evaluation of these guidelines in an independent dataset will be required to evaluate the protocol further. However, the development process using a multi-disciplinary team of practitioners was very effective. In the majority of cases the modifications made to the definitions were to clarify areas without anatomically precise boundaries and to provide additional notes to support contouring accuracy (i.e. BowelBag, Rectum, PenileBulb). In these cases the dosimetric outcomes found in the cross sectional study will be directly comparable to other studies using these definitions. In the case of the vagina and sacral contours which were developed for this study, guidelines to not exist. The dosimetric relationship of these structures to late toxicity outcomes will be piloted in the cross sectional study. However, the male and female genitalia contours developed for this project had the relationship of these organs to late toxicity in mind and are therefore different to the external genitalia OAR definitions provided by the AGITG as they exclude skin and subcutaneous tissue. The results of the cross sectional analysis for these organs may not be directly comparable therefore to other studies. For future evaluation of the prospective study dosimetric data this could be an area to evaluate further through comparing acute and late toxicity outcomes of the external genitalia structures with and without skin and subcutaneous tissues.

The use of deformable registration between CT and MRI was evaluated within this study. Whilst this process is not validated for use in clinical practice, initial studies in with head and neck cancer patients showed favourable results(275, 276). However, this qualitative evaluation of patients treated with pelvic radiotherapy found that the usefulness of this software was outweighed by a number of issues/limitations: anatomical distortions caused by the patients not being scanned for their MRI in the treatment position, pre-operative diagnostic MRI scans matched to post-operative

treatment scans, poor quality MRI scans, and differences in bladder and rectal distension. This study did not seek to evaluate the usefulness of this software to improve target volume definitions but similar issues are likely to impact on the target tissues as well. To use MRI/CT fusion to improve pelvic anatomy contouring, the patient needs to at the minimum be scanned in the treatment position for their diagnostic MRI scan. At this point, further quantitative evaluation of the registration process with multiple practitioners is required to develop this use in clinical practice.

The chapter also outlines the complex contouring process required to retrospectively contour the cohort of cross sectional patients and described the methods and technology developed to combine doses for patients treated with two different treatment phases. With the introduction of IMRT/VMAT techniques treatment in two or more phases will no longer be as common in the future, however, the dose combination processes used in this study may be useful for calculating the effect of combining doses for patients requiring retreatment due to disease recurrence and for who may require replanning during treatment. This chapter also outlined the technical processes involved with exporting DVH data from the treatment planning system and demonstrated that DVH data can be exported from patients treated in clinical practice for use in dosimetric analysis on a large scale. To implement this process more widely within clinical practice a number of modifications would be required to ensure that the data extracted could be easily analysed, in particular the TPS would require implementation of standard naming for all contours (OAR and target organs) to ease the combination and analysis of data. Further evaluation of these processes will take place with the patients treated in the prospective study as part of post-doctoral work.

Chapter 8 Dosimetry, patient and clinical factors influencing patient reported toxicity in patients treated with pelvic radiotherapy: A Cross sectional study

8.1 Introduction

This chapter aims to evaluate the dosimetric, clinical and patient factors impacting on patient-reported late toxicity in patients treated with pelvic (chemo)radiotherapy for anal, rectal, cervical and endometrial cancer. This chapter will also include an overview of the socio-demographic and clinical data of the sample, the prevalence of patient-reported toxicity in the different cancer sites and evaluate the clinical usefulness of applying a principal component analysis (PCA) to dosimetric data.

As survival rates for patients with pelvic malignancies continue to improve, measuring treatment related toxicity and evaluating methods to modify treatment regimes to reduce complications is critical. Advances in precision radiotherapy techniques aim to reduce complications. However, these precision techniques are relatively new and are not implemented extensively in all organisations within the United Kingdom or used to treat all cancer sites at the current time. Development of predictive models for normal tissue complications requires a detailed evaluation of the relationship between dosimetric, patient and clinical factors, as well as accurate measures of toxicity. The previous chapters have evaluated the importance of selecting a suitable toxicity outcome measure for use within this project and described the benefits of using patient-reported outcomes (PRO) over clinician-reported toxicity grading systems. This chapter focuses on the analysis of the dosimetric factors associated with each toxicity outcome and other clinical and patients factors that have been reported to have an impact on the severity of toxicity outcomes, such as patient co-morbidities, for example diabetes(131); medications such as angiotensin-converting enzyme inhibitors (ACEi) and statins(301); and treatment factors such as concurrent chemotherapy, brachytherapy and surgery (282). Through dosimetric evaluation using existing conventional three-dimensional (3D) external beam radiotherapy (EBRT) techniques the findings from this study may be used as a foundation on which to design future clinical trials examining precision radiotherapy.

Studies evaluating late toxicity in patients treated with radiotherapy for pelvic malignancies suggest that up to 50% of patients have long-term gastrointestinal (GI)

side effects(93). Symptoms associated with bladder and sexual dysfunction are also prevalent, as reviewed in Chapter 3(127, 302). Clinical studies have shown that dose volume histogram (DVH) metrics correlate with patient toxicity outcomes although the relationship is complex(281). Normal tissue complication probability (NTCP) models reduce complex dosimetric and anatomical information within a risk model, such as the most widely used NTCP model, the Lyman-Kutcher-Burman (LKB) model(40). However, one of the key limitations of the LKB model is the lack of inclusion of clinical risk factors within the model(126). Including clinical information within NTCP models has been found to improve their predictive power, and will also increase their usefulness within clinical practice(303).

Previous studies evaluating the relationship between dosimetry and toxicity outcomes within the pelvis have mainly focused on prostate cancer and used clinician-reported outcomes, focusing on severe toxicity grades or binary complication outcomes(92, 126, 130, 131, 304-306). A number of studies have also not included clinical and patient factors alongside DVH metrics within the outcome modelling despite evidence demonstrating benefits of their inclusion(130, 303, 307). However, a number of recent dosimetric studies have used validated PROs to evaluate adverse events, although they have mainly focused on GI toxicity(15, 308-310). The three studies evaluating prostate cancer EBRT corroborated previously validated models of DVH rectal parameters and clinician-reported toxicity using PRO outcomes for GI toxicity and concluded that further validation of PRO use in dosimetric models should remain a priority(15, 309, 310). Han and colleagues directly compared acute toxicity (diarrhoea) reporting by patients and clinicians to dosimetric parameters in anal cancer patients(308). The relatively small sample size (n=58) limited the conclusions they were able to draw from the comparative analysis between physician and patient's toxicity scoring and dosimetric parameters. However, good agreement was found between EORTC-QLQ instruments and clinician reporting using CTCAE for the diarrhoea item (CTCAE ≥ 1: 61% vs. EORTC ≥ 'quite a bit': 65%; McNemar test P=0.62) and sore skin/skin reaction item (100% vs 95%; McNemar test P=0.48). DVH parameters (using cumulative volumes) were associated with both clinician and PRO outcomes for the diarrhoea item(308).

Two recent studies have evaluated vaginal stenosis and dosimetric parameters in patients treated with EBRT for rectal and anal cancer. In the study by Mirabeau-Beale and colleagues, vaginal stenosis was assessed using the patient's medical record to ascribe a grade by using a modified version of CTCAE version 4(285). No dosimetric correlations were found in their analysis; however using case note review to retrospectively grade toxicity will limit the quality of the outcome data. In addition, the

authors provided no anatomical description of vaginal organ contouring in the paper(285). In the study by Son and colleagues, vaginal stenosis was evaluated in rectal and anal cancer patients using the difference between the maximum size of vaginal dilator used before and after treatment in the second study(286). In the analysis, vaginal stenosis was associated with multiple dosimetric parameters using cumulative DVH, mean and maximum dose and generalised equivalent uniform dose within the regression model(286). The generalised equivalent uniform dose (gEUD) model offers a single metric to describe non-uniform dose distributions taking into account dose heterogeneities and if given to the whole organ uniformly is expected to lead to the same complication rate as the original dose distribution(40, 286). Anal cancer patients received a significantly higher dose than the rectal cancer patients to all DVH parameters and gEUD <35Gy and mean dose <43Gy were associated with a reduced risk of severe vaginal stenosis(286). Interestingly, patients with self-reported <40% compliance using dilators (three times a week) were more likely to have toxicity(286). Within this study, vaginal stenosis will be evaluated using the EORTC-QLQ CX24 vaginal functioning items. Based on the potential weaknesses found in the description of vaginal stenosis within the CTCAE using PRO may provide a more accurate assessment of symptomatic toxicity and therefore relate more accurately to dosimetric data.

8.1.1 Using Principal Component Analysis to analyse DVH

The initial step in evaluating the relationship between toxicity and dose delivered to the associated organs at risk (OAR) requires the reduction of the 3D radiotherapy treatment data to two-dimensions (2D). The 2D representations of the data are called dose-volume histograms (DVH). Within the DVHs spatial information about the location of high or low dose areas within a structure is lost. For some organs, previous studies have segmented OARs attempting in part to acknowledge this data reduction, for example the study by Stenmark and colleagues where the rectum was segmented into three parts, inferior, mid and superior rectum(15). Within this study, these suggestions have been followed with segmentation of the rectum and intestinal cavity (BowelBag) at lumbar spine level L3 (see Chapter 7 for further details).

One of the challenges with studying normal tissue DVHs in comparison to tumour DVHs is the increased heterogeneity of the dose distribution and greater variation between patients thus the model applied is improved if it considers the dose heterogeneity. A number of studies have evaluated the relationship between the DVH parameters within the pelvis and toxicity for different OARs and have found significant relationships(15, 130, 131, 286, 310). However, the summary DVH parameters used

have differed between studies, with some studies opting to evaluate differences in toxicity using a single DVH parameter, such as volume at a particular dose point (V), dose at a particular volume cut off (D) or maximal dose (Dmax)(15, 307-310). Using a single volume threshold, such as V20 (percentage of an OAR treated to 20Gy) describes a single data point on a DVH curve and therefore potentially loses important dosimetric information, which may discriminate between treatment plans(126). Similarly, the same value for V20 can occur for an infinite number of different dose distributions which may be associated with very different risks(40). The dose volume parameters are also highly correlated with each other, with the correlations arising from fixed beam geometries and treatment techniques(132). For example, the volume treated to 10Gy is will be spatially adjacent to the volume treated to 15Gy within a particular OAR. Others have compared dosimetric information to toxicity by reducing a DVH curve to surrogate values such as the mean dose (Dmean) or generalised equivalent uniform dose (gEUD)(285, 286, 304). However, these parameters are limited in their ability to describe the variability within DVH data and therefore may not be suitable to apply to data sets with heterogenous dosimetry, for example when combining multiple techniques or treatment sites within a single analysis(311).

A number of studies have explored the use of a principal component analysis (PCA) as a means to explain and compress the correlated variability of the DVH data(126, 130-132). PCA is a statistical tool for establishing patterns between correlated items within a data set. The process effectively groups together correlated data points, reducing the data to a few parameters which describe the whole data set. With DVH data PCA quantifies the variability in a DVH dataset and separates out DVHs with similar morphology (i.e. similar relative volumes treated with comparable doses). PCA characterises the individual DVHs into a few parameters, the ‘principal components’ (PCs). The aim is to explain the individual DVHs and their variability by a few PCs allowing comparison between groups of similar DVHs in relation to their risk of toxicity. This means that instead of having a DVH described by 70 data points divided into 1Gy bins, for OAR volumes treated to 70Gy, a patient’s DVH may be explained by few PCs that explain a high proportion of the variability within the data. This reduction in the DVH data allows for more manageable modelling of the impact of the DVH in causing dose related symptoms in patients without the loss of potentially important information found with other simpler modelling techniques. The PCs may then be assessed within a regression analysis to evaluate the dosimetric relationship with toxicity outcomes. Ideally, the PCs should more sharply describe patient-to-patient dosimetric variance than arbitrary volumetric or dosimetric indices, such as V40 or D50, and provides a way to characterise the variability in the dosimetry using relatively few indices. As the PCs are also uncorrelated, unlike other dosimetric parameters, using a PCA may

increase the chance of revealing significant correlations between outcomes and dosimetry if these variations exist. PCA also provides a clear framework for deciding how many parameters dominate the DVH morphology in comparison to selecting single volume or dose parameters for which the selection is purely empirical.

However, despite the benefits of using PCA, the interpretation of the PCA outcomes is more challenging. By incorporating the whole of the DVH within the PCA model interpreting the dosimetric meaning of the outcomes is more complex to attain. PCA creates the PC modes by segregating the cumulative volumes of each OAR exposed by variance using linear combinations of these original DVH variables. The relative contribution of each DVH in the PCs is based on the size of the variance and the level of redundant information contained(132). In comparison, selecting single DVH points allows ease of interpretability of findings however, relevant information from other parts of the DVH may be lost by these models(130). The PCA covariance matrix, rather than the correlation matrix is used within the analysis(130). The covariance matrix is appropriate for use in samples where the variables are measured in comparable units and the differences in variance found between the different variables are important for interpretation. After the initial PCA, a second rotation of the components may be beneficial to simplify the structure of the components. An orthogonal varimax rotation rotates the axis of the PCA so that the vertices remain perpendicular to each other and has been used in previous research to obtain PCs using DVH data that are simpler to interpret(132).

Within this study the analysis will compare multiple different EBRT treatment regimes to the pelvis. PCA has been used successfully in this setting before through conversion of the DVHs from treatment regimes with different fractionation schedules into linear-quadratic biologically effective dose delivered in 2Gy fractions using an $\alpha/\beta=3Gy$[2](126). One of the criticisms of this study was that differences in the model could be explained by differences in technique, with the separation in the model explained by differences in patients treated in 2Gy/fraction compared to patients treated with 2.5Gy/fraction(312). To address this issue, potential confounding factors will be introduced into the regression analysis though including dose per fractionation into the model and through evaluating the models separately for each cancer site. A number of authors have recommended incorporating heterogenous dosimetric datasets into NTCP models to explore dosimetric parameters that arise as a result of combining different treatment techniques within a single analysis(132, 312). By including multiple

[2] $\alpha/\beta=3Gy$ is used to describe the radiobiological properties of the normal tissues and their late effects. The EQD2 is calculated by:
EQD2 = Total dose *((Total dose/number of fractions) + α/β)/(2+ α/β)

techniques from different tumour sites within the analysis potentially the data can describe not only patient-to-patient variability within a single technique (which may be demonstrated in the regression analysis if a PC relates to a toxicity outcome for a particular cancer site) but also variability between different techniques (which may be demonstrated if there is no effect on the model when dose per fractionation and diagnosis are evaluated), increasing the generalisability of the outcomes.

8.1.2 Aims

This chapter aims to use a validated PRO measure within a cross-sectional study to describe the prevalence of late adverse events (AE) up to five years post pelvic radiotherapy treatment and validate the use of the PRO instrument in clinical practice. The study further aims to examine the associations between patient-reported toxicity, patient clinical data and radiotherapy dosimetric data to explore predictive models linking radiotherapy treatment to toxicity severity.

This study is innovative in the inclusion of multiple cancer sites treated within the pelvis, creating heterogenous dosimetry data for analysis, the use of validated PRO measures to evaluate toxicity and the inclusion of multiple normal tissue site end-points relating to the toxicity outcome data. By considering the complexity of the individual patient characteristics and treatments received alongside consideration of the spectrum of toxicity outcomes, this study aims to optimise the understanding of the dosimetric relationship to patient toxicity within the pelvis.

To avoid repetition within the introduction and methods, Chapter 8 includes all data from the cross sectional study. The results section presents the overall patient characteristics of the sample and the results from the EORTC-QLQ C30(67). The results of each group of toxicity items – urinary, bowel, female and male sexual dysfunction and low back pain - and related OAR dosimetric analyses are then laid out in turn. The discussion evaluates the overall findings from the study and considers the models developed for each symptom group in turn.

8.2 Methods

8.2.1 Patient sample

The study cohort comprised men and women with anal, rectal, cervical and endometrial cancer treated between 2009 and 2014 at the Institute of Oncology

Outpatient Clinic at St James's Hospital, Leeds with radical (curative) pelvic external beam radiotherapy (EBRT). Patient were eligible if they had received standardised radical 3D conformal radiotherapy, Intensity Modulated Radiotherapy (IMRT) or volume modulated arc radiotherapy (VMAT) in four cancer sites 1) Radical (chemo)radiotherapy for anal cancer; 2) Pre-operative adjuvant (chemo)radiotherapy for rectal cancer; 3) Radical (chemo)radiotherapy for cervical cancer; and 4) Post-operative radiotherapy for endometrial/uterine cancer and cervical cancer. Patients were eligible regardless of disease status at the time of the evaluation. Disease status including recurrence was recorded.

The National Research Ethics Service Leeds East Committee approved the study following ethical review (13-YH-0156). Patients were eligible for the study if they were 18 years or older, able to read and understand English and were not exhibiting overt psychopathology or serious cognitive dysfunction. All participants provided written informed consent. Eligible patients on long term follow up were identified by clinical staff screening the clinic appointment lists, and were contacted by letter from their named consultant in advance of their appointment inviting them to take part in the study. This approach was necessary to allow patients the opportunity to consider taking part in the study prior to their appointment, as patients on long term follow up have infrequent hospital visits (typically every 6-12 months). This letter also provided patients with their online log in details to enable them to complete a single quality of life (QOL)/symptom assessment questionnaire electronically in advance of their clinic appointment if they wished. Alternatively patients were able to complete the questionnaire on touch screen computers during their clinic visit, on paper before, during or after their clinic appointment or online after their clinic appointment. After their clinic visit patients who had not completed the questionnaire but had consented to take part received two letter reminders to complete the questionnaire at monthly intervals. Full details of the approach taken are described in Chapter 6.

8.2.2 Summary of radical treatment

8.2.2.1 Anal cancer treatment details

Patients with stages T1-4 with node positive or negative disease received EBRT 30Gy in 15 fractions in phase 1 to the whole pelvis (large parallel opposed fields) followed immediately by Phase 2, 20Gy in 10 fractions to the GTV with 3cm margins (using a 3 or 4 field technique) combined with Mitomycin on day 1 (12mg/m2) and 5FU days 1-4 and 29-32 (1000mg/m2). Patients with a T1N0 squamous cell anal cancer with a primary tumour <1cm (or patients treated adjuvantly following local excision) received 30Gy in 15 fractions EBRT with concurrent Mitomycin day 1 (12mg/m2) and 5-

Flurouracil (5FU) chemotherapy days 1-4 (1000mg/m2). The EBRT was delivered to the gross tumour volume (GTV) with a 3cm margins using a 3 or 4 field technique.

8.2.2.2 Rectal cancer treatment details

As decided by our local multidisciplinary team (MDT), patients with rectal adenocarcinoma staged T2-3 with a clear circumferential resection margin (CRM) received neoadjuvant short course EBRT (SCRT) 25Gy in 5 fractions followed by total mesorectal excision (TME) surgery within 7-14 days. Patients with a threatened or involved CRM received neoadjuvant long course EBRT (LCRT) 45Gy in 25 fractions with either (oral) capecitabine (900mg/m2 bd) chemotherapy on days of radiotherapy or 5FU (350mg/m2) daily on weeks 1 and 5 with leucovorin. Patients then received a pelvic MRI to assess tumour response at six weeks post completion of radiotherapy. If patients had no evidence of disease progression they would proceed to TME surgery. The clinical target volume (CTV) included the primary tumour, mesorectum and internal iliac nodes using a 3 or 4 field technique. Patients who are unable to receive CRT, received neoadjuvant short course EBRT (SCRT) 25Gy in 5 fractions followed by a delay of six weeks to assess response prior to evaluation for TME surgery.

8.2.2.3 Cervical cancer treatment details

Patients with Stage 1B2-IV cervical squamous cell carcinoma are offered definitive treatment with EBRT 48Gy in 24 fractions over 32-34 days with weekly cisplatin (40mg/m2) followed by intracavity brachytherapy (ICBT) 21Gy in 3 fractions over 14 days (with no gap between EBRT and ICBT). Patients not able to receive brachytherapy received a Phase 2 boost 18Gy in 10 fractions over 12-14 days to the macroscopic tumour at the time of diagnosis plus a 2cm margin. The CTV included the nodal CTV (macroscopic nodal volume plus a 1cm margin), bilateral parametrial tissue, uterus, upper 2cm of normal vagina, and pelvic lymph nodes (parametrial, obturator, presacral (down to level of S2/3 junction), internal, external and common iliac. Paraaortic and common iliac nodes are included when involved and inguinal nodes in stage IIIA disease).

Post surgery, patients with positive nodes, involved parametrium or a resection margin <5mm received adjuvant EBRT 45Gy in 25 fractions over 32-34 days. Additional concurrent weekly cisplatin chemotherapy was considered in adjuvant patients treated with IMRT/VMAT with >1 positive node or poor prognostic factors. A brachytherapy boost, 12Gy in 3 fractions given on consecutive days post EBRT was considered in adjuvant patients with close margins or invasion of parametria. The CTV included the

parametrial tissue, upper 2cm of the vagina and pelvic lymph nodes (parametrial, obturator, presacral down to level of S2/3 junction), internal, external and common iliac as well as lower paraaortic and common iliac nodes when involved).

8.2.2.4 Endometrial cancer treatment details

Adjuvant post operative EBRT was offered (if appropriate) in patients with Stage IB serous/clear cell, and Stage IIIa, IIIc for all grades and histology. Adjuvant EBRT is considered in patients with Stage Ib grade 3, Stage II and completely resected IVb. Adjuvant patients receive EBRT 45Gy in 25 fractions over 32-34 days and in patients with cervical involvement phase 2 brachytherapy 12Gy in 3 fractions is additional considered. The CTV is the same as the CTV described for the patients with cervical cancer treated adjuvantly previously.

8.2.3 OAR dose constraints

OAR contouring was not standard for the majority of patients treated during the eligible time frame however for patients treated with VMAT in the adjuvant gynaecological cancer setting some dose constraints to normal tissues were applied over the treatment period. These were: Small bowel V40Gy ≤ 3%, Rectum V55Gy ≤ 5%, Bladder V45Gy ≤ 35%, Femoral headV30Gy ≤ 35%.

8.2.4 Radiotherapy planning

Full details of the process of radiotherapy planning are given in Chapter 6. All patients had axial computed tomography (CT) slices with a maximum of 5mm slice thickness. Individual CT planning scans were combined with pre-existing anatomical structures, three-dimensional dose matrix and the original treatment plan (or plans) parameters. Delineation of OAR was not mandatory for treatment and therefore all OAR were retrospectively contoured using the protocol devised in Chapter 6. For patients treated in two phases and 5Gy fractionation schedules the physical doses to each voxel in the dose matrix (grid size 0.3cm) for each treatment phase were combined to generate the equivalent dose in 2Gy fractions (EQD2) using an α/β=3Gy(126). Cumulative DVHs and absolute volumes for each OAR were exported in 0.1Gy dose bins. The cumulative DVHs in 0.1Gy dose bins were used to extract the EQD2 in 1Gy dose increments using an α/β=3Gy for all OARs for patients treated with 1.8Gy fractionation schedules for use in further analysis. Dose bins of 1Gy were used to calculate the cumulative DVH for each OAR, the summary DVH measures: Dose at a cumulative volume of 50% (D50), Mean dose (Dmean) and Maximum dose (Dmax) and the unrotated and varimax rotated PCs.

8.2.5 Outcome measures

The questionnaire comprised the validated cancer specific EORTC core questionnaire ((EORTC QLQ-C30) and the disease specific modules for each cancer site (cervical-CX24; endometrial –EN24 and anal and rectal (gastrointestinal - GI) patients – CR29) with additional items from the EORTC item bank advocated through the development work of this project(67, 313-316). These included additional items on sexual dysfunction for the GI cancer patients taken from the cervical cancer module (CX24) and the prostate cancer module (PR25) and items on bowel and urinary urgency for all patients taken from the endometrial cancer module (EN24). This approach has been used in other trials to good effect(14, 21). For the majority of items a four-point Likert-type scale is used for the questionnaire. The item responses are converted through a linear transformation for both individual and scaled items onto a 0-100 scale. Higher scores for the symptom items reflect a higher level of symptoms and higher scores for the function items reflect a better level of functioning(129).

8.2.6 Sample size

Sample size calculations were carried out using GPower 3.1 by Ada Keding (statistician)(317) and based on regressing symptomatic toxicity evaluated through the PRO measures on DVH in the presence of a maximum of five covariates. Cohen's f^2 relates to the amount of variance explained by the regression model with one predictor of interest (DVH) and five other clinical/demographic covariates(318). To detect a moderate effect size of DVH (f^2 =0.15) with 90% power, a minimum sample size of 73 is required for each disease site. To detect large effect sizes (f^2 =0.35) evaluating the impact of DVH a minimum sample of 33 is required.

8.2.7 Analysis

I carried out all analysis and data management for this project with support from Gill Santorelli (statistician); John Fenwick (medical physicist); Sindu Vivekanadan (clinical oncology registrar) and Damianos Christophides (medical physicist). Gill supported development of the project, the set up of the Stata syntax and advised on the regression analysis; John advised on the development of the project, the use, application and analysis of the PCA; Sindu advised on the PCA analysis; and Damianos validated the results of the regression analysis using an alternative method (described later).

Data was analysed using Stata/SE 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13.1. College Station, TX: StataCorp LP), IBM SPSS Statistics 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) and Anaconda Python distribution (Continuum Analytics Inc., TX, USA; https://www.continuum.io/downloads) and R statistical programming language (R Core Team (2015), Vienna, Austria; https://www.r-project.org). Analysis of the EORTC QLQ-C30 and disease specific modules and handling of missing data were performed according to the EORTC guidelines, using a process of imputing for missing values in scale responses(i.e. grouped items)(129, 319). The PRO item responses were assessed as continuous outcomes on the linear scale (0-100) and assessed as a categorical variable for different types of toxicity experienced (e.g. bowel or sexual dysfunction). There is no research on the EORTC QLQ items to challenge the non-linearity of the items(129, 319). The scoring manual recommends using the EORTC-QLQ scales based upon an unweighted summed score using the Likert method of summated scales(129). The constituent items within each scale are summed assuming (1) that it is appropriate to give each item equal weight and (2) that the items are graded on a linear/ equal-interval scale. These simple scoring systems have been found to be robust(320) and reasonable to use for many purposes(321).

The potential predictors of the PRO outcomes included the dosimetric variables from the PCA, summary dosimetric factors (D50, Dmean and Dmax) and percentage volume of each OAR in 5Gy increments as well as all clinical factors, listed in table 8.1. Clinical factors with a prevalence of less than 5% were not included in the regression analysis. PCA was performed using IBM SPSS Statistics 22 on the full dataset for each OAR in turn, irrespective of the toxicity profile. The covariance matrix was used for the analysis and an additional varimax rotation performed on the data set. The PCs and individual patient coefficients related to each PC generated from the analysis were extracted for use within the regression analysis. The PCs included in the models accounted for more ≥1% of the variability within the data. To establish the dosimetric links between the resulting PC data to the original DVH data each OAR had a reconstructed DVH calculated using the following calculation:

$$Original\ DVH_d = Mean\ DVH_d + \left(PC_{d,i} \times Coefficient_i\right)$$

Where *d*= the dose increment, for example the original and mean DVH at 30Gy and *i*= the PC number, for example principal component 1 (PC1) and the coefficient for an individual patient related to PC1.

To evaluate the dosimetric characteristics of each PC for each OAR further, the PCs were plotted against the dose with the aim of establishing the relevant dose ranges. In addition scatterplots of the dominant OAR PCs over the alternative summary dosimetric variables, such as Dmean, were plotted to evaluate the related DVH properties of the PCs.

Table 8-1: Clinical data collected

Category	Information
Tumour	Type, stage, pathology, grade
Patient	Age, smoking history, alcohol use, ethnicity, BMI co-morbidities (e.g. diabetes, inflammatory bowel disease), previous abdominal surgery history
Treatment	Total dose, number of fractions, dose per fraction, treatment technique, use of brachytherapy, use of chemotherapy, use of surgery, concurrent medications (e.g. statins, ACEi)

Descriptive statistics and linear regression analyses were performed using Stata/SE 13.1. PRO and clinical data were summarised using descriptive statistics for each disease site. Three backward stepwise regression models were used to identify predictors of PRO scores as sample size calculations were estimated based on a maximum of five co-variates within the model. In model 1, associations between PRO scores and clinical data (patient and treatment characteristics) were assessed using a significance level of 10% ($p<0.1$) to determine potentially significant covariates. In model 2, dosimetric predictors were modelled (PCs were included in the 'PCA model'; Dmax, Dmean and D50 included in the 'Summary dosimetric parameters model' and cumulative volume initially in 10Gy increments into the 'Cumulative volume model'), again using $p<0.1$ to determine significance. The PCA analysis was the principal dosimetric model evaluated within this project. The additional dosimetric models were evaluated to explore and compare outcomes of the different models. In model 3, all significant dosimetric and clinical variables from models 1 and 2 were entered into a final model, retaining those where $p<0.05$. The accuracy of the final linear model was validated using the bootstrapping method based on the lmg metric(322) as implemented in R via the 'relaimpo' package(323). The bootstrapping method validation was carried out by Damianos Christophides.

8.3 Results

8.3.1 Patient characteristics, questionnaire completion method and oncological treatment

During the recruitment period, 481 patients were approached and asked if they wanted to participate in the study. Of these, 315 (65%) consented, and 85 (18%) declined. A further 76 patients (16%) did not take part in the study for the following reasons: 66

patients (14%) were not seen in clinic to follow up on the invitation to take part in the study and 10 (2%) patients left the trial before either providing written consent (but had completed the questionnaire online) or after consenting but declining to complete the questionnaire. At the point of analysis it transpired that 5 patients (1%) were ineligible for further analysis as they only received adjuvant brachytherapy rather than EBRT for endometrial cancer. Table 8.2 shows a summary of the demographic characteristics of the sample. Due to small numbers of patients not of white British ethnicity, ethnicity was not incorporated into the regression analysis.

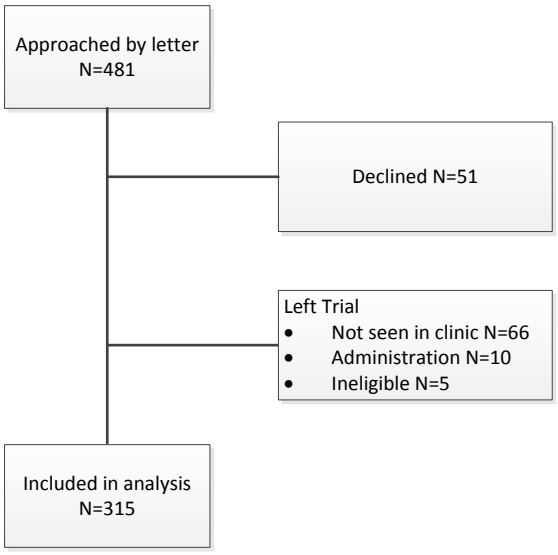


Figure 8-1: CONSORT diagram of recruitment

Table 8-2: Patient demographics

Ethnicity	Number of patients	Percent
White British	266	84.4%
Not stated	32	10.2%
Asian/White Asian	5	1.6%
Black African/Black Caribbean White	3	1.0%
Other	9	2.9%
Total	315	100.0%
Marital status	**Number of patients**	**Percent**
Married/ Civil Partnership	180	57.1%
Cohabiting	44	14.0%
Separated/Divorced	35	11.1%
Widowed	23	7.3%
Single	31	9.8%
Not stated	2	0.6%
Total	315	100.0%
Employment status	**Number of patients**	**Percent**
Working full time (30+ hours/week)	73	23.2%
Working part time (<30 hours/week)	46	14.6%
Unable to work (disability/illness)	34	10.8%
Retired	144	45.7%
Other	16	5.1%
Not stated	2	0.6%
Total	315	100.0%
Continued education after school	**Number of patients**	**Percent**
No	151	47.9%
Yes	163	51.7%
Not stated	1	0.3%
Total	315	100.0%
Degree or professional qualification	**Number of patients**	**Percent**
No	218	69.2%
Yes	96	30.5%
Not stated	1	0.3%
Total	315	100.0%

Of the 315 eligible patients who completed a questionnaire 95 patients had a diagnosis of anal cancer (30%; males n=27, female n=68); 74 had a rectal cancer diagnosis (24%; males n=48, females n=26); 49 patients had a diagnosis of endometrial cancer (16%); 97 had a cervical cancer diagnosis (31%). Patients mean age was 60.5 years (SD13.5). For full oncological and treatment characteristics see table 8.3 and 8.4. 5.8% of gynaecological cancer patients received VMAT. Table 8.5 summarises comorbidities, smoking status, alcohol use and BMI and table 8.6 summarises medication use. The median duration of follow up from treatment was 2 years (IQR: 1.4-3.5; mean 2.45; SD1.21). Factors with a prevalence of less than 5% were not included in the regression analysis.

Table 8-3: Gastrointestinal cancer characteristics and treatment

ANAL CANCER			RECTAL CANCER		
Histology	**Number of patients**	**Percent**	**Histology**	**Number of patients**	**Percent**
Squamous cell carcinoma	84	89.4%	Adenocarcinoma	70	94.6%
Adenocarcinoma	4	4.3%	Carcinoma	2	2.7%
Basaloid squamous cell carcinoma	2	2.1%	Basaloid squamous cell carcinoma	2	2.7%
Other	4	4.4%	Total	74	100.0%
Total	94	100.0%			
Recurrence	**Number of patients**	**Percent**	**Recurrence**	**Number of patients**	**Percent**
No	88	93.6%	No	54	73.0%
Yes	6	6.4%	Yes	20	27.0%
Total	94	100.0%	Total	74	100.0%
T stage	**Number of patients**	**Percent**	**T stage**	**Number of patients**	**Percent**
1	15	16.0%	1	2	2.7%
2	39	41.5%	2	18	24.3%
3	19	20.2%	3	39	52.7%
4	15	16.0%	4	9	12.2%
X	4	4.3%	X	2	2.7%
Unknown	2	2.2%	Unknown	4	5.4%
Total	94	100.0%	Total	74	100.0%
N stage	**Number of patients**	**Percent**	**N stage**	**Number of patients**	**Percent**
0	51	54.3%	0	22	29.7%
1	13	13.8%	1	31	41.9%
2	13	13.8%	2	12	16.2%
3	4	4.3%	X	5	6.8%
X	11	11.7%	Unknown	4	5.4%
Unknown	2	2.1%	Total	74	100.0%
Total	94	100.0%			
M stage	**Number of patients**	**Percent**	**M stage**	**Number of patients**	**Percent**
0	84	89.4%	0	47	63.5%
1	3	3.2%	1	11	14.9%
X	7	7.4%	X	12	16.2%
Total	94	100.0%	Unknown	4	5.4%
			Total	74	100.0%
Histology grade	**Number of patients**	**Percent**	**Histology grade**	**Number of patients**	**Percent**
Low / Well Differentiated	11	11.7%	Low / Well Differentiated	2	2.7%
Medium/ Moderately Differentiated	19	20.2%	Medium/ Moderately Differentiated	41	55.4%
High/ Poor Differentiated	14	14.9%	High/ Poor Differentiated	4	5.4%
Unknown	50	53.2%	Unknown	27	36.5%
Total	94	100.0%	Total	74	100.0%

Concurrent chemotherapy	**Number of patients**	**Percent**	**Concurrent chemotherapy**	**Number of patients**	**Percent**
No	6	6.4%	No	42	56.8%

ANAL CANCER			RECTAL CANCER		
Yes	88	93.6%	Yes	32	43.2%
Total	94	100.0%	Total	74	100.0%
Surgery	**Number of patients**	**Percent**	**Surgery**	**Number of patients**	**Percent**
No	86	91.5%	No	20	27.0%
Yes	8	8.5%	Yes	54	73.0%
Total	94	100.0%	Total	74	100.0%
Type of surgery	**Number of patients**	**Percent**	**Type of surgery**	**Number of patients**	**Percent**
AP resection	5	5.3%	Anterior resection	22	29.7%
Defunctioning stoma	3	3.2%	AP resection	18	24.3%
N/A	86	91.5%	Other rectal surgery (including Hartmann's procedure)	4	5.4%
Total	94	100.0%	Defunctioning stoma	2	2.7%
			TEMS	4	5.4%
			Pelvic exteneration	1	1.4%
			Liver surgery	1	1.4%
			Other	2	2.7%
			N/A	20	27.0%
			Total	74	100.0%

Key: AP – abdominal perineal

Table 8-4: Gynaecological cancer characteristics and treatment

CERVICAL CANCER			ENDOMETRIAL CANCER		
Histology	**Number of patients**	**Percent**	**Histology**	**Number of patients**	**Percent**
Squamous cell carcinoma	71	73.2%	Endometrioid adenocarcinoma	24	50.0%
Adenocarcinoma	10	10.3%	Serous cystadenocarcinoma	11	22.9%
Adenosquamous carcinoma	6	6.2%	Mixed cell adenocarcinoma	7	14.6%
Carcinoma	3	3.1%	Clear cell adenocarcinoma	2	4.2%
Small cell carcinoma	3	3.1%	Carcinosarcoma	2	4.2%
Other	3	3.1%	Other	2	4.2%
Unknown	1	1.0%	Total	48	100.0%
Total	97	100.0%			
Recurrence	**Number of patients**	**Percent**	**Recurrence**	**Number of patients**	**Percent**
No	85	87.6%	No	39	81.3%
Yes	12	12.4%	Yes	9	18.8%
Total	97	100.0%	Total	48	100.0%
FIGO Stage of Primary diagnosis	**Number of patients**	**Percent**	**FIGO Stage of Primary diagnosis**	**Number of patients**	**Percent**
1a2	1	1.0%	1a	2	4.2%
1b	2	2.1%	1b	5	10.4%
1b1	9	9.3%	2	6	12.5%
1b2	14	14.4%	2a	2	4.2%
2a	1	1.0%	2b	1	2.1%
2b	59	60.8%	3	1	2.1%
3a	2	2.1%	3a	13	27.1%
3b	3	3.1%	3b	1	2.1%
4a	4	4.1%	3c1	4	8.3%
4b	1	1.0%	3c	6	12.5%
Unknown	1	1.0%	3c2	3	6.3%
Total	97	100.0%	4b	2	4.2%
			Unknown	2	4.2%
			Total	48	100.0%
Histology grade	**Number of patients**	**Percent**	**Histology grade**	**Number of patients**	**Percent**
Low / Well Differentiated	8	8.2%	Low / Well Differentiated	9	18.8%
Medium/ Moderately Differentiated	46	47.4%	Medium/ Moderately Differentiated	9	18.8%
High/ Poor Differentiated	35	36.1%	High/ Poor Differentiated	28	58.3%
Unknown	8	8.2%	Unknown	2	4.2%
Total	97	100.0%	Total	48	100.0%
Concurrent chemotherapy	**Number of patients**	**Percent**	**Concurrent chemotherapy**	**Number of patients**	**Percent**
No	11	11.3%	No	48	100.0%
Yes	86	88.7%	Total	48	100.0%
Total	97	100.0%			
Surgery	**Number of patients**	**Percent**	**Surgery**	**Number of patients**	**Percent**
No	86	88.7%	No	2	4.2%
Yes	11	11.3%	Yes	46	95.8%
Total	97	100.0%	Total	48	100.0%

CERVICAL CANCER			ENDOMETRIAL CANCER		
Type of surgery	**Number of patients**	**Percent**	**Type of surgery**	**Number of patients**	**Percent**
TAH, BSO +	4	4.1%	TAH, BSO +	41	85.4%
Vaginal hysterectomy	1	1.0%	Vaginal hysterectomy	4	8.3%
Wertheim's hysterectomy	5	5.2%	Other	1	2.1%
Pelvic exteneration	1	1.0%	Unknown	2	4.2%
N/A	86	88.7%	Total	48	100.0%
Total	97	100.0%			
Brachytherapy	**Number of patients**	**Percent**	**Brachytherapy**	**Number of patients**	**Percent**
No	22	22.7%	No	39	81.3%
Yes	75	77.3%	Yes	9	18.8%
Total	97	100.0%	Total	48	100.0%

Key: TAH- Total Abdominal Hysterectomy; BSO – Bilateral salpingo-oophrectomy.

Table 8-5: Comorbidities, smoking status, alcohol use and BMI

Current smoker	Number of patients	Percent
No	205	65.1%
Yes	48	15.2%
Unknown	62	19.7%
Total	315	100.0%
Alcohol use	**Number of patients**	**Percent**
Nil	50	15.9%
Occasional	120	38.1%
Moderate	43	13.7%
Heavy	21	6.7%
Unknown	81	25.7%
Total	315	100.0%
Body Mass Index (BMI)	**Number of patients**	**Percent**
BMI<20	11	3.5%
BMI 20-24.9	85	27.0%
BMI 25-29.9	77	24.4%
BMI>30	83	26.3%
Unknown	59	18.7%
Total	315	100.0%
Musculoskeletal conditions	**Number of patients**	**Percent**
No	221	70.2%
Yes	93	29.5%
Not stated	1	0.3%
Total	315	100.0%
Diabetes diagnosis	**Number of patients**	**Percent**
No	287	91.1%
Yes	27	8.6%
Not stated	1	0.3%
Total	315	100.0%
Ischaemic disease diagnosis (cardiac and non-cardiac)	**Number of patients**	**Percent**
No	289	91.7%
Yes	25	7.9%
Not stated	1	0.3%
Total	315	100.0%
Inflammatory bowel disease	**Number of patients**	**Percent**
No	310	98.4%
Yes	4	1.3%
Not stated	1	0.3%
Total	315	100.0%
Previous abdominal surgery	**Number of patients**	**Percent**
No	178	56.5%
Yes	136	43.2%
Not stated	1	0.3%
Total	315	100.0%

Table 8-6: Medication use

On an anticoagulant	Number of patients	Percent
No	273	86.7%
Yes	40	12.7%
Not stated	2	0.6%
Total	315	100.0%
Statins	**Number of patients**	**Percent**
No	259	82.2%
Yes	54	17.1%
Not stated	2	0.6%
Total	315	100.0%
Angiotensin Converting Enzyme inhibitors	**Number of patients**	**Percent**
No	275	87.3%
Yes	38	12.1%
Not stated	2	0.6%
Total	315	100.0%
Proton pump inhibitors	**Number of patients**	**Percent**
No	252	80.0%
Yes	61	19.4%
Not stated	2	0.6%
Total	315	100.0%
Hormone Replacement Therapy	**Number of patients**	**Percent**
No	287	91.1%
Yes	22	7.0%
Not stated	6	1.9%
Total	315	100.0%
Non-Steroidal Anti-inflammatory Drugs	**Number of patients**	**Percent**
No	294	93.3%
Yes	15	4.8%
Not stated	6	1.9%
Total	315	100.0%
Antidepressants	**Number of patients**	**Percent**
No	270	85.7%
Yes	39	12.4%
Not stated	6	1.9%
Total	315	100.0%

Overall 64% of patients completed the questionnaire online and 36% on paper. There were no differences in gender between choice of completion method: Online completion: Males 65% (n=50) vs Females 63% (n=153) and Paper completion: Males 35% (n=27) vs Females 37% (n=89). However, there were differences in the method of questionnaire completion by age group with a trend towards more patients completing the questionnaire on paper with increasing age (see figure 8.1). Out of the 328 patients who completed the questionnaire 107 patients completed the survey online prior to their clinic visit (33%); 65 (20%) patients completed the survey online during their hospital visit, either using a computer (n=45:14%) or a touch-screen kiosk (n=20; 6%) and 22 (7%) completed online after their clinic visit. 71 patients completed the survey on paper during their hospital visit (22%); 41 contacted the research team to request

completion on paper prior to their clinic visit (13%) and 22 (7%) completed their survey on paper following their visit and posted the results back.

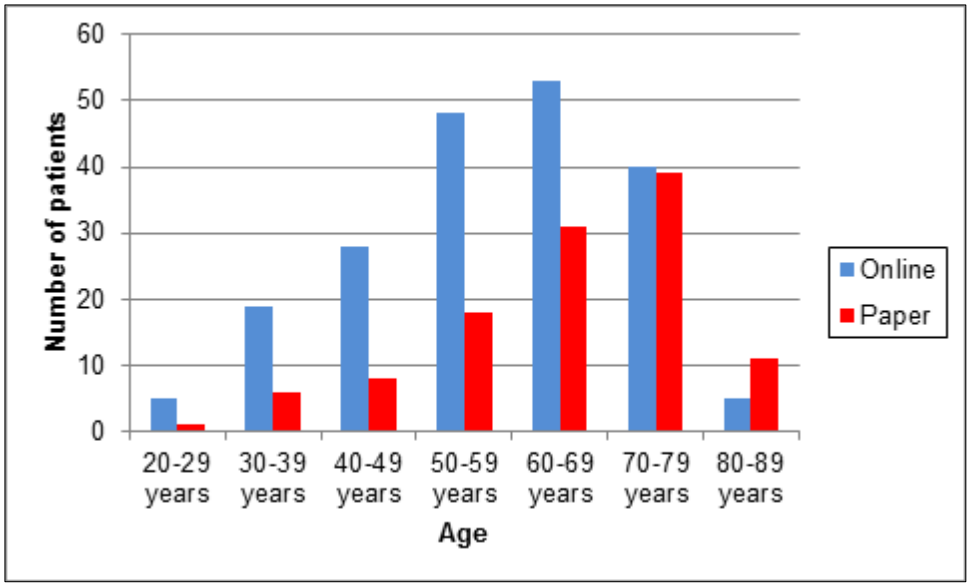


Figure 8-2: Method of questionnaire completion by age

8.3.2 EORTC QLQ-C30 summary

Overall patients within the sample had low symptom and high functioning scores within the EORTC-QLQ core questionnaire (C30). Patients overall QOL scores had a mean score of 69 (SD22.3; median 75). The only items to reach a mean/median score equivalent to a patient response of 'a little' (score 33.3) were fatigue and insomnia (Table 8.7).

Table 8-7: EORTC QLQ-C30 summary

EORTC-QLQ C30 item	Mean score (0-100)	SD	Median score (0-100)	Lower quartile (0-100)	Upper quartile (0-100)
Overall QOL*	69	22.3	75	58.3	83.3
Physical functioning*	80.1	21.4	86.7	66.7	100
Role functioning*	77.7	28.4	83.3	66.7	100
Emotional functioning*	76.3	22.1	75	66.7	91.7
Cognitive functioning*	82	21.4	83.3	66.7	100
Social functioning*	75.9	28.3	83.3	66.7	100
Fatigue	**32.3**	**26.5**	**33.3**	11.1	44.4
Nausea & vomiting	6.6	14.1	0	0	16.7
Pain	23.7	29.5	16.7	0	33.3
Dyspnoea	19.4	27.6	0	0	33.3
Insomnia	**33.2**	**32.2**	**33.3**	0	66.7
Appetite loss	12.9	23.1	0	0	33.3
Constipation	14.6	24.5	0	0	33.3
Diarrhoea	15.4	25.1	0	0	33.3
Financial issues	13.5	25.1	0	0	33.3

*Functioning items (Higher score represents better functioning). Scores with no asterisk represent Symptom items (Higher scores represent worse symptoms).

Many of the items in the EORTC-QLQ C30 are not readily associated with particular pathophysiological process affecting OAR. Therefore, the remainder of the results section will only include the diarrhoea item from EORTC-QLQ C30, as used in a previous study(308), and will instead focus on the key areas where patients treated with pelvic radiotherapy experience toxicity that may be related to end organ damage, namely urinary, bowel, sexual function and low back pain. Each section will provide a summary of the overall symptoms experienced by the participants followed by a detailed evaluation of the PCA of each relevant organ at risk and then the results of the regression analyses combining clinical and dosimetric factors.

8.3.3 Urinary symptoms

A summary of the EORTC-QLQ scores for urinary symptoms is presented in table 8.8. Urinary frequency was the symptom with the highest symptom score (Mean 43.4; SD29.4) followed by urinary urgency (Mean 30; SD32.4). Overall summary urinary symptom score showed similarities across all cancer sites with mean scores ranging between 22.57 and 26.5. When the urinary symptom scale for male and female patients was evaluated separately for the GI patients no differences were found (Males Mean 24.3; SD15.36 vs Females Mean 27.0; SD14.8), however the scores for urinary urgency varied with higher mean score for women (Females Mean 33.5; SD33.1 vs Males Mean 18.9; SD27.6).

Table 8-8: Summary of urinary scores

Urinary symptoms (all cancer sites)	N	Mean	S.D.	Minimum	Lower quartile	Median	Upper quartile	Maximum
Urinary incontinence	309	19.4	26.4	0	0	0	33.3	100
Urinary frequency	310	**43.4**	**29.4**	0	33.3	33.3	66.7	100
Dysuria	310	7.3	18.5	0	0	0	0	100
Urinary urgency	310	**30**	**32.4**	0	0	33.3	33.3	100
Summary urinary scores by diagnosis								
Cervical urinary summary score	96	22.6	18.7	0.0	8.3	16.7	33.3	83.3
Endometrial urinary summary score	47	26.5	22.0	0.0	8.3	25.0	41.7	91.7
Anal urinary summary score	94	26.2	15.1	0.0	16.7	25.0	33.3	66.7
Rectal urinary summary score	74	25.2	15.1	0.0	16.7	25.0	33.3	66.7
GI urinary summary score	168	25.8	15.1	0.0	16.7	25.0	33.3	66.7

8.3.3.1 Principal component analysis of Bladder OAR

For some symptoms evaluated within this study potentially multiple OARs may be related to the pathophysiological changes resulting in patient symptoms. For the urinary symptoms however, this study evaluated a single OAR, the bladder. This section will describe the process of the PCA in detail, demonstrating the relationship between the original DVH data set and the PCA outcomes. Full details of all OAR contouring are found in Chapter 7. A summary of mean and maximum doses for all OARs is shown in table 8.9.

The initial PCA resulted in 6 unrotated PCs and co-efficients. Figure 8.4b shows the original cumulative volumes of bladder treated for each individual patient at 1Gy, plotted in blue. The calculated DVH, using the calculation:

$$Original\ DVH_{1Gy} = Mean\ DVH_{1Gy} + \left(PC_{1Gy,1} \times\ Coefficient_1\right)$$

for each individual patient was then calculated and plotted using the unrotated PCs. The same calculation was carried out for each of the remaining PCs from PC2-PC6. The process was repeated for the volumes of bladder receiving doses in excess of 10Gy, 20Gy, 30Gy, 40Gy, 50Gy, 60Gy. Therefore, for each patient the volumes receiving doses in excess of 1Gy, 10Gy, 20Gy, 30Gy, 40Gy, 50Gy, 60Gy were established (original DVH), ranked in descending order and plotted against the individuals calculated DVH using the PCA PCs and co-efficients. This process was repeated for the PCs and coefficients resulting from the varimax rotation. The graphs (figure 8.3 and 8.4) graphically demonstrate the transformation of the original DVH into the grouped PCs and how the PC reduces the variability of the data. It is possible to see in areas where the dose is homogenous for all individuals, such as bladder volumes receiving doses in excess of 1Gy, that the calculated DVH data points for all PCs cover the same percentage volume (essentially 100%) as the original DVH. In addition, there is little difference between the calculated DVHs with the unrotated (figure 8.4b) and varimax rotated (figure 8.3a) PCs at 1Gy. However, in areas where more heterogenous dose distributions are seen, for example for volumes receiving in excess of 40Gy, the calculated DVHs from the varimax rotated components more closely resemble the original cumulative volume data points. This is seen graphically by the calculated DVHs for the unrotated components falling in horizontal lines describing a particular volume of bladder treated for each PC. In contrast, the calculated DVH data points for the varimax rotated PCs at 40Gy more closely follow the sigmoid shape of the original DVH data. The calculated PCs for the unrotated PCs describe the cumulative DVH at particular thresholds but appear to less closely resemble the original data. This may demonstrate the benefit of using the varimax

rotation as a means of improving the coverage of the variability in the dataset, particularly at dosimetric points, such as V30, V40 and V50 where the distribution of dose is more heterogenous.

However, to further evaluate this relationship and confirm the accuracy of the PCA the ratio between the original DVH compared to the calculated DVH using the varimax components was evaluated for each 10Gy increment (1, 10, 20, 30, 40, 50, 60, 70Gy). The resulting mean ratio overall was 1:0.96 (Range of ratios: minimum 0.68 – maximum 1.01 excluding 60-70Gy calculations; including 60/70Gy: 0.07 to 4.03) suggesting very good representation and coverage of the original data using the PCA components. In comparison, the coverage using the unrotated components was not as succinct with a mean ratio of 1:1.27 (minimum -1.62 – maximum 1.60 excluding 60-70Gy calculations; including 60/70Gy: -1.83 to 14.0). The average ratio of the calculated DVHs compared to the mean DVHs for both the unrotated and varimax components for bladder volumes treated to 1, 10, 20, 30, 40, 50, 60, 70Gy was 1:1 for both techniques. Using this method it was possible to establish that the varimax rotated data more closely resembled the original data set and this may arguably be beneficial to interpreting the data and future modelling. However, the use of PCA as a technique in dosimetric modelling is not well established and remains open to interpretation.

The first 6 principal components accounted for 96% of the DVH variability. The correlation of PCs to the DVH indices are illustrated in figure 8.5. For the varimax components: PC1 describes the correlated variability of the DVH data around the mean DVH in the range 5-50Gy, this is also demonstrated in the scatterplots correlating PC1 and Dmean in figure 8.6. PC2 describes the high dose regions (40-65Gy); PC3 describes the intermediate dose regions (25-50Gy); PC4 correlates with the low dose regions (1-25Gy); PC5 describes the anticorrelated variability in the intermediate dose region with increased relative volumes in the higher dose region (42.5-53Gy) and simultaneously decreased relative volumes in the intermediate dose region 32-42.5Gy. PC6 in comparison describes decreased relative volumes in low (10-20Gy) and high dose regions (42-52Gy) and increased relative volumes the intermediate dose region (32-43Gy)

Table 8-9: Summary of Mean and Maximum Doses (to 1cc) for all OARs

BLADDER	**N**	**Mean (Gy)**	**SD**	**Min (Gy)**	**Max (Gy)**
Anal Bladder Dmean	91	34.1	12.5	1.4	53.6
Rectal Bladder Dmean	72	26.2	7.2	10.6	41.8
Endometrial Bladder Dmean	46	39.3	5.9	26.5	57.7
Cervical Bladder Dmean	94	48.1	5.2	32.8	64.8
Anal Bladder Dmax	91	47.4	9.8	3.0	57.0
Rectal Bladder Dmax	72	43.2	6.7	21.0	70.0
Endometrial Bladder Dmax	46	47.5	5.1	44.0	63.0
Cervix Bladder Dmax	94	52.9	6.2	46.9	70.0
BOWELBAGL3	**N**	**Mean (Gy)**	**SD**	**Min (Gy)**	**Max (Gy)**
Anal BowelBagL3 Dmean	90	8.9	5.7	0.5	26.1
Rectal BowelBagL3 Dmean	72	8.7	4.0	2.0	19.3
Endometrial BowelBagL3 Dmean	47	20.5	5.2	9.4	33.9
Cervical BowelBagL3 Dmean	94	28.6	5.0	11.9	41.1
Anal BowelBagL3 Dmax	90	41.1	16.3	2.0	57.9
Rectal BowelBagL3 Dmax	72	43.0	6.6	21.0	70.0
Endometrial BowelBagL3 Dmax	47	48.0	5.0	45.0	62.0
Cervix BowelBagL3 Dmax	94	53.5	6.3	47.0	70.0

ANORECTUM	**N**	**Mean (Gy)**	**SD**	**Min (Gy)**	**Max (Gy)**
Endometrial AnoRectum Dmean	45	34.3	9.3	0.7	59.7
Cervical AnoRectum Dmean	93	45.7	8.1	18.7	66.2
Endometrial AnoRectum Dmax	45	46.4	7.4	10.9	63.0
Cervix AnoRectum Dmax	93	52.4	6.0	46.0	70.0
INFERIOR RECTUM	**N**	**Mean (Gy)**	**SD**	**Min (Gy)**	**Max (Gy)**
Endometrial RectumInferior Dmean	45	21.0	15.3	0.5	59.0
Cervical RectumInferior Dmean	94	33.1	16.9	1.7	65.6
Endometrial RectumInferior Dmax	45	33.6	17.5	1.0	61.0
Cervix RectumInferior Dmax	94	45.6	13.7	3.0	66.0
MID RECTUM	**N**	**Mean (Gy)**	**SD**	**Min (Gy)**	**Max (Gy)**
Endometrial RectumMid Dmean	46	38.5	11.3	0.5	61.1
Cervical RectumMid Dmean	94	49.1	8.5	5.4	67.6
Endometrial RectumMid Dmax	46	45.6	8.5	1.0	62.0
Cervix RectumMid Dmax	94	51.6	7.0	17.0	69.0
SUPERIOR RECTUM	**N**	**Mean (Gy)**	**SD**	**Min (Gy)**	**Max (Gy)**
Endometrial RectumSuperior Dmean	46	37.0	11.3	2.2	59.0
Cervical RectumSuperior Dmean	94	49.2	6.3	28.7	66.6
Endometrial RectumSuperior Dmax	46	45.0	8.5	12.0	63.0
Cervix RectumSuperior Dmax	94	52.4	5.9	45.9	70.0

VAGINA	**N**	**Mean (Gy)**	**SD**	**Min (Gy)**	**Max (Gy)**
Anal Vagina Dmean	66	46.7	8.5	19.9	55.4
Rectal Vagina Dmean	25	38.4	7.0	20.1	50.8
Endometrial Vagina Dmean	45	38.8	10.3	0.5	59.7
Cervical Vagina Dmean	81	45.3	6.7	16.8	64.9
Anal Vagina Dmax	66	49.4	8.0	23.0	57.0
Rectal Vagina Dmax	25	42.3	5.2	21.0	52.0
Endometrial Vagina Dmax	45	45.6	8.6	1.0	63.0
Cervix Vagina Dmax	81	49.5	3.7	45.0	66.0
FEMALE GENITALIA	**N**	**Mean (Gy)**	**SD**	**Min (Gy)**	**Max (Gy)**
Anal Female_genitalia Dmean	66	44.9	9.3	17.8	54.2
Rectal Female_genitalia Dmean	26	19.7	14.2	1.5	46.9
Endometrial Female_genitalia Dmean	47	12.6	13.0	0.5	40.6
Cervical Female_genitalia Dmean	93	23.3	18.8	1.6	64.6
Anal Female_genitalia Dmax	66	50.1	8.4	23.0	58.0
Rectal Female_genitalia Dmax	26	32.3	14.7	2.0	52.0
Endometrial Female_genitalia Dmax	47	23.5	18.7	1.0	58.0
Cervix Female_genitalia Dmax	93	35.3	18.9	3.0	66.0

SACRUM	N	Mean (Gy)	SD	Min (Gy)	Max (Gy)	PENILE BULB	N	Mean (Gy)	SD	Min (Gy)	Max (Gy)	MALE GENITALIA	N	Mean (Gy)	SD	Min (Gy)	Max (Gy)
Endometrial Sacrum Dmean	47	33.2	6.4	6.5	42.7	Anal PenileBulb Dmean	24	46.1	8.6	21.5	52.6	Anal Male_genitalia Dmean	24	24.0	12.2	3.0	46.8
Cervical Sacrum Dmean	94	42.7	4.3	32.3	55.9	Rectal PenileBulb Dmean	44	25.3	18.8	1.5	52.8	Rectal Male_genitalia Dmean	46	6.4	6.2	0.5	35.6
Endometrial Sacrum Dmax	47	45.8	4.0	38.9	61.0	Anal PenileBulb Dmax	24	47.8	8.8	22.0	54.0	Anal Male_genitalia Dmax	24	46.6	9.4	22.0	56.0
Cervix Sacrum Dmax	94	51.6	5.5	45.0	68.0	Rectal PenileBulb Dmax	44	27.9	19.6	2.0	64.0	Rectal Male_genitalia Dmax	46	29.1	15.0	1.0	54.0

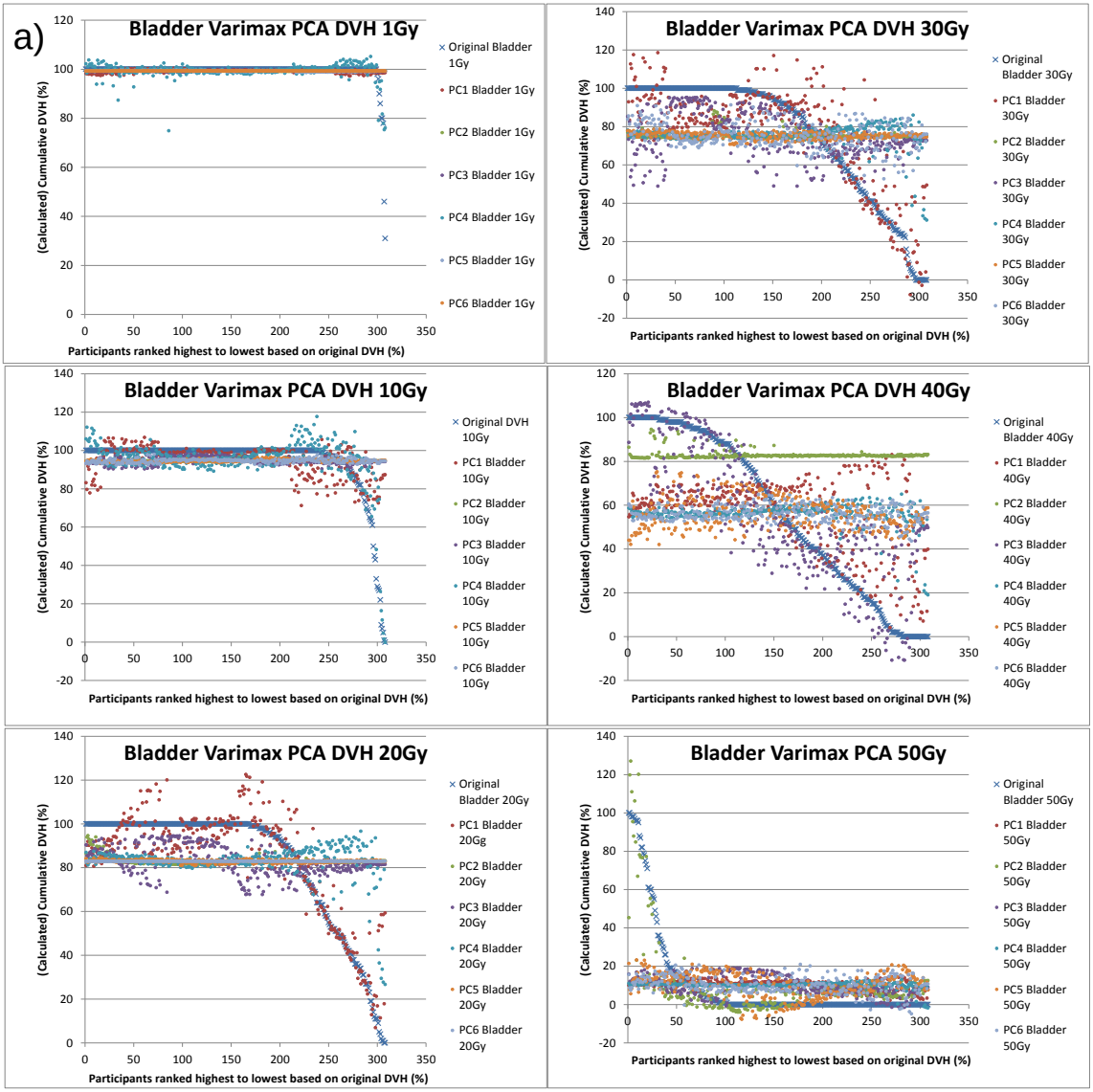


Figure 8-3:Bladder PCs vs original DVH: Varimax

a) Original and calculated DVH using PCs with a Varimax rotation with participants ranked in descending order based on their original DVH..

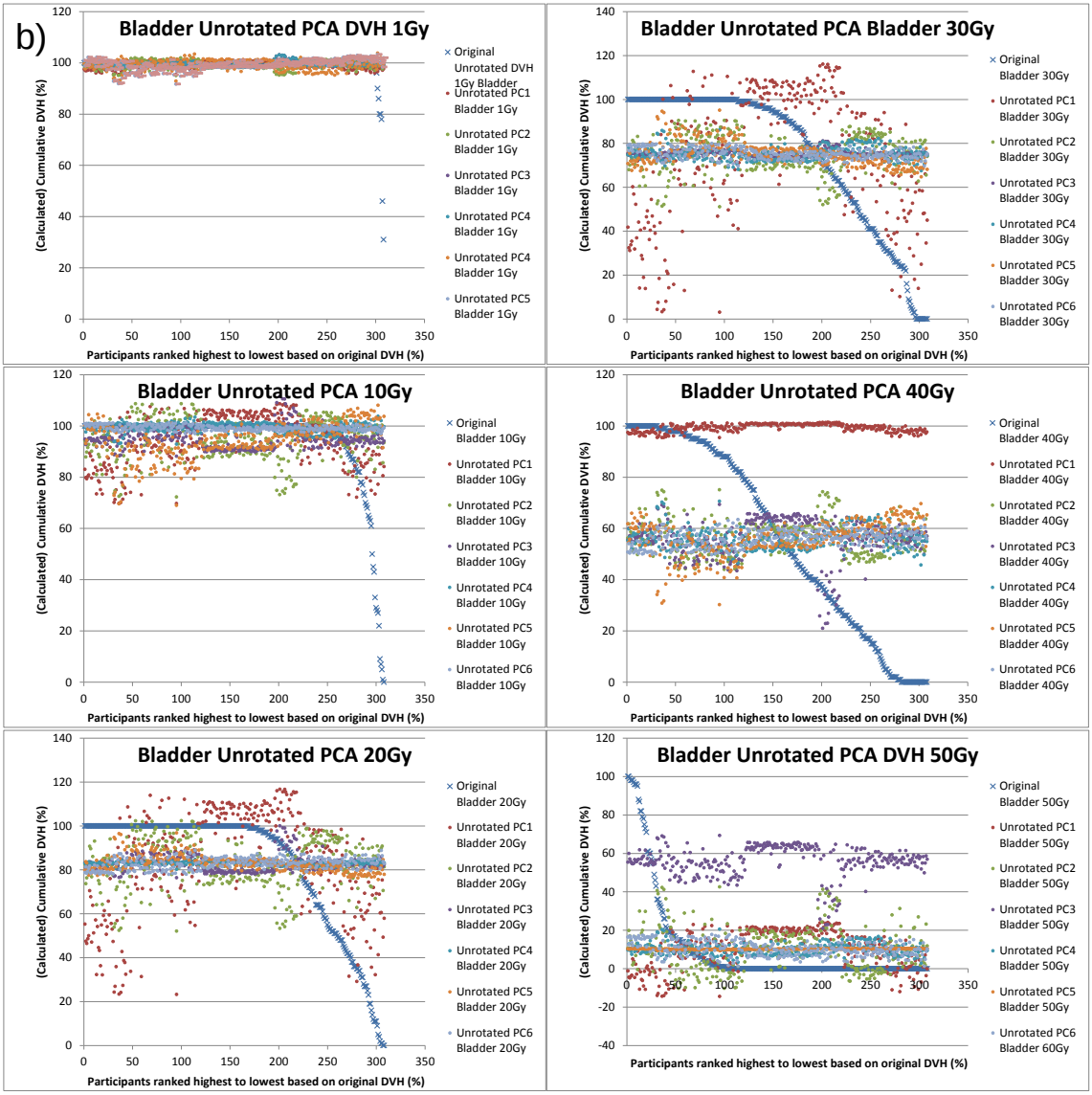


Figure 8-4: Bladder PCs vs original DVH: Unrotated

(b) Original and calculated DVH using PCs with no rotation with participants ranked in descending order based on their original DVH

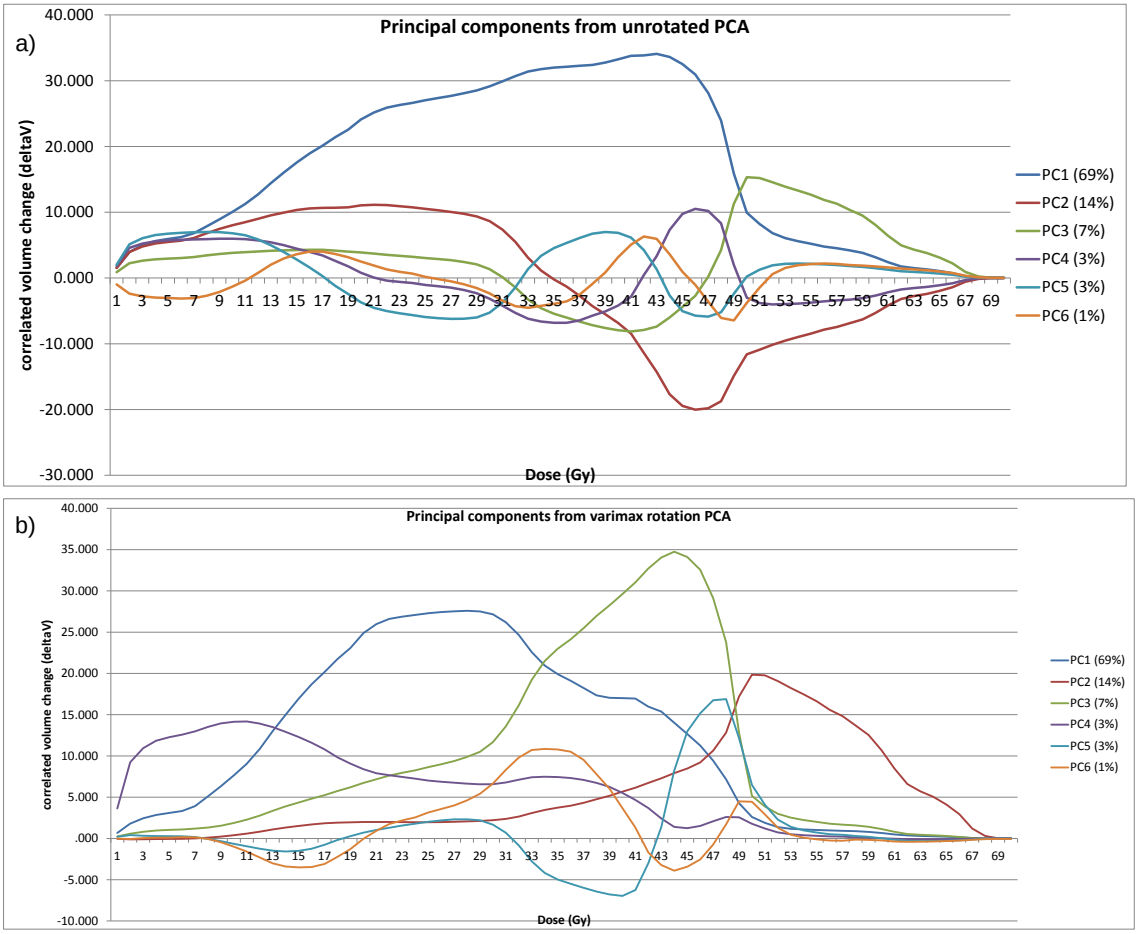


Figure 8-5: Bladder Principal components

resulting from a) Unrotated PCA and b) Varimax rotation. Percentage of data set variability described by each PC shown.

Whilst the relationship between the unrotated PCs and the original DVH summary dosimetric factors, such as Dmean may be clearer (Figure 8.5) the original DVH data is more closely aligned with the PCs from the varimax (orthogonal) rotation (Figure 8.4). Figure 8.6 shows the relationship with PC1, PC2 and PC3 and Dmean using the PCs from the varimax rotation (a) and the unrotated factors (b).

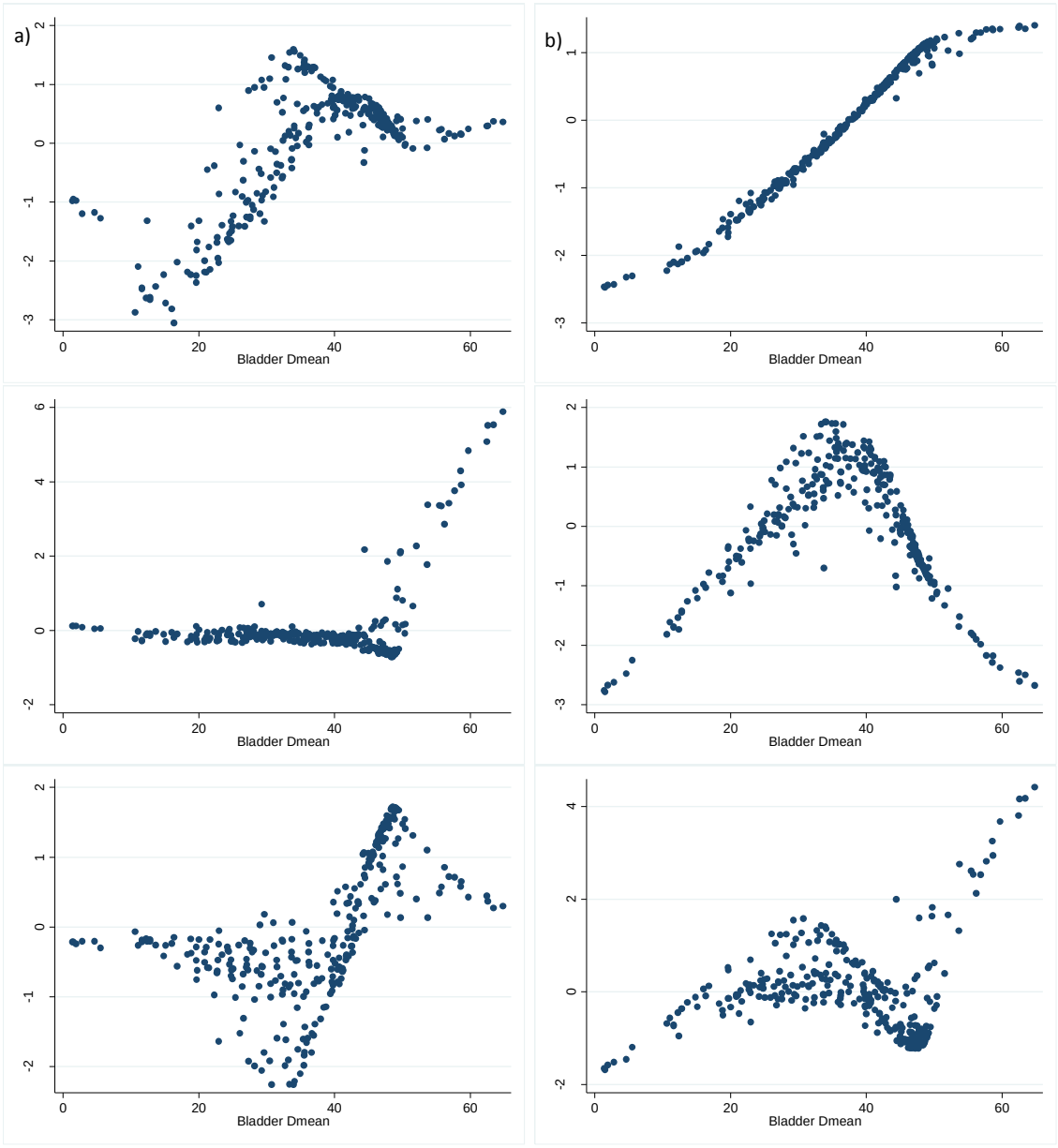


Figure 8-6: Scatterplots of the first three Bladder PCs

to show relationship to Dmean: a) with Varimax rotation and b) with unrotated PCs

8.3.3.2 Urinary symptom regression analyses

Baseline urinary symptoms were not available for the cross sectional analysis but are known to be important in predicting urinary symptom outcomes(131). However, the associations between clinically important comorbidities, treatment and patient characteristics and each bladder symptom were explored using a backwards stepwise linear regression model (Model 1). Potential explanatory factors considered were: gender, BMI, age, smoking status, diagnosis, presence of recurrent disease, dose per fraction, concurrent chemotherapy, surgery, brachytherapy, VMAT technique, time since start of EBRT, medication use (ACEi, statins and NSAIDs), and co-morbidities:

DM, ischaemic disease (cardiac and vascular) and pre-existing renal problems(131). Factors with a prevalence of less than 5% were not included in the regression analysis.

In model 2, dosimetric factors were included into a backwards stepwise linear regression model. All 6 PCs from the PCA were included into PCA model and these findings were compared to summary dosimetric variables Dmean, Dmax and D50 in the Summary dosimetric parameter model and cumulative volume in 10Gy increments in the cumulative volume model initially which were further refined based on the analysis outcomes to smaller DVH increments. In model 3 (final model), all significant dosimetric and clinical variables from models 1 and 2 were entered into a final model, retaining those where p<0.05. A summary of the main findings are shown in table 8.10. The outcomes of each dosimetric model (with significant clinical factors) are presented in the summary table along with the final model to demonstrate the differential impact of the different dosimetric parameters on the model. The outcomes for each toxicity item are described in detail in the following sections.

Table 8-10: Summary of urinary symptom regression analysis

MODEL	PCA model	Summary dosimetric parameter model	Cumulative volume model	FINAL MODEL	FINAL MODEL	FINAL MODEL
VARIABLES	**Urinary Frequency**	**Urinary Frequency**	**Urinary Frequency**	**Urinary Frequency**	**Urinary Urgency**	**Urinary Incontinence**
Bladder PC2	3.920** (0.653 - 7.188)			3.920** (0.653 - 7.188)	-4.722** (-8.461 - -0.983)	
BMI					1.198*** (0.520 - 1.875)	0.736*** (0.210 - 1.262)
Female gender					15.72*** (6.179 - 25.25)	12.78*** (5.310 - 20.25)
Bladder PC6	-3.517** (-6.772 - -0.262)			-3.517** (-6.772 - -0.262)		
Bladder Dmax		0.499** (0.0993 - 0.899)				
Bladder V43			0.0620 (-0.184 - 0.308)			
Bladder V45			-0.0605 (-0.443 - 0.322)			
Bladder V47			0.104 (-0.192 - 0.401)			
Surgery						-7.692** (-14.59 - -0.794)
Observations	300	298	300	300	245	252
R-squared	0.033	0.020	0.016	0.033	0.099	0.101

Regression coefficient presented at the top of each column with 95% confidence interval in parentheses
*** p<0.01, ** p<0.05, * p<0.1

8.3.3.2.1 Urinary frequency

Urinary frequency was not associated with any significant clinical factors in the multivariate linear regression model. However, urinary frequency was associated with a number of dosimetric factors – Bladder PC2 and PC6 in the PCA model and Dmax in the Summary dosimetric model. In the summary dosimetric model only Dmax was significant at the 5% level (95%CI 0.1 - 0.9, p= 0.015) and was no longer significant

when included in the final model. These factors consider similar dosimetric features. PC2 describes the high dose regions (40-65Gy) and Dmax considers maximum dose regions. Both factors are associated with an increase in urinary frequency scores: PC2: Coeff 3.9; 95%CI 0.7 - 7.2; p=0.02 and Dmax: Coeff 0.5; 95%CI 0.1-0.9 p=0.02. PC6 also describes the high dose regions with decreased relative volumes between 42-52Gy and is associated with a reduction in urinary frequency scores of 3.5 (PC6: Coeff -3.5; 95%CI -6.8 to -0.3; p=0.03). There was no association between dose per fractionation and urinary frequency.

When each cancer site was evaluated separately, PC6 remained significant only for the anal cancer patients (PC6: Coeff -4.3; 95%CI -8.3 to -0.3; p=0.04) and PC2 for the endometrial cancer patients (PC2: Coeff 15.7; 95%CI 1.5- 29.8; p=0.03). Dmax remained significant only for the rectal cancer patients: (Dmax: Coeff 1.0; 95%CI 0.2-1.8; p=0.013). These findings suggest that these dosimetric factors are describing the patient-to-patient variability within the treatment techniques used for the different cancer sites rather than describing a dosimetric factor that describes the variability in the whole data set. Thus the variability in toxicity can be explained by the differences between patients treated in the anal cancer group for PC6, for the endometrial patients for PC2 and for the rectal cancer patients for Dmax.

Table 8.10 also presents the arbitrary results achieved when including the single point cumulative DVHs within the regression analysis. V43 shows a relative increase in urinary frequency score of 0.062, V45 a decrease in score of -0.061 and V47 an increase in score 0.104. The single point cumulative DVHs followed similar arbitrary effects on patient scores when included in the regression analyses for all OARs within this project. Whilst in some cases initial individual volumetric indices may have been found to be significant, closer examination of the regions around the significant factor found similar arbitrary effects on the scores as seen in this example.

This table also demonstrates the greater contribution provided by the PCA to explain the differences in toxicity scores found in comparison to the summary dosimetric or the single point cumulative DVHs. Whilst the R^2 values are low within all of these models, the PCA model describes a greater proportion of the variance and the PCs have higher regression coefficients (relating to a greater change in toxicity scores) than the other dosimetric factors.

8.3.3.2.2 Urinary urgency

Female patients scored 15.7 points higher than males on the urinary urgency item (95%CI 6.2 - 25.3; p=0.001) and increases in BMI (kg/m2) increased urinary urgency scores by 1.2 (95%CI 0.5 -1.9; p=0.001). PC2 was associated with a 4.7 reduction in urinary urgency scores (95%CI -8.5 to -1.0; p=0.01) and is associated with the high dose regions around 40-65Gy. When each cancer site was evaluated separately, the dosimetric effect of PC2 remained significant only in the cervical cancer patient group: PC2: Coeff -4.6; 95%CI -8.5 to -0.7; p=0.02).

8.3.3.2.3 Urinary incontinence

No dosimetric factors were predictive of urinary incontinence. Increasing BMI (Coeff 0.7; 95%CI 0.2 – 1.3; p=0.006), women (Coeff 12.8; 95%CI 5.3-20.3; p=0.001) and patients who did not receive surgery (Coeff 7.6; 95%CI 14.6-0.8; p=0.03) were predictive of worse urinary incontinence scores (see table 8.10).

8.3.4 Bowel symptoms

A summary of bowel symptoms is presented in table 8.11. Bowel urgency was the symptom with the highest symptom score with a mean score of 41.2 (SD33.9), followed by symptoms of flatulence (Mean 37.3; SD32.5) and bowel frequency (Mean 30.2; SD25.0). Overall summary bowel symptom score showed similarities across all cancer sites with mean scores ranging between 20.8 and 32.8.

Table 8-11: Summary of bowel symptoms

Bowel symptoms: all cancer sites	N	Mean	S.D.	Minimum	Lower quartile	Median	Upper quartile	Maximum
Faecal Incontinence	308	22.2	28.0	0.0	0.0	0.0	33.3	100.0
Bowel urgency (not including patients with a stoma)	249	**41.2**	**33.9**	0.0	0.0	33.3	66.7	100.0
Diarrhoea	315	15.5	25.1	0.0	0.0	0.0	33.3	100.0
Constipation	315	14.6	24.5	0.0	0.0	0.0	33.3	100.0
Bowel symptoms: GI and Cervical patients								
PR Bleeding	263	4.8	14.3	0.0	0.0	0.0	0.0	100.0
Bowel symptoms: GI and Endometrial patients								
Flatulence	210	**37.3**	**32.5**	0.0	0.0	33.3	66.7	100.0
Bowel symptoms Gynaecological patients only								
Abdominal cramps	142	23.0	29.2	0.0	0.0	0.0	33.3	100.0
Bowel symptoms: GI patients only								
Bowel frequency	106	**30.2**	**25.0**	0.0	16.7	25.0	50.0	100.0
Stoma frequency	59	18.9	23.9	0.0	0.0	16.7	33.3	100.0
Embarrassed about bowels	166	26.7	30.8	0.0	0.0	33.3	33.3	100.0
Summary bowel scores by diagnosis								
Cervical bowel summary score	97	22.4	18.7	0.0	6.7	20.0	33.3	73.3
Endometrial bowel summary score	46	20.8	18.6	0.0	6.7	20.0	33.3	73.3
Anal bowel summary score*	77	28.7	21.3	0.0	13.3	26.7	40.0	93.3
Rectal bowel summary score*	29	**31.5**	**24.3**	0.0	6.7	26.7	46.7	93.3
GI bowel summary score including bowel urgency item*	106	**32.8**	**22.4**	0.0	16.7	27.8	44.4	94.4
Stoma summary score*	60	26.5	22.1	0.0	13.3	20.0	33.3	100.0

* These grouped scores are not part of a validated scale but items are grouped as in other questionnaires as a summary score

8.3.4.1 Principal component analysis of Bowel OARs

The bowel symptoms reported by patients could relate to a number of normal tissues. In all patients the intestinal cavity (BowelBag) was contoured, stopping at L3 of the lumbar spine to create the parameter BowelBagL3. In the gynaecological patients the AnoRectum and rectum segmented into three parts were also contoured: inferior rectum (ischial tuberosities to 3cm superior), middle (next 3cm) and superior rectum (top of the middle rectum to sigmoid flexure). The rectum is part of the target organ, and therefore not an OAR, in the gastrointestinal (GI) patients. In contrast in the gynaecological cancer patients the rectum is an avoidance organ.

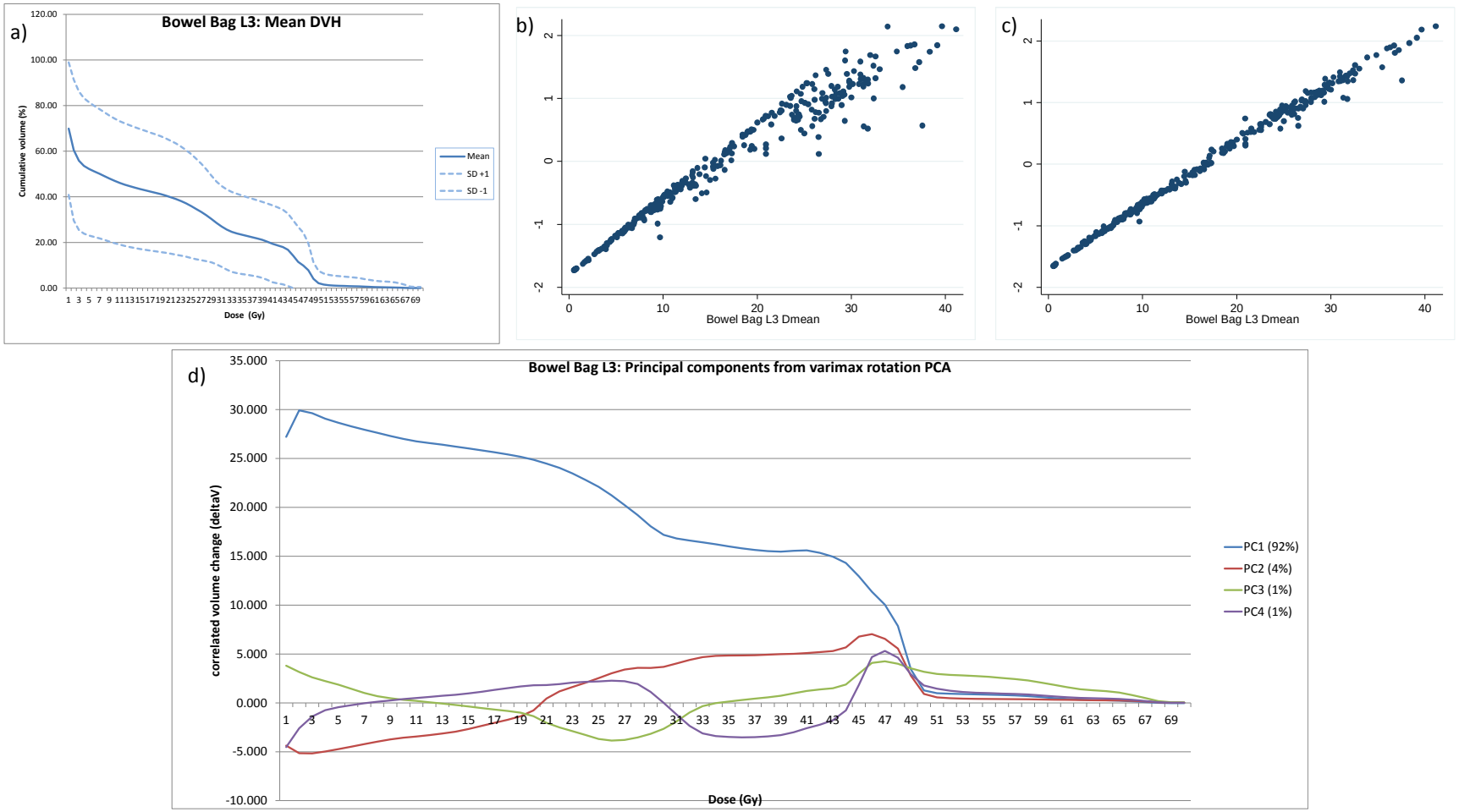
8.3.4.1.1 Bowel Bag L3 PCA

The first 4 principal components accounted for 98% of the DVH variability. The mean ratio of the original DVH compared to the calculated DVH at 30Gy using the varimax rotated components was 1:0.99. The correlation of PCs to the DVH indices are

illustrated in figure 8.7. PC1 describes the correlated variability of the DVH data set around the mean DVH in the range 1-50Gy, this is also demonstrated in the scatterplots correlating PC1 and Dmean in figure 8.7. PC2 describes the anticorrelated variability with decreased relative volumes in the low dose region 1-20Gy and simultaneously increased relative volumes in the intermediate to high dose region 20-50Gy. PC3 in comparison describes increased relative volumes in low (1-10Gy) and higher dose regions (32-70Gy) and decreased relative volumes the intermediate dose region (15-32Gy). PC4 describes decreased relative volumes in dose regions 1-5Gy and 30-45Gy and increased relative volumes in dose regions 5-30Gy and 45-50Gy.

Figure 8-7: Bowel Bag L3 DVH summary graphs:

(a) Mean cumulative DVH (b) PC1 with varimax rotation vs Dmean (c) PC1 with no rotation vs Dmean (d)Correlation of principal components to dose (EQD2)



8.3.4.1.2 AnoRectum PCA

The first 5 principal components accounted for 97% of the DVH variability. The mean ratio of the original AnoRectum DVH compared to the calculated DVH at 30Gy using the varimax rotated components was 1:1. The correlation of PCs to the DVH indices are illustrated in figure 8.8. PC1 and PC2 describe the correlated variability of the DVH data set around the mean DVH in the range 1-65Gy, with PC1 describing the lower dose regions (1-40Gy) and PC2 describing the intermediate dose region (20-50Gy). This is also demonstrated in the scatterplots correlating PC1 and PC2 vs Dmean in figure 8.8. PC3 describes high dose regions 45-65Gy as does PC4 (40-70Gy). PC5 describes the intermediate dose region between 40-50Gy.

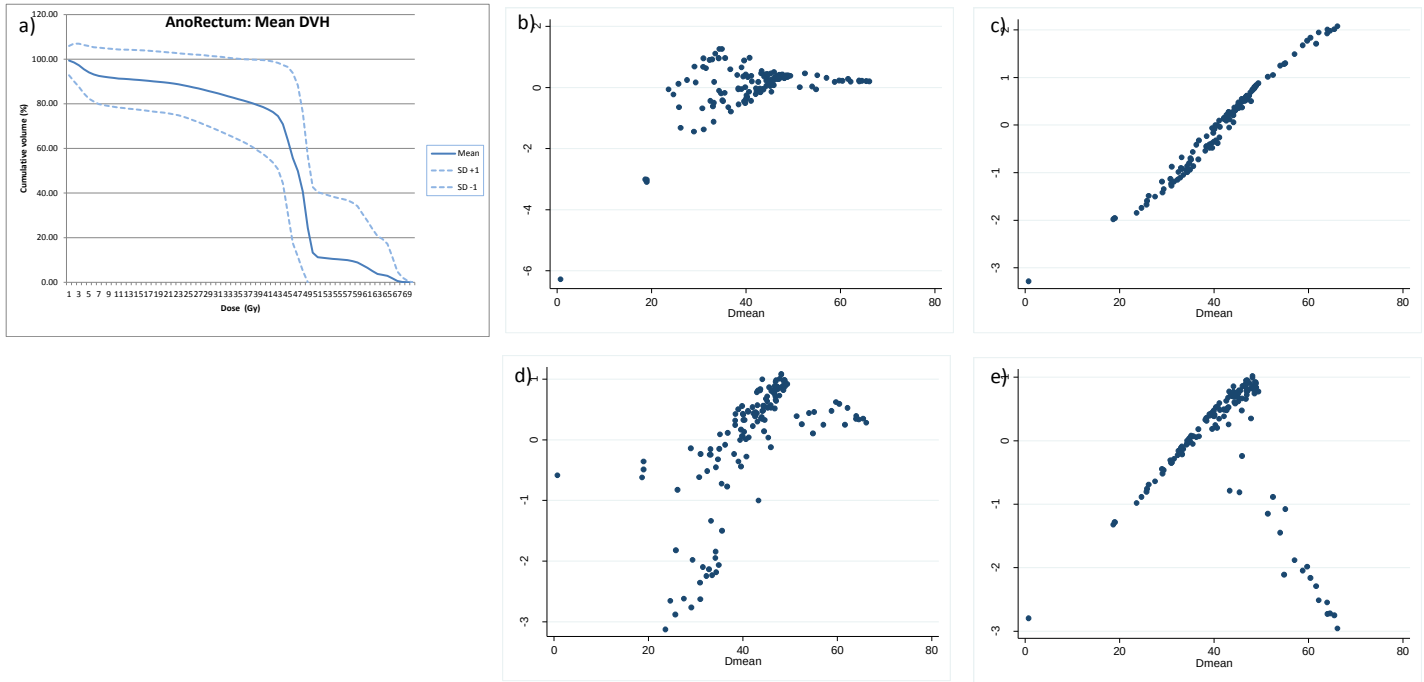
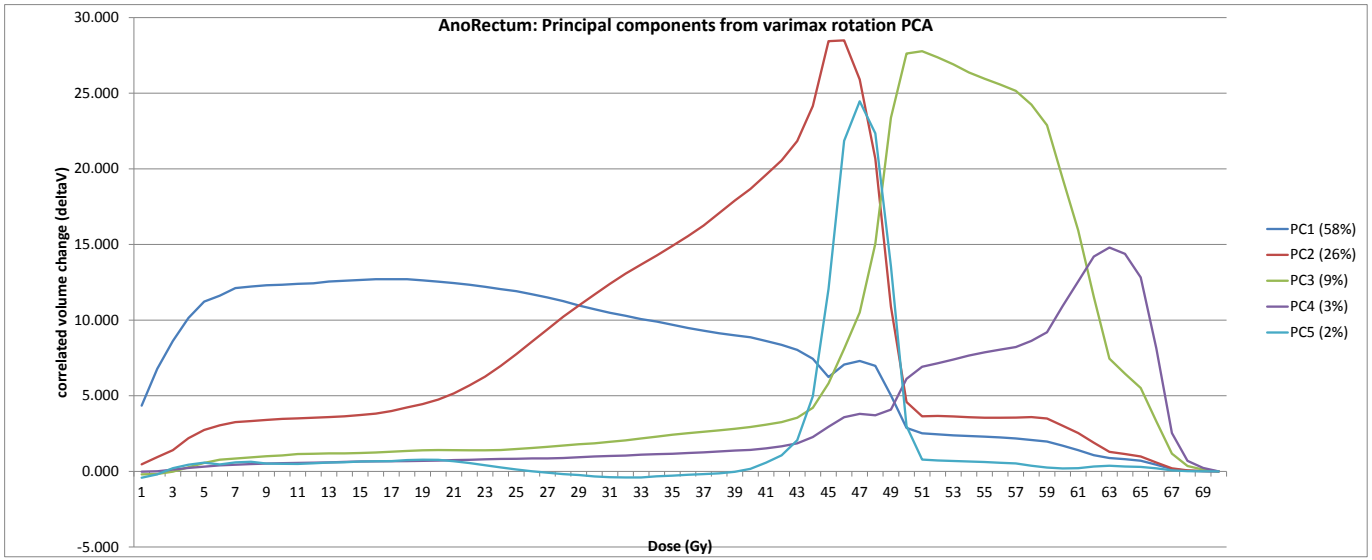


Figure 8-8: AnoRectum DVH summary graphs:

(a) Mean cumulative DVH (b) PC1 with varimax rotation vs Dmean (c) PC1 with no rotation vs Dmean (d) PC2 with varimax rotation vs Dmean (e) PC2 with no rotation vs Dmean (f)Correlation of principal components to dose (EQD2) (following page)

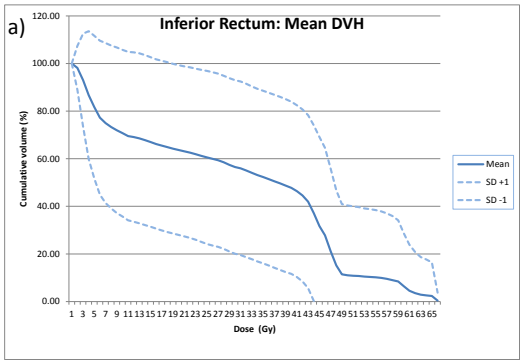

AnoRectum: Principal components from varimax rotation PCA
correlated volume change (deltaV)
30.000
25.000
20.000
15.000
10.000
5.000
0.000
-5.000
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51 53 55 57 59 61 63 65 67 69
Dose (Gy)
PC1 (58%)
PC2 (26%)
PC3 (9%)
PC4 (3%)
PC5 (2%)

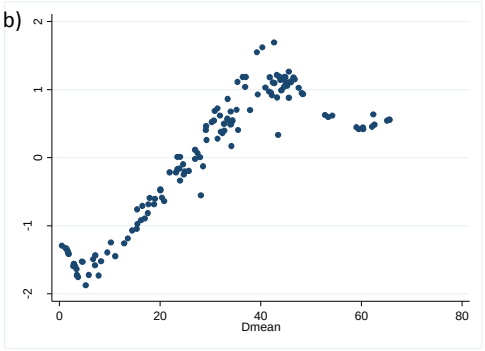
8.3.4.1.3 Inferior Rectum PCA

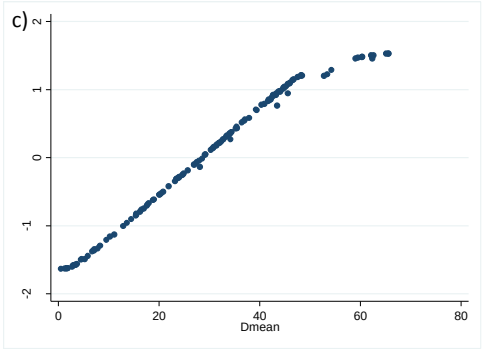
The first 4 inferior rectum principal components accounted for 97% of the DVH variability. The mean ratio of the original DVHs compared to the calculated DVH at 30Gy using the varimax rotated components was 1:0.96. The correlation of PCs to the DVH indices are illustrated in figure 8.7. PC1 describes the correlated variability of the DVH data set around the mean DVH in the range 1-65Gy. This is also demonstrated in the scatterplots correlating PC1 vs Dmean in figure 8.7. PC2 describes high dose regions 40-65Gy. PC3 broadly describes decreased relative volumes in the low dose region 1-5Gy and high dose region 44-48Gy and simultaneously increased relative volumes in the intermediate region 5-44Gy and high dose region 48-65Gy. PC4 describes the anticorrelated variability with decreased relative volumes in the low dose region 1-15Gy and simultaneously increased relative volumes in the intermediate to high dose region 15-50Gy.

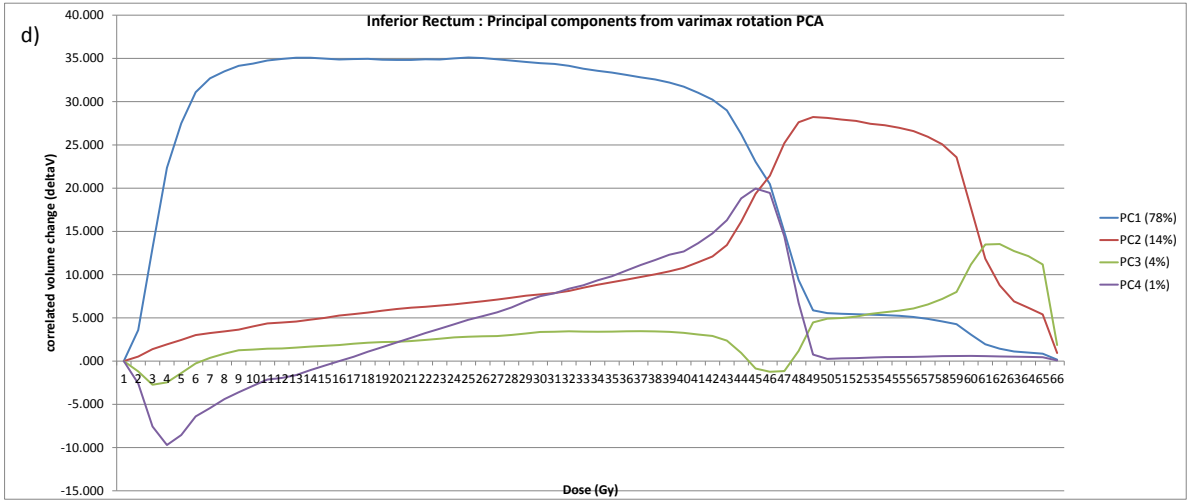
Figure 8-9: : Inferior Rectum DVH summary graphs:

(a) Mean cumulative DVH (b) PC1 with varimax rotation vs Dmean (c) PC1 with no rotation vs Dmean (d) Correlation of principal components to dose (EQD2)









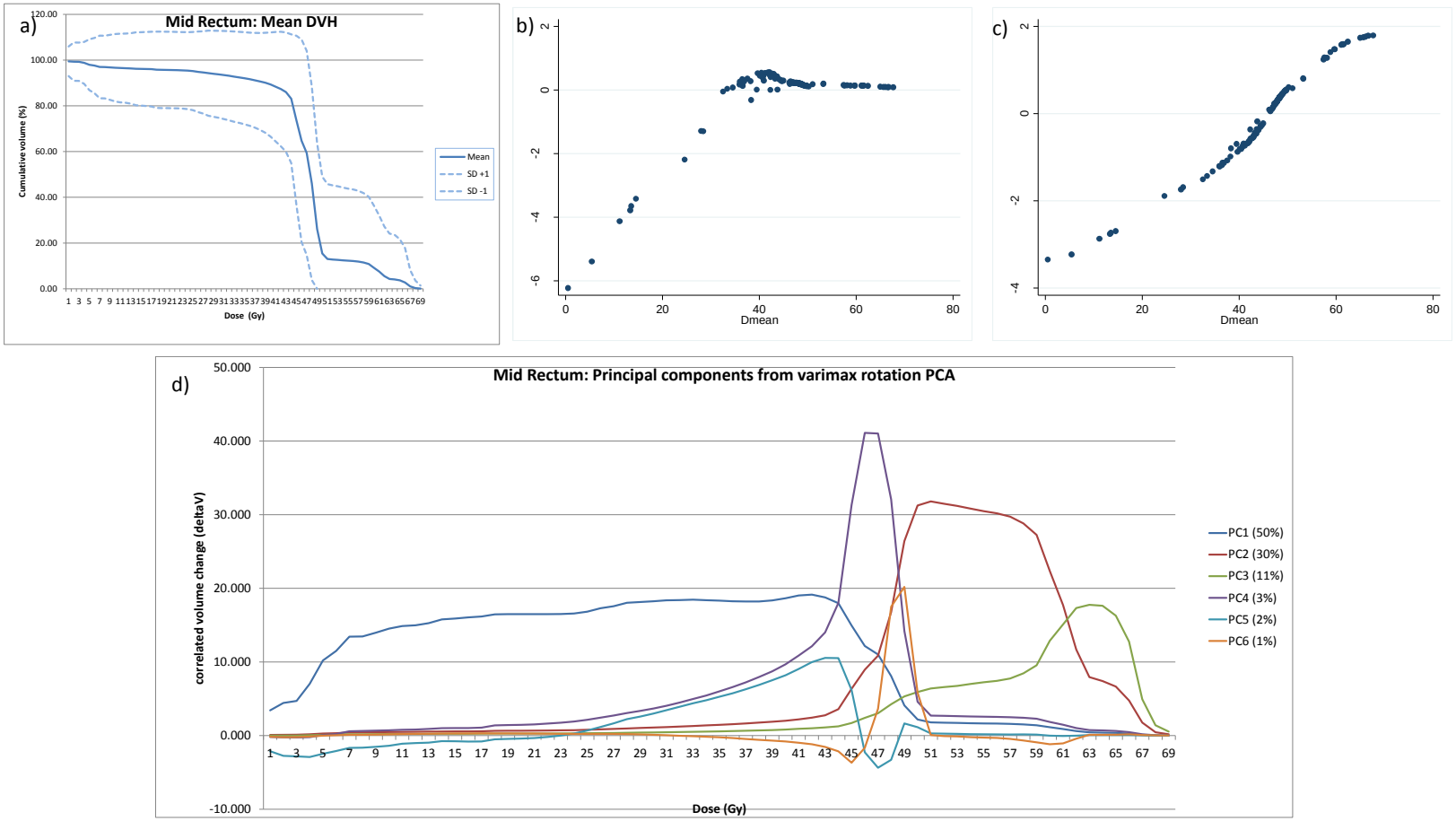


Figure 8-10 Mid Rectum DVH summary graphs

(a) Mean cumulative DVH (b) PC1 with varimax rotation vs Dmean (c) PC1 with no rotation vs Dmean (d) Correlation of principal components to dose (EQD2)

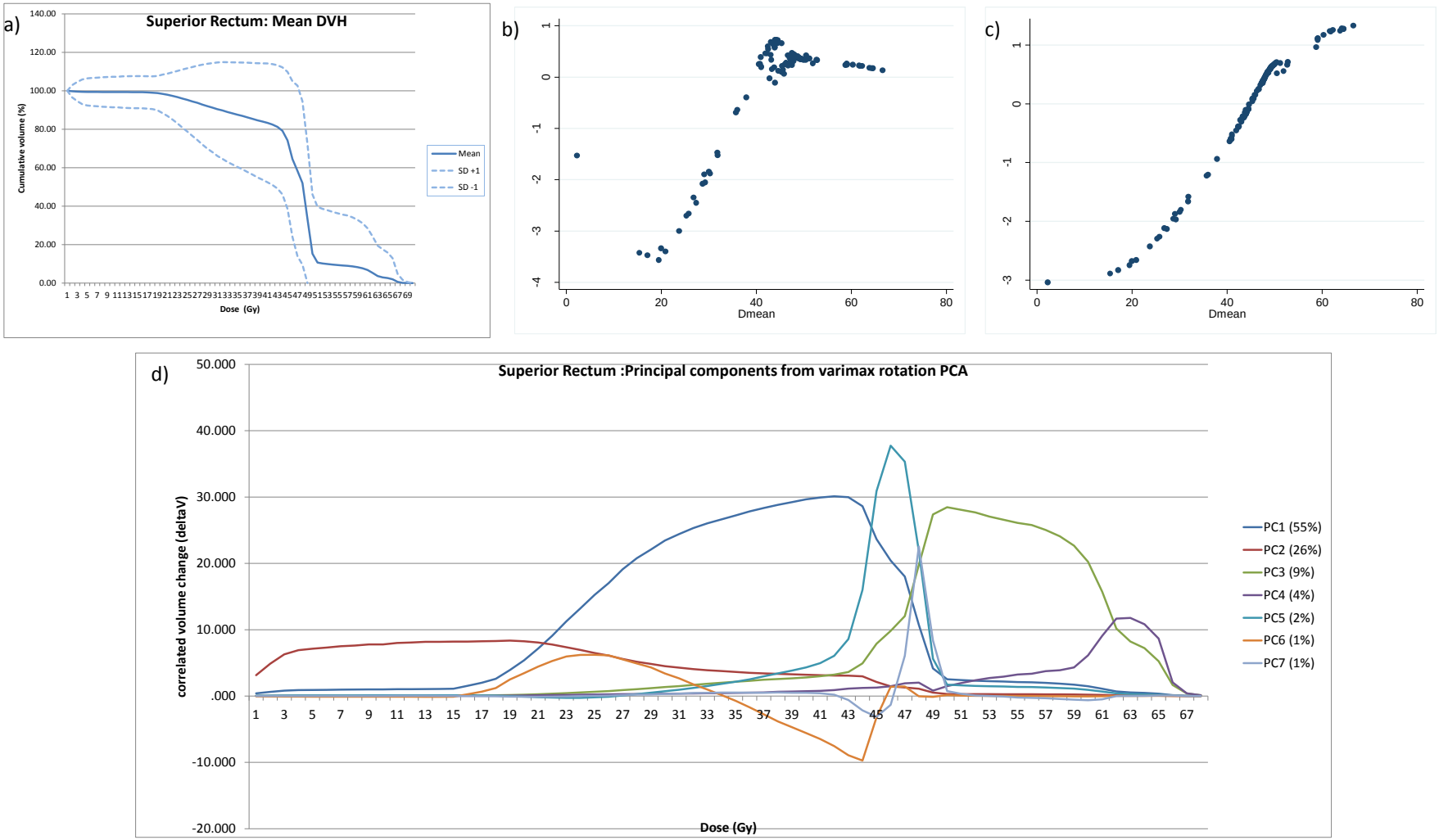


Figure 8-11Superior Rectum DVH summary graphs:

(a) Mean cumulative DVH (b) PC1 with varimax rotation vs Dmean (c) PC1 with no rotation vs Dmean (d) Correlation of principal components to dose (EQD2)

8.3.4.1.4 Mid Rectum PCA

The first 6 mid rectum principal components accounted for 97% of the DVH variability. The mean ratio of the original DVH compared to the calculated DVH at 30Gy using the varimax rotated components was 1:1. The correlation of PCs to the DVH indices are illustrated in figure 8.10. PC1 describes the correlated variability of the DVH data set around the mean DVH in the range 1-50Gy. This is also demonstrated in the scatterplots correlating PC1 vs Dmean in figure 8.10. PC2 describes high dose regions 43-70Gy and PC3 also describes high dose regions between 46-70Gy. PC4 describes the intermediate dose region between 30-50Gy. PC5 describes both decreased relative volumes in the low dose region 1-25Gy and high dose region 46-49Gy and simultaneously increased relative volumes in the intermediate region 25-46Gy. PC6 describes a narrow dose region with decreased relative volumes in dose region 40-46Gy and increased relative volumes between 46-50Gy.

8.3.4.1.5 Superior Rectum

The first 7 superior rectum principal components accounted for 98% of the DVH variability. The mean ratio of the original DVH compared to the calculated DVH at 30Gy using the varimax rotated components was 1:1. The correlation of PCs to the DVH indices are illustrated in figure 8.11. PC1 describes the correlated variability of the DVH data set around the mean DVH in the range 15-50Gy. This is also demonstrated in the scatterplots correlating PC1 vs Dmean in figure 8.11. PC2 describes low dose regions 1-40Gy and PC3 describes high dose regions between 43-67Gy. PC4 also describes high dose regions between 50-65Gy. PC5 describes the intermediate dose region between 35-50Gy. PC6 describes increased relative volumes in the low dose region 15-35Gy and simultaneously decreased relative volumes in the intermediate region 35-45Gy. PC7 describes a narrow dose region with decreased relative volumes in dose region 43-46Gy and increased relative volumes between 46-50Gy.

8.3.4.2 Bowel symptom regression analyses

Baseline GI symptoms and data on acute GI toxicity were not available for the cross sectional analysis however, clinically important comorbidities, treatment and patient characteristics were included into an exploratory backwards stepwise linear regression model for each bowel symptom item. Potential explanatory factors considered were: gender, BMI, age, smoking status, diagnosis, presence of recurrent disease, dose per fraction, concurrent chemotherapy, surgery, VMAT technique, time since start of EBRT, medication use (ACEi, statins, anticoagulants and NSAIDs), and co-morbidities: DM, ischaemic disease (cardiac and vascular) and previous abdominal surgery (121, 126, 303, 306). The prevalence of inflammatory bowel disease was 1.3% (n=4) and was therefore not included in the regression analysis. Dosimetric factors were modelled as

described in the previous section on the bladder analysis before significant clinical and dosimetric factors were included into the final backward stepwise regression model. Table 8.12 shows a summary of the significant findings for all symptoms.

Table 8-12: Bowel symptom regression analysis summary

CANCER SITES INCLUDED IN ANALYSIS	ALL CANCER SITES			ALL (except patients with a stoma)	GYNAECOLOGICAL CANCERS (GYNAE)- RECTAL OARs		GI ONLY	GI and CERVICAL	GYNAE ONLY
MODEL	FINAL	FINAL	Cumulative Volumetric model	FINAL	FINAL	FINAL	FINAL	FINAL	FINAL
VARIABLES	Faecal incontinence	Diarrhoea	Diarrhoea	Bowel Urgency	Bowel Urgency	Bowel Urgency	Bowel Frequency	PR Bleeding	Abdominal cramps
BowelBagL3 PC3	5.216*** (1.564 - 8.868)	3.395** (0.664 - 6.125)		7.308*** (2.858 - 11.76)				2.915*** (0.860 - 4.970)	
BMI	0.862*** (0.250 - 1.474)			1.154*** (0.392 - 1.916)	1.180** (0.176 - 2.185)	1.191** (0.185 - 2.197)			
Time since RT (yrs)				4.336** (0.538 - 8.133)					
AnoRectal PC2					8.079** (1.314 - 14.84)				
AnoRectal PC3					-6.832** (-12.32 - - 1.345)				
Mid Rectum PC2						-6.490** (-12.20 - - 0.781)			
Age							-0.496*** (-0.850 - - 0.141)		
ACEi							12.00** (1.423 - 22.58)		
BowelBagL3 PC1		3.249** (0.524 - 5.974)							
BowelBagL3 PC4		-4.934*** (-7.671 - - 2.197)							
BowelBagL3 V20			0.623*** (0.374 - 0.871)						
BowelBagL3 V35			-0.736*** (-1.099 - - 0.372)						
Statins									-17.86** (-32.18 - - 3.545)
Observations	246	305	305	203	109	109	165	254	142
R-squared	0.053	0.074	0.077	0.105	0.132	0.090	0.092	0.030	0.042

Regression coefficient presented at the top of each column with 95% confidence interval in parentheses
*** p<0.01, ** p<0.05, * p<0.1

8.3.4.2.1 Faecal Incontinence

Faecal incontinence was evaluated with all patient groups assessing the clinical factors and BowelBagL3 dosimetric variables. In addition dosimetric features of the AnoRectum and segmented rectum (inferior, mid and superior parts) were evaluated in the gynaecological patients group. Increasing BMI was associated with an increase in faecal incontinence symptoms (Coeff 0.9; 95%CI 0.3 -1.5; p=0.01) in a multivariate regression model with PC3 for BowelBagL3 where BowelBagL3 PC3 was associated with an increased faecal incontinence score of 5.2 (95%CI 1.6-8.9; p=0.01). BowelBagL3 PC3 describes increased relative volumes in low (1-10Gy) and higher dose regions (32-70Gy) and decreased relative volumes the intermediate dose region (15-32Gy). When each cancer site was evaluated separately, the dosimetric effect of PC3 was not significant in any cancer site suggesting this PC describes dosimetric variations between individual patients across all cancer sites and treatment techniques used. Dose per fraction however, almost reached significance in the regression model associated with an increase in faecal incontinence score of 5.4 with increasing dose per fraction, suggesting a possible effect of dose per fraction in this model (95%CI -0.2 to 11.1; p=0.06). No other dosimetric factors (Cumulative volumes or summary variables – Dmax, Dmean and D50) were significant in the multivariate regression analysis evaluating the impact on faecal incontinence scores for BowelBagL3 or for the AnoRectum or segmented rectum.

8.3.4.2.2 Diarrhoea

Diarrhoea was evaluated in all patient groups and was only significant in the regression analysis with three of the PC dosimetric factors of BowelBagL3 PC1, PC3 and PC4 and V20 and V35. No clinical parameters or dosimetric parameters associated with the rectum were found to be significant in the multivariate regression. PC1 (correlated with the mean DVH) and PC3 (correlated with increased relative doses in between 1-10Gy and 32-70Gy and decreased relative doses between 15-32Gy) were associated with 3 points increase in diarrhoea scores (PC1: 95%CI 0.5-6.0; p=0.02; PC3: 95%CI 0.7-6.1; p=0.02). PC4 in comparison was associated with a 5 point decrease in diarrhoea scores (95%CI -7.7 to -2.2; p<0.001) and is correlated with decreased relative dose volumes between 1-5Gy and 30-45Gy and increased relative dose volumes between 5-30Gy and 45-50Gy.In a combined regression analysis with all dosimetric factors only V20 and V35 remained significant, however, V20 was associated with a increase in diarrhoea score (Coeff 0.6; 95%CI 0.4-0.9; p=<0.001) and V35 with a decrease in score (Coeff -0.7; 95%CI -1.1 to -0.4; p<0.001). When the cumulative DVHs were included in the final model with the PCs the PCs were no longer significant whilst the cumulative DVH remained significant. Because the relationship between the toxicity outcomes and the cumulative DVHs does not make clinical sense, the final model

retained included only the PCs. No effect of dose per fractionation or diagnosis was evident, however when the use of VMAT techniques was added into the model with the PC1, PC3 and PC4 there was a trend towards reduction of diarrhoea symptoms (Coeff -12.2; 95%CI -25.0, 0.6; p=0.06).

8.3.4.2.3 Bowel urgency

The bowel urgency item was included in the questionnaires for all patients except for the GI patients with a stoma. Bowel urgency was the most prevalent symptom following pelvic radiotherapy treatment (Mean 41.2; SD33.9). As for faecal incontinence scores, BMI and BowelBagL3 PC3 were associated with increases in bowel urgency toxicity scores within the multivariate regression model: PC3 coeff 7.5 (95%CI 3.0-11.9; p=0.001); BMI coeff 1.2 (95%CI 0.4-1.9; p=0.003) along with increasing time since radiotherapy treatment leading to improvements in bowel urgency scores (Coeff -4.2; 95%CI -0.6 to -8.0; p=0.02). Dose per fraction had no effect on the model (p=0.32). When each cancer site was evaluated separately, BMI only remained a significant factor in the cervical cancer group (Coeff 1.4; 95%CI 0.3-2.7; p=0.01). As for the faecal incontinence analysis, when each cancer site was evaluated separately the dosimetric effect of PC3 was not significant in any cancer site, although there was a trend towards significances in the cervical cancer group (Coeff 6.8; 95%CI -0.7 to 14.4; p=0.08). The effect of time since treatment was only seen in the GI cancer patients (Anal: coeff -7.7; 95%CI -0.7 to -14.7; p=0.03; Rectal: coeff -12.9; 95%CI -1.0 to 24.8; p=0.04).

BMI and two dosimetric components, AnoRectum PC2 and PC3, significantly impacted on bowel urgency scores for the gynaecological cancers. Increasing BMI was associated with an increased bowel urgency score of 1.2 (95%CI 0.2-2.2; p=0.02); AnoRectum PC2 was associated with an increase in bowel urgency score of 8.1 (95%CI 1.2-14.8; p=0.02) and describes the mean dose in the intermediate dose region (20-50Gy) whereas AnoRectum PC3, describing a higher dose region (45-65Gy) was associated with a decrease in bowel urgency score (Coeff -6.8; 95%CI -12.3 to -1.3; p=0.02). Dose per fraction had no impact on the model (p=0.3). Evaluating each cancer site separately found that AnoRectum PC3 was significant only for the cervical cancer group (Coeff -7.8; 95%CI -13.8 to -1.9; p= 0.01). In comparison, AnoRectum PC2 described the model for both cancer sites in combination. Time since EBRT was not significant.

In the gynaecological cancer patients an additional effect of surgery on patients urgency scores was found in multivariate regression with BMI. Patients receiving

surgery as part of their treatment, who received adjuvant EBRT were found to have lower bowel urgency scores than those who had radial pelvic radiotherapy as their definitive treatment (Coeff -18.3; 95%CI -31.4 to -5.3; p=0.01). However, the addition of dosimetric factors into the model meant the surgical parameter was no longer significant (not shown in the table).

No inferior rectum PC dosimetric factors or summary factors (Dmean/D50/Dmax) were significant in the regression analysis, however, V45 was significant in a univariate analysis with an increase in bowel urgency score of 0.2 (95%CI 0.02 – 0.32; p=0.02) with a trend towards significance in the multivariate regression analysis with BMI (95%CI -0.01 to 0.3; p=0.06; not shown in table).

PC2, associated with high dose regions (46-70Gy), for the mid rectum was associated with a decrease in bowel urgency score of 6.5 (95%CI -12.2 to -0.8; p=0.03) in a multivariate regression with BMI (Coeff 1.2; 95%CI 0.1-2.2; p=0.02). Dose per fraction was not significant in the model however, when each cancer site was evaluated separately, the dosimetric effect of PC2 remained significant only in the cervical cancer patient group: PC2: Coeff -7.9; 95%CI -14.0 to -1.9; p=0.01) as did the effect of BMI (Coeff 1.2; 95%CI 0.1-2.3; p=0.04)

No dosimetric factors for the superior rectum were significant in the regression analysis with bowel urgency.

8.3.4.2.4 Bowel frequency

Bowel frequency was evaluated in the GI cancer patients. BowelBagL3 dosimetric parameters were not significant in the regression analysis, however clinical factors, age and ACEi use were found to significantly impact on patients frequency scores, with a trend towards females suffering higher frequency scores (p=0.06). ACEi use (17% of patients reported use) increased patient's bowel frequency scores by 11.8 (95%CI 1.3-22.4; p=0.03) and increasing age was associated with a 0.5 point decrease in the score (95%CI -0.8 to -0.1; p=0.01).

8.3.4.2.5 Flatulence

Despite flatulence being a prevalent symptom amongst the GI and endometrial sample (Mean 37.3; SD32.5) no dosimetric or clinical factors were significant in the multivariate regression analysis. Dosimetric evaluation was not possible for the AnoRectum and segmented rectum due to the small sample of endometrial cancer patients (n=38).

8.3.4.2.6 Per Rectal (PR) bleeding

PR bleeding is a low incidence symptom in this patient sample (Mean 4.8; SD14.3) and is evaluated only in the GI and cervical cancer patients. No clinical factors were significant in the multivariate linear regression analysis and only BowelBagL3 PC3 was significant in the univariate analysis with an increase in PR bleeding of 2.9 (95%CI 0.9-5.0; p=0.01). PC3 is associated with increased relative dose volumes in low dose regions (1-10Gy) and high dose regions (32-70Gy) and decreased relative volumes in the intermediate dose regions 30-45Gy. No effect of dose per fractionation or diagnosis was seen.

8.3.4.2.7 Abdominal Cramps

Only the gynaecological cancer patients were required to respond to the item on abdominal cramps and only the intestinal cavity (BowelBagL3) is likely to relate pathophysiologically to this symptom. No intestinal cavity dosimetric factors were significant in the regression analysis. Only statin use out of the clinical factors was found to have an impact on this symptom, with fewer abdominal cramp symptoms experienced by patients on statins (Coeff: -17.9; 95%CI -32.2 to -3.5; p=0.02) although the confidence interval is wide with only 14% on statins in the gynaecological patient sample.

8.3.5 Female Sexual Dysfunction

A summary of the EORTC-QLQ scores for female sexual dysfunction symptoms is presented in table 8.13. Sexually active patients were a mean age of 51 years (SD13.4), slightly lower than the mean age of all female patients (Mean 58.7; SD14.0). Overall, 32% of female patients with anal cancer were sexually active, responding to the question ‘During the past 4 weeks have you been sexually active?’ with a response of ‘a little’, ‘quite a bit’ or ‘very much’ (n=21/66); 36% of rectal cancer female patients (n=8/22); 20% of endometrial cancer patients (n=9/46) and 42% of cervical cancer patients (n=39/93). Only 8% of women did not respond to the item on sexual activity (n=20). The 75 patients who reported to be sexually active (33%) reported experiencing a high prevalence of sexual dysfunction symptoms. The overall mean sexual functioning score was 60.1 (SD28.6) with mean symptom scores between 36.6 (SD28.6) and 44.1 (SD35.4) for aspects of vaginal function equivalent to score between ‘a little’ and ‘quite a bit’. Patients who used vaginal dilators (n=50) also reported high levels of vaginal symptoms with mean scores for vaginal dryness and

stenosis between 40.8 (SD30.6) and 50.3 (SD33.4). Patients reported very low libido levels (mean 14.8; SD24.2).

Table 8-13: Summary of EORTC-QLQ female sexual functioning scores

Female vaginal/sexual symptoms	N	Mean	S.D.	Minimum	Lower quartile	Median	Upper quartile	Maximum
Female sexual activity*	227	**14.4**	**22.1**	0.0	0.0	0.0	33.3	100.0
Female enjoyment of sex*	70	**50.5**	**29.4**	0.0	33.3	33.3	66.7	100.0
Female libido*	88	**14.8**	**24.2**	0.0	0.0	0.0	33.3	100.0
Overall sexual/vaginal functioning*	75	**60.1**	**28.6**	8.3	33.3	66.7	83.3	100.0
Vaginal shortening	73	**38.4**	**37.5**	0.0	0.0	33.3	66.7	100.0
Vaginal stenosis	74	**44.1**	**35.4**	0.0	33.3	33.3	66.7	100.0
Dyspareunia	72	**36.6**	**28.6**	0.0	0.0	33.3	66.7	100.0
Vaginal dryness	73	**42.0**	**34.7**	0.0	0.0	33.3	66.7	100.0
Vaginal dilator responses								
Vagina short/tight	49	**50.3**	**33.4**	0.0	33.3	33.3	66.7	100.0
Vaginal dryness	49	**40.8**	**30.6**	0.0	33.3	33.3	66.7	100.0
Pain on dilator use	50	26.7	26.9	0.0	0.0	33.3	33.3	100.0

*Functioning items (Higher score represents better functioning). Scores with no asterisk represent Symptom items (Higher scores represent worse symptoms).

8.3.5.1 Principal component analysis of female sexual OARs

Female genitalia and vagina were contoured as OAR in all female patients, excluding parts of the organ included in the GTV.

8.3.5.1.1 Vagina PCA

The first 8 principal components accounted for 96% of the DVH variability. The mean ratio of the original DVH compared to the calculated DVH at 30Gy using the varimax rotated components was 1:1.01. The correlation of PCs to the DVH indices are illustrated in figure 8.12. PC1 describes the correlated variability of the DVH data set around the mean DVH in the range 1-50Gy, this is also demonstrated in the scatterplots correlating PC1 and Dmean in figure 8.12. PC2 describes the mean DVH in the intermediate dose region 20-50Gy. PC3 and PC4 describe increased relative volumes in higher dose regions 40-65Gy and 40-50Gy respectively. PC5 describes the region between 20-35Gy, PC6 the region between 35-50Gy and PC7 between 35-45Gy. PC8 describes increased relative volumes between 40-43Gy and 47-55Gy and 1-20Gy and simultaneously decreased relative volumes in dose region 43-47Gy.

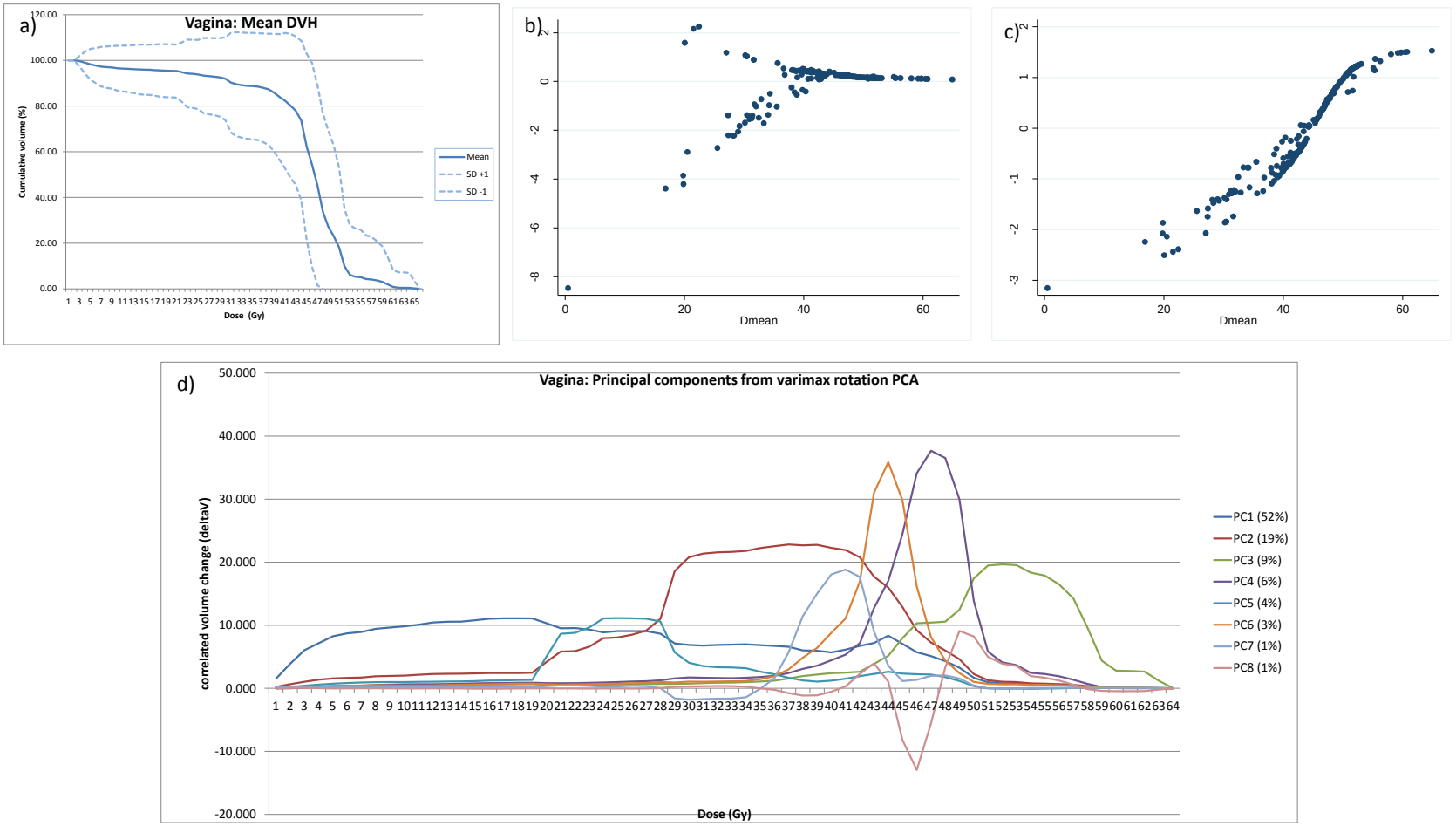


Figure 8-12: Vagina DVH summary graphs:

(a) Mean cumulative DVH (b) PC1 with varimax rotation vs Dmean (c) PC1 with no rotation vs Dmean (d)Correlation of principal components to dose (EQD2)

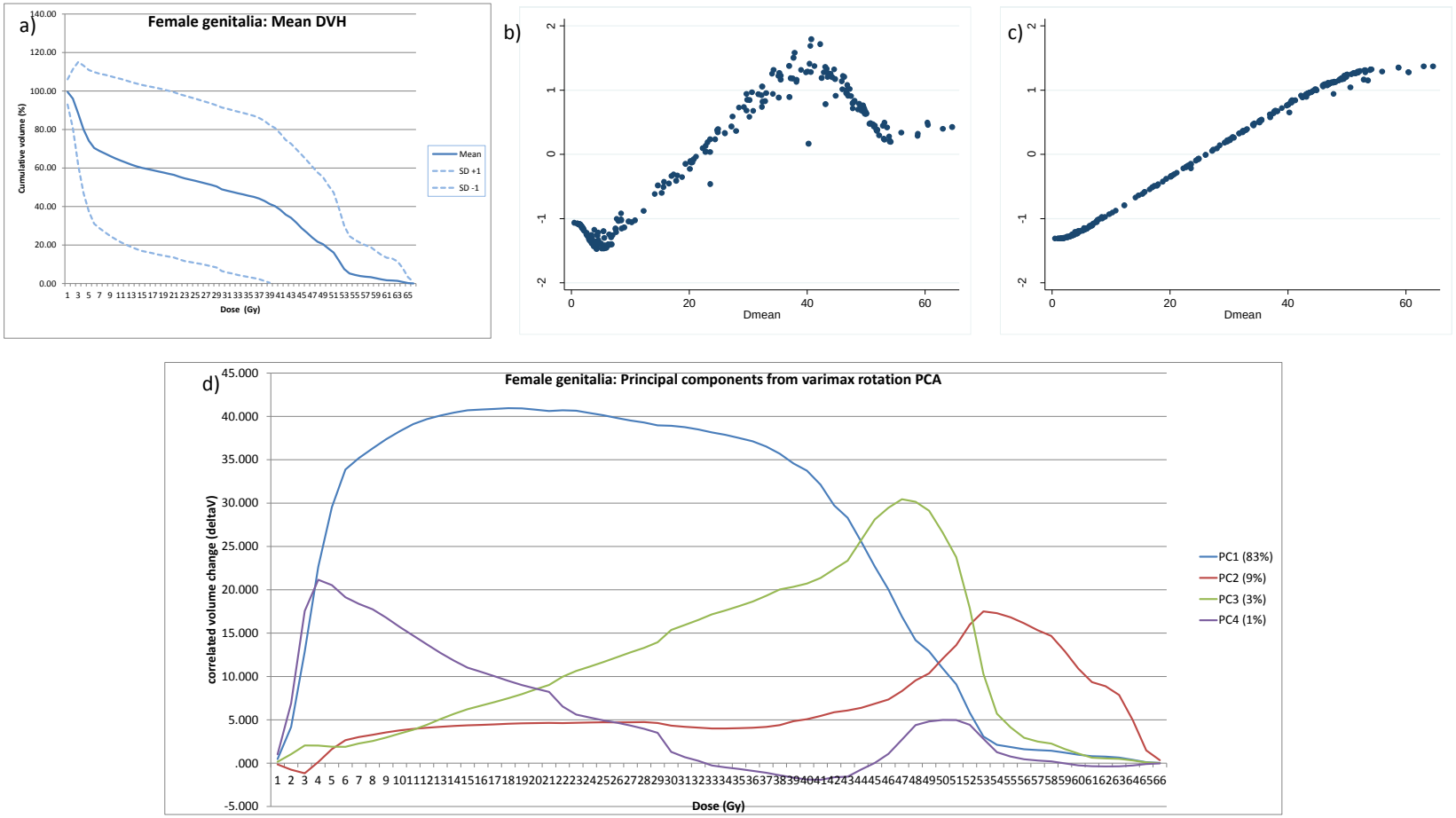


Figure 8-13: Female genitalia DVH summary graphs:

(a) Mean cumulative DVH (b) PC1 with varimax rotation vs Dmean (c) PC1 with no rotation vs Dmean (d)Correlation of principal components to dose (EQD2)

8.3.5.1.2 Female genitalia

The first 4 principal components accounted for 96% of the DVH variability. The mean ratio of the original DVH compared to the calculated DVH at 30Gy using the varimax rotated components was 1: 0.94. The correlation of PCs to the DVH indices are illustrated in figure 8.13. PC1 describes the correlated variability of the DVH data set around the mean DVH in the range 1-55Gy, this is also demonstrated in the scatterplots correlating PC1 and Dmean in figure 8.13. PC2 describes the mean DVH in the intermediate to high dose region 40-65Gy. PC3 describes increased relative volumes between 1-55Gy with a peak between 41-52Gy. PC4 describes increased relative volumes between 1-34Gy and 44-58Gy and simultaneously decreased relative volumes in dose region 34-44Gy.

8.3.5.2 Female sexual dysfunction symptom regression analyses

Baseline data on sexual activity and menopausal status was not available for the cross sectional analysis. Clinically important comorbidities, treatment and patient characteristics were included into an exploratory backwards stepwise linear regression model for each female sexual dysfunction symptom. Potential explanatory factors considered were: age, smoking status, diagnosis, presence of recurrent disease, dose per fraction, concurrent chemotherapy, surgery, brachytherapy, VMAT technique, time since start of EBRT, medication use (hormone replacement therapy(HRT), and co-morbidities: DM, ischaemic disease (cardiac and vascular), depression(285, 286). Dosimetric factors for each OAR were separately included into a backwards stepwise linear regression model before combining all significant factors in a final model. As the female genitalia structure does not describe vaginal function it was not included as an OAR in the analysis for items vaginal stenosis/shortening/dryness. The outcome items on vaginal dilator related symptoms were not included in the regression analysis as these items are not validated. Table 8.14 shows a summary of the final regression models for all symptoms with significant results.

8.3.5.2.1 Overall sexual/vaginal functioning

This item summarises the scores from four items to create a scaled item: vaginal stenosis, shortening, dryness and dyspareunia. Increasing age and use of HRT were both associated with improved female sexual function scores throughout the regression analysis: Age Coeff 0.7; 95%CI 0.2-1.3; p=0.02; and HRT Coeff 20.3; 95%CI 4.2-36.5 p=0.01. PC3 for the vagina OAR was found to worsen female sexual function scores by 6.7 points (95%CI -12.6 to -0.9; p=0.02) and describes the highest dose region between 40-65Gy. Dose per fractionation had no effect on the model. The main effect of the model when each cancer site was evaluated separately was found in the cervical

cancer group with a worsening of function of 11.5 points (95%CI -17.2 to -5.9; p=<0.001), however it must be noted that included in this analysis cervical cancer patients contributed the largest number into the sample (n=30), followed by anal cancer patient (n=15) then endometrial and rectal with three patients each included. V50 and D50 were also significantly associated with worsening female sexual function (V50: coeff -0.3; 95%CI -0.5 to -0.1; p=0.002 and D50 -1.2; 95%CI -2.1 to -0.4; p=0.004). These two factors were only significant in the cervical cancer patient group when each cancer site was evaluated separately. When all dosimetric parameters were included in the final model, none remained significant. Although the R^2 values were greater for the models including V50 and D50 the regression coefficient value was greatest for the PC3 parameter. These exploratory analyses may reveal challenges with including a scaled questionnaire item (vaginal functioning) that contains multiple symptoms within a regression model evaluating the impact of radiotherapy on different pathophysiological processes.

The female genitalia dosimetric parameters had no effect on this model.

Table 8-14: Female sexual dysfunction symptom regression analysis summary

MODEL	PCA model FINAL MODEL	Summary dosimetric parameter model	Cumulative volume model	PCA model	Summary dosimetric parameter model	Cumulative volume model	FINAL MODEL	FINAL MODEL	PCA model FINAL MODEL	Cumulative volume mode	FINAL MODEL	PCA model FINAL MODEL	Cumulative volume mode
VARIABLES	**Vaginal functioning**	**Vaginal functioning**	**Vaginal functioning**	**Vaginal stenosis**	**Vaginal stenosis**	**Vaginal stenosis**	**Vaginal stenosis**	**Vaginal shortening**	**Vaginal dryness**	**Vaginal dryness**	**Dyspareunia**	**Sexual enjoyment**	**Sexual enjoyment**
Vagina PC3	-6.707** (-12.49 - -0.921)			10.22*** (3.416 - 17.02)			7.380** (0.290 - 14.47)						
Age	0.764*** (0.263 - 1.265)	0.756*** (0.272 - 1.241)	1.014*** (0.506 - 1.522)	-1.177*** (-1.766 - -0.588)	-1.143*** (-1.726 - -0.560)	-1.209*** (-1.794 - -0.623)	-1.194*** (-1.765 - -0.623)	-0.795** (-1.468 - -0.122)	-0.660* (-1.341 - 0.0214)	-0.609* (-1.275 - 0.0563)	-0.526** (-1.018 - -0.0336)		
HRT use	20.50** (4.463 - 36.54)	21.56*** (5.981 - 37.15)	18.99** (3.703 - 34.28)	-27.78*** (-46.65 - -8.919)	-28.79*** (-47.53 - -10.05)	-28.89*** (-47.62 - -10.15)	-29.47*** (-47.77 - -11.18)	-24.43** (-45.39 - -3.467)					
Vagina D50		-1.265*** (-2.088 - -0.441)			1.507*** (0.517 - 2.497)		1.104** (0.0636 - 2.145)						
Vagina V50			-0.295*** (-0.463 - -0.127)							0.313*** (0.0888 - 0.537)			
Vagina V55						0.593*** (0.226 - 0.960)							
Vagina PC6									11.93*** (3.317 - 20.54)				
Female genitalia PC4											-7.027** (-13.77 - -0.285)		
Female genitalia PC1												-7.813** (-14.49- -1.13)	
Female genitalia V30													-0.210** (-0.369 - -0.0516)
Observations	71	70	71	71	70	71	70	73	69	69	70	68	68
R-squared	0.204	0.250	0.274	0.283	0.291	0.297	0.335	0.129	0.113	0.114	0.131	0.076	0.096

Regression coefficient presented at the top of each column with 95% confidence interval in parentheses *** p<0.01, ** p<0.05, * p<0.1

8.3.5.2.2 Vaginal tightening/stenosis

Similar findings were found in the regression model for vaginal stenosis with Vagina PC3 associated with worse vaginal stenosis symptoms (Coeff 10.3; 95%CI 3.6-17.0; p=0.003) and age and HRT use associated with improved symptom scores (Age: coeff -1.2; 95%CI -1.8 to -0.6; p<0.001 and HRT: coeff -27.7; 95%CI -46.3 to -9.1; p=0.004). Dose per fractionation had no impact on the model and the main effect was seen in cervical cancer patients (Coeff: 15.5; 95%CI 8.7-23.0; p<0.001). D50 and V55 were also associated with worsening vaginal stenosis symptoms when included separately in the model with age and HRT and were only significant for cervical cancer patients but the model was better explained by PC3 (D50: coeff. 1.5; 95%CI 0.5-2.4; p=0.004 and V55: coeff 0.6; 95%CI 0.2-1.0; p=0.002). The final model was improved by including PC3 and D50 along with increasing age and HRT use. When each cancer site was evaluated separately, the dosimetric effect of PC3 and D50 was not significant in any cancer site suggesting this model describes dosimetric variations between individual female patients across all cancer sites and treatment techniques used.

8.3.5.2.3 Vaginal shortening

The regression model found increasing age and HRT use to be associated with improved scores for the vaginal shortening item (Age: coeff -0.7; 95%CI -1.4 to -0.03; p=0.04 and HRT: coeff -23.8; 95%CI -44.6 to -3.1; p=0.03). Surgery was not significant in the model, however only a small sample of endometrial cancer patients were sexually active (n=9). No dosimetric factors for the vagina OAR were found to be significant in the regression model.

8.3.5.2.4 Vaginal dryness

The best multivariate regression model found Vagina PC6 to be associated with worsening vaginal dryness when incorporated into the final model with age (although this clinical parameter was not significant in the model). PC6 was associated with increasing vaginal dryness symptom scores by 11.9 points (95%CI 3.3-20.5; p=0.007) and describes the dose region between 35-50Gy. No effect of dose per fractionation was found and this dosimetric factor was only significant in the cervical cancer patients when each cancer site was evaluated separately. V50 was also significant in the regression model with age (age was again not significant) but the change in score was small (Coeff 0.3; 95%CI 0.1-0.5; p=0.007) and again this factor was only significant in

cervical cancer patients when the cancer sites were assessed separately and was no longer significant when included in the final model.

8.3.5.2.5 Dyspareunia

Vaginal dosimetric factors were not significant in the multivariate regression analysis with this item. Age and PC4 for female genitalia OAR both improved dyspareunia scores. Increasing age was associated with a reduction in dyspareunia of 0.5 (95%CI -1.0 to -0.03; p=0.04) and PC4, describing increased relative volumes between 1-34Gy and 44-58Gy and decreased relative volumes in dose region 34-44Gy, was associated with a 7.0 point reduction in dyspareunia scores (95%CI -13.8 to -0.3; p=0.04). Dose per fraction had not effect on the model. When each cancer site was evaluated separately a trend towards the main effect of PC4 was found in the model for the anal cancer patient group (Coeff: -11.9; 95%CI -24.4 to 0.52; p=0.06).

8.3.5.2.6 Sexual enjoyment

This item asked the question 'Was sexual activity enjoyable for you?' Only two dosimetric factors were associated with this item in a univariate model. Female genitalia PC1, describing the mean DVH, was associated with a 7.8 point decrease in enjoyment scores (95%CI -14.4 to -1.1; p=0.02). Dose per fraction and diagnosis had no additional effects on the model. V30 for female genitalia was also associated with a significant reduction in sexual enjoyment (Coeff -0.2; 95%CI -0.4 to -0.1; p=0.01). Whilst there was no effect of dose per fraction evaluation of each diagnosis separately found a trend towards significance in the anal cancer patient group (Coeff -0.4; 95%CI -0.8 to 0.02; p=0.06). Anal cancer patients on average received much higher mean doses than the other cancer sites (see table 8.9). The addition of VMAT technique into the model improved sexual enjoyment scores although this was not significant (Coeff 26.2; 95%CI -0.7, 53; p=0.06).

8.3.6 Male Sexual Dysfunction

A summary of the EORTC-QLQ scores for male sexual dysfunction symptoms is presented in table 8.15. Sexually active patients were a mean age of 57 years (SD14.4) lower than the mean age of all male patients (Mean 66.2; SD10.4). Overall, 52% of male patients with anal cancer were sexually active (n=12/23) and 40% of rectal cancer male patients (n=18/45). Only 14% of men did not respond to the items on sexual activity or impotence (n=11). Mean scores for impotence were 55.4 (SD37.6) equivalent to a score between 'a little' and 'quite a bit'. For the 30 patients who were sexually active, the overall sexual functioning score was 60.6 (SD27.1) comprising of

items on enjoyment of sex, erectile problems, ejaculation problems and concerns about feeling sexually intimate. Libido scores were higher than for the female patients but were still low (Mean 31.9; SD 27.1).

Table 8-15: Summary of EORTC-QLQ male sexual functioning scores

Male sexual symptoms	N	Mean	S.D.	Minimum	Lower quartile	Median	Upper quartile	Maximum
Sexual Activity*	68	**20.1**	**26.5**	0.0	0.0	0.0	33.3	100.0
Male libido*	72	**31.9**	**27.1**	0.0	0.0	33.3	66.7	100.0
Impotence	68	**55.4**	**37.6**	0.0	33.3	66.7	100.0	100.0
Male enjoyment of sex*	29	**62.1**	**30.5**	0.0	33.3	66.7	100.0	100.0
Ejaculation problems	30	**33.3**	**40.1**	0.0	0.0	0.0	66.7	100.0
Intimacy concerns	30	30.0	36.5	0.0	0.0	16.7	66.7	100.0
Overall male sexual functioning*	30	**60.6**	**27.1**	0.0	41.7	62.5	83.3	100.0

*Functioning items (Higher score represents better functioning). Scores with no asterisk represent Symptom items (Higher scores represent worse symptoms).

8.3.6.1 Principal component analysis of male sexual OARs

The penile bulb and male genitalia were contoured as OAR in all male patients.

8.3.6.1.1 Penile Bulb PCA

The first 4 principal components accounted for 95% of the DVH variability. The mean ratio of the original DVH compared to the calculated DVH at 15Gy using the varimax rotated components was 1: 0.95. The correlation of PCs to the DVH indices are illustrated in figure 8.14. PC1 describes the correlated variability of the DVH data set around the mean DVH in the range 1-50Gy. PC2 describes the correlated variability of the DVH data set around the mean DVH between 40-50Gy. Dmax is also highly correlated with PC1. This is also demonstrated in the scatterplots correlating PC1, PC2, and Dmean in figure 8.14. PC3 describes the mean DVH in the intermediate dose region 20-45Gy. PC4 describes increased relative volumes in the dose regions 35-50Gy.

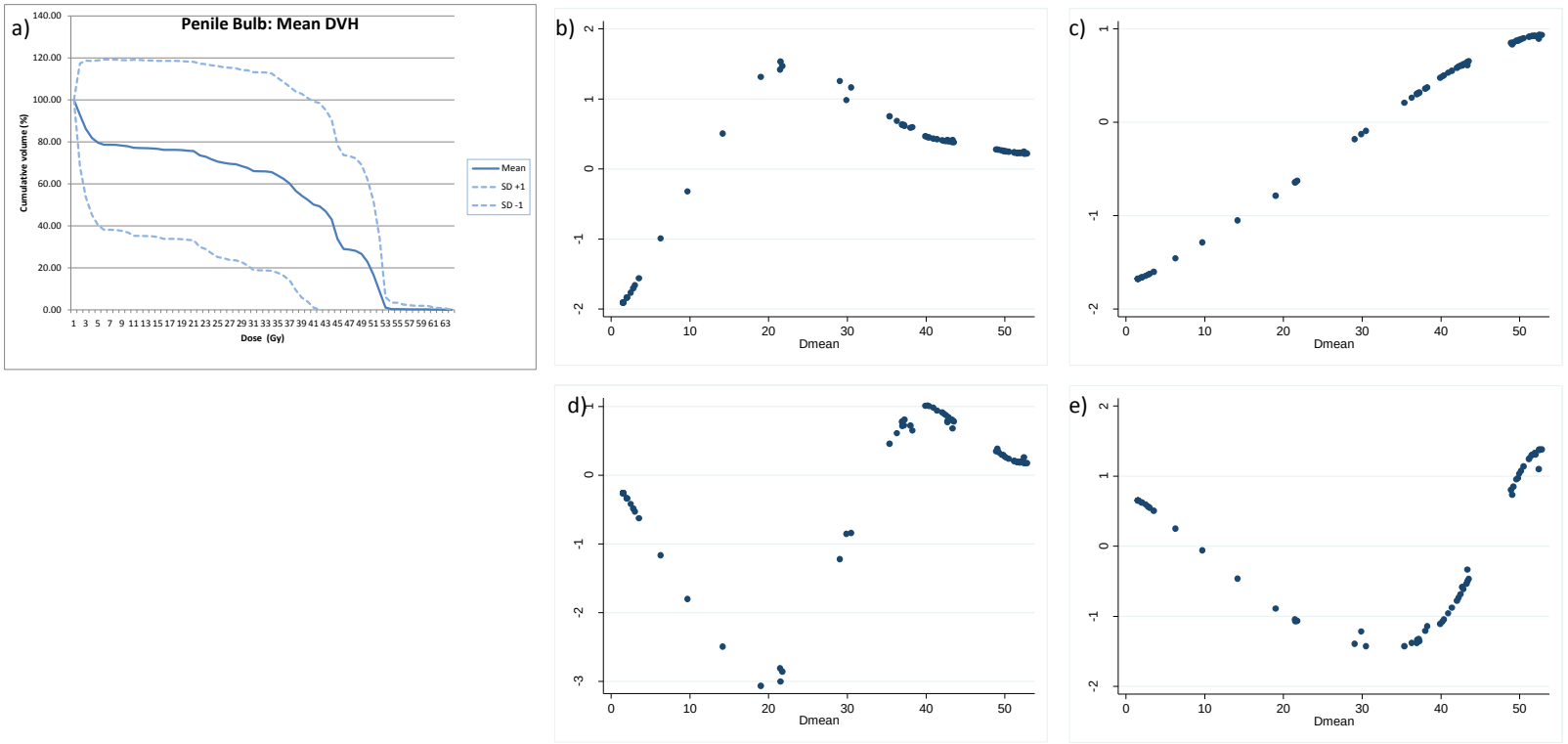
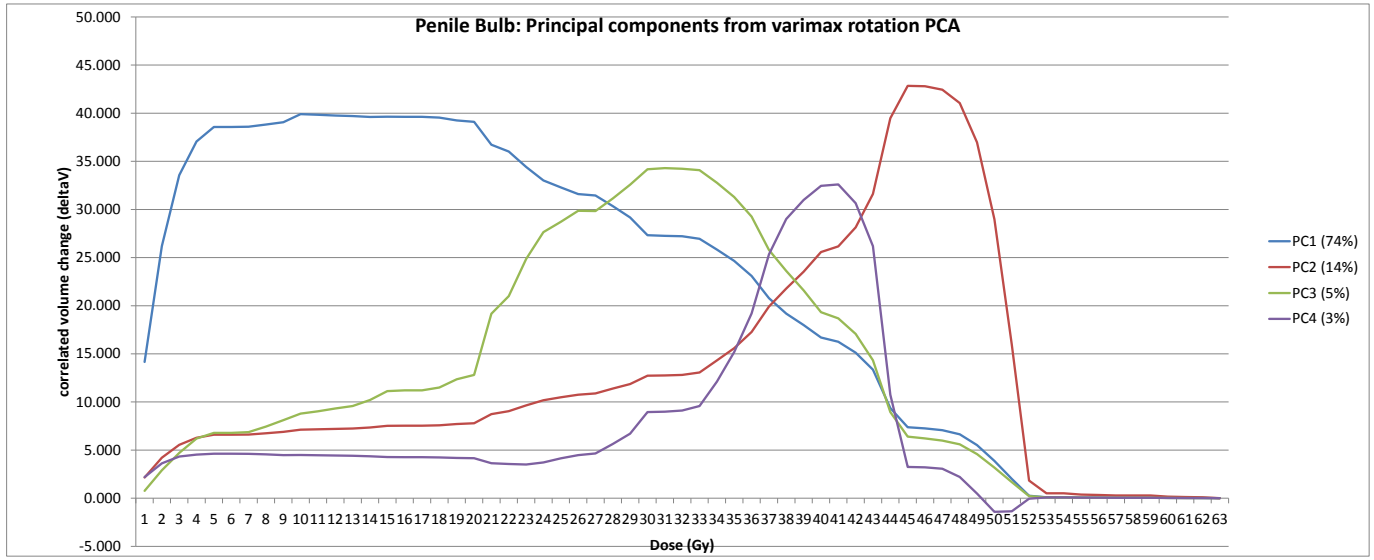
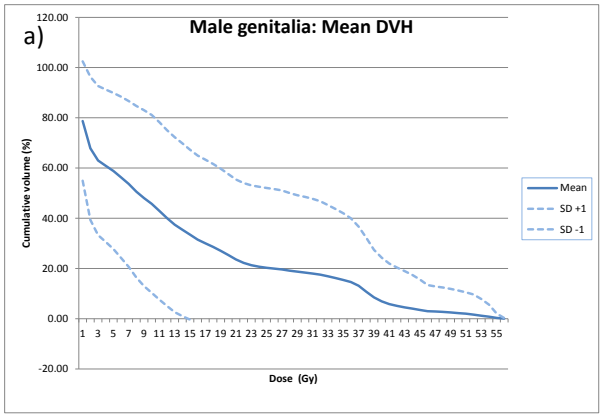
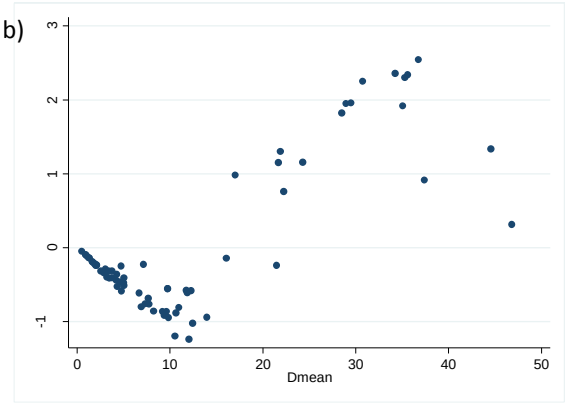


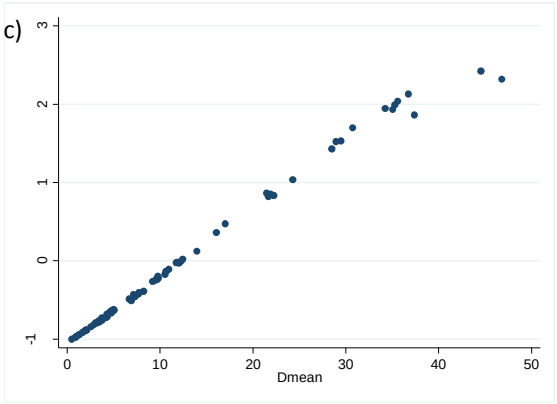
Figure 8-14: Penile Bulb DVH summary graphs

(a) Mean cumulative DVH (b) PC1 with varimax rotation vs Dmean (c) PC1 with no rotation vs Dmean (d) PC2 with varimax rotation vs Dmean (e) PC2 with no rotation vs Dmean (f)Correlation of principal components to dose (EQD2) (see next page)


Penile Bulb: Principal components from varimax rotation PCA
correlated volume change (deltaV)
50.000
45.000
40.000
35.000
30.000
25.000
20.000
15.000
10.000
5.000
0.000
-5.000
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63
Dose (Gy)
PC1 (74%)
PC2 (14%)
PC3 (5%)
PC4 (3%)







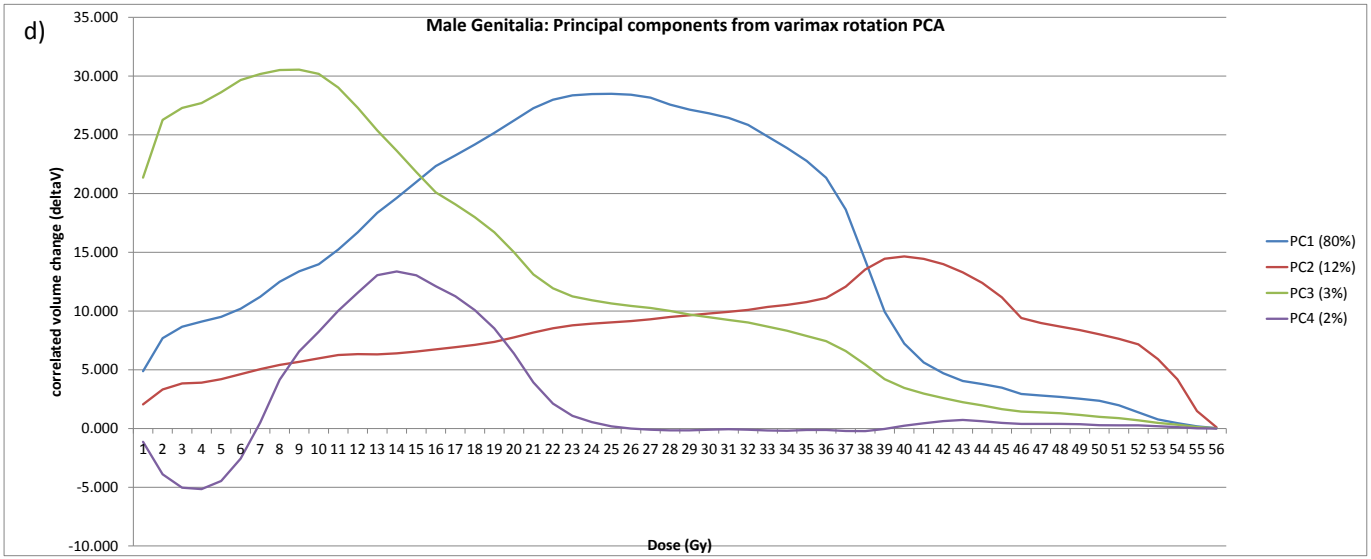


Figure 8-15: Male genitalia DVH summary graphs:

(a) Mean cumulative DVH (b) PC1 with varimax rotation vs Dmean (c) PC1 with no rotation vs Dmean (d)Correlation of principal components to dose (EQD2)

8.3.6.1.2 Male genitalia

The first 4 principal components accounted for 98% of the DVH variability. The mean ratio of the original DVH compared to the calculated DVH at 20Gy using the varimax rotated components was 1:0.73. The correlation of PCs to the DVH indices are illustrated in figure 8.15. PC1 describes the correlated variability of the DVH data set around the mean DVH in the range 1-45Gy. This is also demonstrated in the scatterplots correlating PC1 and Dmean in figure 8.15. PC2 describes a broad range of doses between 1-55Gy. PC3 describes the low dose region between 1-25Gy. PC4 describes decreased relative volumes between 1-7Gy and simultaneously increased relative volumes in dose region 7-25Gy.

8.3.6.2 Male sexual dysfunction symptom regression analyses

Baseline data on sexual activity and sexual functioning status was not available for the cross sectional analysis. Clinically important comorbidities, treatment and patient characteristics were included into an exploratory backwards stepwise linear regression model for each male sexual dysfunction symptom. Potential explanatory factors considered were: age, BMI, smoking status, diagnosis, presence of recurrent disease, dose per fraction, concurrent chemotherapy, surgery, time since start of EBRT, and co-morbidities: DM, ischaemic disease (cardiac and vascular), depression. Dosimetric factors for each OAR were separately included into a backwards stepwise linear regression model before combining with clinical factors within a final model. Table 8.16 shows a summary of the significant findings for all symptoms.

Table 8-16: Male sexual dysfunction symptom regression analysis summary

MODEL	PCA Model FINAL MODEL	Summary dosimetric parameter model	FINAL MODEL
VARIABLES	**Impotence**	**Impotence**	**Male libido**
Penile Bulb PC1	20.01*** (9.318 - 30.70)		
BMI	2.229** (0.204 - 4.253)	2.732** (0.676 - 4.788)	
Age	1.278** (0.312 - 2.245)	1.279** (0.311 - 2.247)	-0.909*** (-1.523 - -0.295)
Surgery	29.94*** (10.89 - 49.00)	37.39*** (16.89 - 57.89)	
Penile Bulb Dmax		1.057*** (0.490 - 1.624)	
Observations	50	50	72
R-squared	0.363	0.362	0.111

Regression coefficient presented at the top of each column with 95% confidence interval in parentheses
***p<0.01, ** p<0.05, * p<0.1

8.3.6.2.1 Impotence

Increasing age, increasing BMI, surgery and PC1 for the penile bulb were associated with worse erectile function. Increasing age was associated with a deterioration in erectile function seen with an increase in symptoms of 1.3 points (95%CI 0.3-2.2;

p=0.01), increasing BMI increased symptoms scores by 2.2 points (95%CI 0.2-4.3; p=0.03), surgery increased scores by 29.9 points (95%CI 10.9-49.0; p=0.003) and PC1 of the penile bulb, which describes the mean DVH, increased scores by 20 points (95%CI 9.3-30.7; p<0.001). Dmax for the penile bulb was also highly significant in as a dosimetric factor in the multivariate regression model with age, BMI and surgery increasing impotence symptoms (Coeff 1.1; 95%CI 0.5-1.6; p<0.001). However, including Dmax within the model along with PC1 meant the dosimetric factors were no longer significant. Therefore, the final model retained PC1 as this explained a greatest change in symptoms than Dmax. Dose per fraction had no effect on these models but evaluating each diagnosis separately found the main effects of both models in the rectal cancer patient group. No dosimetric parameters from the male genitalia OAR were associated with impotence.

8.3.6.2.2 Other male sexual dysfunction items

As only 30 male patients reported sexual activity in this analysis the regression models for the remaining sexual function items (ejaculation problems, intimacy concerns, sexual enjoyment) found no dosimetric effects with either OAR and only increasing age was significant at the 5% level associated with a reduction in the sexual interest score (Coeff. -0.9; 95%CI -1.5 to -0.3; p=0.004).

8.3.7 Low back pain

The EORTC-QLQ mean score for low back pain in the gynaecological cancer patients was 34.0 (SD33.8; Median 33.3, IQR 0-66.7). The back pain item is only included in the EN24 and CX24 questionnaires.

8.3.7.1 Principal component analysis for Sacrum

The first 4 principal components accounted for 97% of the DVH variability. The mean ratio of the original DVH compared to the calculated DVH at 20Gy using the varimax rotated components was 1: 0.98. The correlation of PCs to the DVH indices are illustrated in figure 8.16. PC1 describes the correlated variability of the DVH data set around the mean DVH in the range 1-50Gy. This is also demonstrated in the scatterplots correlating PC1 and Dmean in figure 8.16. PC2 describes a higher dose region between 40-65Gy. PC3 describes the intermediate dose region 35-50Gy and PC4 describes decreased relative volumes in the dose regions 1-15Gy and simultaneously increased relative dose volumes between 15-47Gy.

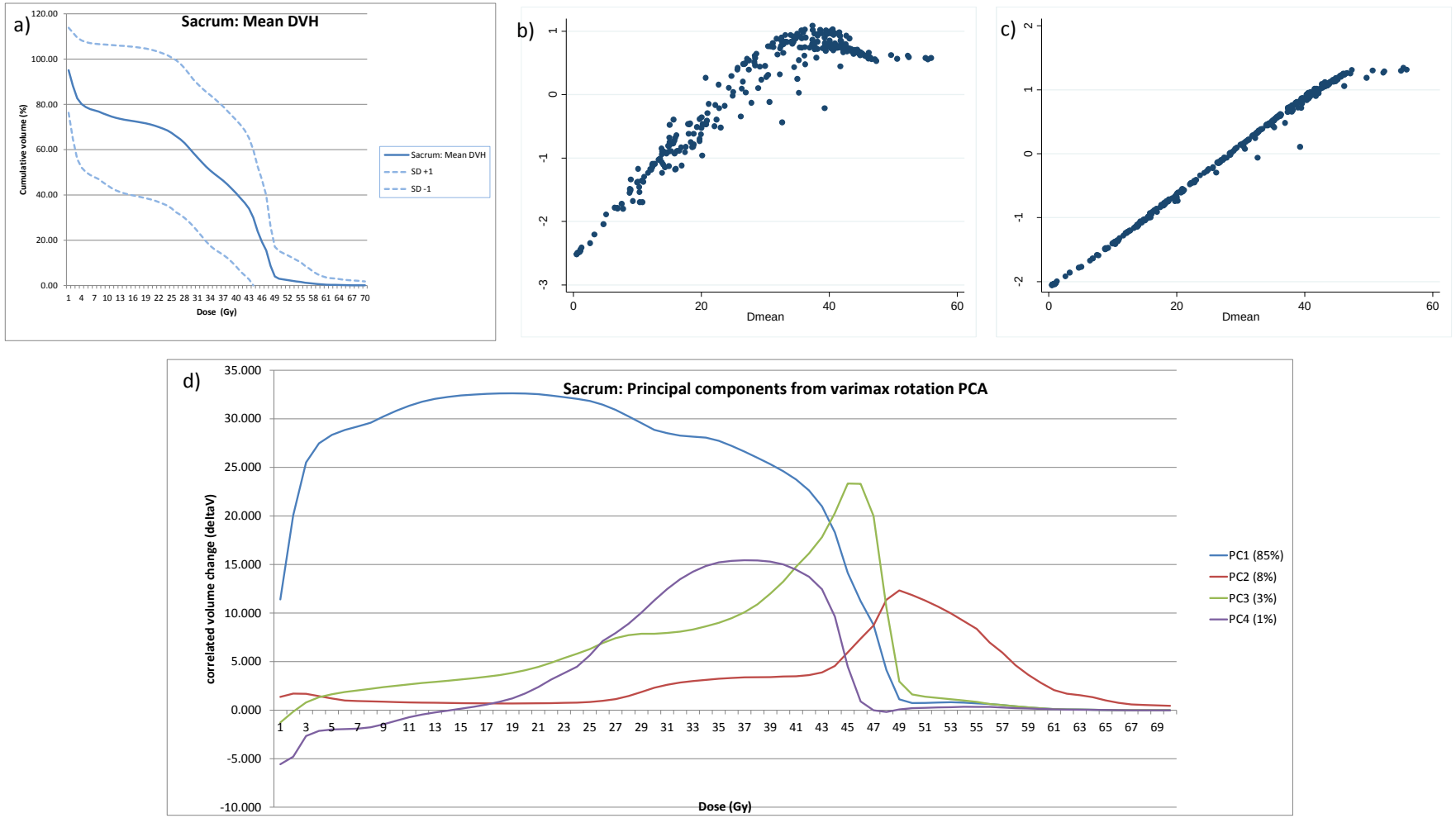


Figure 8-16: Sacrum DVH summary graphs:

(a) Mean cumulative DVH (b) PC1 with varimax rotation vs Dmean (c) PC1 with no rotation vs Dmean (d)Correlation of principal components to dose (EQD2)

8.3.7.2 Low back pain symptom regression analyses

Baseline data on physical functioning activity was not available for the cross sectional analysis. Clinically important comorbidities, treatment and patient characteristics were included in an exploratory backwards stepwise linear regression mode. Potential exploratory factors considered were: age, BMI, diagnosis, presence of recurrent disease, dose per fraction, concurrent chemotherapy, surgery, time since start of EBRT, and pre-existing musculoskeletal conditions. Dosimetric factors were separately included into a backwards stepwise linear regression model before combining with clinical factors to produce the final model. Table 8.17 shows a summary of the significant findings. BMI, the presence of musculoskeletal comorbidities (including osteoporosis, osteoarthritis and rheumatoid arthritis) and having surgery as part of treatment were associated with an increase in low back pain scores. Dosimetric correlations were seen with reduction in low back pain scores for D50 and PC1 in separate analyses with the clinical factors (D50 Coeff -1.6;95%CI -2.7,-0.5; p=0.006; PC1 Coeff -35.3;95%CI -51.4, -13.1; p=0.001). Both dosimetric factors only remained significant for patients who received EBRT for endometrial cancer when each cancer site was evaluated separately in the regression analysis (D50 coeff -1.8; 95%CI -3.1 to -0.5; p=0.008 and PC1 coeff -33.3; 95%CI -50.1 to -16.5; p=0.001). When D50 was included in the model with PC1 D50 was no longer significant.

Table 8-17: Low back pain symptom regression analysis summary

MODEL	PCA Model FINAL MODEL	Summary dosimetric parameters model
VARIABLES	Low Back Pain	Low Back Pain
Sacrum PC1	-32.26*** (-51.38 - -13.13)	
BMI	1.087** (0.123 - 2.052)	1.041** (0.0386 - 2.042)
Musculoskeletal conditions	21.64*** (7.681 - 35.61)	19.69*** (5.328 - 34.06)
Surgery	36.46*** (16.54 - 56.37)	
Concurrent chemotherapy	39.21*** (17.59 - 60.83)	25.89** (4.922 - 46.87)
Sacrum D50		-1.591*** (-2.719 - -0.463)
Observations	110	108
R-squared	0.240	0.161

8.4 Discussion

As seen in previous studies, pelvic radiotherapy is associated with bowel, urinary, sexual and musculoskeletal adverse events that may be linked with both clinical and dosimetric parameters. Within this study, the EORTC-QLQ C30 and disease-specific modules were evaluated as effective measures to collect pelvic radiotherapy toxicity information from patients on long term follow up in routine clinical practice, using both electronic and paper methods to record the information, with a high uptake rate in our

clinical population. The results of regression analysis demonstrate the PRO toxicity data collected from patients treated with different combinations of treatment for multiple tumour sites can be combined with dosimetric and clinical parameters to provide a foundation on which to develop predictive models of toxicity in future studies. This study also found PCA to be an efficient method to describe and analyse a heterogenous dosimetric dataset, taking into account treatment technique (through analysing the regression models by diagnosis and VMAT use) and dose per fraction as important dosimetric confounding factors, to explain the variations in toxicity seen within the regression analysis.

8.4.1 Application of PRO data collection in routine practice

Only 18% of patients approached by letter declined to take part in the study when approached face to face suggesting that completion of PROs in routine clinical practice is acceptable for a whole population of patients treated with pelvic radiotherapy on long term follow up. The use of Internet based methods is feasible for a range of age groups, education level and employment status and allows patients to complete the measure prior to their clinical follow up within their home environment. Paper based methods provided a viable alternative but additional resources would be required for data entry prior to data viewing by clinical teams and analysis in future applications. Patients were also happy to complete the PRO measure during their clinic appointment whilst waiting to be seen and after their appointment, with the same percentage of patients completing the survey online and on paper at these time points. To maximise uptake of PRO completion a combination of approaches – Internet and paper; at home and in clinic – may be most effective.

8.4.2 EORTC-QLQ for symptomatic toxicity reporting

As has been seen in multiple clinical trial settings, the EORTC-QLQ system is effective in evaluating the prevalence of late toxicity following pelvic radiotherapy. This study has demonstrated the use of these validated PRO measures in a clinical practice setting to evaluate the prevalence of symptomatic toxicity in a population cohort of patients treated with pelvic radiotherapy over the past 1-5 years. Similar patterns of prevalence are seen in this cohort as compared to recent trial data, with higher scores for fatigue and sleeping problems(14, 57), urinary frequency(57), urinary urgency(302, 324), bowel urgency(302, 324), flatulence(324), vaginal dysfunction(14, 18) and impotence(14). The levels of missing data for the sexual activity item for both men and women was very low in comparison to clinical trial reports (14% and 8% respectively) and was also low for the impotence item (8%). This may suggest that within a clinical practice context patients are more open about responding to potentially more sensitive

items. The prevalence of symptoms over time appears similar regardless of duration since radiotherapy for all symptoms within this analysis except for bowel urgency in the GI cancer patients who had some improvement in their symptoms with time. This lack of variability over time was seen in the study by Adams and colleagues who evaluated patients previously treated over a longer time period from 1-11 years and found no appreciable differences(302). The trajectory of symptoms over the first one year following radiotherapy will be assessed within the prospective study (Chapter 9) but longer follow up is required to fully evaluate these findings further.

Data is not available to clarify what constitutes a minimally important difference in the EORTC-QLQ scores and how to interpret the scores when evaluated using a cross sectional methodology at either the individual or group level. Within a single item, a score of 0 relates to a patient response of ‘not at all’, a score of 33.3 score is a linear transformation from the patient response category ‘a little’, as compared to 66.6 corresponding to a response ‘quite a bit’ and 100 ‘very much’. A number of symptom items within the analysis had mean scores of 33.3 or more. Pragmatically one could assume that a response of ‘a little’ describes a symptom that patients suffer with but is not impacting sufficiently on their daily lives to score more highly, and this is certainly the suggestion from the cognitive interview data analysis in Chapter 5. This would mean a score of 33.3 be considered a minimally important difference and one requiring further discussion to consider potential management interventions. However, this interpretation may underreport toxicity and further evaluation of the minimally important differences for each item in turn is necessary to provide accurate recommendations for using EORTC-QLQ in interpreting cross sectional data.

Similar challenges arise when determining what constitutes an important change in symptoms when interpreting the regression analysis results for predictive outcome modelling. Early evaluation on EORTC-QLQ C30 found that patients who completed the module on two separate occasions and rated their perceived change in their ratings between the two occasions found that patients who rated their symptoms had changed ‘a little’ had a mean score change between 5 and 10 points, those who perceived a ‘moderate’ change in symptoms had a change in mean scores between 10 to 20 points and for ‘very much’ change greater than 20(244). It is not clear if these interpretations can be applied to the regression model outcomes.

8.4.3 Principal component analysis

PCA allowed the complex and heterogeneous OAR DVH data for four different cancer sites treated with different techniques and doses to be described with a few PCs for

each OAR. Although DVH data is strongly correlated within treatment techniques using a heterogenous data set allowed for different patterns of correlations among dose volume parameters to be segregated. This was seen in some of the regression analyses where the main effect of the model was found within a separate cancer site rather than describing the DVH dataset as a whole. A number of authors have recommended incorporating heterogenous dosimetric datasets into toxicity analysis to explore across treatment dosimetric parameters to strengthen the generalisability of the outcomes and as a means to resolve issues with using highly correlated data within regression analyses(132, 312). Previous research has included data from a single cancer site treated using two different fractionation schedules(126) however, this is the first study to combine multiple pelvic treatment sites and fractionation schedules within a single analysis.

Through exploring the outcomes of the PCA analysis alongside models developed using the cumulative DVHs and summary dosimetric factors (Dmean, Dmax and D50) it was possible to see the greater contribution provided by the PCs within the regression models to explain the differences in toxicity seen. Therefore using a PCA increased the chance of revealing significant correlations in the data if they were present and may allow generalisation of the outcomes to patients treated with different dose and fractionation schedules, which is not possible with the other dosimetric parameters.

8.4.4 Regression analysis

Understanding the combination of dosimetric and clinical factors and their impact on patient symptoms following pelvic radiotherapy is important for future development of individualised treatment, patient care and supportive interventions(92).

8.4.4.1 Urinary symptoms

Prospective research has found baseline symptoms to provide the strongest predictors of urinary incontinence and frequency within an analysis with dosimetric and other clinical data(131). Unfortunately this information was not available for this analysis due to the cross sectional nature of the trial. Two PCs, PC2 and PC6, describing increased relative volumes in high dose regions were associated with increases in urinary frequency scores as was Dmax supporting the view that patients with bladder volumes receiving greater radiation doses are more at risk of urinary frequency. PC2 in this analysis appeared to describe the endometrial patient group, PC6 the anal cancer treatment, and Dmax the rectal cancer group. On the contrary, PC2 described a relative decrease in urinary urgency scores within the cervical cancer group in a

regression where female patients and increasing BMI were associated with increased urinary urgency scores. Urinary incontinence was also related to increasing BMI and female gender as well as patients who did not receive surgery scoring more highly. BMI has been found in other studies of gynaecological cancer patients to be predictive of worse urinary incontinence scores(11). Prevalence of urinary incontinence is higher in women within the general population and increases with age, with rates of severe incontinence approximately twice those of men in the 70-80 year old age group(325). The higher rates in patients not receiving surgery may be a surrogate for patients receiving chemoradiotherapy as a definitive treatment as is the case for anal and cervical cancer patients but evaluation is required.

Bladder PC2 is highly correlated with Dmean at higher doses (40-65Gy). In a prospective study of prostate EBRT by Yahya and colleagues, PC1 describing the mean dose between 0-70Gy was found to correlate with urinary frequency symptoms(131). Further modelling of urinary symptoms within a prospective setting will be key to understanding the opposing effects of PC2 on the bladder and describing more fully the impact of treatment technique when data on baseline symptoms and change from baseline scores may be incorporated into the analysis.

QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) aimed to extensively review the normal tissue dose constraints from the literature to provide a clear overview(92). For the bladder, dose limits of 40-50Gy were recommended for gynaecological cancer patients but clear dose tolerances were not clearly ascertained due to a paucity of evidence demonstrating a clear dose response and challenges associated with organ motion and distension(283). Our findings provide some evidence to support the dose limit of 40-50Gy in endometrial cancer and support this constraint in anal cancer patients. However, the results also support the suggestion from the QUANTEC review that different parameters may be necessary to describe bladder complications for different cancer sites. The different Bladder PCs found in this analysis appeared to describe different treatment techniques as when each cancer site was evaluated separately the model only retained significance for a single cancer site.

8.4.4.2 Bowel symptoms

Bowel urgency was the most prevalent symptom in all patients without a stoma and this finding supports other research findings that around 30-40% of patients post pelvic radiotherapy are affected with bowel urgency(326-329). When all cancer sites were included in the analysis, BMI and PC3 for BowelBagL3 OAR increased patient's bowel urgency scores. BowelBagL3 PC3 described the increased relative volumes in low (1-

10Gy) and high dose regions (32-70Gy) with decreased relative volumes in the intermediate dose region and described a cross treatment parameter (15-32Gy). BowelBagL3 PC3 and BMI were similarly significant variables within the regression analysis for faecal incontinence. BowelBagL3 PC3 and BowelBagL3 PC1 (associated with mean DVH) were associated with increasing diarrhoea symptoms. PC4 (correlated with decreased relative volumes in dose regions 1-5Gy and 30-45Gy and increased relative volumes in dose regions 5-30Gy and 45-50Gy) was associated with a decrease in diarrhoeal symptoms. These three PCs described different regions of segregation of individuals with similar DVH morphology in all cancer sites and were seen to describe variation across different treatment. BowelBagL3 PC3 was also found to increase PR bleeding scores, although the prevalence of this adverse event was very low.

V45 has been found to be a significant predictor of increased acute GI toxicity in patients treated with both 3D-conformal(282) and IMRT techniques in gynaecological cancers and prostate cancer, where the intestinal cavity OAR was contoured(121, 330). QUANTEC found a lack of dosimetric modelling for late toxicity associated with intestinal cavity or small bowel OARs but concluded that limiting V45 to <195cc for the intestinal cavity would be likely to reduce late as well as acute toxicity risk(282). These conclusions broadly fit with our findings that relative increased volumes in the high dose region (BowelBagL3 PC3) are associated with increased toxicity scores for bowel urgency, diarrhoea, PR bleeding and faecal incontinence. The multiple PCs associated with diarrhoea are more challenging to explain. The complexity of the findings could be related to the lower incidence of this symptom in our sample and the challenges patients described when reporting on this item in the questionnaire in Chapter 5, with the item reflecting changes in stool consistency, as well as bowel frequency and urgency. The issue may also relate to variation in the movement of small bowel within the BowelBag contour or could reflect additional treatments such as the presence of a stoma.

AnoRectum and Mid Rectum PCs were also associated with changes in bowel urgency along with BMI in the gynaecological cancer patients. AnoRectum PC2 was associated with increasing bowel urgency scores and describes the intermediate dose regions (20-50Gy) across different treatment regimes. In contrast AnoRectum PC3 and MidRectum PC2 both describe increased relative volumes in the high dose regions (45-65Gy and 46-70Gy respectively) and were correlated with reductions in bowel urgency scores with the main effect of these parameters found in the cervical cancer group. Previous studies have focused on rectal toxicity in prostate cancer patients where external beam doses are higher than in our sample (typically 66-78Gy). These studies converge on

cumulative DVHs >V65-V70Gy associated with increased toxicity(15, 126, 309, 310). Intermediate and high dose regions were significantly associated with toxicity in the review analysis carried out by QUANTEC(278). However, the authors commented that this finding could be explained by the high correlation between high and intermediate Vdoses or that the volume exposed to intermediate doses contributes to tissue repair and recovery of the higher dose regions. These findings are interesting as the rectal volumes treated to V70 occurred at a very low incidence for the gynaecological cancer sample in this study compared to prostate patients - Mean and median V70 values for AnoRectum, inferior, mid and superior rectum are <1% in this study vs the median V70 for whole rectum 11.7%, inferior 7.0%, mid 24.4% and superior rectum 1.3% in the paper by Stenmark and colleagues(15). However, in comparison at intermediate doses (V40) a much greater proportion of the AnoRectum is irradiated in the gynaecological patients in this study with a median of 83.6% vs median V40 in the prostate cancer group of 29.7%; inferior rectum 43.7% vs 26.3%; mid rectum 100% vs 62.0% and superior rectum 98.5% vs 13.9%(15). Increased relative volumes in the intermediate dose region of the AnoRectum describing variation across both endometrial and cervical treatments is related to a substantial increase in bowel urgency symptoms. This model requires further analysis with an independent data set to evaluate these findings further. The low incidence of volumes treated to high doses may explain the lack of correlations between other bowel symptoms and rectal OAR dosimetric outcomes in this study.

This analysis found that statin use was associated with a reduction in abdominal cramps in the gynaecological cancer patients. Wedlake and colleagues reported similar findings in a study where GI symptoms improved through use of statins during and after pelvic radiotherapy(301). In this sample, patients statin use at the time of entry into the study was recorded as data on whether patients had been taking statins at the time of treatment was not availably consistently. This finding may provide additional support to the findings of Wedlake et al. that sustained use of statins may provide longer-term GI protection post pelvic EBRT(301). Within this analysis ACEi use alone was associated with increased bowel frequency and did not have the protective GI effect recorded by Wedlake et al. when used in combination with statins(301). These findings require further exploration in prospective models with larger sample sizes.

8.4.4.3 Female sexual dysfunction

Increasing age was associated with improved scores for all vaginal items. This may reflect patient expectations that as they get older they will experience menopausal symptoms and compensate for this within their responses. HRT use was also found to

improve overall vaginal functioning, vaginal stenosis and vaginal shortening scores although in the sample of sexually active patients only 22 patients (29%) were recorded as taking HRT with a mean age of 43.5 (SD10.6). This is an interesting finding as HRT (or the combined oral contraceptive pill in younger patients) is used in patients who are pre- or peri-menopausal before EBRT treatment and use is encouraged until age 50 for patients with no contraindications. A systematic review on interventions to support vaginal physical dysfunction following pelvic radiotherapy did not review the literature on HRT use in pelvic radiotherapy related vaginal stenosis but found topical oestrogens to have some evidence (level 1c) to support their use(90).

Vagina PC3, V50 and D50 were associated with worse overall vaginal functioning when combined with HRT and age in the multivariate regression analysis. Vagina PC3 describes increased relative volumes in the highest dose region between 40-65Gy and was also correlated with worse vaginal stenosis scores in association with D50. These findings broadly corroborate the findings from the study in anal and rectal cancer patients by Son and colleagues where mean vaginal doses <43Gy and gEUD <35Gy were found to be associated with reduced risk of severe vaginal stenosis based on maximum dilator size(286). The contouring of the vagina in the Son et al study differed slightly in the superior border from the OAR contour in this study with the vaginal contour extending up to the uterus rather than the inferior border of the cervix as it did in our study. The inclusion of gynaecological cancer patients within our study also led to restrictions on the superior border based on GTV extension. Vagina PC6 relating to increased relative volumes in the dose region 35-50Gy was associated with worse vaginal dryness with the main effect of the model seen in the cervical cancer group. Previous research has not evaluated this symptomatic outcome and further evaluation in independent datasets is necessary to evaluate this finding further. Similarly further evaluation is necessary for the findings that female genitalia PC4, correlated with increased relative volumes in between 1-34Gy and 44-58Gy and decreased volumes between 34-44Gy, increased dyspareunia and female genitalia PC1 (describing the mean DVH) and V30 reduced enjoyment of sex. The trend towards these PCs having significance for these symptoms in the anal cancer group is not surprising due to the tumour position and the treatment technique used.

8.4.4.4 Male sexual dysfunction

In comparison to the female dysfunction scores, increasing age was associated with worse erectile function and reduced libido. Increasing age has been found to be an important clinical factor in other studies of erectile dysfunction following pelvic EBRT(331, 332). Increasing BMI was also associated with worse erectile function

scores has been seen as a risk factor in the general population along with increasing age(333). Surgery was also found to be an important factor in addition to EBRT in predicting worse erectile function supported by the findings from the Dutch TME rectal cancer study and CRO7 trial(156, 158). The penile bulb OAR has been considered as an anatomical surrogate for the erectile apparatus as the actual structures involved are not yet determined(287). Using the recommended OAR contouring guidelines for penile bulb, PC1 for the penile bulb, describing the mean DVH, and Dmax were both associated with significantly worse erectile function with the main dosimetric effect of the model seen in the rectal cancer group. Interestingly the anal cancer patient group had the higher doses to Dmean and Dmax in this study (table 8.9), suggesting further evaluation of this finding is required. The QUANTEC review recommended limiting mean dose to 95% of the structure to <50Gy based on a number of studies reporting on penile bulb dose in prostate cancer EBRT(287). These findings add evidence in different cancer sites and may suggest lower mean and maximum doses to the penile bulb may also affect erectile function.

8.4.4.5 Low back pain

In the gynaecological cancer patients the incidence of low back pain was increased with a diagnosis of a musculoskeletal condition, increasing BMI, receiving surgery and concurrent chemotherapy. Previous studies have found associations with increased risk of sacral insufficiency fractures and a diagnosis of osteoporosis following pelvic irradiation in rectal cancer patients (334). In gynaecological cancer patients, a trend towards increasing back pain reported in patient medical records was seen in patients treated with concurrent chemotherapy(335). No dosimetric models were available to compare the dosimetric associations with PC1 and D50 and a reduction in back pain scores and previous evaluations of the impact of total EBRT dose on the incidence of pelvic insufficiency fractures have been conflicting(292, 336). Further evaluation in multiple cancer sites is required to evaluate this model further.

8.4.5 Limitations

A cross sectional method was used to evaluate late toxicity and although this limits the ability to conclude if the prevalence of symptoms reported is a true reflection of complications related to treatment or in fact related to existing problems, it was necessary due to time restrictions on completion of a thesis within three years. This may be of particular relevance for bladder symptoms where pre-existing bladder problems are predictive of worse late urinary symptoms(131). Whilst the analysis incorporates dosimetric data from multiple cancer sites using different treatment

techniques, the predictive modelling is mainly based on 3D-conformal treatment with only 17 endometrial and 2 cervical cancer patients treated with VMAT techniques. Whilst this analysis is on historical data the models developed will provide a guide towards development of dosimetric OAR models for newer, more precise techniques.

For the majority of OARs standardised contouring has been used with reference to detailed protocols developed through extensive quality assurance and training to ensure reproducibility. For non-standard OAR contouring for male and female sexual organs the extent of the contours was discussed with consultant radiologists and clinical oncologists with international expertise in radiotherapy contouring with the end organ pathophysiological process of late toxicity in mind. Although this may limit the comparability of the sexual organ dosimetric models to other studies relatively little data exist in this area at the current time. In particular it will be important to evaluate whether the dosimetric and anatomical models developed for non-standardised sexual organ OARs in this study translate to other institutions.

Finally, the patients in this study had a median of 2 years follow up following EBRT treatment, which may limit the applicability to longer-term adverse events and underestimate toxicity as severity may still increase over time. However, in a study looking specifically at toxicity differences using PROs between patients treated 1-5 year post treatment and those treated 6-11 years ago found no significant differences between the two groups(302).

8.4.6 Future work

Currently radical radiotherapy is broadly individualised for patients through planning on each patients' simulation CT scan, based on tumour size and position and through managing which patients, taking into account age and comorbidities, may be suitable for concurrent chemotherapy (if applicable). Although dose constraints for normal tissues exist for many of the pelvic organs, much of the rectal and penile bulb dosimetric data has been extrapolated from clinical trials involving prostate cancer patients and may not be generalizable to other patient groups(278, 287). OAR data for bladder and small bowel/intestinal cavity whilst involving more heterogeneous tumour sites, remain without clear models on which to base dose constraints on(92, 282, 283).

This analysis explored the role of PCA as a research tool to assess the impact of dosimetric factors on toxicity outcomes and has demonstrated the application across multiple cancer sites and treatment techniques, including IMRT, within the pelvis.

Despite the limitations of using a cross sectional trial design without such data it would challenging, if not impossible, to design effective predictive models. Future prospective trials can then be used to validate and refine predictive models derived resulting in a better understanding of the causes of toxicity in patients. This study creates a foundation for future clinical trials seeking to evaluate treatment approaches, which aim to avoid certain late toxicities randomly compared with standard protocols. Through developing the application of PCA and probability modelling within clinical trials and in clinical practice, the management of patient treatment may be better individualised to decrease the probability of radiotherapy related toxicities.

The following chapter explores the prospectively collected PRO results of patients treated with pelvic radiotherapy in anal, cervical, endometrial and rectal cancer.

Chapter 9 Electronic and paper collection of patient reported toxicity in patients treated with pelvic radiotherapy: A Prospective feasibility study

9.1 Introduction

The use of patient reported outcomes (PROs) in cancer clinical trials is now widespread. The United States (US) Food and Drug Administration (FDA) have set out rigorous guidelines for the development and use of PROs as both primary and secondary trial outcomes(45). Best practice guidelines for collection and use of PRO data within clinical practice have also been established in the International Society for Quality of Life Research (ISOQOL) *User's Guide for Implementing Patient-Reported Outcomes Assessment in Clinical Practice* and the key recommendations outlined in earlier chapters(337).

It is expensive to collect prospective longitudinal data due to high administrative and staffing costs of collecting repeated questionnaires alongside communication with patients. Using Internet-based PRO data collection has been estimated to be four times cheaper than paper collection with cost savings for printing, paper, postage, storage and data entry(338, 339). Internet-based methods have also been found to improve compliance rates over paper methods(114). Internet-based methods also enable real-time integration into patient's electronic records allowing immediate availability of PRO results in multiple formats (for example graphical and tabular)(111). However, it may be preferable to include the option for completion of questionnaires using paper-based methods alongside Internet-based methods within a cohort study design to maximise response rate and inclusivity for a whole clinical population(339).

The use of PRO assessments in clinical practice has focused on the monitoring of toxicity and health related quality of life (HRQOL) associated with systemic treatments. Currently, the longest mean duration of follow up using PROs collected electronically is eight months, on a cohort of patients treated with multiple courses of chemotherapy(113). In this study by Judson and colleagues, all patients with access to a home computer with Internet access and email who were being treated with chemotherapy for lung, gynaecologic, breast, and genitourinary cancer were eligible until they completed treatment. With weekly email reminders the average monthly

compliance was 83% (SD25%) and weekly compliance 62% (SD30%), demonstrating the feasibility of PRO data collection longitudinally over a long time period. However, participants were in regular contact with the hospital as they were all on active chemotherapy treatment. In comparison, a longitudinal study of patients treated with radical radiotherapy in clinical practice would involve both an acute period during which patients would be attending the hospital daily for treatment and also long term follow up with periods of weeks and months without contact with the hospital.

In two studies of a clinical practice cohort of patients treated with radical radiotherapy for gynaecological malignancies, paper PRO compliance rates ranged from 99% immediately after treatment completion, to 27% at 6 weeks following completion of radiotherapy, 37% at one year and 25% at 3 years(12, 340). Within a randomised clinical trial (RCT) setting patients treated with chemoradiotherapy for lung cancer completed electronic PROs at baseline, weekly during treatment and once at week 12 with a 69% compliance rate at week 12 post treatment(134). However, within clinical practice, the feasibility of electronic PRO data collection in the long-term follow up of patients treated with radical radiotherapy has not been evaluated. As seen in the systematic review, higher rates of symptomatic late toxicity were reported using PRO data as compared to clinician reporting. It may therefore be beneficial to prospectively collect PRO data to accurately establish the prevalence and trajectory of acute symptomatic toxicity during and in the first few months after radiotherapy, particularly at time points when clinicians do not routinely review patients.

9.1.1 Aims

This chapter provides an interim analysis of the findings from the prospective study. This descriptive analysis aims to characterise patient's self-reported baseline symptoms, acute and late self-reported toxicity during and in the first year following pelvic radiotherapy for patients with anal, rectal, cervical and endometrial cancers treated with curative intent. In addition, this chapter aims to evaluate the initial findings regarding the feasibility and acceptability of longitudinal PRO data collection alongside routine clinical care over a period of one year using both electronic and paper methods. This is evaluated through consideration of recruitment and attrition rates, compliance and analysis of the feedback questionnaires from patients who have completed the study. Case studies will illustrate the clinician view of the PRO toxicity results. Following study completion in June 2016, future analysis will evaluate the clinical and treatment related factors associated with patient reported toxicity and used to validate the dosimetric models developed within the cross sectional study.

9.2 Methods

9.2.1 Patient sample

The study cohort comprised men and women with anal, rectal, cervical and endometrial cancer treated between May 2014 and June 2015 at the Institute of Oncology Outpatient Clinic at St James's Hospital, Leeds with radical (curative) pelvic external beam radiotherapy (EBRT). Patients were eligible if they received standardised radical 3D conformal radiotherapy, Image Modulated Radiotherapy (IMRT) or volume modulated arc radiotherapy (VMAT) in four cancer sites: 1) radical (chemo)radiotherapy for anal cancer; 2) neoadjuvant (chemo)radiotherapy for rectal cancer; 3) radical (chemo)radiotherapy for cervical cancer; and 4) adjuvant radiotherapy for endometrial cancer and cervical cancer. Patients were also eligible if they were receiving radical radiotherapy for pelvic recurrence in these tumour sites.

The National Research Ethics Service Leeds East Committee approved the study following ethical review (13-YH-0156). Patients were eligible for the study if they were 18 years or older, able to read and understand English and were not exhibiting overt psychopathology or serious cognitive dysfunction. All participants provided written informed consent. Clinical staff identified eligible patients during their initial consultation and introduced patients to the research team. Full details of the approach taken are described in Chapter 6. Patients were aware that the PRO data collection was for research, and although the data would be available to clinicians (within Leeds Teaching Hospitals) the process was not designed to replace any existing clinical structures.

9.2.2 Summary of curative radiotherapy

Details of curative treatment received for all tumour sites are outlined in full in the previous chapter. This section provides a brief summary of the treatment regimes with a focus on the impact the different schedules have on the assessment times in this study. There are six different treatment regimes for the eligible patients in this study and 10 different study arms as the male and female patients received different questionnaires in the gastrointestinal cancer (GI) groups.

1. Short course radiotherapy for rectal cancer (male and female) (SCRT): Patients received 25Gy in 5 fractions over a week followed by total mesorectal excision (TME) surgery within 7-10 days
2. Short course radiotherapy and delay for rectal cancer (male and female) (SCRT delay): Patients receive 25Gy in 5 fractions over a week followed by an MRI scan at six weeks to assess response before consideration of TME surgery
3. Long course chemoradiotherapy for rectal cancer (male and female) (LCRT): Patients receive 5 weeks of EBRT (45Gy in 25 fractions) with concurrent chemotherapy (capecitabine or 5-flurouracil (5FU) followed by an MRI scan at six weeks to assess response before consideration of TME surgery
4. Anal cancer patients (male and female): Patients receive 3-5 weeks of chemoradiotherapy as their definitive treatment, as outlined in the previous chapter, with the majority of patients receiving 5 weeks of EBRT. Within the anal cancer patient group, IMRT was introduced during study recruitment. The IMRT volumes followed the UK national protocol recommendations(341). Patients with T1-2N0 squamous cell anal cancer received 50.4Gy in 28 fractions to the gross tumour volume (GTV) with concurrent Mitomycin on day 1 (12mg/m2) and 5FU days 1-4 and 29-32 (1000mg/m2) and 40Gy in 28 to the clinical target volume (CTV). Patients with stages T3/4 or TanyN+ received 40Gy in 28 fractions to the inguinal nodes (elective nodal volume: ENV), 50.4Gy in 28 fractions to the gross nodal volume and 53.2Gy in 28 fractions to the GTV with concurrent chemotherapy as before. Organs at risk (OAR) contouring was only standard for patients treated with anal cancer IMRT: Small bowel 30Gy ≤ 200cc, 35gy ≤150cc, 45Gy ≤ 20cc, 53.2Gy 0cc; Bladder 35Gy ≤5%, 40Gy ≤35%, 50Gy≤5%; Femoral heads 30Gy≤5%, 40Gy≤35%, 44Gy≤5%; External genitalia 20Gy≤5%, 30Gy≤35%, 40Gy≤5%.
5. Cervical cancer patients: receive 5 weeks of concurrent chemoradiotherapy (48Gy in 28 fractions with weekly cisplatin) followed by brachytherapy (21Gy in 3 fractions over 14 days) as their definitive treatment. Post operative patients receive 5 weeks of EBRT (45Gy in 25 fractions) with some patients (with close margins or invasion of parametria) receiving brachytherapy 12Gy in 3 fractions on consecutive days following EBRT.
6. Endometrial cancer patients: Following their surgery, (patients with fully resected FIGO stage 3a, 3c and 4 disease are also offered a six cycle course of three weekly carboplatin and paclitaxel chemotherapy post operatively) patients receive 5 weeks of EBRT (45Gy in 28 fractions). Patients with cervical involvement are also offered brachytherapy 12Gy in 3 on consecutive days following EBRT.

9.2.3 Assessment

Baseline questionnaires were completed at time of consent prior to or within 0-4 days of starting radiotherapy treatment. At this time patients opted to either complete the questionnaires online, receiving either email or letter reminders, or to complete paper questionnaires which were posted to them. Patients were invited to complete the questionnaires at different time points depending on treatment received. These time points broadly coincided with usual follow up schedules for patients. Patients are seen weekly during treatment, at week six post treatment completion, then at 3, 6, 9 and 12 months following completion of EBRT. Following recommendations from health professionals, two PRO assessments during treatment at week 2 and week 5 were suggested rather than weekly evaluation and an additional PRO assessment at two weeks following EBRT completion to coincide with potentially the timing of greatest toxicity when patients are not routinely reviewed by clinicians(see table 9.1 and chapter 4). All patients were invited to complete questionnaires at six common time points baseline, week 2 after the start of radiotherapy treatment, week 7, week 26 (six months following treatment completion), week 39 (9 months) and week 52 (12 months).

Table 9-1: Schedule of PRO assessment times for prospective study

Grouped timings for analysis	Week of clinic appointment (Day 1 is start of RT)	Short course rectal Male/ Female	Short course and delay rectal Male/ Female	Long course rectal Male/ Female	Anal Male/ Female	Cervical	Endometrial
Baseline	Baseline						
Week 2	Week 2	Surgery at week 2-3					
Week 5	Week 5						
Week 7	Week 7						
N/A	Week 8		Surgery at week 8				
Week 11	Week 11			Surgery at week 11			
	Week 14						
Week 18	Week 17						
	Week 19						
Six months (Week 26)	Week 26						
	Week 29						
	Week 31						
9 months (Week 39)	Week 38						
	Week 41						
	Week 43						
12 months (Week 52)	Week 50						
	Week 52						
	Week 55						
	Total number of questionnaires	7	7	8	9	9	9

Shaded area: Invitation to complete PRO assessment sent

Short course – 5 days radiotherapy. All other external beam radiotherapy schedules are over 5 weeks.

Anal, cervical and endometrial cancer patients received additional invitations to complete questionnaires at week 5 during treatment, week 11 and week 18. Rectal cancer patients follow up schedules were modified to allow for recovery time following surgery following health professional recommendations (Chapter 4). For the first seven weeks of follow up on the study, one reminder was sent out 7 days after the initial invitation. For the remainder of the study two reminders at 7 and 14 days after the initial invitation were sent out. This is due to the differences in the scheduling for the later invitations, with periods of 3 months between the invitations. Email and letter reminders were managed using the tracker system (Microsoft Access) as described previously in Chapter 6. Occasionally, patients who were seen by researchers informally when they attended their hospital follow-up appointments were reminded about questionnaire completion. This occurred on occasion during the recruitment period if patients were seen in the waiting area whilst recruiting new patients.

Electronic results were immediately available for viewing by clinical staff in patient's electronic health records (EHR). At the start of the study paper results were not available to staff in the EHR. However following staff feedback all paper results were also inputted into QTool and the results made available.

Socio-demographic data including patients' age, gender, marital status, level of education and employment status was collected at the start of the study. Clinical information including primary tumour site, stage of disease, current status of disease (e.g. evidence of disease recurrence) and the treatment regimen, along with BMI, smoking and alcohol use was recorded from the medical notes at study entry and disease status updated at the time of analysis. Medical information detailing co-morbidities, previous surgery, and current medications was provided by patient self-report at study entry.

9.2.4 Outcome measures

As in the cross sectional study, patients completed the validated cancer specific EORTC core questionnaire ((EORTC QLQ-C30) and the disease specific module for the relevant cancer site (cervical- CX24; endometrial –EN24 and anal and rectal (gastrointestinal - GI) patients – CR29) with additional items from the EORTC item bank selected through the development work of this project and used in the cross sectional study(67, 313-316). For the majority of items a four-point Likert-type scale is used for the questionnaire and the item responses are converted through a linear transformation for both individual and scaled items onto a 0-100 scale. Higher scores

for symptom items reflect a higher level of symptoms and higher scores for the function items reflect a better level of functioning(129). For single symptom items, a score of 0 relates to a patient response of ‘not at all’, a score of 33.3 score is a linear transformation from the patient response category ‘a little’, as compared to 66.6 corresponding to a response ‘quite a bit’ and 100 ‘very much’. For functional items a score of 100 represents a patients with no impact on their functioning, 66.6 relates to ‘a little’ impact on function, 33.3 ‘quite a bit’ and 0 ‘very much’. As discussed in Chapter 8, mean scores of 33.3 or more for symptom items or 66.6 or less could be considered as responses requiring further discussion with patients to consider potential management interventions. Minimal important differences were classified as a change in score of 5-10 points, moderate differences as a change between 10-20 points and large differences to be change in score greater than 20 points(244).

9.2.5 Sample size

The sample size was based on the estimated number of patients treated with pelvic radiotherapy in Leeds Cancer Centre over a one year period in anal, cervical, endometrial and rectal cancer. Approximately 365 patients were estimated to receive treatment over a one year period: 35 anal cancer patients, 40 cervical, and 40 endometrial, and 250 rectal cancer patients. The target recruitment number was estimated at 130 patients: 16 anal cancer patients, 18 cervical, and 18 endometrial, and 78 rectal cancer patients. This estimation allowed for a 70% recruitment rate and 35% attrition rate(20). The number of rectal cancer patients was reduced to 78 patients based on the sample size estimates described in Chapter 8, where a mimimum sample size for each disease site of 73 was required to detect moderate effect sizes of DVH (f^2=0.15).

9.2.6 Statistical analysis

Data was analysed using Stata/SE 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13.1. College Station, TX: StataCorp LP). PRO scores over time, clinical data and feedback questionnaires were summarised using descriptive statistics. Analysis of the EORTC QLQ-C30 and disease specific modules and handling of missing responses within a questionnaire were performed according to the EORTC guidelines, using a process of imputing for missing values in scaled responses(129). As patients were able to access the questionnaire online at any time and postal reminders were sent, on occasion patients completed more than one questionnaire during a particular time period. The mean of these item responses was used for the analysis. An interim analysis of the reasons for patients leaving the trial will be presented along with an

evaluation of the rate of recruitment to the study. Evaluation of the reasons for missing questionnaires will be considered when the full analysis is completed.

9.3 Results

In total, 158 patients were eligible to participate in the study between 1st May 2014 and 16th April 2015, meeting the estimated rate of recruitment, and 132 consented to take part (84%) (Figure 9.4 in section 9.3.2.2 shows a CONSORT diagram). Of these, three patients were excluded from the analysis: two patients left the trial prior to completion of the baseline questionnaire (one stated she was 'too busy' to take part and the other provided no specific reason) and one patient died before the start of radiotherapy. Of the remaining 129 patients, 16 left the trial over the course of the follow up period: 10 patients died; two stated they were too unwell to continue; one patient following pelvic extenteration surgery felt the questions on the survey were no longer relevant; two felt uncomfortable completing the questionnaires and one provided no reason. The mean duration of follow up at the time of this interim analysis is 9.5 months (41 weeks) and median time 9.8 months (42 weeks; range 0.5 to 12 months). At the time of writing, all patients have completed the six months (Week 26) follow up time point.

The characteristics of the 26 patients who did not take part in the study broadly reflected the characteristics of the study population, although more often women declined to take part (female n=19 (73%) vs. male n=7 (27%)). The mean age for decliners was 66 years (range: 47 to 87 years). Six patients had a diagnosis of anal cancer (23%); six cervical (23%); three endometrial (12%) and 11 rectal (42%). Three patients were not entered for administrative reasons. One patient was not approached following a doctor's decision and two patients became ineligible. Twenty patients actively declined to take part, with one patient stating they did not want to take part in a study with one year follow up and four patients stating there was too much else going on at the time to consider taking part. The remaining 15 did not provide a reason.

9.3.1 Baseline characteristics and choice of questionnaire completion method

One hundred and twenty nine patients were included in the analysis: 27 with a diagnosis of anal cancer (21%), 18 cervical (14%), 11 endometrial (8%) and 73 with rectal cancer (57%). Recruitment in the endometrial cancer subgroup was slower than expected. This is because patients who were previously treated with EBRT now receive brachytherapy alone, following the outcomes of the PORTEC-2 trial showing a

reduction in toxicity and no impact on survival with brachytherapy(23). Seventy eight participants were female (60%) and 51 were male (40%). The mean age of patients in the trial was 64 years (SD12.4; range 32 to 94 years) but this differed according to diagnosis: cervical patients had the lowest mean age of 54 years (SD15.2; range 32 – 78); anal patients had a mean age of 60 years (SD12.2; 38-88); endometrial patients mean age was 65 years (SD7.9; 51-77) and rectal patients mean age was 67 years (SD10.7; 43-94). A summary of patient demographics, treatment and tumour characteristics are provided in tables 9.2-9.5.

Table 9-2: Summary demographics

Ethnicity	**Number of patients**	**Percent**
White British	93	72.1%
Not stated	32	24.8%
Asian/White Asian	2	1.6%
Other White background	2	1.6%
Total	129	100.0%
Marital status	**Number of patients**	**Percent**
Married/ Civil Partnership	70	54.3%
Cohabiting	10	7.8%
Separated/Divorced	15	11.6%
Widowed	20	15.5%
Single	14	10.9%
Total	129	100.0%
Employment	**Number of patients**	**Percent**
Working full time (30+ hrs/week)	25	19.4%
Working part time (<30 hrs/week)	13	10.1%
Unable to work(disability/illness)	16	12.4%
Retired	70	54.3%
Other	4	3.1%
Not stated	1	0.8%
Total	129	100.0%
Continue education after school	**Number of patients**	**Percent**
No	61	47.3%
Yes	68	52.7%
Total	129	100.0%
Degree or professional qualification	**Number of patients**	**Percent**
No	85	65.9%
Yes	43	33.3%
Not stated	1	0.8%
Total	129	100.0%

Table 9-3: Gastrointestinal cancer tumour characteristics

ANAL CANCER			RECTAL CANCER		
Histology type	**Number of patients**	**Percent**	**Histology type**	**Number of patients**	**Percent**
Squamous cell carcinoma, NOS	23	85.2%	Squamous cell carcinoma, NOS	3	4.1%
Adenocarcinoma, NOS	1	3.7%	Adenocarcinoma, NOS	65	89.0%
Neoplasm, malignant	1	3.7%	Neoplasm, malignant	2	2.7%
Cloacogenic carcinoma	1	3.7%	Carcinoma, NOS	2	2.7%
Basaloid squamous cell carcinoma	1	3.7%	Basaloid squamous cell carcinoma	1	1.4%
Total	27	100.0%	Total	73	100.0%
Tumour stage	**Number of patients**	**Percent**	**Tumour stage** (using T staging and Number staging systems)	**Number of patients**	**Percent**
1	3	11.1%	1	4	5.5%
2	12	44.4%	2	10	13.7%
3	6	22.2%	3	30	41.1%
4	4	14.8%	Stage IIIA*	4	5.5%
Unknown	2	7.4%	Stage IIIB**	21	28.8%
Total	27	100.0%	Stage IIIC***	3	4.1%
			Unknown	1	1.4%
			Total	73	100.0%
Node stage	**Number of patients**	**Percent**	**Node stage**	**Number of patients**	**Percent**
0	13	48.1%	0	21	28.8%
1	3	11.1%	1	29	39.7%
2	3	11.1%	2	18	24.7%
3	8	29.6%	3	5	6.8%
Total	27	100.0%	Total	73	100.0%
Metastasis stage	**Number of patients**	**Percent**	**Metastasis stage**	**Number of patients**	**Percent**
0	18	66.7%	0	47	64.4%
1	8	29.6%	1	21	28.8%
Unknown	1	3.7%	Unknown	5	6.8%
Total	27	100.0%	Total	73	100.0%

Key: *Stage IIIA: relates to TNM staging T1, N1, M0 or T2, N1, M0; **Stage IIIB - T3, N1, M0 or T4, N1, M0; ***Stage IIIC - any T, N2, M0

Table 9-4: Gynaecological cancer tumour characteristics

ENDOMETRIAL CANCER			CERVIX CANCER		
Histology	**Number of patients**	**Percent**	**Histology**	**Number of patients**	**Percent**
Adenocarcinoma, NOS	2	18.2%	Squamous cell carcinoma, NOS	10	55.6%
Endometrioid adenocarcinoma, NOS	3	27.3%	Adenocarcinoma, NOS	4	22.2%
Serous cystadenocarcinoma, NOS	2	18.2%	Carcinoma, NOS	1	5.6%
Mixed cell adenocarcinoma	1	9.1%	Serous cystadenocarcinoma, NOS	1	5.6%
Carcinosarcoma, NOS	1	9.1%	Adenosquamous carcinoma	1	5.6%
Clear cell adenocarcinoma, NOS	1	9.1%	Mucinous cystadenocarcinoma, NOS	1	5.6%
Mullerian mixed malignant tumor	1	9.1%	Total	18	100.0%
Total	11	100.0%			
FIGO Stage	**Number of patients**	**Percent**	**FIGO Stage**	**Number of patients**	**Percent**
1b	2	18.2%	1b1	1	5.6%
2	2	18.2%	2b	16	88.9%
3a	2	18.2%	3b	1	5.6%
3c1	2	18.2%	Total	18	100.0%
3c2	3	27.3%			
Total	11	100.0%			
Histology Grade	**Number of patients**	**Percent**	**Histology Grade**	**Number of patients**	**Percent**
Low / Well Diff	1	9.1%	Low / Well Diff	1	5.6%
Medium/ Mod Diff	4	36.4%	Medium/ Mod Diff	7	38.9%
High/ Poor Diff	5	45.5%	High/ Poor Diff	5	27.8%
Unknown	1	9.1%	Unknown	5	27.8%
Total	11	100.0%	Total	18	100.0%

Table 9-5: Treatment received by cancer site and evidence of recurrence at point of interim analysis

Treatment received and disease status at time of interim analysis	ANAL CANCER		RECTAL CANCER		ENDOMETRIAL CANCER		CERVICAL CANCER	
Concurrent chemotherapy	**Number of patients**	**Percent**	**Number of patients**	**Percent**	**Number of patients**	**Percent**	**Number of patients**	**Percent**
Yes	27	100.0%	45	61.6%	0	0.0%	13	72.2%
No	0	0.0%	28	38.4%	11	100.0%	5	27.8%
Total	27	100.0%	73	100.0%	11	100.0%	18	100.0%
Surgery	**Number of patients**	**Percent**	**Number of patients**	**Percent**	**Number of patients**	**Percent**	**Number of patients**	**Percent**
Yes	2	7.4%	62	84.9%	11	100.0%	1	5.6%
No	25	92.6%	11	15.1%	0	0.0%	17	94.4%
Total	27	100.0%	73	100.0%	11	100.0%	18	100.0%
Brachytherapy					**Number of patients**	**Percent**	**Number of patients**	**Percent**
Yes					3	72.7%	16	11.1%
No					8	27.3%	2	88.9%
Total					11	100.0%	18	100.0%
Disease recurrence during trial	**Number of patients**	**Percent**	**Number of patients**	**Percent**	**Number of patients**	**Percent**	**Number of patients**	**Percent**
Yes	2	7.4%	5	6.8%	3	27.3%	0	0.0%
No	25	92.6%	68	93.2%	8	72.7%	18	100.0%
Total	27	100.0%	73	100.0%	11	100.0%	18	100.0%

9.3.2 Patient reported outcomes using the EORTC-QLQ system

9.3.2.1 Completion methods used

At the time of recruitment, 73 patients (57%) stated they would complete the questionnaires online; however, through the course of the study 12 of them converted to completing the questionnaires on paper. The reasons given at the time were varied: not checking emails regularly, using someone else's email/computer and perceived ease of completing on paper. More women initially opted to complete the questionnaire on paper (49%) as compared to the men (35%). Table 9.6 shows a breakdown of the method used to complete the questionnaires by gender and age group. As observed in the cross sectional study, older patients tended to favour paper methods although interestingly the youngest age group (30-39 years) had more patients completing on paper by the end of the study (Paper n=3; 60% vs. Online n=2; 40%) although the participant numbers are small.

Table 9-6: Methods used to complete questionnaire

	Method used to complete questionnaire		Online entry	Paper entry	Changed from online to paper entry	Total
Gender	Female	Number of participants	33	38	7	78
		Percent	42.3%	48.7%	9.0%	100.0%
	Male	Number of participants	28	18	5	51
		Percent	54.9%	35.3%	9.8%	100.0%
Grouped Age	30-39 years	Number of participants	2	2	1	5
		Percent	40.0%	40.0%	20.0%	100.0%
	40-49 years	Number of participants	6	4	3	13
		Percent	46.2%	30.8%	23.1%	100.0%
	50-59 years	Number of participants	15	11	1	27
		Percent	55.6%	40.7%	3.7%	100.0%
	60-69 years	Number of participants	24	12	5	41
		Percent	58.5%	29.3%	12.2%	100.0%
	70-79 years	Number of participants	13	18	1	32
		Percent	40.6%	56.3%	3.1%	100.0%
	80-89 years	Number of participants	1	8	1	10
		Percent	10.0%	80.0%	10.0%	100.0%
	90-99 years	Number of participants	0	1	0	1
		Percent	0.0%	100.0%	0.0%	100.0%
	Total	Number of participants	61	56	12	129
		Percent	47.3%	43.4%	9.3%	100.0%

9.3.2.2 Overall completion: interim review

Figure 9.1 shows an overview of recruitment and questionnaire completion rates by study arm at the six common time points where all patients were expected to have completed a questionnaire – baseline, week 2 after the start of radiotherapy treatment, week 7, week 26 (six months following treatment completion), week 39 (9 months) and week 52 (12 months). At the time of the interim analysis, all patients had been invited to complete the questionnaire at six months. At baseline, only 2 patients of the 129 included in the analysis had missing data (98% compliance); week 2 completion rate was 68%; week 7 was 63% and at six months completion was 62%. For the longer duration of follow up overall completion rates were 47% at 9 months and 47% at a year, including only patients who had been invited to take part at the later time-points.

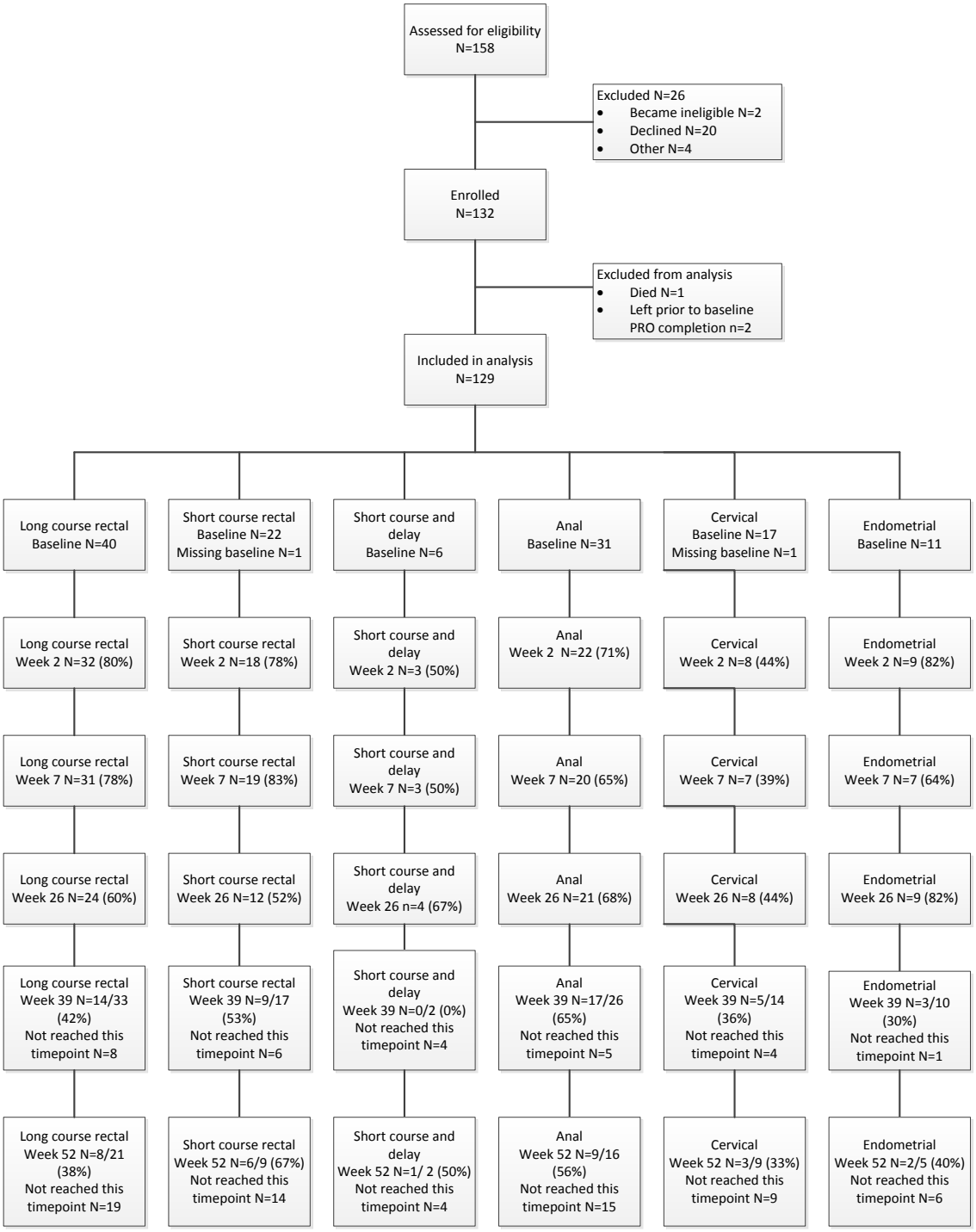


Figure 9-1: CONSORT diagram of recruitment and questionnaire completion rates

9.3.2.3 EORTC-QLQ C30 results

Due to the small sample sizes in each study arm the following results are presented as a descriptive analysis.

Overall mean baseline EORTC global quality of life (QOL) and functional scores prior to pelvic radiotherapy were greater than 68. These scores were similar for all disease groups except for the short course and delay study arm (n=6) where patients reported a mean QOL score of 50 (SD25.3). This group of patients is considered unfit for standard neoadjuvant treatment and this is reflected in their baseline scores. Overall QOL returned to baseline or close to baseline levels by one year (Figure 9.2). Similarly physical, role, emotional, social and cognitive (not shown) functioning all returned to close to baseline levels by the six months to a year (Figure 9.3). Large differences in role functioning scores and moderate differences in social functioning were seen at week 7 from baseline. The lowest scores are seen around week 5 for the long course rectal (LCRT), cervical, endometrial and anal cancer study arms corresponding with the final week of EBRT with recovery seen by week 7, with the exception of the LCRT group. The scores for QOL and role, social, emotional and physical functioning in the LCRT group do not improve prior to surgery and only begin to show improvements at the six month time point (Week 26). Long course rectal patients also reported lower function item scores at the Week 18 point corresponding with recovery from their surgery (at Week 11). Cervical and anal cancer patients had a noticeably greater deterioration in overall QOL and physical, role and social functioning during treatment with chemoradiotherapy in comparison to the other treatment arms.

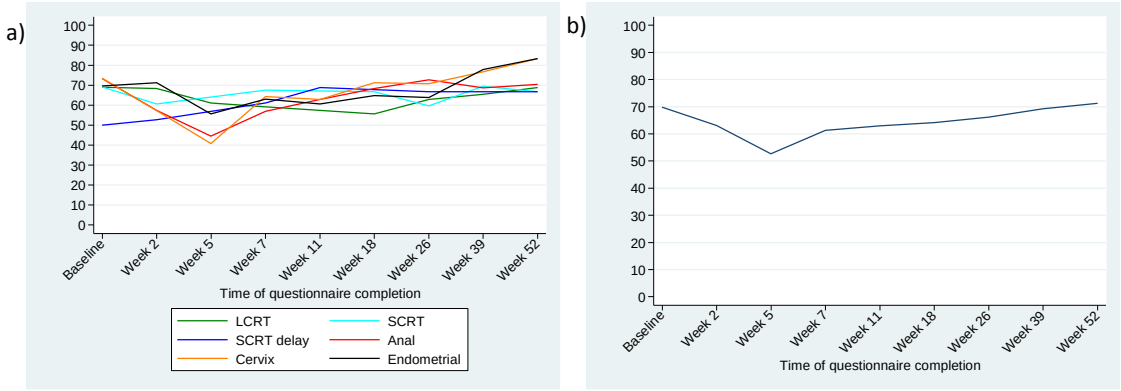


Figure 9-2: Overall Quality of life (QOL)

(a) By treatment arm (b) All groups (higher score=better functioning)

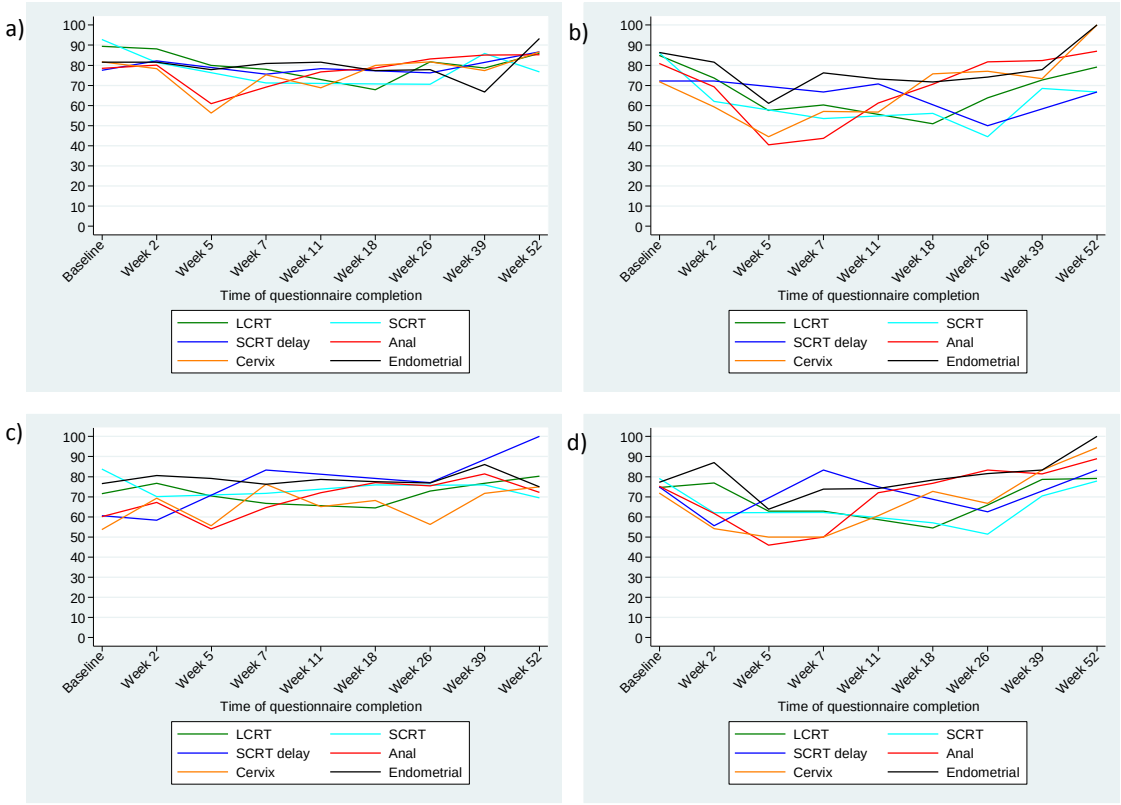


Figure 9-3:Functioning scores:

(a) Physical functioning (b) Role functioning (c) Emotional functioning (d) Social functioning (higher score=better functioning)

By six months, a number of mean functional symptom scores were still lower than baseline levels, for example role and social functioning (table 9.3). However, the trend in the patients who had completed the later questionnaires at 9 and 12 months was improvement to baseline (role functioning) or better than baseline levels (social functioning). Emotional functioning scores had already improved from baseline at six months reflecting the stressful and challenging time around the start of treatment for patients.

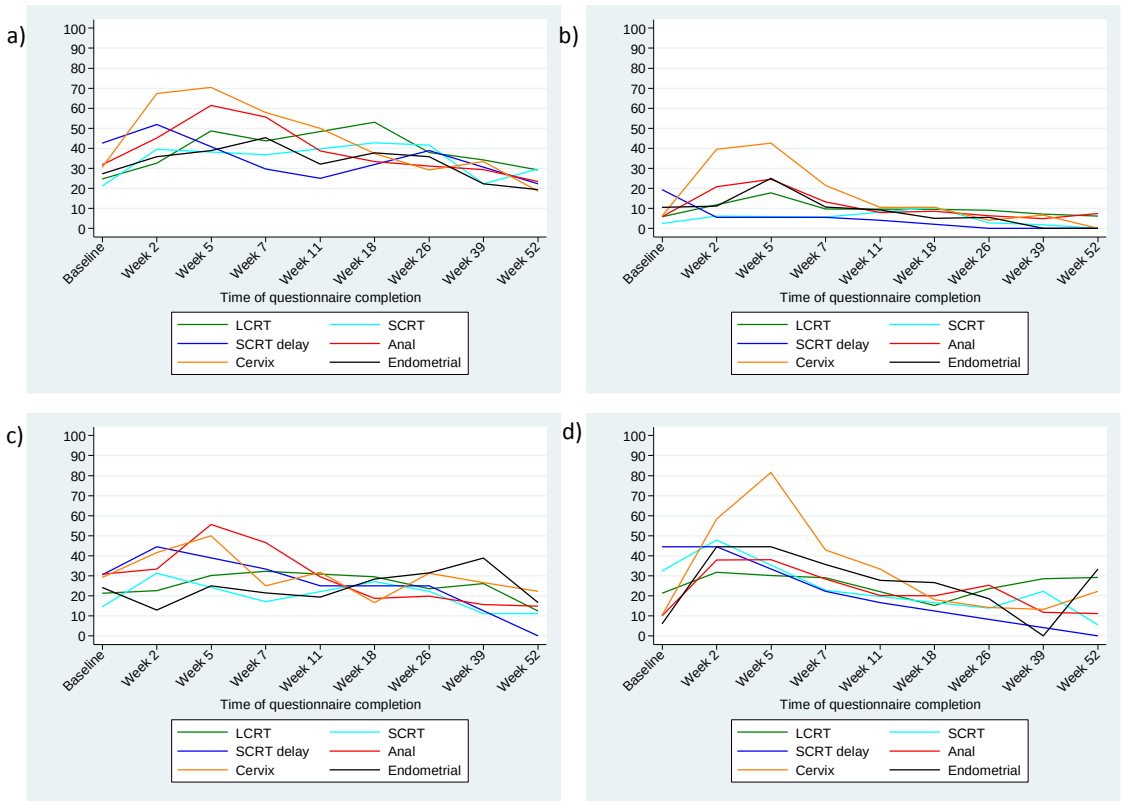


Figure 9-4: EORTC-QLQ C30 Symptoms:

(a) Fatigue (b) Nausea and vomiting (c) Pain (d) Diarrhoea (higher score= worse symptoms)

Note that the scores for patients at all time points are presented in the graphs, but the scores shown in the tables are only at the time points common to all groups (as described in the Assessments section of this chapter).

Table 9-7: EORTC-QLQ C30 Scores for all patients over time

EORTC-QLQ C30 item	N	Mean Score	SD	Min Score	Max Score	EORTC-QLQ C30 item	N	Mean Score	SD	Min Score	Max Score	EORTC-QLQ C30 item	N	Mean Score	SD	Min Score	Max Score
BASELINE						**WEEK 7**						**WEEK 39**					
Global Health status*	123	69.8	21.5	0.0	100.0	Global Health status*	87	61.3	18.9	16.7	100.0	Global Health status*	48	69.3	22.3	0.0	100.0
Physical functioning*	123	85.0	20.0	0.0	100.0	Physical functioning*	86	74.5	18.0	20.0	100.0	Physical functioning*	48	81.4	18.1	33.3	100.0
Role functioning*	123	82.0	26.8	0.0	100.0	Role functioning*	87	**56.2**	29.5	0.0	100.0	Role functioning*	48	75.7	29.2	0.0	100.0
Emotional functioning*	123	68.3	25.2	0.0	100.0	Emotional functioning*	87	69.4	22.4	0.0	100.0	Emotional functioning*	48	78.3	21.5	25.0	100.0
Cognitive functioning*	123	83.1	17.9	25.0	100.0	Cognitive functioning*	87	76.7	21.1	16.7	100.0	Cognitive functioning*	48	84.0	19.1	33.3	100.0
Social functioning*	123	75.4	27.5	0.0	100.0	Social functioning*	87	**60.3**	30.5	0.0	100.0	Social functioning*	48	78.8	25.4	0.0	100.0
Fatigue	123	27.7	24.4	0.0	100.0	Fatigue	87	**45.7**	26.4	0.0	100.0	Fatigue	48	29.4	24.0	0.0	100.0
Nausea and Vomiting	123	6.4	15.5	0.0	100.0	Nausea and Vomiting	87	10.5	14.8	0.0	66.7	Nausea and Vomiting	48	4.9	10.8	0.0	50.0
Pain	123	24.3	29.6	0.0	100.0	Pain	87	30.8	31.8	0.0	100.0	Pain	48	20.5	26.0	0.0	100.0
Dyspnoea	123	10.7	20.6	0.0	100.0	Dyspnoea	87	18.2	24.2	0.0	100.0	Dyspnoea	48	17.4	29.2	0.0	100.0
Insomnia	123	**36.7**	31.8	0.0	100.0	Insomnia	87	**44.6**	31.0	0.0	100.0	Insomnia	48	25.0	28.8	0.0	100.0
Appetite loss	123	19.4	27.9	0.0	100.0	Appetite loss	86	29.3	28.7	0.0	100.0	Appetite loss	48	10.4	19.6	0.0	66.7
Constipation	123	21.0	28.4	0.0	100.0	Constipation	87	17.2	25.3	0.0	100.0	Constipation	48	13.9	24.6	0.0	100.0
Diarrhoea	123	18.7	26.4	0.0	100.0	Diarrhoea	87	28.9	30.7	0.0	100.0	Diarrhoea	48	18.1	25.7	0.0	100.0
Financial problems	123	14.2	27.6	0.0	100.0	Financial problems	87	15.3	28.2	0.0	100.0	Financial problems	47	9.2	23.8	0.0	100.0
WEEK 2						**WEEK 26**						**WEEK 52**					
Global Health status*	88	**63.0**	18.4	25.0	100.0	Global Health status*	78	**66.1**	19.2	16.7	100.0	Global Health status*	29	71.3	17.9	33.3	100.0
Physical functioning*	89	83.2	17.4	26.7	100.0	Physical functioning*	78	79.6	18.4	33.3	100.0	Physical functioning*	29	84.4	17.2	46.7	100.0
Role functioning*	89	69.9	26.6	0.0	100.0	Role functioning*	78	67.5	30.4	0.0	100.0	Role functioning*	29	82.2	22.7	33.3	100.0
Emotional functioning*	89	72.3	20.8	12.5	100.0	Emotional functioning*	78	73.0	25.3	0.0	100.0	Emotional functioning*	29	75.3	22.3	33.3	100.0
Cognitive functioning*	89	80.3	21.1	0.0	100.0	Cognitive functioning*	78	79.9	16.2	33.3	100.0	Cognitive functioning*	29	82.8	16.4	33.3	100.0
Social functioning*	89	68.7	28.0	0.0	100.0	Social functioning*	78	70.1	29.2	0.0	100.0	Social functioning*	29	85.1	20.1	33.3	100.0
Fatigue	89	**41.1**	23.6	0.0	100.0	Fatigue	78	**35.6**	22.3	0.0	88.9	Fatigue	29	25.5	20.1	0.0	88.9
Nausea and Vomiting	89	15.3	18.3	0.0	100.0	Nausea and Vomiting	78	6.0	11.1	0.0	50.0	Nausea and Vomiting	29	4.0	11.5	0.0	50.0
Pain	89	28.3	28.7	0.0	100.0	Pain	78	24.1	26.9	0.0	100.0	Pain	29	13.8	20.0	0.0	83.3
Dyspnoea	87	12.3	17.7	0.0	66.7	Dyspnoea	77	18.2	25.1	0.0	100.0	Dyspnoea	29	13.8	20.9	0.0	66.7
Insomnia	88	**32.8**	28.1	0.0	100.0	Insomnia	77	**35.9**	31.9	0.0	100.0	Insomnia	29	31.0	32.0	0.0	100.0
Appetite loss	89	27.2	30.0	0.0	100.0	Appetite loss	78	15.4	23.8	0.0	100.0	Appetite loss	29	10.3	20.1	0.0	66.7
Constipation	89	14.2	26.2	0.0	100.0	Constipation	78	7.3	14.9	0.0	66.7	Constipation	29	16.1	24.6	0.0	100.0
Diarrhoea	89	**40.3**	28.7	0.0	100.0	Diarrhoea	77	20.3	25.5	0.0	100.0	Diarrhoea	29	17.2	22.9	0.0	100.0
Financial problems	89	13.1	23.8	0.0	100.0	Financial problems	78	11.5	26.2	0.0	100.0	Financial problems	29	9.2	21.6	0.0	100.0

N= Number of patients. *Functioning items (Higher score represents better functioning). Scores with no asterisk represent Symptom items (Higher scores represent worse symptoms).

All mean symptom scores from the EORTC-QLQ C30, except insomnia, were less than 33.3 at baseline (equivalent of a patient response of ‘a little’) and in the main returned to baseline levels by six months (see table 9.7 and figure 9.4). Mean fatigue and dyspnoea scores remained higher than baseline at six months but showed a trend toward returning to baseline in the patients who had completed questionnaires at the later time-points. Overall fatigue items showed a moderate change from baseline scores at week 7 (a change of 18 points) and large differences (21.6 point increase) in diarrhoea scores. During treatment, anal and cervical cancer patients experienced greater changes from baseline scores for fatigue, nausea and vomiting, pain and diarrhoea items, with fatigue and diarrhoea taking longer to resolve. Nausea and vomiting was particularly associated with the cervical cancer patients, reflecting the use of the emetic-inducing cisplatin chemotherapy treatment. Pain was more severe during and acutely after treatment in the anal cancer group who experience severe radiation skin reactions as a treatment side effect. The acute diarrhoea scores were markedly higher for the cervical cancer patients, which may reflect the greater treatment volume from 3D conformal treatments used to treat these patients.

9.3.2.4 Urinary symptoms

This section describes the trajectory of the urinary symptom items included in all disease specific questionnaires: dysuria, urinary incontinence, frequency and urgency. Baseline urinary frequency mean scores were greater than 33.3 but otherwise baseline urinary symptom scores were low. Dysuria, and to a lesser degree urinary frequency, were worst acutely during and in the few weeks after treatment as expected returning to baseline level by six months, related to irradiation of the bladder causing local irritation (figure 9.5 and table 9.8).

Urinary urgency appeared to be worse in the cervical and anal cancer groups following treatment with overall mean scores (in all treatment groups) at six months 6.4 points higher than baseline representing a minimally important difference(244). Urinary incontinence scores returned to baseline levels by six months. When the data were evaluated by gender, similar patterns were seen (data not shown).

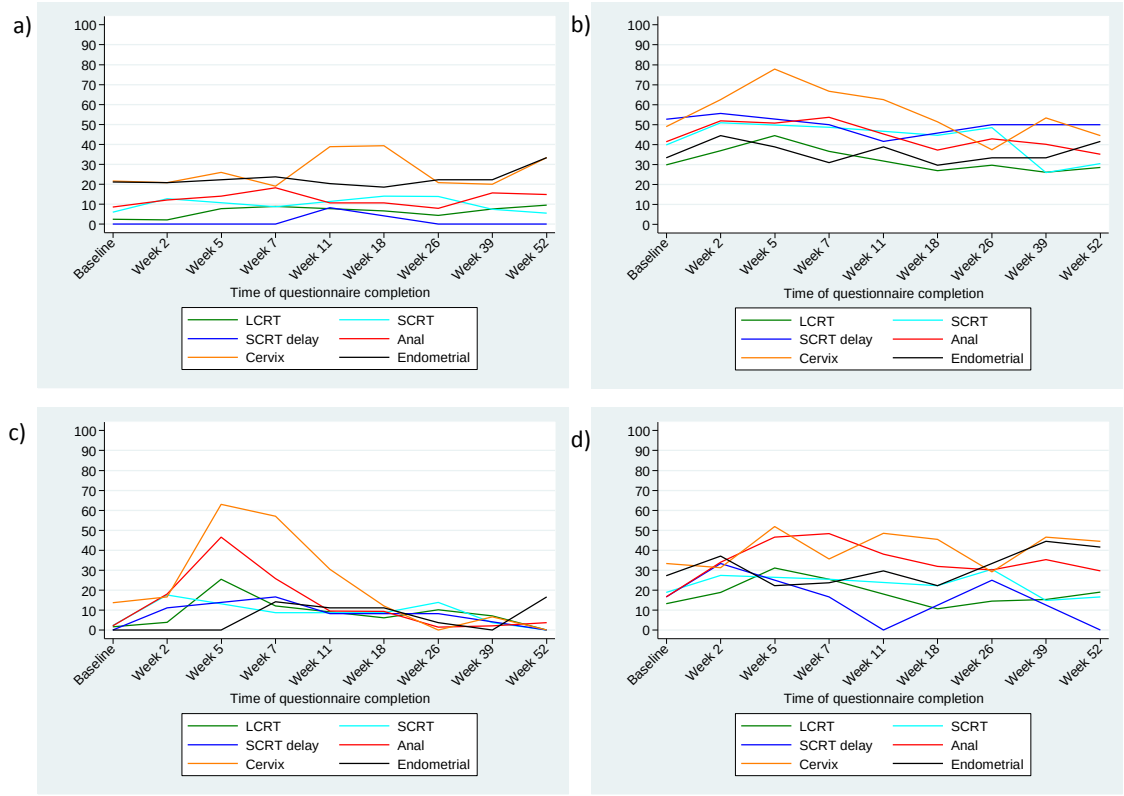


Figure 9-5: Urinary symptoms

(a) Urinary incontinence (b) Urinary frequency (c) Dysuria (d) Urinary urgency (higher score= worse symptoms).

Note the SCRT and delay patients were not invited to complete a questionnaire at Week 5.

Table 9-8: Urinary symptom items

Timing of completion	EORTC item	N	Mean score	SD	Minimum score	Maximum score
Baseline	Urinary Incontinence	127	8.7	17.4	0.0	100.0
	Urinary frequency	127	**38.3**	**24.6**	0.0	100.0
	Dysuria	127	3.3	12.3	0.0	100.0
	Urinary urgency	127	19.2	25.5	0.0	100.0
Week 2	Urinary Incontinence	88	10.0	19.7	0.0	100.0
	Urinary frequency	90	**47.0**	23.9	0.0	100.0
	Dysuria	89	11.0	21.8	0.0	83.3
	Urinary urgency	89	27.7	29.2	0.0	100.0
Week 7	Urinary Incontinence	85	12.9	21.3	0.0	100.0
	Urinary frequency	85	**45.7**	23.3	0.0	100.0
	Dysuria	85	18.6	25.4	0.0	100.0
	Urinary urgency	85	31.4	29.6	0.0	100.0
Week 26	Urinary Incontinence	77	10.4	18.9	0.0	66.7
	Urinary frequency	77	**38.5**	23.0	0.0	83.3
	Dysuria	76	6.6	18.9	0.0	100.0
	Urinary urgency	77	25.5	26.4	0.0	100.0
Week 39	Urinary Incontinence	47	12.8	17.8	0.0	66.7
	Urinary frequency	48	**34.4**	29.9	0.0	100.0
	Dysuria	47	4.3	16.5	0.0	100.0
	Urinary urgency	47	27.7	30.5	0.0	100.0
Week 52	Urinary Incontinence	28	14.3	24.7	0.0	100.0
	Urinary frequency	28	**34.5**	24.4	0.0	83.3
	Dysuria	29	2.3	8.6	0.0	33.3
	Urinary urgency	28	25.6	27.0	0.0	100.0

N= Number of patients.

9.3.2.5 Bowel Symptoms

Baseline mean scores were higher for GI symptoms than urinary symptoms with bowel urgency and flatulence scores >30 (Table 9.9). This is not surprising as the study sample includes patients with GI malignancies who will present with bowel symptoms. Per rectal bleeding improved dramatically by week 7 reducing from 24.9 points to 3.9 (large clinical difference) by Week 26 (six months) reflecting the effective treatment of the GI malignancies. Faecal incontinence, buttock pain, and bowel frequency scores increased during treatment showing a trend towards resolution by six months and even improvement in many cancer sites (Figure 9.6). Flatulence scores remain relatively static in comparison to the other symptoms over the treatment and follow up period.

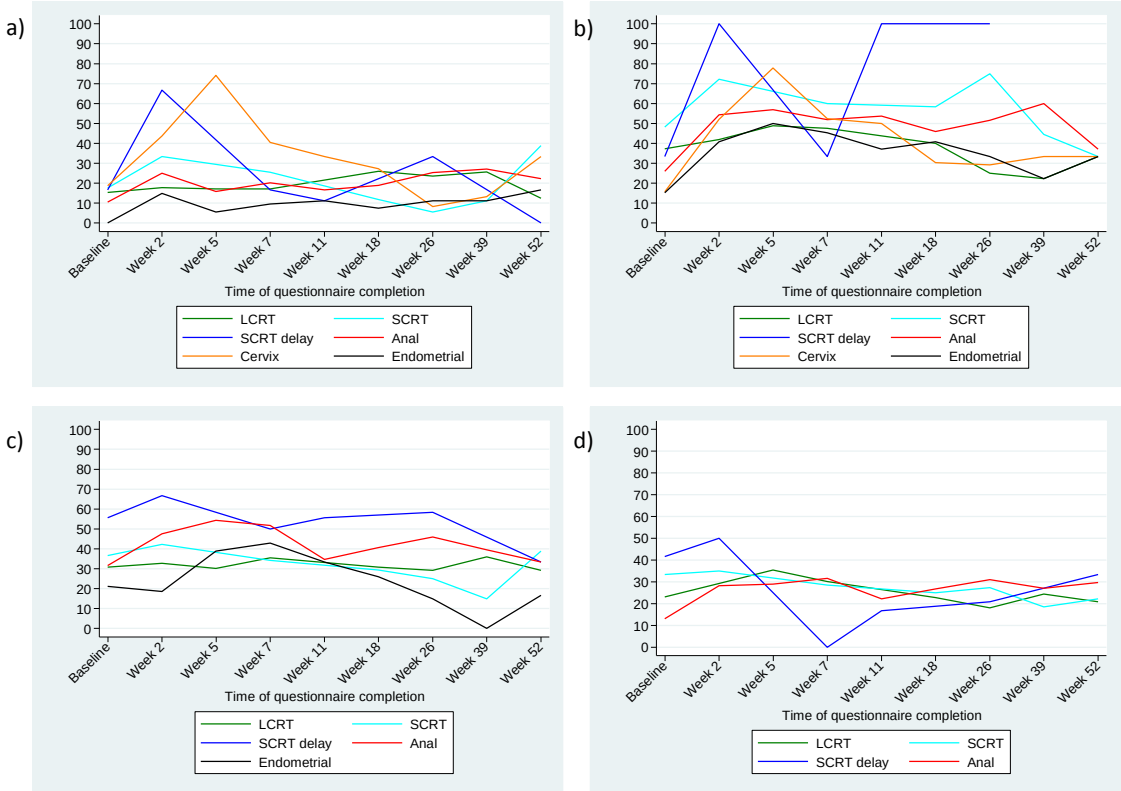


Figure 9-6: Bowel symptoms

(a) Faecal incontinence (b) Bowel urgency (c) Flatulence (GI and endometrial patients) (d) Stool frequency (GI patients only) (higher score= worse symptoms). Note the SCRT and delay patients were not invited to complete a questionnaire at Week 5 and include a sample of only 6 patients.

Mean bowel urgency scores for all participants at six months remained at 44.9 (a moderate difference from baseline), the highest of all GI symptoms present following pelvic radiotherapy. For patients completing at later time-points the mean score for bowel urgency does reduce to near baseline levels. This symptom will be interesting to evaluate after the full one-year follow up.

Table 9-9: Bowel symptom scores

Timing of Completion	EORTC item	N	Mean Score	SD	Min Score	Max Score
Baseline	Faecal Incontinence	121	13.6	22.2	0.0	100.0
	Per Rectal Bleeding	116	24.9	30.3	0.0	100.0
	Buttock pain***	116	23.7	33.4	0.0	100.0
	Flatulence**	106	**32.5**	30.2	0.0	100.0
	Stool Frequency*	94	23.1	20.3	0.0	66.7
	Embarrassed about bowels*	93	20.6	30.7	0.0	100.0
	Bowel urgency	113	30.8	34.2	0.0	100.0
Week 2	Faecal Incontinence	85	25.5	28.0	0.0	100.0
	Per Rectal Bleeding	81	25.1	28.2	0.0	100.0
	Buttock pain***	81	**37.0**	34.0	0.0	100.0
	Flatulence**	78	**37.8**	28.3	0.0	100.0
	Stool Frequency*	69	30.8	19.8	0.0	66.7
	Embarrassed about bowels*	68	26.2	31.6	0.0	100.0
	Bowel urgency	76	**51.5**	31.1	0.0	100.0
Week 7	Faecal Incontinence	85	21.0	27.0	0.0	100.0
	Per Rectal Bleeding	78	10.3	18.1	0.0	66.7
	Buttock pain***	79	**36.9**	36.1	0.0	100.0
	Flatulence**	78	**40.2**	29.5	0.0	100.0
	Stool Frequency*	71	29.2	24.1	0.0	100.0
	Embarrassed about bowels*	71	26.1	29.5	0.0	100.0
	Bowel urgency	71	**50.5**	31.2	0.0	100.0
Week 26	Faecal Incontinence	78	18.8	25.5	0.0	100.0
	Per Rectal Bleeding	68	3.9	10.8	0.0	33.3
	Buttock pain***	68	18.1	27.3	0.0	100.0
	Flatulence**	70	**33.3**	28.9	0.0	100.0
	Stool Frequency*	60	24.4	20.7	0.0	66.7
	Embarrassed about bowels*	61	30.6	32.4	0.0	100.0
	Bowel urgency	46	**44.9**	30.8	0.0	100.0
Week 39	Faecal Incontinence	46	21.0	28.4	0.0	100.0
	Per Rectal Bleeding	45	6.7	18.3	0.0	100.0
	Buttock pain***	45	18.5	27.1	0.0	100.0
	Flatulence**	41	30.1	33.2	0.0	100.0
	Stool Frequency*	38	24.1	20.8	0.0	66.7
	Embarrassed about bowels*	38	28.1	29.5	0.0	100.0
	Bowel urgency	29	**46.0**	35.0	0.0	100.0
Week 52	Faecal Incontinence	29	23.0	23.7	0.0	100.0
	Per Rectal Bleeding	26	2.6	9.1	0.0	33.3
	Buttock pain***	27	14.8	21.4	0.0	66.7
	Flatulence**	26	32.1	24.0	0.0	100.0
	Stool Frequency*	24	25.0	16.3	0.0	66.7
	Embarrassed about bowels*	24	25.0	26.5	0.0	100.0
	Bowel urgency	21	**34.9**	26.8	0.0	100.0

Key: N= Number of patients. *– Item asked in GI questionnaire only; ** - Item asked in GI and endometrial questionnaires; *** - Item asked in GI and cervical questionnaires.

9.3.2.6 Sexual activity

94% (n=73) of women responded to the question regarding sexual activity and 82% of men (n=42) at baseline. Baseline sexual activity scores at baseline were low, with an overall mean score for this item of 13.5 in men (SD 24.5) and 9.1 in women (SD 16.0). Only 17 women (23%) reported some level of sexual activity at baseline and 13 men (31%). Sexual activity reduced during the five-week treatment period (for patients on

chemoradiotherapy) but mean scores for sexual activity returned to baseline line levels by six months for both men and women (Figure 9.7 and Tables 9.10 and 9.11).

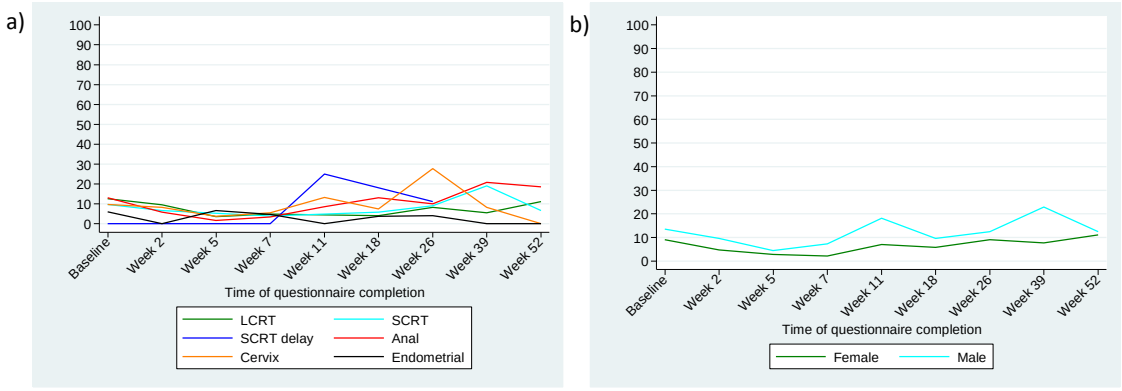


Figure 9-7:Sexual activity

(a) Overall sexual activity by treatment arm (b) Sexual activity by gender (higher score=better functioning)

9.3.2.6.1 Female sexual dysfunction

Baseline sexual/vaginal functioning scores, made up of the four symptom items: vaginal dryness, dyspareunia, vaginal stenosis and shortening, were high at baseline with patients reporting minimal symptoms (see table 9.10 and figure 9.8). Symptoms increased during treatment and peaked around week 18. By six months, sexual/vaginal functioning mean scores were reduced by 31.5 points from baseline (large difference) with the greatest change in function seen with worsening vaginal stenosis scores. The baseline vaginal stenosis mean score was 3.7 (SD 10.8) and this increased to 48.1 (SD 37.7) in the nine patients who remained sexually active (large difference).

Similarly high symptom scores were seen in patients using vaginal dilators. These items, reflecting similar items related to vaginal function during sexual activity, were included following comments from health professionals during interview that additional useful data on vaginal function could be ascertained from patients using dilators. Patients are not using vaginal dilators prior to treatment with radiotherapy (and thus no baseline data is provided). However, the symptoms described using vaginal dilators in patients who are not sexually active may be considered as a surrogate for vaginal function. In the 13 patients using vaginal dilators at six months their stenosis score ('Vaginal dilator short or tight') was 48.7 (SD 44.3) with associated high scores in painful and dry insertion. For the small number of patients who completed the questionnaire at the later time points, there appears to be some improvement in vaginal functioning.

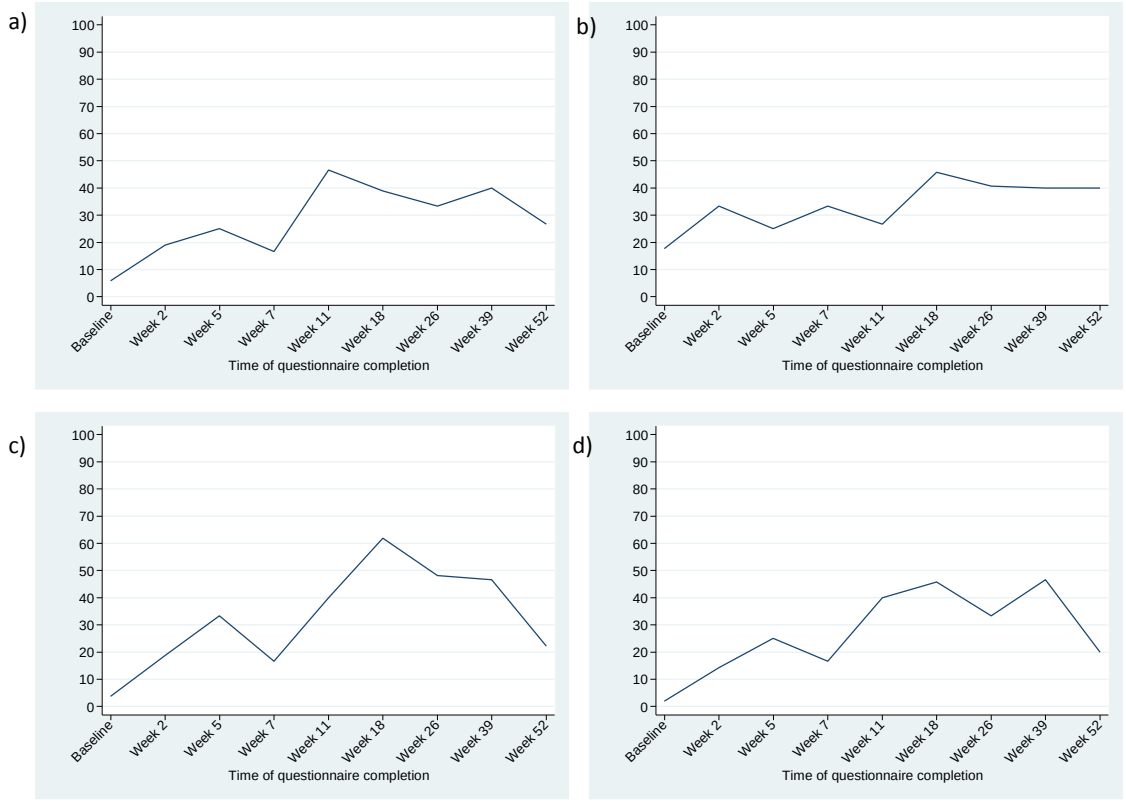


Figure 9-8: Vaginal symptoms

(a) Dyspareunia (b) Vaginal dryness (c) Vaginal stenosis (d) Vaginal shortening (higher score= worse symptoms). **Table 9.10** shows the number of respondents at each time point (N= responses to Sexual/Vaginal functioning score)

Table 9-10: Female sexual dysfunction scores

Timing of Completion	EORTC item	N	Mean Score	SD	Min Score	Max Score
Baseline	Sexual Activity*	73	**9.1**	16.0	0.0	66.7
	Sexual Enjoyment*	17	**51.0**	29.1	0.0	100.0
	Sexual/vaginal functioning*	17	92.6	9.3	66.7	100.0
Week 2	Sexual Activity*	52	**4.8**	11.6	0.0	33.3
	Sexual Enjoyment*	7	**47.6**	17.8	33.3	66.7
	Sexual/vaginal functioning*	8	80.0	9.7	66.7	100.0
	Vaginal dilator dry	1	0.0	.	0.0	0.0
	Vaginal dilator short or tight	1	0.0	.	0.0	0.0
	Vaginal dilator painful	1	0.0	.	0.0	0.0
Week 7	Sexual Activity*	47	**2.1**	8.2	0.0	33.3
	Sexual Enjoyment*	2	**33.3**	47.1	0.0	66.7
	Sexual/vaginal functioning*	2	79.2	17.7	66.7	91.7
	Vaginal dilator dry	4	0.0	0.0	0.0	0.0
	Vaginal dilator short or tight	4	8.3	16.7	0.0	33.3
	Vaginal dilator painful	4	0.0	0.0	0.0	0.0
Week 26	Sexual Activity*	44	**9.1**	20.8	0.0	100.0
	Sexual Enjoyment*	8	**41.7**	23.6	0.0	66.7
	Sexual/vaginal functioning*	9	**61.1**	34.6	0.0	100.0
	Vaginal dilator dry	13	**43.6**	43.9	0.0	100.0
	Vaginal dilator short or tight	13	**48.7**	44.3	0.0	100.0
	Vaginal dilator painful	12	**47.2**	48.1	0.0	100.0
Week 39	Sexual Activity*	26	**7.7**	14.3	0.0	33.3
	Sexual Enjoyment*	5	**46.7**	29.8	0.0	66.7
	Sexual/vaginal functioning*	5	**56.7**	33.0	8.3	91.7
	Vaginal dilator dry	6	**27.8**	39.0	0.0	100.0
	Vaginal dilator short or tight	6	**33.3**	36.5	0.0	100.0
	Vaginal dilator painful	6	**27.8**	39.0	0.0	100.0
Week 52	Sexual Activity*	15	**11.1**	16.3	0.0	33.3
	Sexual Enjoyment*	5	**46.7**	18.3	33.3	66.7
	Sexual/vaginal functioning*	5	71.7	28.6	33.3	100.0
	Vaginal dilator dry	5	**33.3**	40.8	0.0	100.0
	Vaginal dilator short or tight	5	**33.3**	40.8	0.0	100.0
	Vaginal dilator painful	5	**26.7**	43.5	0.0	100.0

N= Number of patients. *Functioning items (Higher score represents better functioning). Scores with no asterisk represent Symptom items (Higher scores represent worse symptoms).

9.3.2.6.2 Male sexual dysfunction

Mean scores at baseline for impotence were 31.0 (SD 38.6)(Table 9.11 and Figure 9.9). 43 patients responded to this item (84% response rate) and 13 patients on the study reported to be sexually active (31% of those who responded to this item; n=42). All male patients are invited to complete the items on libido and impotence regardless of sexual activity level but only sexually active patients complete the items on ejaculation problems, concerns about sexual intimacy and enjoyment, which make up the overall sexual functioning scale. Baseline mean scores for overall sexual function were 79.0 (SD 22.3). This score steadily declined over time with the patients completing at six months and nine months reporting an overall mean score around 65 (SD 22-8-24.3).

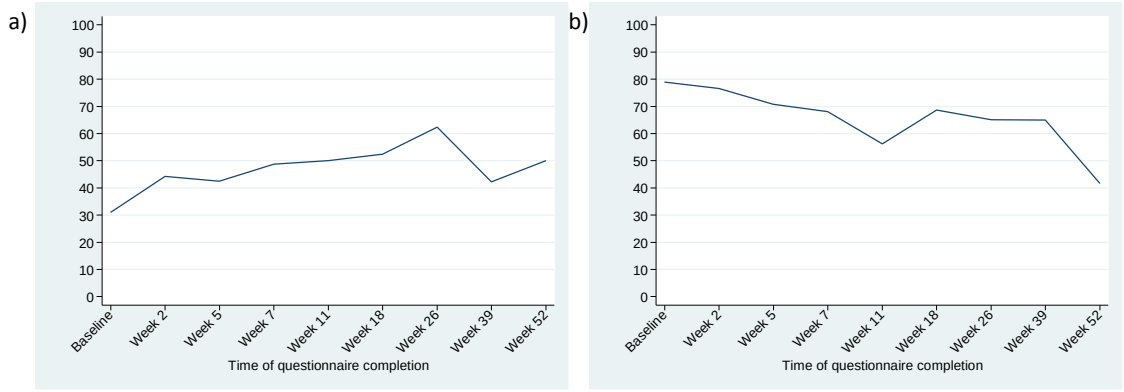


Figure 9-9: Male sexual function

(a) Impotence (higher score= worse symptoms) (b) Overall male sexual functioning score (higher score=better functioning)

The main impact on overall sexual function appear to be the deterioration in erectile function with mean impotence symptom scores increasing from 31.0 at baseline to 62.3 (SD 39.3) at six months (large difference). Ejaculation problems showed a large difference in scores from baseline to six months, with a 25.3-point increase in mean score. Unsurprisingly a corresponding reduction in sexual enjoyment was observed with scores reducing from 75.0 (SD 25.1) to 44.4 (SD 27.2) at six months. Concerns regarding intimacy remained similar at all time points. Due to the small numbers of male participants it was inappropriate to look for differences in response between different treatment arms.

Table 9-11: Male sexual dysfunction scores

Timing of Completion	EORTC item	N	Mean Score	SD	Min Score	Max Score
Baseline	Sexual Activity*	42	**13.5**	24.5	0.0	100.0
	Impotence	43	31.0	38.6	0.0	100.0
	Ejaculation problems	13	12.8	32.0	0.0	100.0
	Sexual intimacy	13	20.5	37.4	0.0	100.0
	Sexual interest	44	**31.4**	33.8	0.0	100.0
	Sexual enjoyment*	12	75.0	25.1	33.3	100.0
	Sexual functioning*	13	79.0	22.3	41.7	100.0
Week 2	Sexual Activity*	31	**9.7**	17.6	0.0	66.7
	Impotence	26	**44.2**	44.0	0.0	100.0
	Ejaculation problems	8	12.5	35.4	0.0	100.0
	Sexual intimacy	8	20.8	24.8	0.0	66.7
	Sexual interest	31	**22.6**	26.0	0.0	66.7
	Sexual enjoyment*	8	**62.5**	27.8	33.3	100.0
	Sexual functioning*	8	76.6	15.7	58.3	100.0
Week 7	Sexual Activity*	32	**7.3**	14.0	0.0	33.3
	Impotence	27	**48.8**	37.2	0.0	100.0
	Ejaculation problems	6	5.6	13.6	0.0	33.3
	Sexual intimacy	6	**33.3**	21.1	0.0	66.7
	Sexual interest	34	**17.2**	19.5	0.0	66.7
	Sexual enjoyment*	6	**44.4**	17.2	33.3	66.7
	Sexual functioning*	6	68.1	13.4	58.3	91.7
Week 26	Sexual Activity*	24	**12.5**	19.2	0.0	66.7
	Impotence	23	**62.3**	39.3	0.0	100.0
	Ejaculation problems	7	**38.1**	35.6	0.0	100.0
	Sexual intimacy	7	23.8	37.1	0.0	100.0
	Sexual interest	24	**22.2**	23.4	0.0	66.7
	Sexual enjoyment*	6	**44.4**	27.2	0.0	66.7
	Sexual functioning*	7	**65.1**	24.3	25.0	91.7
Week 39	Sexual Activity*	16	**22.9**	31.5	0.0	100.0
	Impotence	15	**42.2**	42.7	0.0	100.0
	Ejaculation problems	7	**47.6**	26.2	33.3	100.0
	Sexual intimacy	8	20.8	30.5	0.0	66.7
	Sexual interest	16	31.3	31.0	0.0	100.0
	Sexual enjoyment*	8	**54.2**	24.8	33.3	100.0
	Sexual functioning*	8	**64.9**	22.8	33.3	91.7
Week 52	Sexual Activity*	8	**12.5**	24.8	0.0	66.7
	Impotence	8	**50.0**	30.9	0.0	100.0
	Ejaculation problems	1	**33.3**	.	33.3	33.3
	Sexual intimacy	1	**33.3**	.	33.3	33.3
	Sexual interest	8	**20.8**	24.8	0.0	66.7
	Sexual enjoyment*	1	**0.0**	.	0.0	0.0
	Sexual functioning*	1	**41.7**	.	41.7	41.7

N= Number of patients. *Functioning items (Higher score represents better functioning). Scores with no asterisk represent Symptom items (Higher scores represent worse symptoms).

9.3.2.7 Miscellaneous items

A number of other symptoms are common side effects of pelvic radiotherapy and concurrent or adjuvant chemotherapy used (Figure 9.10). At baseline pre-existing concerns regarding weight were present in the cervical and GI patients in which this (function) item was asked (mean score 79.2; SD 29.0). Pre-existing back pain was also

present in the gynaecological cancer patients who were asked this question (mean score 31.0; SD 33.9). Otherwise other mean baseline scores were ≤10.

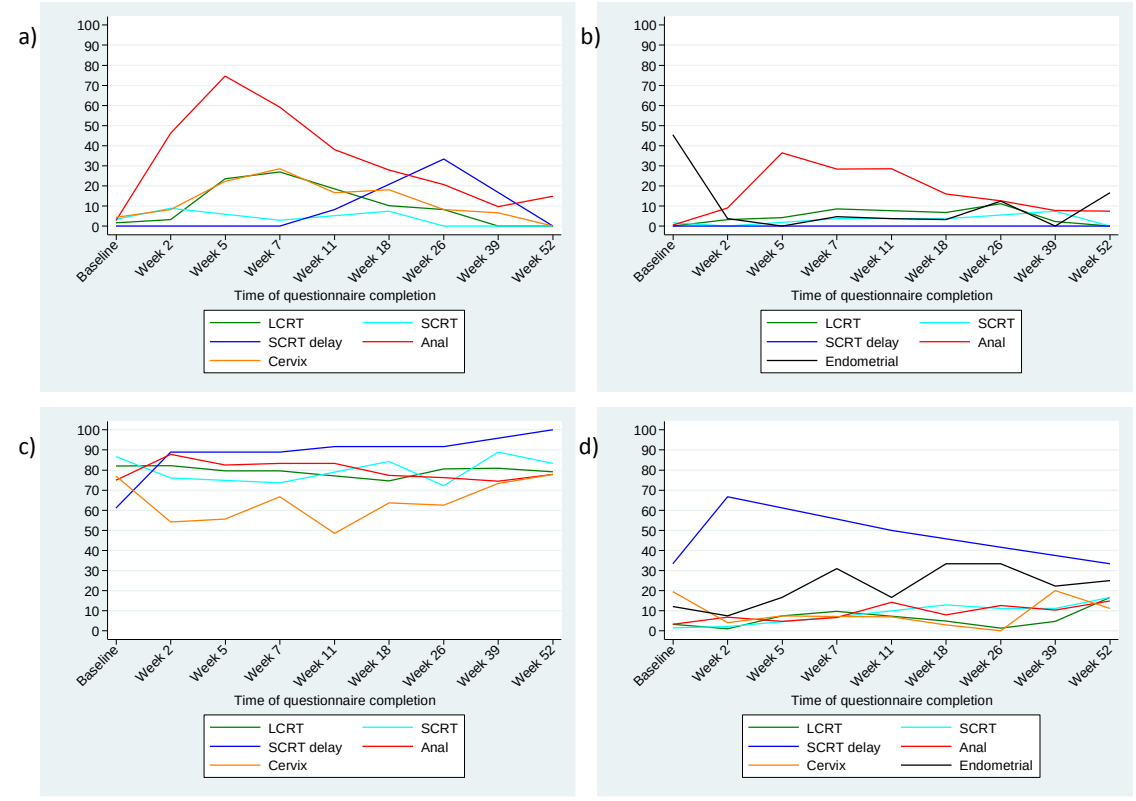


Figure 9-10:Miscellanous symptoms:

(a) Skin reaction (b) Hair loss (c) Weight worries (d) Lymphoedema. Note the numbers in the short course and delay group are very small (n=6 at baseline).

The skin reaction item was created specifically for this project for use in anal cancer patients who are known to suffer with radiation skin reaction during treatment ('Have you had any changes to your skin treated with radiotherapy?'). As expected anal cancer patients had the greatest increase in skin reaction mean scores with a peak score at week 5, with on-going symptoms at week 7, resolving over the next few weeks with some residual changes noted at six months in the anal cancer group (Figure 9.10a). These changes to the external skin in the pelvis are also reflected in the greater increase in hair loss scores reported in the anal cancer group during treatment and in the acute follow up period, with pubic hair loss being a common side effect of treatment. Most endometrial cancer patients have completed chemotherapy in the few weeks prior to commencing pelvic radiotherapy and therefore started with higher baseline hair loss mean scores than the other groups, which then resolved.

An additional item regarding concern about weight (taken from EORTC-QLQ CR29) was added to the cervical cancer questionnaire following interviews with health professionals. The clinician interviewed noted that patients commonly complained

about weight gain during chemotherapy treatment due to the concurrent use of corticosteroids to reduce their chemotherapy side effects. This pattern of toxicity is observed in figure 9.10c with cervical patients mean scores deteriorating to a greater extent during treatment than the GI patients.

Lymphoedema was most commonly seen in the endometrial cancer population as expected (Figure 9.10d). This is a common side effect following surgery including pelvic nodal removal. The lymphoedema item was added to the GI questionnaire, as it is a known side effect for anal cancer patients following irradiation of the inguinal nodal regions. There appears to be a trend towards an increase in mean scores for the anal cancer patient from a mean baseline score of 3.33 (SD 10.2) to 12.7 (SD 22.3) by six months. The line for the short course and delay patients is difficult to interpret due to the small number of patients in this treatment group (n=6).

9.3.2.8 Case examples

To demonstrate the clinician view and illustrate the potential use of the PRO data in clinical practice this section provides case examples from two patients. The first patient (Figure 9.11) shows the graphs of the scaled item responses over time from a 61 year-old female with a diagnosis of T4N0V1M0 high rectal adenocarcinoma. She was treated with neoadjuvant concurrent chemoradiotherapy (45Gy in 25 fractions with capecitabine) between August 2014 to the beginning of October 2014. She had an anterior resection on 21 December 2014 with complete regression following neoadjuvant treatment (histologyypT0, ypN0, ypM0 V0 R0; 0/26 lymph nodes). Her graphs show she started of with high levels of fatigue, associated with lower physical functioning scores and these have now resolved following treatment. She had a peak of pain post surgery. In a recent consultation she reported intermittent diarrhoea and constipation, which she is managing, seen in her bowel symptom score of 40. Prior to treatment she was not sexually active (show by the dotted line on the graph), however since June she has resumed sexual activity with good function.

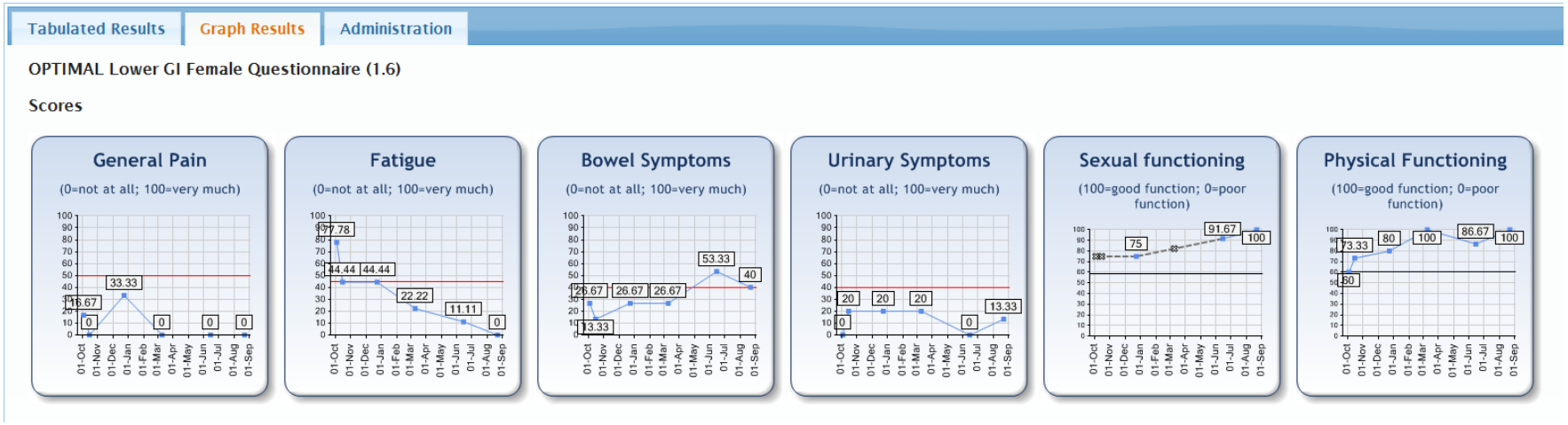
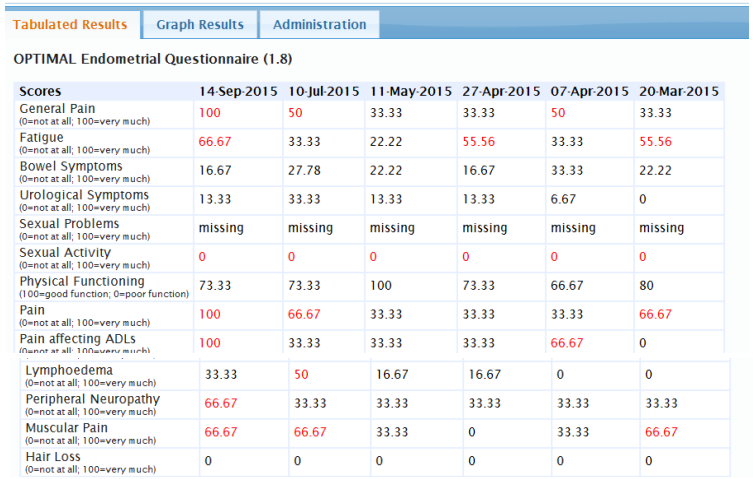


Figure 9-11: Case study 1



Tabulated Results | Graph Results | Administration

OPTIMAL Endometrial Questionnaire (1.8)

Scores	14-Sep-2015	10-Jul-2015	11-May-2015	27-Apr-2015	07-Apr-2015	20-Mar-2015
General Pain (0=not at all; 100=very much)	100	50	33.33	33.33	50	33.33
Fatigue (0=not at all; 100=very much)	66.67	33.33	22.22	55.56	33.33	55.56
Bowel Symptoms (0=not at all; 100=very much)	16.67	27.78	22.22	16.67	33.33	22.22
Urological Symptoms (0=not at all; 100=very much)	13.33	33.33	13.33	13.33	6.67	0
Sexual Problems (0=not at all; 100=very much)	missing	missing	missing	missing	missing	missing
Sexual Activity (0=not at all; 100=very much)	0	0	0	0	0	0
Physical Functioning (100=good function; 0=poor function)	73.33	73.33	100	73.33	66.67	80
Pain (0=not at all; 100=very much)	100	66.67	33.33	33.33	33.33	66.67
Pain affecting ADLs (0=not at all; 100=very much)	100	33.33	33.33	33.33	66.67	0
Lymphoedema (0=not at all; 100=very much)	33.33	50	16.67	16.67	0	0
Peripheral Neuropathy (0=not at all; 100=very much)	66.67	33.33	33.33	33.33	33.33	33.33
Muscular Pain (0=not at all; 100=very much)	66.67	66.67	33.33	0	33.33	66.67
Hair Loss (0=not at all; 100=very much)	0	0	0	0	0	0

Figure 9-12: Case study 2

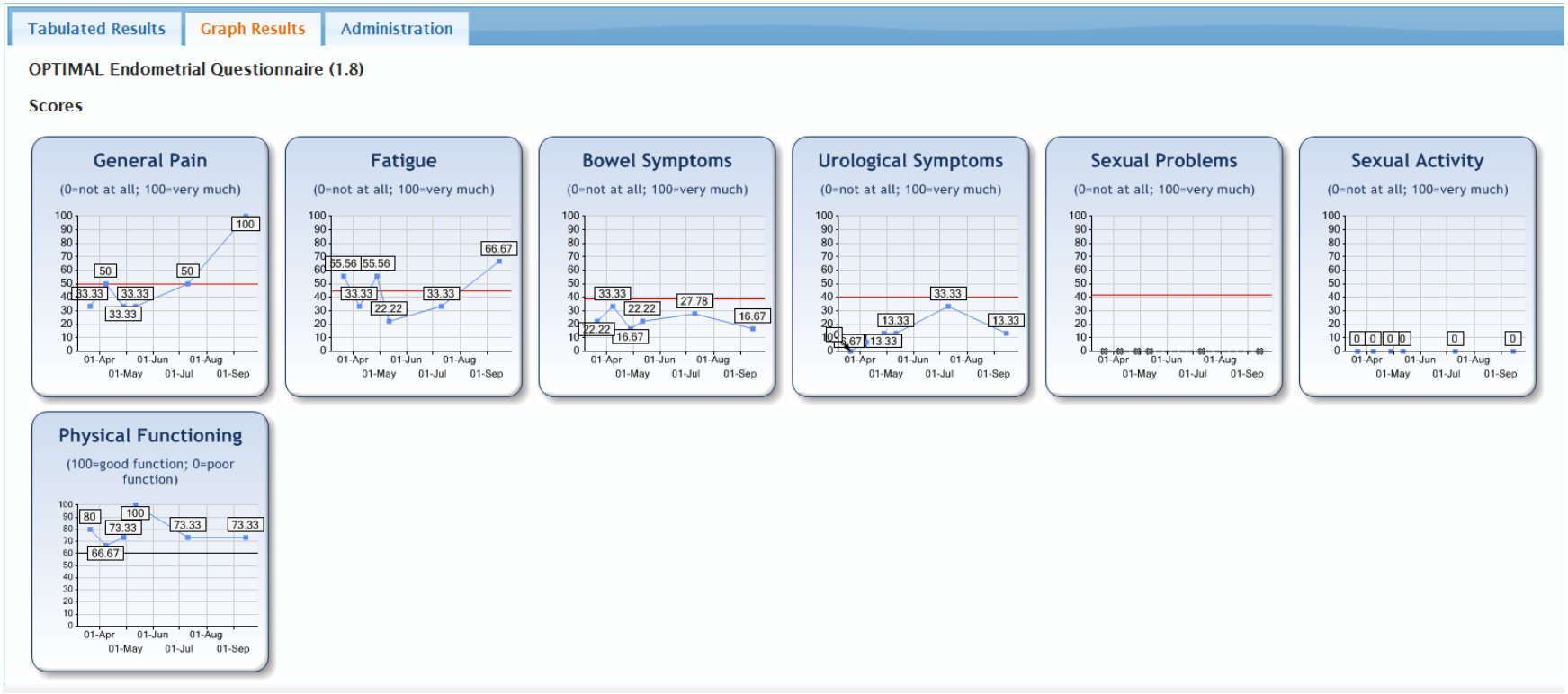


Figure 9-13: Case study 2

The second case study shows the results of a 52 year-old female with a diagnosis of Stage 3a grade 1 endometrioid adenocarcinoma of the endometrium. She was treated with a total abdominal hysterectomy and bilateral salpingo-oophorectomy in September 2014, followed by six cycles of adjuvant chemotherapy with three-weekly Carboplatin and Paclitaxel. Her graphical results start in March 2015 prior to starting pelvic radiotherapy (45Gy in 25 fractions) followed by vault brachytherapy (12Gy in 3 fractions) completed. During treatment she reported bowel urgency symptoms, worsening pain and fatigue (see figure 9.12 and 9.13). Whilst her bowel symptoms have resolved since July 2015 she has presented with significant peripheral neuropathy symptoms associated with pain and fatigue (see figure 9.12). These symptoms are currently under investigation and management.

9.3.3 Feedback questionnaire results

A slightly modified version of the feedback questionnaire piloted in the pilot study was used to gather feedback from patients who had completed the study. At the time of data export 28 out of the 43 patients who had completed the study at the time of interim analysis provided feedback (65.1%).

Of the 28 patients who completed the feedback questionnaire, the majority of patients used online methods, either using a home computer (n=10; 36%), a mobile device (n=4; 14%) or using hospital touch-screen computers (n=1; 4%). Twelve patients used paper and post methods (41%). One participant did not report their method. On average patients reported they completed the questionnaire before and after their hospital consultations 50% of the time (Table 9.12). Patients responded to the question: 'If you did complete the questionnaire on any occasion before seeing your hospital team did you find it useful?' with the majority reporting it was useful 'all the time' 29% (n=8), 'sometimes' (n=13; 46%), and 'not useful' 25% (n=7). The reasons given for the process being useful were improved communication (n=5; 18%); allowed them time to think about their problems in advance (n=10; 36%); gave patients more confidence (n=5; 17%); and helped patients to remember their concerns (n=9; 32%). Patients who did not find completing the questionnaire useful before their consultation gave the following reasons: the doctors did not review the results (n=3; 11%); no problems to report (n=8; 29%); the questions were not relevant (n=3; 11%) and free text responses: '*My treatment after radiotherapy was in York*' and '*The same questions were asked. As it is a year on, I felt the questions could be different*'.

77% of patients reported that they found the questionnaire easy to understand (n=22) and 61% (n=17) felt the questions included questions that reflected their experience with 25% of patients reporting the survey reflected their experience ‘sometimes’ (n=7). Twenty three patients felt the number of questions asked was acceptable (82%) with only one patient reporting there were too many questions (4%). The majority of patients did not consider the questionnaire completion changed their interaction with their clinical teams (n=19; 68%).

Of the twelve patients who responded to the functionality of completing the questionnaires online, the majority of patients found using the website and login process ‘very easy’ (n=7) or ‘easy’ (n=3) (Table 9.12). Only one patient reported they required support from the research team during the course of the study for online completion. The majority of patients using the online system opted to receive emails (n=9). The majority received emails to their own account but two patients received emails via a family member and reported they found this process ‘very easy’ to manage. In the main patients completed the questionnaires at home (n=10) but one patient found using the hospital touch-screen computers useful ‘sometimes’. Most patients reported they would be happy to continue to use a similar system in the future (n=11).

Home Internet access was not available for four patients (14%). Reasons for choosing paper methods were provided with the majority of patients considering paper methods to be easier (n=8; 29%). Other reasons were a lack of confidence with computers (n=2; 7%); preference for paper-based methods (n=3; 11%); and not owning a computer or mobile device (n=5; 18%).

Table 9-12: Summary of feedback responses

QUESTIONNAIRE ITEM		
When did you usually complete the questionnaires?	**Number of patients**	**Percent**
Before being seen by a member of the clinical team	14	50.0%
After seeing a member of the clinical team	14	50.0%
Total	28	100.0%
If you did complete the questionnaire on any occasion before seeing your hospital team did you find it useful?	**Number of patients**	**Percent**
No	7	25.0%
Yes	8	28.6%
Sometimes	13	46.4%
Total	28	100.0%
Did you find the survey easy to read and understand?	**Number of patients**	**Percent**
No	1	3.6%
Yes	22	78.6%
Sometimes	3	10.7%
Not stated	2	7.1%
Total	28	100.0%
Did the survey include questions that reflected your experience?	**Number of patients**	**Percent**
No	2	7.1%
Yes	17	60.7%
Sometimes	7	25.0%
Not stated	2	7.1%
Total	28	100.0%
What did you think about the number of questions in the survey?	**Number of patients**	**Percent**
Too many	1	3.6%
About right	22	78.6%
I would have answered more	1	3.6%
Not sure	2	7.1%
Not stated	2	7.1%
Total	28	100.0%
Do you think completing the questionnaires changed your interactions with your hospital teams?	**Number of patients**	**Percent**
No	19	67.9%
Yes	3	10.7%
I'm not sure	4	14.3%
Not stated	2	7.1%
Total	28	100.0%
RESPONSES OF PATIENTS COMPLETING THE QUESTIONNAIRE USING INTERNET METHODS		
How easy or difficult did you find it to get onto the study website?	**Number of patients**	**Percent**
Very easy	8	28.6%
Easy	3	10.7%
Difficult	1	3.6%
N/A or not stated	16	57.1%
Total	28	100.0%
How easy or difficult did you find it to log in with your username and password?	**Number of patients**	**Percent**
Very easy	7	25.0%
Easy	3	10.7%
Difficult	1	3.6%
N/A or not stated	17	60.7%
Total	28	100.0%
Did you have to contact the research team to ask for help at any point	**Number of patients**	**Percent**
No	10	35.7%
Yes	1	3.6%
N/A or not stated	17	60.7%
Total	28	100.0%
If you were asked, would you continue to answer similar questionnaires using this Internet system (for example, before future hospital appointments)?	**Number of patients**	**Percent**
Definitely	7	25.0%
Very likely	3	10.7%
Unsure	1	3.6%
N/A or not stated	17	60.7%
Total	28	100.0%

Free text responses to suggestions for additional questionnaire items included: '*It would have been helpful to add any concerns. Say a space at the end of the questionnaire for comments'; '[items] regarding sexuality after treatment'; 'I would like questions relating to the long-term side effects of radiotherapy. Also re the anxiety of patients'.* This final item suggestion regarding long-term side effects was addressed in an interview with this patient and related to her concerns about secondary malignancies following radiotherapy treatment.

Free text responses regarding perceived barriers to completing the questionnaires were *'[having a] catheter in place'; 'Personal relationships'*; and two patients who reported they did not feel the items were relevant for them (one male patient with a diagnosis of rectal cancer and one female with an anal cancer diagnosis).

9.4 Discussion

This is an interim, descriptive analysis of the prospective study. The initial findings suggest longitudinal collection of electronic and paper PRO with integration into EHR is feasible and acceptable for patients over a median nine-month follow up period. The recruitment and attrition rates were favourable(48) and initial patient feedback was broadly positive. Response rates at six months (62%) were similar to the 12-week response rate (69%) seen in the study using electronic PRO collection by Judson and colleagues(113) and at seven weeks were more than twice as high as response rates seen at six weeks in a paper based study collecting PRO data in clinical practice in patients treated with radiotherapy for gynaecological cancer(12). These findings reflect the improve completions rates seen in other studies using electronic PRO data collection as compared to paper based methods(114). However, enabling the option of paper completion increased the recruitment rates and allowed inclusivity to the whole clinical population. Although, it was interesting to note in the feedback questionnaire that only a small percentage of patients did not have access to home Internet/computers and therefore a number of patients chose to complete on paper despite the option of Internet-based methods at home.

Overall these early findings provide encouraging evidence that electronic methods are feasible and acceptable for use in clinical practice in the long term follow up of patient treated with radiotherapy and provide good quality data. Within the full analysis of the data from this study, the relationship between missing questionnaires and PRO

completion method, admissions to hospital, proximity to death and disease recurrence will be evaluated.

The PRO data collected provided detailed information on the trajectory and severity of acute and early late toxicity experienced by patients treated with pelvic radiotherapy. Bowel urgency and sexual dysfunction were symptoms with the greatest change in mean score from baseline to six months and this reflected the higher mean scores seen for these items in the cross sectional study. This study provides early evidence that the use of the EORTC-QLQ C30 and disease-specific modules in clinical practice to evaluate pelvic radiotherapy related toxicity is effective and provides an accurate means of systematically collecting toxicity data. The trajectory of symptom and function scores was as expected and reflects similar rates of acute and late symptomatic toxicity commonly experienced by patients treated with pelvic radiotherapy(12, 18, 158, 308, 342). Further evaluation of the use of the EORTC-QLQ system in clinical practice in multi-centre trials is required to validate this instrument in clinical practice. However, this study provides good pilot data on the acute symptom trajectory for these treatment regimes and could be used to guide further work.

The additional items included in the GI and cervical questionnaires added useful data, in particular the items on skin reaction and lymphoedema in the anal cancer patients and the item on weight concerns in the cervical cancer group. The skin item in particular was essential to measure the significant deterioration in scores seen in the anal cancer patients and was developed specifically for this project as the EORTC-QLQ anal cancer module is in development(143). In comparison to the low rates of symptoms or functional problems seen in items from the EORTC-QLQ C30 in the cross sectional study, the usefulness of these items was clear when used in a prospective design setting. The acute deterioration in QOL, physical functioning and emotional and social challenges experienced by patient during cancer diagnosis and treatment was clearly seen. For the symptom items, acute diarrhoea scores deteriorated significantly during treatment but had resolved by six months. This reflects the lower level of diarrhoea symptoms seen at a later follow up time point measured in the cross sectional study where a mean score of 15.4 (SD25.1) was reported. Pain, nausea and fatigue were also high during and acutely after treatment reflecting the acute toxicities associated with pelvic (chemo)radiotherapy.

This study has a number of strengths. It is the first study to report on the use of PRO integration within patient EHR in clinical practice. It also has the longest mean/median duration of follow up using electronic methods of PRO data collection. This study also

has limitations. The conclusions are limited as this is an interim analysis and only provides a descriptive analysis of the results. The study arms have small sample sizes so the analysis is limited to a descriptive evaluation and therefore the interpretation of the results is limited. The decision was made to include multiple treatment regimes to have a variety of different pelvic radiotherapy techniques included to allow dosimetric evaluation of heterogeneous data in relation to PRO toxicity in the future analysis. No formal training was provided to patients or staff on how to use the PRO information in the consultation. This may have led to a number of comments from patients in the feedback survey regarding clinical staff not reviewing or discussing their results with them; in addition the full integration of PRO results into EHR outside of Leeds Cancer Centre is not available. Patients treated with rectal and endometrial cancer will be followed up at the hospital where they received their surgery and thus includes surrounding cancer units. It will be interesting to evaluate in the full analysis of the feedback data if differences in the place of follow up care impacted on patient's experience negatively. Further qualitative data will be collected and analysed from patients and staff interviews to evaluate the weaknesses of the current study in more detail to provide recommendations for future work in this area.

The full benefit of this research may not be fully realised at this point due to incomplete follow up. Following study completion in June 2016, full analysis of the missing data and reasons for this will illuminate weaknesses in the study design. The relationship between PRO severity and clinical and treatment related factors will be evaluated and used to validate the dosimetric models developed within the cross sectional study. However, it is clear prospective electronic PRO data collection over a long time period is possible with minimal intervention from research staff. Although paper collection improved inclusivity, which is important in clinical practice, the demands on research time were greater in terms of on going costs and time. Favourable response rates were seen at six months suggesting these methods of PRO data collection provide an effective model to generate high rates of good symptomatic toxicity information from patients. The electronic platform piloted in this study provides early evidence that collection of PRO data with integration into EHR allows a consistent and systematic method to record adverse event data. This information may be used at an individual level to identify and monitor patients suffering from toxicity (as seen in the case studies), and at an organisational level to evaluate the relationships between toxicity outcomes and individual treatment and patient information to improve future therapies. The data may also influence the increasing use of PROs in the acute phase of treatment in trials.

Future analysis will explore detailed feedback on the study processes through patient and staff interviews to improve future studies in this area. The optimal number and timing of questionnaire completion will be considered as some patients reporting on the feedback questionnaire did not find it useful to report symptoms at all time points. The PRO, patients and treatment data will be used as an independent data set to validate the dosimetric models developed in the cross sectional study and provide a starting point to evaluate the usefulness of systematic PRO data collection in clinical practice to improve future radiation treatment.

Chapter 10 Conclusions, discussions and future directions

10.1 Conclusions

This PhD had two main objectives:

1) Evaluate the feasibility and acceptability of routine electronic patient reported outcome (PRO) collection within clinical practice in patients treated with pelvic radiotherapy
2) Assess the relationship between PRO late toxicity, radiotherapy dosimetric data and clinical factors.

Before testing these objectives within two clinical studies, several important methodological and practice issues were addressed:

- Selection of a PRO instrument to effectively measure acute and late radiotherapy related toxicity in patients treated with anal, rectal, endometrial and cervical cancer using multiple methods: systematic and literature reviews, content analysis of PROs, interviews with health professionals and patients and expert panel discussion.
- Set up of electronic integration of PRO data into individual patients electronic health records (EHR) for use in clinical practice
- Development of a research data-capture system able to import existing clinical data from EHR for validation and use within research analysis
- Set up of a tracker system to monitor patients on the prospective study
- Pilot study of feasibility of electronic PRO and paper collection and electronic integration into EHR in clinical practice
- Development of an organs at risk (OAR) contouring protocol for use in clinical practice by a multidisciplinary team
- Set of technical processes to enable dose-volume histogram (DVH) data export from treatment planning systems (TPS) in a format suitable for analysis

The studies reported in this thesis were carried out over a three year period with over 500 participants taking part. This chapter discusses and synthesises the key findings of the thesis.

10.1.1 Chapter 3: Systematic and Literature reviews

The results of the systematic review highlighted the lack of reporting standards for both clinician and patient-reported adverse events (AE) in randomised controlled trials (RCTs) of rectal cancer. The frequency of AE symptom reporting was consistently lower in clinician reported studies than those reported using PROs. The clinician-reported papers overall presented less detailed toxicity information than the PRO studies, with a tendency to report only the more serious toxicities and group symptoms relating broadly to a single organ unit together. There was also a lack of clinician-reported data on sexual dysfunction. In the literature reviews for all four chosen cancer sites the validated toxicity reporting measures used in both clinician and patient reported studies were similar. The two instruments most commonly used in the systematic and literature reviews - EORTC-QLQ system and Pelvic Symptom Questionnaire – along with the patient reported version of the CTCAE (the gold standard for clinician-reporting in cancer trials), NCI-PROCTCAE, were taken forward to the following study where their content was analysed through interviews with health professionals and an inductive content analysis.

10.1.2 Chapter 4: Content analysis and health professional interviews

The qualitative analysis of the content and clinical relevance of the three PROs found no one PRO, or group of PROs, covered all toxicity items expected in these cancer sites. Overall, the EORTC-QLQ-C30 and relevant cancer specific modules had the least number of missing items for use in the longitudinal follow up of patients with anal, cervical, endometrial and rectal cancer treated with (chemo)radiation. This questionnaire system was selected for use within the clinical studies. This evaluation piloted the use of an innovative mixed qualitative methods approach to evaluate the content of existing validated PROs. The use of an inductive content analysis technique to compare multiple questionnaires with the CTCAE proved an effective method to highlight missing items in each of the PROs evaluated. The domains and codes discussed in the health professional interviews were then integrated into the content analysis coding framework. This combined approach was valuable as whilst expert opinion was helpful in highlighting relevant missing items and envisioning the application of the PRO intervention in practice the analysis revealed no consensus on design and wording preferences. Combining the two methods provided a clear and transparent process through which to select the PRO with the best coverage of adverse event items for use in clinical practice in patients treated with pelvic radiotherapy.

10.1.3 Chapter 5: Cognitive interviews

Patients in the cognitive interview study found the EORTC-QLQ system easy to complete and suitable for use within this project. This study piloted the use of qualitative methodology to assess the differences between clinician and patient grading of AE through an evaluation of content validity of the EORTC-QLQ system and the CTCAE. Whilst quantitative studies often find differences in patients and clinician reporting of AE, the qualitative methods used in this study revealed that the discrepancies in toxicity grading between patient and clinician might be due to inherent differences in the grading descriptions in the two scoring systems. Therefore, it is not that clinicians are under-reporting symptoms per se but for some items may be unable to score a patient's symptoms more severely due to the restrictions implicit in the CTCAE description.

10.1.4 Chapter 6: Setting up the clinical studies and pilot study

The pilot study (n=31) found both the electronic and paper versions of the EORTC-QLQ to be relevant and acceptable to the sample population and provided a platform to test the PRO integration into EHR, approach methods and data management processes for the clinical studies.

10.1.5 Chapter 7: Protocol development for organ at risk contouring and methods used for dose-volume histogram export

The evaluation of existing OAR contouring guidelines found a number of the definitions lacked precision and the modifications developed through work with a multidisciplinary team improved the definitions for use within clinical practice using a multi-professional approach. The chapter also presented pilot work developing definitions for male and female external genitalia and vaginal contouring. Qualitative review of the use of MRI and CT fusion techniques identified the challenges with using image registration within the pelvis using existing clinical pathways. Finally, a solution to combine the dosimetric data for patients treated in more than two phases was developed. The technological and methodological processes developed within this project allow for PRO data to be collected routinely in future studies within our organisation, alongside extraction of detailed clinical data from EHR and DVH data from treatment planning systems providing high quality data for analysis. This new approach has the potential to allow clinicians within our organisation to routinely audit their treatment outcomes.

10.1.6 Chapter 8: Cross sectional study

The cross sectional study, involving 315 patients, demonstrated the associations between PRO late toxicity, collected from multiple cancer sites, and the dosimetric and clinical data. Principal component analysis (PCA) provided an effective research tool to manage heterogeneous DVH data and generate principal components (PCs) for each OAR for use in the regression analysis. This study piloted the application of PCA to describe DVH data from patients treated with multiple radiation techniques. The normal tissue complication models developed for each OAR incorporated dosimetric, treatment information and individual patient characteristics with the future aim of validating the models using the data generated from the prospective study.

10.1.7 Chapter 9: Prospective study

The interim analysis of the prospective study (n=129) provided encouraging findings for the use of longitudinal electronic and paper PRO collection in routine practice over a median 9.8 month period (range 0.5 to 12 months). Recruitment and attrition rates were favourable and response rates at the point of analysis were similar to other studies using electronic methods to collect PRO data and better than previous studies using solely paper methods in clinical practice(12, 48, 113). The PRO results described detailed information on the trajectory and severity of acute and early late toxicity associated with different pelvic radiotherapy regimes. Many treatment-related symptoms resolved by the assessment at six months; however as seen in the cross sectional study results, bowel urgency and sexual symptoms continued to be the most prominent symptoms experienced by patients, showing the greatest deterioration in mean scores from baseline. These early findings suggest longitudinal electronic PRO collection with integration into EHR is feasible and acceptable to patients and the use of the EORTC-QLQ system to evaluate pelvic radiotherapy related toxicity in clinical practice is effective and provides an accurate means of systematically collecting toxicity data.

10.2 Methodological aspects

10.2.1 Study design

The use of a mixed methods approach to this project allowed a multi-faceted exploration of the development and implementation of a complex intervention within clinical practice. The questionnaire selection was arrived at through a rigorous combination of literature reviews, an inductive content analysis of validated PRO measures, interviews with healthcare professionals followed by patient interviews.

Questionnaire development for clinical trials recommends construction using interviews and literature searching(343). This study combined traditional questionnaire development methods and piloted an innovative approach to analysing the content of the most commonly used PROs alongside the health professional interview analysis. This mixed methods approach was used to ensure all important toxicity items were added to the existing validated PROs to extend use in clinical practice. Qualitative research is limited by the small sample sizes used and therefore can lack generalisability. However, the qualitative analyses illuminated potential mechanisms by which clinician and patients report toxicity by evaluating questionnaire content in a way that would not possible using quantitative study design.

The selection of cross sectional design allowed the collection of a relatively large participant sample within the three-year timeframe of this PhD project to assess late radiotherapy related toxicity and the relationship to dosimetric, clinical and patient factors. The sample included multiple cancer sites and treatment regimes. Whilst a cross sectional study design is limited as patients were assessed as a single time-point with participants completing the assessment at different times following the completion of radiotherapy, this confounding factor was included within the regression analysis. The inclusion of multiple treatment techniques was overcome in part through the application of the PCA and also through evaluating dose per fractionation and cancer site within the regression analysis. However, observational studies are potentially subject to bias. Whilst attempts are made to account for all potential confounding factors within the analysis some factors may remain hidden and unrecorded.

The prospective study design provides a good model to address the feasibility and acceptability of longitudinal PRO data collection for patients receiving pelvic radiotherapy, to reveal the strengths and weaknesses of electronic PRO integration in clinical practice. The study was limited in the small sample size numbers for the different treatment regimes. Whilst the interim analysis provides only descriptive data describing the trajectory of toxicity, the data generated from both of these observational studies provides useful information to inform clinical practice and inform the design of future clinical trials.

10.2.2 Statistical analysis

The cross sectional study piloted the use of PCA technique to combine dosimetric data from patients treated from multiple pelvic treatment sites and with different fractionation schedules within a single analysis. Using the principal components generated from the PCA within the regression analysis does not immediately result in dosimetric guidelines

that can be applied to clinical practice. However, the results broadly describe the patterns of DVH associated with worse (or better) toxicity scores and may be used in future research to validate and develop predictive models which may more easily be integrated within routine care. Future work with the normal tissue complication models developed from this study will be described in the following section.

It was recognised that various patient, disease and treatment related factors might influence the toxicity outcomes(303). Information on these factors was collected in both the cross sectional study and prospective study and included within the regression analyses for the cross sectional study. Whilst every effort was made to take into account differences in radiation techniques used within the regression analysis in the cross sectional study, an alternative option would be to include a matched pair analysis from the cohort. For example to compare outcomes in a patient treated with 3D conformal treatment compared to a matched patient treated with intensity modulated radiotherapy (IMRT).

10.2.3 Clinical settings

All studies were conducted in Cancer Research UK (CRUK) Leeds Centre, a specialised tertiary referral centre for radiotherapy. However, whilst all patient receive radiotherapy therapy treatment in Leeds, patients with rectal and endometrial cancer are followed up at satellite hospitals where they received their surgery. This may lead to differences in the attrition rates and missing data within the prospective study, which will be evaluated when follow up for this study is complete.

The psychosocial research team within CRUK Leeds Centre has been active for twenty years and clinicians working within the hospital have been regularly involved in studies involving PRO research. Every effort was made to engage clinical staff members who treat and support patients treated with radiotherapy in the project and to ensure the intervention was relevant to their clinical practice. This led to excellent collaboration and enthusiasm from the clinical teams who were willing to support recruitment positively and led to the fast recruitment rates found in the studies. Conducting a similar study in a different unit may have required more support for training and education during the study to ensure continued good recruitment rates.

Whilst clinical staff were aware of the availability of PRO results for patients on the studies no formal training was provided to recommend how best to use the data within the consultation. Health professionals who follow up patients within Leeds were shown

how to access the results but the use of the results and impact on care was not measured within this study.

10.2.4 Patient reported outcome measures

The EORTC-QLQ system was selected for use within the clinical studies. The validated questionnaire system provided the best coverage of pelvic radiotherapy related toxicity items out of the measures assessed. The system was developed specifically for use in oncology, has been widely used in clinical trials and practice and has a significant amount of information on analysis and interpretation(48, 129, 244). Whilst the questionnaire system was developed for use in studies involving group comparisons and not to interpret results for individual patients, the use of the EORTC-QLQ C30 at an individual level within clinical practice has been previously evaluated(257). When comparing the results from the questionnaire with symptoms reported in the clinical records the data was consistent(257). Within this project the aim of integrating PRO results within clinical practice was to highlight areas of concern for clinicians to explore further rather than as a decision-making tool to change care.

All scales used within the EORTC-QLQ CX24, EN24 and male sexual items used in the GI questionnaire from PR25 met the reliability criterion (Cronbach's alpha) for internal consistency with reliability coefficient scores >0.7(313, 315, 316). EORTC-QLQ CR29 met the criteria for the majority of items (75%)(314) and the EORTC-QLQ C30 met the criteria for all but one scale (role functioning)(67). Cronbach's alpha coefficient of reliability assesses whether the items within a questionnaire are similar in content. The scores range from 0 (low reliability) to 1(high reliability). Whilst for group comparisons the 0.7 reliability criterion level is considered acceptable, for use at an individual level higher reliability levels are recommended(344). If future work is to consider the use of the EORTC-QLQ system as an alternative or adjunct to traditional follow up then further evaluation on decision-making based on individual scores will be required.

10.3 Implications for practice and future research

10.3.1 Using PRO to explore stratified follow up of patients

This study has demonstrated that routine collection and integration of PRO results into patient EHR using a combination of electronic and paper methods is feasible and acceptable to patients treated with pelvic radiotherapy in clinical practice. The recruitment rates for the cross sectional were excellent and longitudinal follow up over

a nine-month period in the prospective study demonstrated low attrition rates and favourable response rates at the point of interim analysis. One of the potential uses of remote monitoring of symptoms using PRO could be to supplement or modify traditional models of routine follow up following cancer treatment.

Traditional follow up in clinical practice following treatment, including curative radiotherapy, involves regular review in hospital outpatient clinics for a period of 5 years(83, 345, 346). The two main aims of follow up are (1) to detect local regional failure where salvage treatment may improve long term outcomes and (2) to detect, monitor and support patients with late toxicity following treatment. These potential benefits must be weighed up against the potential negative consequences of regular follow up; more invasive testing, the psychological impact of the visits and the financial costs to both patient and organisation. Regular surveillance may also not be appropriate for all patients if the option of curative surgery, further radiotherapy or chemotherapy would not be suitable. The current follow up practice for the four chosen cancer sites is variable and complex and not all cancer sites may be amenable to using remote follow-up practices using PROs to monitor for recurrence and toxicity(83, 87, 345, 346).

Longitudinal PRO data capture in clinical practice using electronic methods may offer a number of benefits to improve and potentially risk stratify long term follow up of patients following radiotherapy treatment. In the short term it may be possible to stratify patients on the basis of disease risk, including data from follow up imaging, and complex social needs to reduce hospital visits for patients stratified to a low recurrence risk group whilst still collecting data regarding late toxicity symptoms. A separate study could also evaluate the validity of using PROs to detect recurrence symptoms.

In the longer term, it might be possible to gain additional long term toxicity information from patients treated in clinical practice at later time points when local recurrence is no longer an issue. PROs might also be considered as a method of screening patients presenting with late toxicity symptoms before referral to a specialist, providing baseline data to evaluate the impact of treatment on symptom control.

10.3.2 Developing predictive models of radiation toxicity using probability modelling and informing future trial design

The normal tissue complication models developed from the results of the cross sectional analysis require further evaluation using the longitudinal data gathered in the

prospective study. The use of longitudinally collected PRO data will provide a more accurate measure of treatment related toxicity by analysing the change in mean scores from baseline. The prospective data will also provide an independent data set to further test and validate the models developed.

One of the challenges with the models developed using principal components (PCs) is how to interpret and relate the PCA outcomes for an OAR to an individual patient's dosimetric data and thus potentially modify their treatment. By incorporating the whole of the DVH within the PCA model interpreting the dosimetric meaning of the outcomes is more complex to attain, but arguably uses a more rigorous methodology to explain more of the variance in the data set than by using arbitrary DVH values. Although complex models are less appealing to clinicians as they lack transparency in the decision-making process, we already use complex modelling in our practice. Inverse planning used in IMRT planning uses an optimisation program to solve the inverse problem set up by the dosimetrist. The optimiser is able to create a plan more complex than would be possible by the manual trial and error methods used for forward planning in conformal treatments. Currently dose-constraints for OAR applied to the inverse planning models are not individualised based on clinical risk factors. An extension to the models developed in the cross sectional regression analysis could be to incorporate clinical risk factors and PCs predicting toxicity related symptoms within the process of treatment planning to better optimise treatment outcomes for individual patients. Developing these predictive models using predictive modelling techniques will be a focus of future work.

In addition to developing predictive models for patient outcomes, the PRO data collected in this trial may inform the design of future clinical trials in terms of when to collect PRO data in relation to multi-modal treatment regimes. If regular PRO data collection is established in clinical practice, the large observational datasets will allow evaluation of late toxicity from modern RT techniques such as IMRT, where it is unlikely that large RCTs will be performed.

In summary, the results from this project have found electronic PRO data collection and integration with EHR to be acceptable and feasible in patients treated with pelvic radiotherapy over a nine-month follow up period. The electronic PRO results provide a systematic alternative to symptomatic toxicity reported by clinicians within clinical practice, where routine data on AE is not collected. Use of PRO as an adjunct or alternative to traditional hospital led surveillance may be a favourable model for some tumour sites and requires evaluation in multi-centre trials. Dosimetric and clinical

factors were predictive of patient-reported toxicity. Future work will evaluate these models further using the prospective study data to validate and develop more accurate methods to optimise individual patient treatments.

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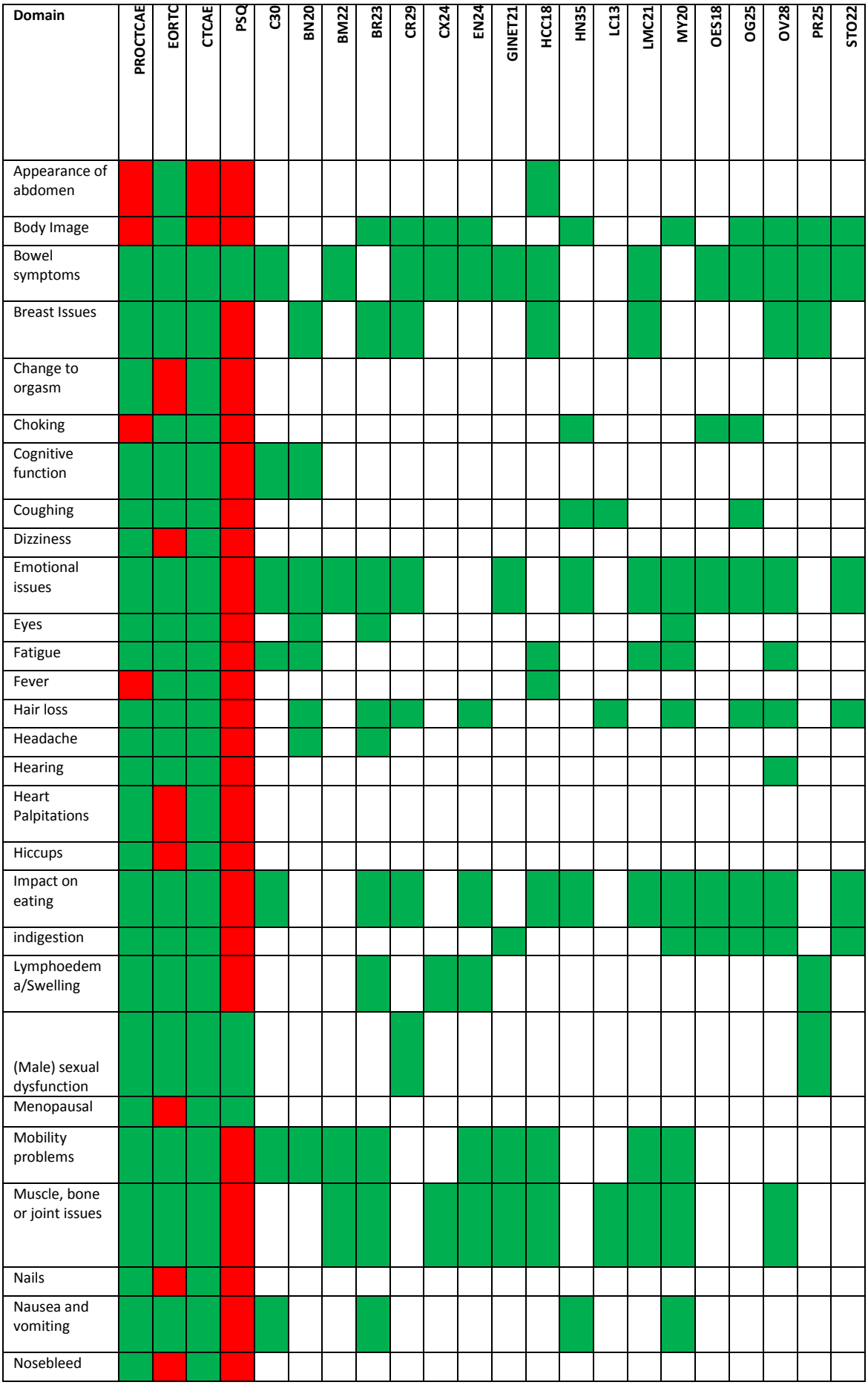
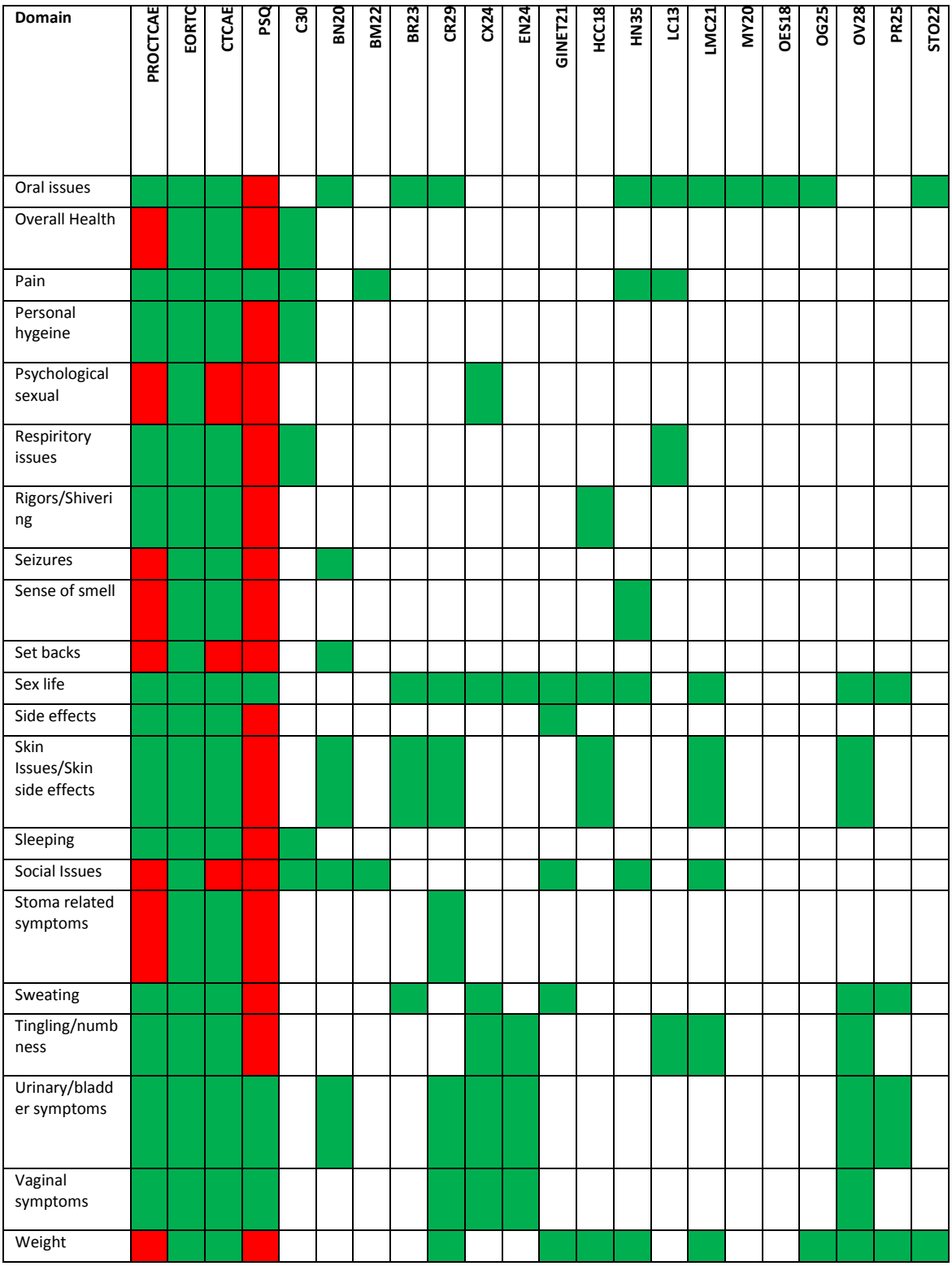
Appendices

Table 10-1: Appendix A: Complete coding summary of all domains found in all PROs and CTCAE




Domain
PROCTCAE
EORTC
CTCAE
PSQ
C30
BN20
BM22
BR23
CR29
CX24
EN24
GINET21
HCC18
HN35
LC13
LMC21
MY20
OES18
OG25
OV28
PR25
STO22
Oral issues
Overall Health
Pain
Personal hygeine
Psychological sexual
Respiritory issues
Rigors/Shivering
Seizures
Sense of smell
Set backs
Sex life
Side effects
Skin Issues/Skin side effects
Sleeping
Social Issues
Stoma related symptoms
Sweating
Tingling/numbness
Urinary/bladder symptoms
Vaginal symptoms
Weight

Appendix B

Table 10-2: EORTC-QLQ items

EORTC QLQ-C30 items (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no right or wrong answers. The information that you provide will remain strictly confidential.

		Not at all	A little	Quite a bit	Very much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4
17.	Have you had diarrhoea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4

25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

EORTC QLQ-CR29 & additional items – anal and rectal patients					
During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
31.	Did you urinate frequently during the day?	1	2	3	4
32.	Did you urinate frequently during the night?	1	2	3	4
33.	Have you had any unintentional release (leakage) of urine?	1	2	3	4
34.	Did you have pain when you urinated?	1	2	3	4
EN	When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
35	Did you have abdominal pain?	1	2	3	4
36.	Did you have pain in your buttocks/anal area/rectum?	1	2	3	4
37.	Did you have a bloated feeling in your abdomen?	1	2	3	4
38.	Have you had blood in your stools?	1	2	3	4
39.	Have you had mucus in your stools?	1	2	3	4
40.	Did you have a dry mouth?	1	2	3	4
HN	Have you had soreness in your mouth?	1	2	3	4
AG	Have you had any soreness to the skin of your hands and feet?	1	2	3	4
41.	Have you lost hair as a result of your treatment?	1	2	3	4
42.	Have you had problems with your sense of taste?	1	2	3	4
EN	Have you had swelling in one or both legs?	1	2	3	4
EN	Have you had tingling or numbness in your hands or feet?	1	2	3	4
AG	Have you had any changes to your skin treated with radiotherapy?	1	2	3	4

43.	Were you worried about your health in the future?	1	2	3	4
44.	Have you worried about your weight?	1	2	3	4
45.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46.	Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
47.	Have you been dissatisfied with your body?	1	2	3	4
48.	Do you have a stoma bag (colostomy/ileostomy)? (please circle the correct answer)	Yes		No	

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
Answer these questions ONLY IF YOU HAVE A STOMA BAG, if not please continue below:					
49.	Have you had unintentional release of gas/flatulence from your stoma bag?	1	2	3	4
50.	Have you had leakage of stools from your stoma bag?	1	2	3	4
51.	Have you had sore skin around your stoma?	1	2	3	4
52.	Did frequent bag changes occur during the day?	1	2	3	4
53.	Did frequent bag changes occur during the night?	1	2	3	4
54.	Did you feel embarrassed because of your stoma?	1	2	3	4
55.	Did you have problems caring for your stoma?	1	2	3	4
AG	Have you had any mucus from your back passage?	1	2	3	4

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
Answer these questions ONLY IF YOU DO NOT HAVE A STOMA BAG					
49.	Have you had unintentional release of gas/flatulence from your back passage?	1	2	3	4
50.	Have you had leakage of stools from your back passage?	1	2	3	4
51.	Have you had sore skin around your anal area?	1	2	3	4
52.	Did frequent bowel movements occur during the day?	1	2	3	4
53.	Did frequent bowel movements occur during the night?	1	2	3	4
54.	Did you feel embarrassed because of your bowel movements?	1	2	3	4
EN	When you felt the urge to move your bowels, did you have to hurry to get to the toilet?	1	2	3	4

EORTC-QLQ CX24 and additional items – cervical					
During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
31.	Have you had cramps in your abdomen?	1	2	3	4
32.	Have you had difficulty in controlling your bowels?	1	2	3	4
33.	Have you had blood in your stools (motions)?	1	2	3	4
EN	When you felt the urge to move your bowels, did you have to hurry to get to the toilet?	1	2	3	4
CR	Did you have pain in your buttocks/anal area/rectum?	1	2	3	4
34.	Did you pass water/urine frequently?	1	2	3	4
35	Have you had pain or a burning feeling when passing water/urinating?	1	2	3	4
36.	Have you had leaking of urine?	1	2	3	4
37.	Have you had difficulty emptying your bladder?	1	2	3	4
EN	When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
38.	Have you had swelling in one or both legs?	1	2	3	4
39.	Have you had pain in your lower back?	1	2	3	4
40.	Have you had tingling or numbness in your hands or feet?	1	2	3	4
41.	Have you had irritation or soreness in your vagina or vulva?	1	2	3	4
42.	Have you had discharge from your vagina?	1	2	3	4
43.	Have you had abnormal bleeding from your vagina?	1	2	3	4
44.	Have you had hot flushes and/or sweats?	1	2	3	4
AG	Have you had any changes to your skin treated with radiotherapy?	1	2	3	4
45.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46.	Have you felt less feminine as a result of your disease or treatment?	1	2	3	4
47.	Have you felt dissatisfied with your body?	1	2	3	4
CR	Have you worried about your weight?	1	2	3	4

EORTC-QLQ EN24 -endometrial					
During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
31.	Have you had swelling in one or both legs?	1	2	3	4
32.	Have you felt heaviness in one or both legs?	1	2	3	4
33.	Have you had pain in your lower back and / or pelvis?	1	2	3	4
34.	When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
35	Have you passed urine frequently?	1	2	3	4
CR	Did you urinate frequently during the night?	1	2	3	4
36.	Have you had leaking of urine?	1	2	3	4
37.	Have you had pain or a burning feeling when passing urine?	1	2	3	4
38.	When you felt the urge to move your bowels, did you have to hurry to get to the toilet?	1	2	3	4
39.	Have you had any leakage of stools?	1	2	3	4
40.	Have you been troubled by passing wind?	1	2	3	4
41.	Have you had cramps in your abdomen?	1	2	3	4
42.	Have you had a bloated feeling in your abdomen?	1	2	3	4
CR	Have you had blood in your stools?	1	2	3	4
43.	Have you had tingling or numbness in your hands or feet?	1	2	3	4
44.	Have you had aches or pains in your muscles or joints?	1	2	3	4
45.	Have you lost hair?	1	2	3	4
46.	Has food and drink tasted differently from usual?	1	2	3	4
47.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48.	Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4

SEXUAL ITEMS					
During the past 4 weeks:		Not at all	A little	Quite a bit	Very much
All	To what extent were you interested in sex?	1	2	3	4
EN	To what extent were you sexually active?	1	2	3	4
	FEMALE (questions used for all female patients on all questionnaires)				
	Answer these questions only if you have been sexually active during the past 4 weeks:				
CX	Has your vagina felt dry during sexual activity?	1	2	3	4
CX	Has your vagina felt short?	1	2	3	4
CX	Has your vagina felt tight?	1	2	3	4
CX	Did you have pain or discomfort during intercourse?	1	2	3	4
CX	Was sexual activity enjoyable for you?	1	2	3	4
	Answer these questions if you have been using vaginal dilators during the past 4 weeks:				
AG	Has your vagina felt dry when using vaginal dilators?	1	2	3	4
AG	Has your vagina felt short and / or tight when using vaginal dilators?	1	2	3	4
AG	Have you had pain when using vaginal dilators?	1	2	3	4
	MALE				
57.	Did you have difficulty getting or maintaining an erection?	1	2	3	4
	Answer these questions only if you have been sexually active during the past 4 weeks:				
PR	Did you have ejaculation problems (e.g. dry ejaculation)?	1	2	3	4
PR	To what extent was sex enjoyable for you?	1	2	3	4
PR	Have you felt uncomfortable about being sexually intimate?	1	2	3	4

Key: EORTC-QLQ additional items: EN – taken from endometrial questionnaire; CR – taken from colorectal questionnaire; CX– taken from cervical questionnaire; PR - – taken from prostate questionnaire; HN - – taken from head and neck questionnaire. AG – created for this project.

Appendix C: Online consent form

Study Title:

Optimising Individual Treatment Regimes and Patient Outcomes through the Use of Patient-Reported Toxicity Assessments in Patients treated with Pelvic Radiotherapy

Name of Researchers involved in this project: Alexandra Gilbert

Please **tick each box** to show that you have read and agree to each statement:

I confirm that I have read and understand the patient information sheet for the above study. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. I am able to do this by contacting the research team on the email address and telephone number provided ☐

I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from St James' Hospital or from Leeds University for the purposes of this research. I give permission for these individuals to have access to my records. ☐

I am happy for the contribution I have already made to be used in the analysis if I choose to withdraw from the study ☐

I agree to take part in the above study ☐

Contact details:

Dr Alexandra Gilbert Clinical Oncology Trainee and Research Fellow

Tel: 0113 206 7516 a.gilbert@leeds.ac.uk

Appendix D: Validation of clinical data

1. Assume gender and ethnicity correct
    a. Select missing data if not entered
2. Diagnosis and Histology
    a. Correct data based on Clinical summary on PPM by a clinical or medical oncologist. This may be found under the 'H tab' or in a clinical letter (it should be the same information). If patients have had disease progression complete if metastatic disease with selecting M1. Otherwise will assume local disease progression.
    b. Note that patients receiving follow up from outside of Leeds the subsequent treatment information may be incomplete (only a small sample of patients – endometrial and rectal from outside Leeds). To contact local research teams for data.
3. Chemotherapy data
    a. Check a few at random to check data is coming in correctly from import (checked previously when initially exporting data from PPM into excel file so should be fine.)
    b. Blank data leave blank
4. Surgery data
    a. Check a few at random to check data is coming in correctly from import (checked previously when initially exporting data from PPM into excel file so should be fine.)
    b. Blank data leave blank
5. Radiotherapy PPM
    a. Review Radiotherapy treatment given in clinician letter. Look for:
        i. Phase 1
        ii. +/- Phase 2 (most anal, some cervix, some endometrial)
        iii. +/- Brachytherapy
    b. Modify brachytherapy dose to correct total dose (e.g. 21Gy for cervix or 26Gy for endometrial cancer (usually). Data either in annotation under brachy entry on PPM or from clinician letters
    c. Do not worry about the external beam data (under heading Teletherapy) as we will use the MOSAIQ data for total dose, fractionation, energy
6. Radiotherapy MOSAIQ
    a. Check a few at random to check data import ok
    b. Do not need to modify otherwise
    c. Does not contain brachytherapy dosing but this is available in the radiotherapy PPM data

Check the start/end dates on PPM and MOSAIQ and decide which ones are most accurate and we will use this in the analysis. Do not need to modify the other dates we will just assume one or the other is accurate.

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