

**Optimising delivery of Stereotactic Ablative Radiotherapy
(SABR) in the pelvis**

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The candidate confirms that the work submitted is his own, except where work which has 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.

This research has been performed by a team, which has included Finbar Slevin, Matthew Beasley, Richard Speight, John Lilley, Louise J Murray and Ann M Henry, among others. The contributions of the candidate and those of others are fully and explicitly indicated as follows:

Chapter 1 (introduction) is based on work from the following jointly authored publications:

i) F. Slevin, M. Beasley, R. Speight, J. Lilley, L. Murray, and A. Henry, Overview of patient preparation strategies to manage internal organ motion during radiotherapy in the pelvis. *Journal of Radiotherapy in Practice*, 2020. **19**(2): p. 182-189.

Finbar Slevin was responsible for conducting this critical review including design, literature search, manuscript preparation, submission and responding to reviewer comments. Ann Henry had the original idea for the critical review. Matthew Beasley provided assistance with figure assembly. All co-authors reviewed the manuscript and provided comments.

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Abstract

Introduction

Multiple considerations exist concerning Stereotactic Ablative Radiotherapy (SABR) in the pelvis, including impact of teaching on target volume/organ at risk (OAR) delineation, the most appropriate target volume and dose fractionation schedules and how these relate to treatment planning, management of pelvic organ motion and optimum practice of pelvic SABR re-irradiation in the absence of high-level evidence.

Materials and Methods

An evaluation of target volume/OAR delineation variation during a national contouring workshop was performed before and after teaching. A planning study was performed to develop a class solution for ultra hypofractionated Extended Nodal Irradiation (ENI). A prospective feasibility study was performed to determine the impact of hyoscine butylbromide (buscopan) on bowel motion artefacts on cone beam computed tomography (CBCT). An international Delphi study was performed to establish consensus for statements to guide practice for pelvic SABR re-irradiation.

Results

Teaching was associated with modest improvements in delineation variation for multiple target volume/OAR structures. Ultra hypofractionated ENI planning appeared feasible. A schedule of 25 Gy in 5 fractions with simultaneous integrated boost to involved node(s) of 30 Gy provided encouraging rates of tumour control probability and low rates of normal tissue complication probability. Trends to improved CBCT overall image quality and reduced bowel motion artefact were observed with administration of both intramuscular and intravenous buscopan. Delivery of buscopan was feasible and well tolerated by participants. Consensus was established for most statements relating to patient selection, pre-treatment investigations, treatment planning and delivery for pelvic SABR re-irradiation. Absence of consensus remained for statements relating to minimum time to re-irradiation, limits on lesion size/number and the most appropriate cumulative constraints for most OARs.

Conclusions

These findings have provided preliminary evidence and the justification for further investigation into several aspects of pelvic SABR in larger confirmatory studies to determine the clinical impact of these interventions.

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Abbreviations

°	Degrees
%	Per cent
α^-	Mean population radiosensitivity
α/β	Alpha/beta ratio
ρ_{clon}	Initial clonogenic cell density
σ_α	Standard deviation of population radiosensitivity
3D-CRT	3-dimensional conformal radiotherapy
4DCT	4-dimensional computed tomography
11C	Carbon 11
18F	Fluorine 18
68Ga	Gallium 68
AAPM	American Association of Physicists in Medicine
ADT	Androgen deprivation therapy
ARTISTIC	Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer
BED	Biologically effective dose
BRCA 1/2	Breast cancer gene 1/2
CBCT	Cone beam computed tomography
CHHiP	Conventional versus Hypofractionated High-dose intensity-modulated radiotherapy for Prostate cancer
CI	Conformity index
cm	Centimetre
cm ³	Cubic centimetre
CONSORT	Consolidated Standards of Reporting Trials
COPP	Clinical Oncology Planning Project
Covid-19	Coronavirus disease
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events

CTRad	Clinical and Translational Radiotherapy Research Working Group
CTV	Clinical Target Volume
D	Total dose
d	Dose per fraction
Dmax	Maximum dose received by a structure
DNA	Deoxyribonucleic acid
DSC	Dice similarity coefficient
DVH	Dose-volume histogram
Dx%/xcc	Dose received by x%/cm ³ of the volume
EBRT	External beam radiotherapy
EMPIRE	Emory Molecular Prostate Imaging for Radiotherapy Enhancement
EPIC	Expanded Prostate Index Composite
EQD2	Equivalent dose in 2 Gy fractions
EORTC	European Organisation for Research and Treatment of Cancer
ENI	Extended Nodal Irradiation
ESTRO	European Society for Radiotherapy & Oncology
FALCON	Fellowship in Anatomic deLineation and CONtouring
FFF	Flattening filter free
GETUG(-AFU)	Genitourinary Group
GI	Gastrointestinal
GTV	Gross Tumour Volume
GU	Genitourinary
Gy	Gray
ICRU	International Commission on Radiation Units and Measurements
IGRT	Image-guided radiotherapy
IGTV	Internal Gross Tumour Volume
IM	Intramuscular

IMRT	Intensity-modulated radiotherapy
IQR	Interquartile range
ISRCTN	International Standard Randomised Controlled Trial Number
ISUP	International Society for Urological Pathology
IRAS	Integrated Research Application System
IV	Intravenous
kV	Kilovolt
LDE	Line domain error
LQ	Linear quadratic
M stage	Metastasis stage
m	Parameter inversely related to the slope at the steepest point of the NTCP curve
mA	Milliampere
MDT	Metastasis-directed therapy
MIP	Maximum intensity projection
MFS	Metastasis-free survival
mg/ml	Milligrams per millilitre
ml	Millilitre
mm	Millimetre
MRI	Magnetic resonance imaging
ms	Milliseconds
MV	Megavoltage
N stage	Nodal stage
n	Volume effect parameter
NCCN	National Comprehensive Cancer Network
NCRI	National Cancer Research Institute
ng/ml	Nanograms per millilitre
NHS	National Health Service
NIHR	National Institute for Health Research
NTCP	Normal tissue complication probability

OAR	Organ at risk
OLIGOPELVIS	Oligometastatic Pelvic Node Relapses of Prostate Cancer
ORIOLE	Observation versus Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer
PACE	Prostate Advances in Comparative Evidence
PCa	Prostate cancer
PEARLS	Primary radiotherapy for Androgen sensitive Prostate cancer patients with Lymph nodes
PET-CT	Positron emission tomography-computed tomography
PI3K/AKT	Phosphatidylinositol-3-Kinase and Protein Kinase B
PIVOTAL	A Study of Prostate and pelvis Versus prostate Alone Treatment for Locally Advanced Prostate Cancer
PIVOTALboost	A Study of Prostate and pelvis Versus prostate Alone Treatment for Locally Advanced Prostate Cancer boost
PLND	Pelvic lymph node dissection
PPI	Patient and Public Involvement
PROM	Patient-reported outcome measure
PRV	Planning organ at Risk Volume
PSA	Prostate specific antigen
PSMA	Prostate specific membrane antigen
PTV	Planning Target Volume
RADICALS-RT	Radiation Therapy and Androgen Deprivation Therapy in Treating Patients Who Have Undergone Surgery for Prostate Cancer
RAVES	Radiotherapy - Adjuvant Versus Early Salvage
REC	Research Ethics Committee
RCR	Royal College of Radiologists
RP	Radical prostatectomy
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SABR	Stereotactic Ablative Radiotherapy

SABR-COMET	Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases
SBRT	Stereotactic Body Radiotherapy
SIB	Simultaneous integrated boost
SPPORT	Short Term Androgen Deprivation Therapy Without or With Pelvic Lymph Node Treatment Added to Prostate Bed Only Salvage Radiation Therapy
SPSS	Statistical Package for the Social Sciences
STOMP	Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer
STORM	Salvage Treatment of OligoRecurrent Nodal Prostate Cancer Metastases
STRIDeR	Support Tool for Re-Irradiation Decisions Guided by Radiobiology
T stage	Tumour stage
TCP	Tumour control probability
TD ₅₀	Dose resulting in 50% probability of a complication
UK	United Kingdom
USA	United States of America
VMAT	Volumetric modulated arc therapy
XVI	X-ray volume imaging

Chapter 1 Introduction

The introduction has been published in part in two critical review articles, as below:

- i) F. Slevin, M. Beasley, R. Speight, J. Lilley, L. Murray, and A. Henry, *Overview of patient preparation strategies to manage internal organ motion during radiotherapy in the pelvis*. *Journal of Radiotherapy in Practice*, 2020. **19**(2): p. 182-189.
- ii) F. Slevin, M. Beasley, W. Cross, A. Scarsbrook, L. Murray, and A. Henry, *Patterns of Lymph Node Failure in Patients With Recurrent Prostate Cancer Post Radical Prostatectomy and Implications for Salvage Therapies*. *Advances in Radiation Oncology*, 2020. **5**(6): p. 1126-1140.

1.1 Stereotactic Ablative Radiotherapy

1.1.1 Definition

Stereotactic Ablative Radiotherapy (SABR) is ultra hypofractionated radiation therapy, which involves the delivery of large doses per fraction in a small number of treatment fractions (usually 1 to 8 fractions) using tight treatment margins, highly conformal delivery techniques with steep dose gradients and daily online image guidance[1, 2].

1.1.2 SABR workflow

The safe and effective delivery of SABR requires close collaboration between a multidisciplinary team of clinical oncologists, medical physicists, treatment planners, therapeutic radiographers and supporting roles. An illustration of a typical SABR workflow, and the individual components which are investigated within each chapter in this thesis, is shown in **Figure 1.1**. Chapter 2 addresses target volume/organ at risk (OAR) delineation through an analysis of the impact of teaching on delineation variation during a SABR contouring workshop. Chapter 3 addresses treatment planning through the design of a class solution for ultra hypofractionated Extended Nodal Irradiation (ENI) in pelvic nodal recurrent prostate cancer (PCa). Chapter 4 addresses image-guided

radiotherapy and motion management through a prospective feasibility study which evaluated the impact of buscopan in reducing cone beam computed tomography (CBCT) bowel motion artefacts during abdominal/pelvic SABR. Chapter 5 addresses multiple components of the workflow through an international Delphi study to develop consensus statements to guide the practice of pelvic SABR re-irradiation.

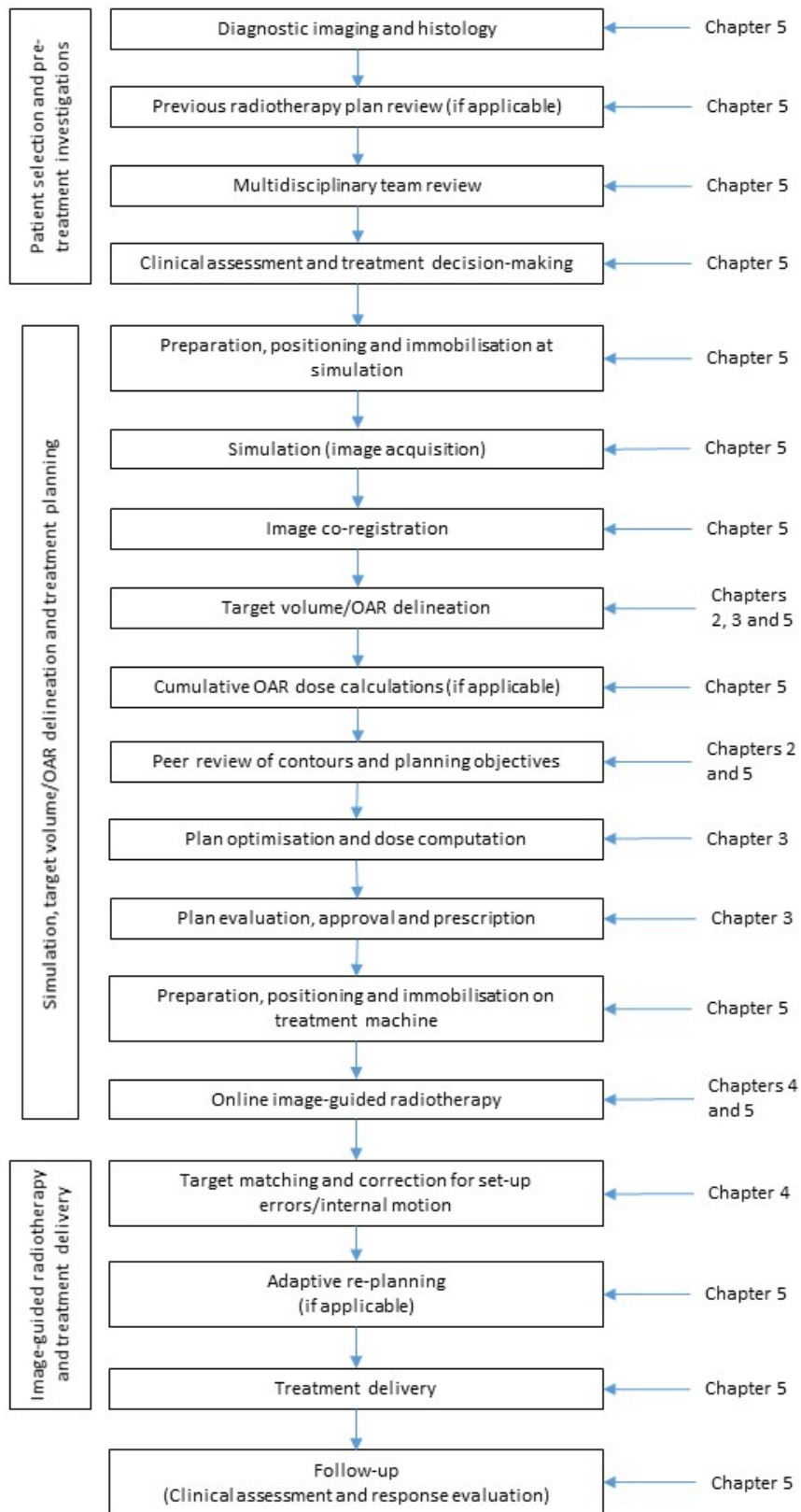


Figure 1.1 SABR workflow illustrating individual components of the treatment pathway and where these are addressed by chapters within this thesis.

1.1.3 Radiobiological and technological considerations

Radiotherapy (RT) is an important component in the management of patients with cancer, and it is used in approximately 50% of cases[3]. RT involves the delivery of ionising radiation, which causes DNA damage and results in cellular apoptosis and death[4]. The aim of RT is to maximise the radiation dose delivered to the tumour and to minimise the dose received by normal tissues. Typically, RT is delivered in the form of high-energy megavoltage (MV) x-rays using a linear accelerator, although other radiation types may be administered and various dedicated treatment platforms exist.

In RT, the relationship between tumour cell kill and normal tissue complications for conventionally fractionated RT (delivered using multiple fractions of 1.8-2 Gy) can be described by the linear quadratic (LQ) model[5]. A number of factors influence tumour control probability (TCP) and normal tissue complication probability (NTCP), including total dose, fraction size, inter-fraction time interval, dose rate, cell cycle phase and tumour hypoxia[6]. The impact of these factors is often described by the 'Five Rs of Radiobiology', which are repair, re-assortment, re-oxygenation, repopulation and radiosensitivity[7]. In the LQ model, cell kill is hypothesised to result from the combination of single or double radiation track hits to DNA[8]. The sensitivity of individual tumours and normal tissues to fraction size can be described by the α/β ratio, which is the ratio of linear (single hit unreparable/lethal DNA lesions) to quadratic (double hit potentially repairable/sublethal DNA lesions) cell kill[6]. Many tumours are considered to have a high α/β ratio (~10 Gy), while the critical late effects for most normal tissues are estimated to have a low α/β ratio (~3 Gy). For such a scenario, the LQ model predicts that conventionally fractionated RT should provide the optimum balance between TCP and NTCP.

However, technological advances in image guidance and treatment delivery mean that larger biologically effective doses (i.e. through dose escalation) than can be achieved with conventionally fractionated schedules can now be safely delivered using SABR[6, 8]. In addition, SABR may induce additional tumour cell kill through enhanced immune response and damage to tumour vasculature. A number of factors may reduce the risk from SABR to normal tissues. Prescription to a peripheral isodose results in a heterogenous dose distribution within the target volume and a rapid fall-off in dose outside of the target volume[6]. This results in a high degree of target conformality and improves sparing of adjacent normal tissues. An isodose distribution for a pelvic

SABR treatment is illustrated in **Figure 1.2**. Some normal tissue OARs may exhibit a parallel arrangement of functional subunits, meaning that organ function can be retained even if several functional subunits are damaged. In addition, a requirement for the safe delivery of SABR is robust patient immobilisation and management of internal organ motion throughout the RT pathway, including the use of online image guidance during treatment delivery, in order to minimise the delivery of dose to surrounding normal tissues[9, 10].

Furthermore, for certain tumours (for example, PCa) the α/β ratio is estimated to be low (~ 1.5 Gy)[11]. A low α/β ratio with respect to adjacent normal tissues would suggest a greater tumour sensitivity to fraction size[5]. This would mean that, compared to conventionally fractionated schedules, either equivalent tumour control for reduced normal tissue late effects or better tumour response for the same level of complications could be achieved with hypofractionation.

1.1.4 Considerations relating to pelvic SABR

There are a number of considerations relating to pelvic SABR. There is considerable internal motion of multiple closely related luminal OARs[12]. With SABR, the maximum point dose to these OARs is likely to be of greater relevance with regards to clinically significant toxicity endpoints than the volume which receives a certain dose[13]. This may impact the dose which can be delivered to the target volume while respecting OAR constraints, especially where these OARs are closely related to the tumour. Multiple soft tissue densities may present a challenge to accurate target volume/OAR delineation, especially with the use of computed tomography (CT) which has limited soft tissue contrast[14]. This is especially relevant for CBCT, which is frequently used for image-guidance of linear accelerator-delivered SABR[15].

These factors may also impact on the safe delivery of SABR re-irradiation[16]. RT is frequently used in the primary management of gynaecological, lower gastrointestinal (GI) and urological malignancies. SABR is increasingly used to treat isolated pelvic recurrences after primary treatment, and there may be overlap between the current and previous treatment. An additional factor concerning re-irradiation is the challenge in accurately determining what dose was previously delivered to OARs, and what further dose can be safely delivered using SABR. Consideration of and, where possible, management of all these factors is important, to minimise the potential for severe early and late toxicities[16-18].

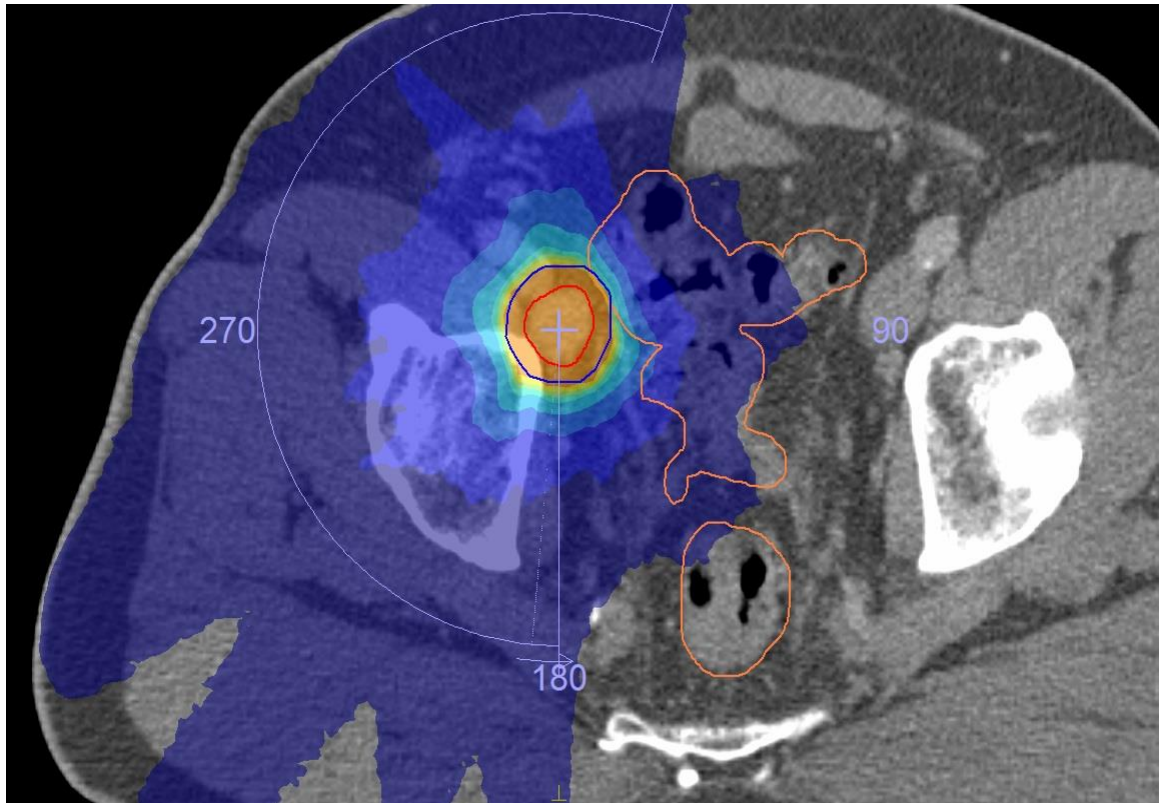


Figure 1.2 Isodose distribution for a right external iliac pelvic nodal SABR plan. Gross tumour volume (red contour), planning target volume (blue contour) and bowel (orange contours) are delineated. Isodoses are shown representing: 30 Gy (orange), 28.5 Gy (yellow), 27 Gy (green), 25 Gy (cyan), 20 Gy (pale blue), 15 Gy (blue), 10 Gy (navy blue) and 5 Gy (royal blue).

1.2 Pelvic organ motion

1.2.1 Importance of pelvic organ motion

Pelvic organs, including bladder, bowel and rectum, are subject to physiological changes in position, shape and volume, with impact from multiple factors including the time of day, hydration and oral intake[12]. During RT, these variations may result in discrepancies between the planned and actual treatment delivered, which could result in geographical miss of the tumour and/or variable dose delivery to adjacent OARs[19]. On-treatment image guidance, for example using CBCT and/or fiducial markers, can guide treatment table shifts to correct for simple translational shifts in organ position, but correction for organ rotation and deformation remains challenging using current technologies[20]. This means that appropriate and consistent patient preparation and positioning strategies remain important, both during acquisition

of simulation images and during delivery of RT[21]. Organ motion may be of particular significance during intensity-modulated RT (IMRT), where more complex dose distributions, dose escalation/boost doses and steep dose gradients are used compared with 3-dimensional conformal RT[12, 20]. This is especially relevant for the safe and effective delivery of highly conformal and hypofractionated treatments like SABR, where small margins around the tumour are used and where geographic miss of the tumour/delivery of excess dose to OARs could have profound clinical implications[9].

1.2.2 Extent of pelvic organ motion

Bladder motion is predominantly determined by bladder filling. This motion tends towards the anterosuperior direction because the pelvic bones and rectum limit bladder expansion posterolaterally[22]. It may also be influenced by muscle invasion in bladder cancer, administration of concurrent chemotherapy and RT toxicity, especially towards the end of a course of treatment[12, 22-24]. In the treatment of bladder cancer, motion in excess of 15 mm in one direction has been observed, and similar bladder motion may occur with the use of either full or empty bladder strategies[25, 26]. Bladder expansion may influence the volume of bowel contained within the pelvis and the position of the seminal vesicles and uterus in prostate and gynaecological RT respectively[12, 27].

Rectal motion is mainly influenced by distension with faeces and gas. The greatest displacements are observed anteriorly in the upper rectum/mesorectum[28, 29]. During rectal cancer RT, inter-fraction tumour positional changes of up to approximately 5 mm have been observed using magnetic resonance imaging (MRI)[30]. The position of the prostate may change considerably with rectal distention[29, 31]. In prostate RT, inferior biochemical/local control has been observed in retrospective studies for patients with a distended rectum at planning[32-34]. The rectum is also primarily responsible for movement of the cervix/upper vagina in gynaecological RT[12]. The influence of bladder/rectal motion on prostate position is illustrated in **Figure 1.3**.

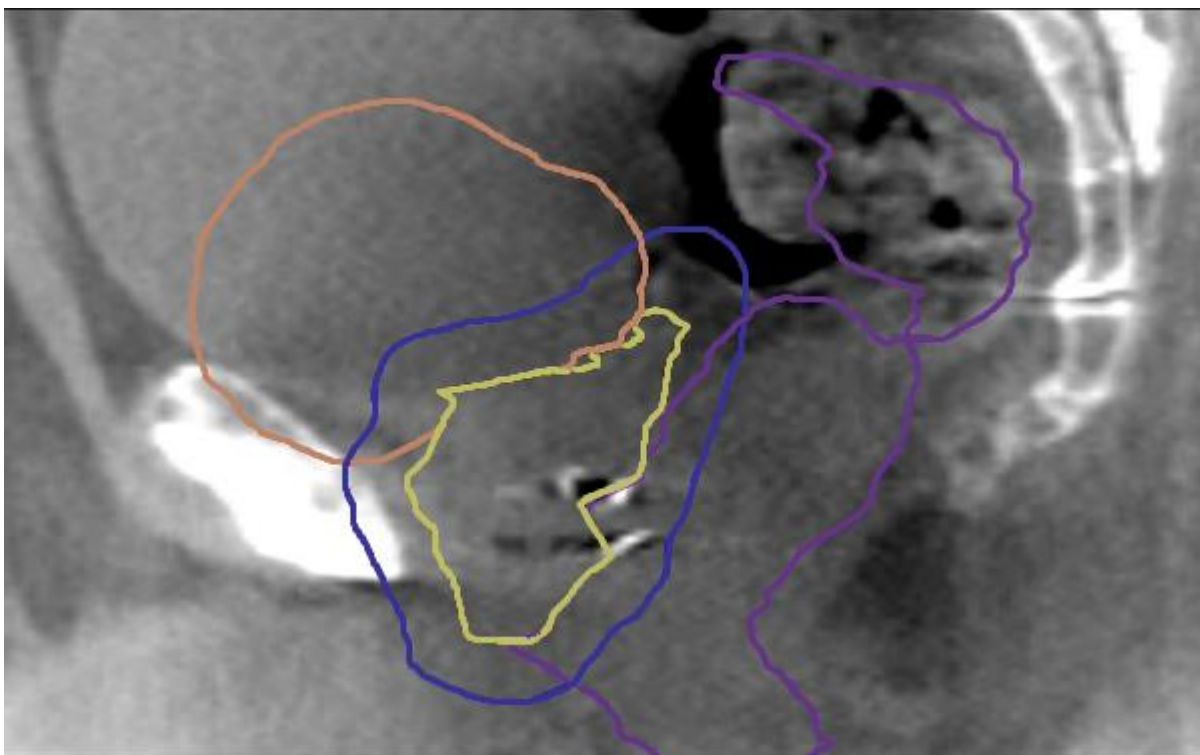


Figure 1.3 Sagittal CBCT on-treatment image with contours from planning CT overlaid (Clinical Target Volume (CTV) prostate and seminal vesicles (yellow), Planning Target Volume (PTV) (blue), bladder (orange) and rectum (purple)). Increase in bladder volume seen compared to planning with expansion superiorly and anteriorly. Increase in mid/upper rectal volume seen compared to planning due to faeces and gas with expansion anteriorly. Motion results in shift in prostate position compared to planning identified by displacement of fiducial markers. Image reproduced from Slevin et al[19].

Bowel is under hormonal/neurological control and exhibits complex peristaltic waves of dilatation and relaxation[35]. Concerning small bowel, this oscillating motion may occur up to 11 times per minute with average amplitude of 7 mm. In addition, large changes in position and volume are seen[36]. Peristaltic waves may occur less frequently in large bowel, although it exhibits considerable variation in luminal diameter as a result of gas and faeces[37]. Planning risk volumes have previously been calculated for bowel to account for its motion during RT[38]. Margins of up to 3 cm might be needed to encompass bowel for the majority of patients throughout RT.

Pelvic lymph nodes are related to vascular anatomy and relevant nodal regions to pelvic RT include internal iliac/obturator, external iliac, common iliac, pre-sacral, mesorectal and inguinal. Where nodal regions are closely related to the pelvic bones, there may be little nodal motion, although greater movement may be seen regarding nodes within the mesorectum[20].

1.2.3 Strategies to manage pelvic organ motion during radiotherapy

A number of strategies may be undertaken to minimise the impact of pelvic organ motion during RT. Selected interventions and the corresponding best available evidence is summarised in **Table 1.1**. Some randomised trials of interventions have been performed[39-42], although much of the evidence concerns small, single centre non-randomised and non-comparative studies, meaning that their findings may not be generalisable[19].

Bladder filling is commonly controlled during pelvic RT, and specific drinking protocols and on-treatment monitoring (for example, with ultrasound) may reduce variability in bladder volume[41, 43, 44]. In addition, a reduction in the volume of small bowel that is irradiated may be obtained[12]. The use of a 'comfortably full' bladder, which may be achieved by bladder voiding followed by drinking 150-300 ml of water, may be more reproducible from simulation to completion of treatment[45].

Typically, an empty rectum is favoured during RT and to minimise variation a number of interventions can be considered including diet, laxatives and enemas[21]. There is no clear evidence to recommend one intervention over another, and some interventions such as laxatives may be poorly tolerated. In prostate RT, randomised trials of endorectal balloons and rectal spacers have demonstrated reduced dose to the rectum and, in the case of rectal spacers, reduced rectal toxicity[40, 42]. However, these potential benefits have to be balanced against factors including patient discomfort/acceptability, the need for additional procedures, staff training and increased treatment times[19].

Regarding bowel, although prone position/belly boards may reduce the volume of bowel in the pelvis and consequently reduce the dose it receives, clinical improvements in bowel toxicity have not necessarily been demonstrated[44]. Regarding SABR, the maximum dose to any loop of bowel close to the target is likely to be of greater relevance than the volume of bowel receiving a certain dose[10, 13]. In addition, prone positioning may be less comfortable for patients and presents issues of stability and reproducibility, which would be of concern during SABR[12, 39]. There remains an absence of alternative interventions to reduce bowel motion or improve reproducibility, meaning that daily online monitoring of bowel position relative to the target is necessary during pelvic SABR[10, 20].

Table 1.1 Summary of selected interventions to manage pelvic organ motion and accompanying level of evidence and grade recommendation

Organ	Intervention	Best level of evidence*	Grade recommendation*
Bladder	Bladder filling	1b	A
Bladder	Ultrasound	2b	B
Rectum	Diet/laxatives	2b	B
Rectum	Enema/suppositories	2b	B
Rectum	Rectal emptying tube	2b	B
Rectum	Endorectal balloon	1b	A
Rectum	Rectal spacer	1b	A
Bowel	Supine versus prone position	1b	A
Bowel	Prone position/belly board	2b	B

*Hierarchy of evidence and grade recommendation based on Oxford Centre for Evidence-based Medicine- Levels of Evidence[46]

Table reproduced from Slevin et al[19].

1.2.4 Quality of radiotherapy imaging and impact of bowel motion

Image quality of CBCT is inferior to diagnostic quality helical CT for several reasons. Low radiation dose protocols are commonly used, without optimisation of scan parameters to account for variation in, for example, patient separation. Large quantities of scattered radiation reach the flat panel detector because of the large field sizes used to image the target and surrounding structures. These factors may result in greater image noise and inferior soft tissue contrast[47-49].

In addition, image projections may take a number of minutes to acquire as the gantry rotates, in contrast to a number of seconds with helical CT[49]. This means that organ motion, including respiratory and cardiac movement, arterial pulsation and displacement of intraluminal bowel gas, can introduce motion artefacts during image reconstruction. Specifically, bowel gas motion results in streak image artefacts on CBCT, which can limit clear identification of the underlying target and/or OARs during image guidance[49, 50].

Image quality can be evaluated using quantitative metrics, such as signal or contrast to noise ratio, but observer-rated scoring of image quality using Likert-type scales is a frequently used method in radiological studies. Although inherently subjective, methods to better standardise this approach include the scoring of image quality against pre-defined criteria (for example, clarity of lesion or OAR), training and statistical analysis of levels of agreement between independent observers[51].

Inferior image quality could be particularly problematic for SABR, where tight margins, steep dose gradients and small number of fractions mean that even small discrepancies in target matching could compromise efficacy of the treatment or deliver excess dose to adjacent OARs.

Motion artefacts also affect other types of imaging which, similarly to CBCT, take a number of minutes to acquire. In diagnostic radiology, there is routine use of anti-peristaltic agents such as hyoscine butylbromide and glucagon during abdominal/pelvic MRI, to reduce bowel motion artefacts and improve the clarity of diagnostic images[52]. However, the use of such agents during RT has not been investigated.

1.3 Prostate cancer

1.3.1 Primary management

Much of the evidence regarding pelvic SABR concerns PCa, and it was also a focus of this thesis. In the following section, PCa is discussed with an emphasis on diagnosis and management in the recurrent disease setting.

PCa is the commonest malignancy in men, with approximately 48,500 new cases diagnosed each year in the UK[53]. Primary localised PCa may be treated using radical prostatectomy (RP), dose-escalated external beam RT (EBRT), brachytherapy or combination EBRT-brachytherapy. EBRT is often combined with neoadjuvant, concurrent and/or adjuvant androgen-deprivation therapy (ADT). Typically, 6 months of ADT is advocated for patients with intermediate risk disease (T2b disease, International Society of Urological Pathology (ISUP) grade 2-3 and/or presenting prostate-specific antigen (PSA) 10-20 ng/ml) and 2-3 years for patients with high risk disease (\geq T3a disease, ISUP grade \geq 4 and/or presenting PSA $>$ 20 ng/ml)[54, 55].

1.3.2 Recurrent prostate cancer

Following primary treatment, patients with PCa are followed up using a combination of clinical assessment and measurement of PSA. A rise in PSA is used to define a state of biochemical failure, which is considered to represent residual local and/or metastatic disease. A number of definitions of biochemical failure exist, but commonly used examples include a rising PSA $>$ 0.2 ng/ml or three consecutive rises post-RP and PSA nadir+2 ng/ml for patients treated with non-surgical therapies[56, 57]. Recurrence after primary treatment is common, especially for patients initially diagnosed with high risk PCa where biochemical failure may occur in up to 50% of patients[58].

For patients treated with RP, internationally there continues to be debate regarding whether adjuvant or early salvage RT in cases of PSA progression should be the standard of care[59]. The recent RADICALS-RT, RAVES and GETUG-AFU 17 phase III trials (and the ARTISTIC meta-analysis of these trials) concluded that adjuvant RT was not superior to early salvage RT for the endpoint of biochemical progression-free survival (PFS)[56, 60-62]. Some authors have questioned whether adjuvant RT should be favoured for patients at high risk of progression post-RP, given that this group was under-represented in these three trials and that longer term evaluation of metastasis-free survival (MFS) in RADICALS-RT is awaited[59, 63]. Nevertheless, in the

UK early salvage RT is considered to be the standard approach in the event of PSA progression post-RP.

The addition of ADT to salvage RT has also been investigated in phase III trials. In GETUG-AFU 16, improved PFS was observed with the addition of 6 months of ADT[64]. In RTOG 9601, an improvement in overall survival was also observed with 2 years of bicalutamide[65]. It has been suggested that variation between the trials regarding the age and risk categories of included patients, duration of follow up and surveillance imaging protocols might explain the different findings regarding overall survival[66]. The hormone therapy element of RADICALS-RT (RADICALS-HD), which randomised between no, 6 months or 2 years of hormone therapy, could provide additional insight into this question[67].

Post-operative prostatic fossa RT is effective, with comparable 5-year event-free survival (defined as biochemical/clinical progression, initiation of further treatment or death from PCa) of 89% versus 88% for adjuvant versus early salvage RT respectively in the ARTISTIC meta-analysis[62]. However, especially for patients initially diagnosed with high-risk PCa, there remains the potential for metastatic spread outside of prostatic fossa RT volumes. The detection of metastatic disease with CT, magnetic resonance imaging (MRI) or bone scintigraphy during early biochemical failure is poor[68, 69]. In contrast, the increased availability of molecular imaging using positron-emission tomography-computed tomography (PET-CT) in early biochemical recurrence has led to identification of patients with low volume metastatic disease (so-called oligometastatic disease), including in pelvic lymph nodes[70].

1.3.3 Oligorecurrent disease

The oligometastatic state is considered to represent an intermediate step between localised and widely disseminated disease[71, 72]. Where metastatic lesions occur following primary treatment, this is termed oligorecurrence[73]. Previously, such patients would typically have been treated with non-curative intent therapies, such as androgen deprivation therapy (ADT) in the case of PCa. Recently however, there has been increasing interest in salvage treatment of oligorecurrent lesions. It is hypothesised that metastasis-directed therapies (MDTs), such as surgery or RT, have the potential to improve outcomes or even provide a second opportunity for cure beyond first relapse[74]. In PCa, if salvage therapies could prevent/delay further waves of metastatic disease, this would be important since MFS is strongly associated with overall survival[75]. Regarding pelvic nodal recurrences, no clear standard of care exists and there

is an absence of phase III evidence as to the optimum approach. Potential options include ADT, docetaxel chemotherapy, novel anti-androgen therapies such as enzalutamide or abiraterone/prednisolone, MDTs or a combination of the above[76-78]. RT is a potentially attractive non-invasive alternative to salvage pelvic lymph node dissection (PLND). RT could be delivered as SABR to the involved node(s) alone or as ENI, where regions of potential microscopic spread are electively treated in addition to definitive treatment of the involved node(s)[79].

1.3.4 The evidence for SABR in oligorecurrent cancer

SABR to the involved node(s) alone has become an increasingly popular method of treating oligorecurrent disease, and is now commissioned by NHS England[80]. It has essentially become a de facto standard of care, despite an absence of phase III evidence to support its use. The strongest evidence to support SABR for oligorecurrent disease is the randomised phase II SABR-COMET trial, which compared SABR to palliative management for patients with primary tumours including breast, colorectal, lung and prostate cancers[81]. In this trial with median follow-up of 51 months, median overall survival was 50 months versus 28 months for the SABR (n=66) versus palliative care (n=33) arms respectively (HR 0.47, 95% CI 0.27-0.81, P=0.006). Grade ≥ 2 toxicity was observed in 29% versus 9% for the SABR and control arms respectively (P=0.026), and despite stringent OAR dose constraints, three patients in the SABR arm died following pulmonary/upper gastrointestinal (GI) complications. In addition to the small study size, concerns regarding the balance of patients with PCa are noted. These comprised 21% of the SABR arm and 6% of the control arm, which might have biased the survival outcomes towards SABR. The findings of SABR-COMET are not directly applicable to pelvic SABR. The majority of patients in SABR-COMET had bone or lung metastases, with few lesions located in the pelvis.

The most appropriate number of lesions that can be treated using SABR while maintaining clinical utility is unknown. During the NHS England Commissioning through Evaluation programme, a limit of 3 lesions was stipulated[82]. In SABR-COMET, more than 90% of patients had 1-3 metastatic lesions treated, with almost half having only a single site of disease[81].

1.3.5 The evidence for SABR in oligorecurrent prostate cancer

Two randomised phase II trials of SABR for PCa oligorecurrence have been reported[78, 83]. These suggest that SABR might delay further disease

progression and the time to commencing ADT. The STOMP trial reported median ADT-free survival of 21 months versus 13 months (HR 0.60, 80% CI 0.40-0.90, P=0.11) for the MDT arm (SABR or salvage PLND) versus surveillance arms respectively[78]. In the ORIOLE trial, the primary endpoint of disease progression at 6 months occurred in 19% versus 61% of patients (P=0.005) in the SABR versus observation arms respectively[83]. The toxicity associated with SABR appears to be low, with no \geq grade 3 adverse events reported in STOMP or ORIOLE after median follow up durations of 36 and 19 months respectively[78, 83]. Despite these promising data, the absence of high-level evidence regarding SABR means that its impact on overall survival is unknown. In addition, in observational studies of pelvic nodal SABR, subsequent relapses often occur within the pelvis. For example, in a multicentre study by Ost et al, 39% of further relapses after pelvic nodal SABR were located in the pelvis[84]. Furthermore, studies of PLND have demonstrated that multiple pathologically involved nodes may be obtained within a single nodal region where either a single PET-CT avid lesion or no avidity is seen pre-operatively[85, 86]. Repeated SABR for further nodal relapses may be significantly compromised by the prior treatment and/or less effective[87].

1.3.6 The potential role for Extended Nodal Irradiation in oligorecurrent prostate cancer

The addition of elective pelvic irradiation to prostate or prostatic fossa irradiation has been investigated in several randomised trials. Two earlier trials in the primary disease setting, RTOG 9413 and GETUG-1, failed to demonstrate a survival benefit, although it is possible that inclusion of patients at low risk of nodal involvement, inadequate coverage of superior pelvic nodal regions or inclusion of patients at very high risk of extrapelvic metastases could have influenced the results[88-91]. Other trials, RTOG 0924 (ClinicalTrials.gov Identifier: NCT01368588) and PIVOTALboost, are currently investigating the addition of ENI in the primary treatment of high risk PCa[92]. In the post-RP salvage setting, the RTOG 0534 SPPORT trial investigated the addition of ENI and/or ADT to prostatic fossa RT. Formal publication of the trial is awaited, although an initial report concluded that disease progression (biochemical or clinical) was reduced with the addition of ENI[93].

ENI in the recurrent disease setting has been evaluated in single-arm phase II trials and is associated with promising outcomes compared with SABR in observational studies[79, 94-96]. In the non-randomised phase II OLIGOPELVIS-GETUG P07 trial, patients with choline PET-CT identified PCa

pelvic nodal recurrence were allocated conventionally fractionated ENI with a boost to involved node(s) with/without prostatic fossa irradiation, depending on whether post-operative prostatic fossa RT had previously been delivered[96]. Half of the patients in OLIGOPELVIS-GETUG P07 had received prior prostate/prostatic fossa irradiation. Where ENI is delivered for pelvic nodal recurrence after primary/post-operative prostatic fossa irradiation, a major concern could be the potential for late bowel toxicity. In OLIGOPELVIS-GETUG P07 however, low toxicity outcomes out to 1 year have been reported, with <5% grade 3 events (all of which were genitourinary (GU)) at 1 year. In addition, no increase in toxicity was observed for patients with prior irradiation. Efficacy and long-term toxicity data from OLIGOPELVIS-GETUG P07 are awaited.

In a recent multicentre European observational study by De Bleser et al, conventionally fractionated ENI was associated with approximately a 10% improvement in 3-year MFS compared with SABR (77% versus 68% for ENI versus SABR respectively, $P=0.01$)[79]. For patients with a single nodal recurrence, 3-year MFS was approximately 95% versus 85% for ENI versus SABR respectively. Late GI toxicity rates were low, with the only \geq grade 3 late toxicities being GU (in 2% of patients). A randomised phase II trial, STORM, is currently in recruitment and is comparing conventionally fractionated ENI plus MDT (either SABR or salvage PLND) and ADT to MDT plus ADT for the primary endpoint of 2-year MFS[97]. However, a phase III comparison between ENI and SABR is required to demonstrate the potential survival advantages provided by ENI.

1.3.7 Hypofractionation and ENI

There is increasing use of moderately (e.g. 20 fractions) and ultra (e.g. 5 fractions) hypofractionated RT schedules in the treatment of PCa[56, 92, 98-100]. IMRT has enabled the safe delivery of hypofractionated ENI with additional simultaneous integrated boost (SIB), while sparing normal tissues such as bowel[101]. In addition to the potential improvement in the therapeutic ratio if the α/β ratio of PCa is low, as discussed in Section 1.2, hypofractionation provides patient convenience/resource benefits[5].

Ultra hypofractionated ENI has been investigated in the primary disease setting in early phase and observational studies, frequently with a SIB to prostate/seminal vesicles[102-104]. In these studies, toxicity appeared to be acceptable, with \leq 5% grade 3 late GU toxicity and no grade 3 late GI toxicity after median follow up durations of 18-30 months. There is minimal data

concerning the use of ultra hypofractionated ENI in the setting of pelvic nodal recurrence, although the primary disease data suggest that it is likely to be safe.

1.3.8 The role of PET-CT in recurrent prostate cancer

A number of PET tracers are available, including carbon 11 (^{11}C) or fluorine 18 (^{18}F) choline, gallium 68 (^{68}Ga) or ^{18}F prostate-specific membrane antigen (PSMA) and ^{18}F fluorocyclobutane-1-carboxylic acid fluciclovine (commonly known as fluciclovine)[105]. There is considerable heterogeneity in the published literature concerning the diagnostic performance of PET-CT tracers in recurrent PCa[106]. There are few direct comparisons and limited phase III evidence. Although multiple systematic reviews and meta-analyses have been performed, the quality of many of the included studies is low[107-116]. Many of these studies are small, single-centre and retrospective with heterogeneous populations of patients, different injected activities of the tracers and lack histopathological correlation of PET-CT positive lesions. Since it is often impractical to obtain histological confirmation, non-invasive methods such as interval imaging or serial PSA measurement are often used as a surrogate measure, but this approach is subject to examination bias[105, 117, 118]. This means that detection rates are often reported, rather than typical attributes of diagnostic performance such as sensitivity/specificity, and subsequently there is a risk of false positive results[70]. The detection of recurrent disease by different PET tracers may also vary depending on several factors, including PSA level, PSA doubling time/velocity, size of metastatic lesion, receipt of anticancer therapies such as ADT and ISUP grade[107].

Nevertheless, it is generally considered that ^{68}Ga PSMA PET-CT is superior to choline or fluciclovine for the detection of metastatic disease, especially at the very low PSA levels characterised by early biochemical recurrence[117, 119-121]. A limited number of prospective comparative studies between PET tracers in the recurrent PCa setting have been performed. In patients with PSA <0.5 ng/ml, detection rates for ^{68}Ga PSMA versus choline range from 42-50% and 12.5-32% respectively[119, 120]. In patients with PSA <2 ng/ml, detection rates for ^{68}Ga PSMA versus fluciclovine range from 53-56% and 26-42% respectively[117, 121]. A summary of performance characteristics of the three PET tracers from prospective comparative studies is shown in **Table 1.2**. Despite the uncertainties inherent in the published literature, these data mean that ^{68}Ga PSMA is likely to be preferred to choline/fluciclovine as the PET tracer of choice. However, there remain a number of questions regarding the use of PET-CT in the recurrent PCa setting, including the optimum tracer, the

most appropriate PSA level at which to perform imaging as well as the clinical benefits and impact on survival of identifying, and treating, low volume metastatic disease at very low PSA levels[106, 122, 123].

Table 1.2 Summary of performance characteristics of available PET-CT tracers from prospective comparative studies in recurrent prostate cancer

<i>Study</i>	<i>Type of study</i>	<i>Type of PET-CT</i>	<i>Population studied</i>	<i>Endpoints</i>	<i>Results</i>
Emmett[119]	Prospective cohort study	68Ga PSMA versus 18F choline	Biochemical recurrence post RP	Detection rates at median PSA of 0.42 ng/ml	68Ga PSMA: 42% 18F choline: 32%
Morigi[120]	Prospective cohort study	68Ga PSMA versus 18F choline	Biochemical recurrence post primary treatment	Detection rates	68Ga PSMA: 50% when PSA <0.5 ng/ml 86% when PSA >2 ng/ml 18F choline: 12.5% when PSA <0.5 ng/ml 57% when PSA >2 ng/ml
Calais[117]	Prospective cohort study	68Ga PSMA versus Fluciclovine	Biochemical recurrence post RP	Detection rates with PSA <2 ng/ml	68Ga PSMA: 56% Fluciclovine: 26%
Pernthaler[121]	Prospective cohort	68Ga PSMA	Biochemical recurrence post	Detection rates with	68Ga PSMA:

	study	versus Fluciclovine	primary treatment	PSA <2 ng/ml	53% Fluciclovine: 42%
Nanni[124]	Prospective cohort study	Fluciclovine versus 11C choline	Biochemical recurrence post RP	Sensitivity and specificity at median PSA 3.35 ng/ml	Fluciclovine: Sensitivity 37% Specificity 67% 11C choline: Sensitivity 32% Specificity 40%

11C, carbon 11; 18F, fluorine 18; 68Ga PSMA, gallium 68 (68Ga) prostate-specific membrane antigen; PSA, prostate-specific antigen

PET-CT has the potential to individualise treatment in the recurrent disease setting. A number of randomised trials to determine the clinical impact of PET-CT tracers, including a multicentre phase III study of 68Ga PSMA PET-CT based salvage RT after RP (NCT03582774), are in progress[106]. The single-centre randomised phase II/III EMPIRE-1 trial of fluciclovine PET-CT for patients with biochemical failure post-RP recently reported[125]. Event-free survival (defined as biochemical or clinical failure) was significantly improved in the fluciclovine arm (76% versus 63%, $P=0.0028$). In addition, fluciclovine led to a change in pre-PET-CT decision making in 35% of patients (addition of ENI to prostatic fossa RT, change to prostatic fossa RT alone or avoidance of RT where metastatic disease was identified). The EMPIRE-2 trial (NCT03762759), which is randomising between 68Ga PSMA and fluciclovine PET-CT, is in progress.

1.3.9 Patterns of pelvic nodal recurrence

The lymphatic drainage from the prostate is primarily to the obturator and internal/external iliac regions, although the pattern of drainage is complex and may not follow a typical sequence[126]. A number of studies have evaluated patterns of pelvic nodal recurrence after primary treatment using PET-CT[122, 127-132]. These patterns vary depending on the primary disease risk and primary treatment (RP versus EBRT), extent of pelvic lymph node dissection where RP was performed, whether post-operative prostatic fossa RT was delivered after RP, use of ADT and the PSA level at the time of imaging[106]. In these studies, recurrent nodal metastases were observed in the internal iliac/obturator (9-28%), external iliac (14-28%), common iliac (9-25%), pre-sacral (1-8%) and para-aortic (2-21%) regions respectively[122, 127-132]. A visual representation of patterns of nodal failure is shown in **Figure 1.4**.

1.3.10 Implications for Extended Nodal Irradiation

A number of studies have mapped PET-CT identified nodal recurrences to typical ENI volumes, to identify the optimum volume which maximises coverage of regions of potential microscopic spread[128, 130, 133]. Prior to a recently published update, the superior border of the Radiation Therapy Oncology Group (RTOG) ENI volume was taken to be the L5/S1 vertebral interspace[134, 135]. In nodal mapping studies, coverage of nodal regions was estimated to improve from 42-44% to 63-93% if the superior border was raised from L5/S1 to the aortic bifurcation (which approximates to the L4/5 vertebral interspace), mainly by improved coverage of the common iliac nodal region (also illustrated in **Figure 1.4**) [128, 130, 133]. In its recent update, the RTOG pelvic lymph node atlas also defined the superior border to be the aortic bifurcation[134]. The use of vascular anatomy is probably more appropriate than vertebral landmarks, given that nodal metastases appear to be localised to major blood vessels and there is variation between individuals regarding the vertebral landmarks for the aortic bifurcation[136]. The aortic bifurcation is also used as the superior border in two ongoing phase II trials of ENI for PCa pelvic nodal relapse, OLIGOPELVIS-GETUG P07 and STORM[96, 97]. However, the optimum nodal volume remains uncertain and some authors have proposed further extensions. De Bruycker et al demonstrated improved coverage of choline PET-CT mapped external iliac nodes by extending the inferior border of the external iliac nodal group distally from its superior aspect to the mid femoral head[128]. The superior border could also be extended cranially beyond the aortic bifurcation. With IMRT, ENI volumes can be safely extended into the para-aortic region (up

to L1/2)[137]. However, the clinical benefits of doing so remain uncertain and this approach ultimately requires validation within a randomised trial. The phase II/III Primary radiotherapy for Androgen sensitive Prostate cancer patients with Lymph nodeS (PEARLS) trial will evaluate whether ENI extended into the para-aortic region improves MFS for patients with primary PCa and involved pelvic and/or para-aortic lymph nodes[138].

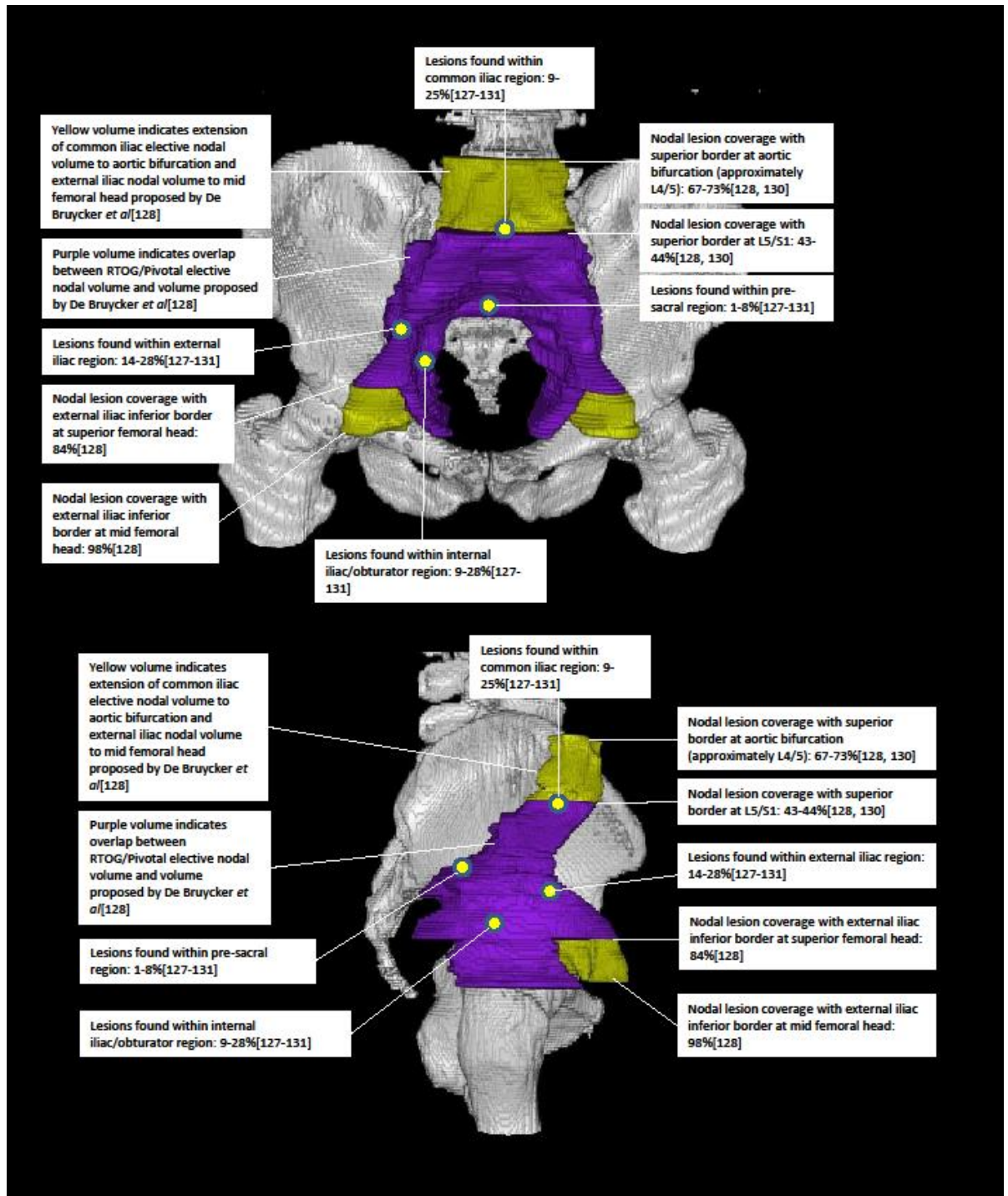


Figure 1.4 Anterior and right lateral views of the pelvis illustrating the locations of nodal metastases evaluated by imaging series in relation to ENI volumes. The purple RT volume represents the overlap between the traditional RTOG volume and the volume recommended by de Bruycker *et al*[128, 135]. The yellow volume represents the extension of this volume in the common iliac/external iliac nodal regions recommended by de Bruycker *et al*[128]. Image reproduced from Slevin *et al*[106].

1.4 Aims

The aims of this thesis are:

- To investigate the impact of teaching during a national contouring workshop on SABR target volume/OAR delineation
- To develop a class solution for ultra hypofractionated ENI for PCa pelvic nodal recurrence following RP and post-operative prostatic fossa RT, and to assess the impact of this strategy on TCP and NTCP
- To investigate the impact of an anti-peristaltic agent (hyoscine butylbromide) on CBCT image artefacts resulting from bowel motion during abdominopelvic SABR
- To establish consensus statements for the practice of SABR re-irradiation in the pelvis using an international Delphi study

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Chapter 2 Evaluation of the impact of teaching on delineation variation during a virtual Stereotactic Ablative Radiotherapy contouring workshop

2.1 Abstract

2.1.1 Introduction

Variation in delineation of target volumes/organs at risk (OARs) is well recognised in radiotherapy and is a significant source of error. This variation may be reduced by several methods including teaching. We retrospectively evaluated the impact of teaching on contouring variation for thoracic/pelvic Stereotactic Ablative Radiotherapy (SABR) during a virtual UK SABR Consortium/Royal College of Radiologists contouring workshop.

2.1.2 Materials and Methods

Target volume/OAR contours produced by workshop participants for three cases were evaluated against reference contours produced by the workshop organisers using DICE similarity co-efficient (DSC) and line domain error (LDE) metrics. Contours were defined on computed tomography (CT) with reference to co-registered magnetic resonance imaging (MRI)/positron emission tomography-computed tomography (PET-CT) images. Pre and post-workshop DSC results were compared using Wilcoxon signed ranks test to determine the impact of teaching during the workshop.

2.1.3 Results

Of 50 workshop participants, paired pre and post-workshop contours were available for 21 (42%), 20 (40%) and 22 (44%) participants for primary lung cancer, pelvic bone metastasis and pelvic node metastasis cases respectively. Statistically significant improvements post-workshop in median DSC and LDE results were observed for 6 (50%) and 7 (58%) of 12 structures respectively, although the magnitude of DSC/LDE improvement was modest in most cases. An increase in median DSC post-workshop ≥ 0.05 was only observed for GTVbone, IGTVlung and SacralPlex and reduction in median LDE > 1 mm was only observed for GTVbone, CTVbone and SacralPlex. Post-workshop, median DSC values were > 0.7 for 75% of structures. For 92% of structures, post-

workshop contours were considered to be acceptable or within acceptable variation following review by the workshop faculty.

2.1.4 Conclusion

This study has demonstrated that virtual contouring training is feasible and that teaching during a virtual SABR contouring workshop for multiple target volumes/OARs was associated with improvements in contouring variation.

2.2 Introduction

Delineation of target volumes and organs at risk (OARs) is a key component of radiotherapy planning, but inter/intra-observer variation in contouring is well recognised and is a significant source of error within treatment workflows[1, 2]. Potential reasons for this variation may include the influence of disease site experience/expertise and skills in cross-sectional image interpretation[2-4]. The consequences of contouring variation may be profound; incorrect delineation is associated with inferior survival outcomes in clinical trials[5, 6].

Various methods exist to minimise contouring variation including delineation protocols, atlases, auto-contours, peer review and teaching[2, 3, 7, 8]. Radiotherapy is a craft specialty, necessitating the acquisition and refinement of contouring skills during clinical practice[9]. To mitigate the potential impact on training of the reduction in junior doctor working hours, smarter and more efficient methods of delivering training are required[10]. Dedicated contouring workshops may be a valuable source of experiential learning especially concerning new radiotherapy techniques[11-13].

Following changes to the commissioning of Stereotactic Ablative Radiotherapy (SABR) in the UK, the Royal College of Radiologists (RCR) and UK SABR Consortium organised a workshop which focused on SABR contouring for lung cancer and bone and nodal oligometastatic disease[14]. The aim of the workshop was to share expertise and experience in SABR techniques and improve participants' contouring skills. Given the Covid-19 pandemic, the workshop took place in virtual format. In this study, we retrospectively evaluated the impact of teaching during the workshop on contouring variation for multiple target volumes/OARs in the thorax and pelvis.

2.3 Methods and Materials

2.3.1 Format of the workshop

The workshop took place on 19th and 22nd October 2020; each session lasted two hours in duration. Participants were UK-based consultants in clinical oncology and the workshop was aimed at those without prior expertise in SABR. Participants were asked to delineate target volumes/OARs for three cases prior to the workshop using the web-based platform EduCase™ (RadOnc eLearning Centre, Inc., Fremont, CA, USA). A video tutorial was provided, which explained how to use EduCase™.

The target volumes/OARs for the three cases were:

Right upper lobe primary lung cancer

- IGTVlung (internal target volume)
- BrachialPlex
- BronchusProx
- Oesophagus
- Spinal_Canal

Left pelvic bone metastasis secondary to breast cancer

- GTVbone (gross tumour volume)
- CTVbone (clinical target volume)
- Femur_Head_Left
- Rectum

Right common iliac lymph node secondary to prostate cancer

- GTVnode
- Bowel_Large
- SacralPlex

Each case was accompanied by a clinical vignette (history, diagnosis, investigations and intended treatment) and instructions detailing which structures were to be delineated and on which axial computed tomography (CT) slices. CT axial slice thickness was 3 mm for the lung cancer case and 1 mm for the bone/node cases. Image co-registration performed in EduCase™ between CT and positron emission tomography-computed tomography (PET-CT) was available for all cases, magnetic resonance imaging (MRI) was available for the nodal and pelvic bone cases, and 4DCT was available for the primary lung case. For the lung cancer case, IGTVlung could be defined on the maximum intensity projection (MIP) scan with reference to the average intensity projection, 0% and 30% respiratory phases.

Pre-workshop contours, anonymised to clinician, were reviewed across the two workshops and teaching was provided for each case including demonstration of a reference contour produced by the workshop faculty. Relevant published contouring guidance and atlases were identified during both sessions. Teaching included clinical cases to illustrate the general principles of patient selection, planning and treatment delivery of SABR for primary lung cancer and oligometastatic disease and a dedicated session for target volume/OAR contouring.

Following each workshop, participants were invited to review/adjust their contours based on the teaching. Final attempts were submitted up to two weeks after the second workshop session. The faculty provided individual written feedback to participants on their post workshop contours.

Participants were asked to provide feedback for individual speaker sessions and the overall workshop experience using a 5-point Likert scale and free text responses.

2.3.2 Analysis of participant contours

Each participant's contours were compared against a reference contour, which was produced by the clinician who led each case discussion during the workshop and peer reviewed by a second faculty member. For each structure, the specific axial CT slices to be contoured was specified; these were non-contiguous and therefore a volume was not obtained. Some participants had delineated contours on slices other than those specified in the case. Therefore, to ensure a fair comparison for all participants, only contours on those pre-specified slices were considered. Participants with only one set of contours (e.g. only pre-workshop contours) were excluded. Participants with two sets of submitted contours but where no changes were made to the post-workshop contours were included.

EduCase™ provides 2-dimensional (i.e. area) Dice similarity coefficient (DSC) and line domain error (LDE) values for individual slices for participant contours compared with the reference contour. DSC is an overlap measure, which measures the intersection of two contours relative to the union and ranges from 0 (zero overlap) to 1 (perfect overlap)[1, 15, 16].

DSC can be calculated by the following formula:

$$\text{DSC} = 2 \times (\text{Area}_{\text{reference}} \cap \text{Area}_{\text{participant}}) / (\text{Area}_{\text{reference}} + \text{Area}_{\text{participant}}) \quad \text{Equation 2.1}$$

[17, 18]

Dice similarity coefficient

where $\text{Area}_{\text{reference}} \cap \text{Area}_{\text{participant}}$ is the intersecting overlap of the two areas and $\text{Area}_{\text{reference}} + \text{Area}_{\text{participant}}$ is the union of the two areas.

LDE is a distance metric within EduCase™, which measures the average absolute Euclidean distance in millimetres between corresponding points on the reference and participant contours.

Since each structure was not a volume but instead a series of individual slices, a summary measure per structure for each participant was produced. The median value of DSC/LDE for each of these slices was calculated for each of the structures contoured by each participant. These median structure DSC/LDE values for participants with both pre and post-workshop contours were exported into IBM-SPSS Statistics for Windows version 26 (IBM Corp., Armonk, NY, USA). Each of the included contours were reviewed by two of the authors (Finbar Slevin and Romélie Rieu) to identify potential reasons for low DSC/high LDE values.

Following the workshop, the faculty reviewed participants' post-workshop contours and provided a score (acceptable, within acceptable variation or unacceptable) and written feedback.

2.3.3 Statistical considerations

The median DSC/LDE and inter-quartile range (IQR) are presented as summary statistics for all the participants' median structure DSC/LDE values pre and post-workshop, since a normal distribution of data could not be assumed and also to minimise the influence of outlying values. Box and whisker plots were produced by importing data into R 3.6.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) using the ggplot2 library[19]. A statistical comparison of the median DSC/LDE for each participant's structures pre and post-workshop was undertaken using the Wilcoxon signed ranks test in SPSS, since this was paired data. A P value of <0.05 was taken to indicate a statistically significant difference.

2.4 Results

Fifty participants registered for the workshop and 43 submitted at least one set of contours for each of the cases. Of these 43 participants, 21 (49%), 20 (47%) and 22 (51%) participants produced pre and post-workshop contours for the lung cancer, pelvic bone metastasis and pelvic node metastasis cases respectively. A summary of the DSC/LDE values pre and post-workshop and results of statistical comparisons are shown in **Table 2.1**. The spread of the median DSC/LDE values for each structure across all of the participants is illustrated in **Figure 2.1**.

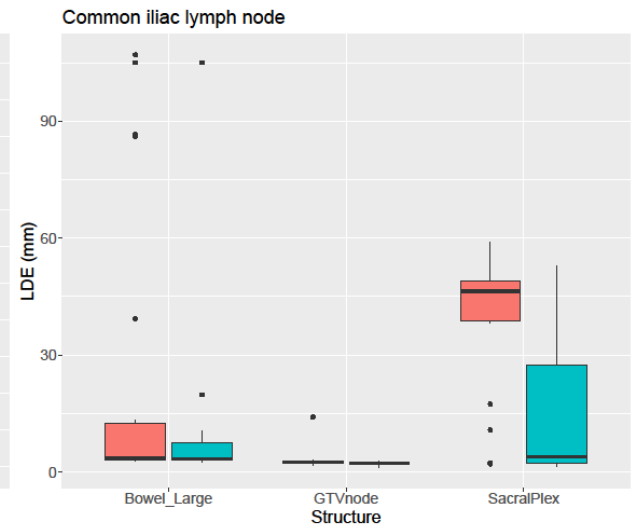
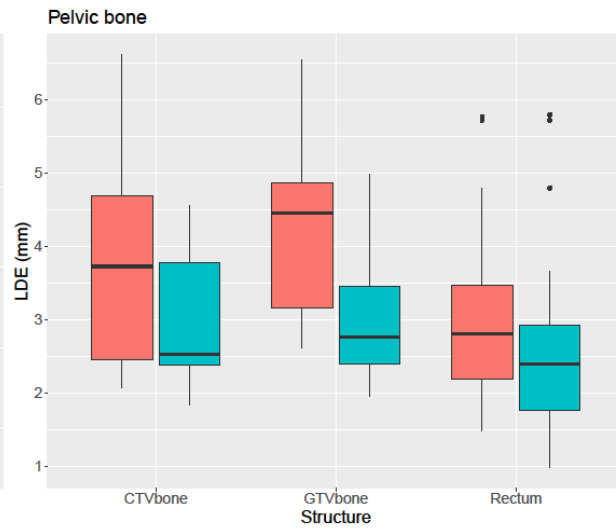
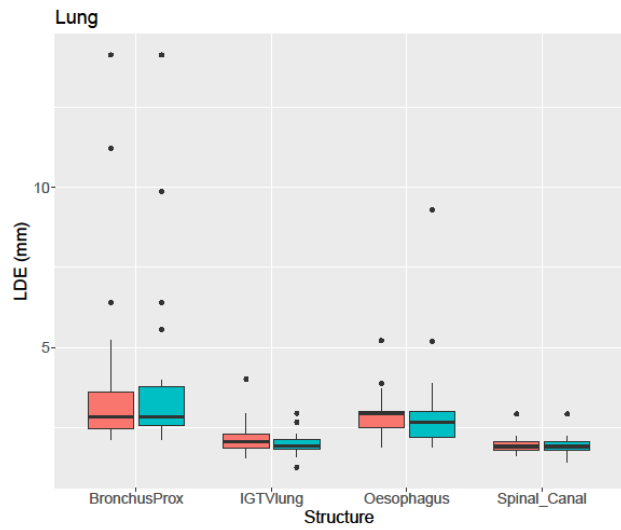
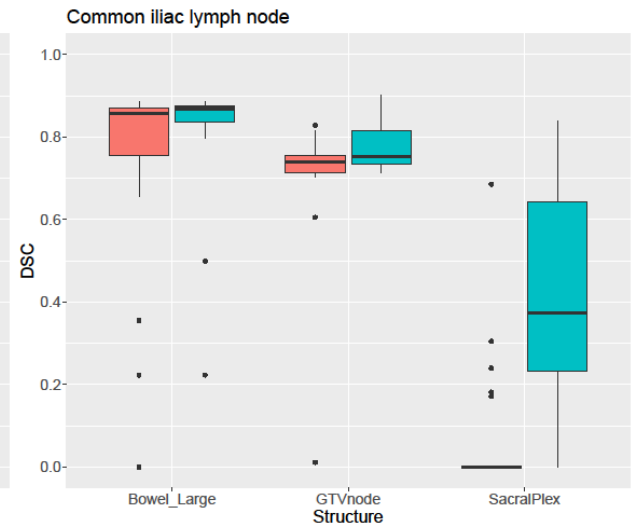
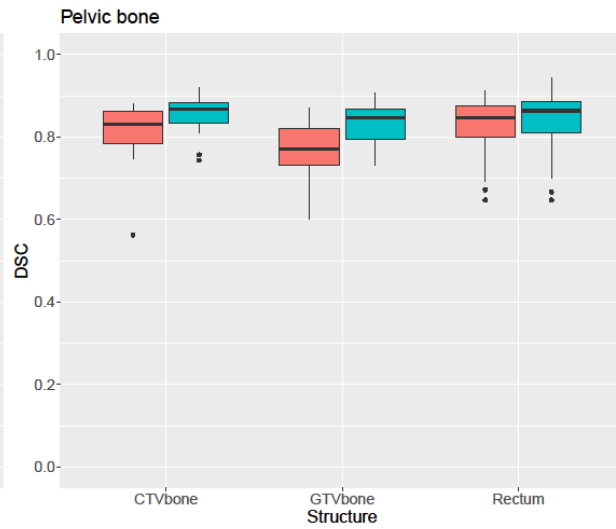
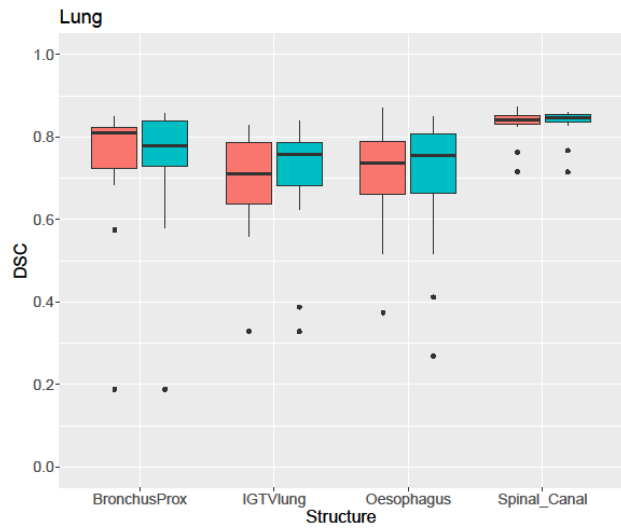
Table 2.1 Summary of median Dice similarity coefficient (DSC) and line domain error (LDE) measurements before/after teaching for each structure

Structure	Number of participants	Median DSC pre (IQR)	Median DSC post (IQR)	P value from Wilcoxon signed ranks test (* indicates statistically significant result)	Median LDE pre (mm) (IQR)	Median LDE post (mm) (IQR)	P value from Wilcoxon signed ranks test (* indicates statistically significant result)	Comments
GTVnode	21	0.74 (0.71-0.76)	0.75 (0.73-0.82)	0.003*	2.56 (2.23-2.76)	2.28 (1.85-2.61)	0.005*	
Bowel_Large	22	0.86 (0.72-0.87)	0.87 (0.82-0.88)	0.023*	3.61 (3.05-19.92)	3.31 (2.97-8.93)	0.028*	
SacralPlex	22	0 (0-0.04)	0.37 (0.21-0.68)	<0.001*	46.39 (33.11-	3.80 (2.31-	<0.001*	Some participants

					49.11)	32.56)		delineated SacralPlex based on CT atlas and others used MRI
GTVbone	20	0.77 (0.72- 0.83)	0.85 (0.78- 0.87)	0.002*	4.45 (3.15- 4.94)	2.76 (2.39- 3.70)	0.001*	
CTVbone	20	0.83 (0.78- 0.87)	0.87 (0.83- 0.88)	0.035*	3.73 (2.43- 5.09)	2.53 (2.34- 3.78)	0.037*	
Rectum	20	0.85 (0.78- 0.88)	0.86 (0.81- 0.89)	0.023*	2.81 (2.03- 3.57)	2.40 (1.75- 3.25)	0.009*	
IGTVlung	20	0.71 (0.63- 0.79)	0.76 (0.66- 0.79)	0.311	2.07 (1.86- 2.41)	1.94 (1.82- 2.18)	0.029*	

BronchusProx	21	0.81 (0.72-0.83)	0.78 (0.72-0.84)	0.730	2.84 (2.37-3.80)	2.83 (2.41-3.87)	0.953	
Oesophagus	21	0.74 (0.66-0.79)	0.76 (0.66-0.81)	0.140	2.93 (2.50-3.06)	2.67 (2.20-3.02)	0.308	
Spinal_Canal	21	0.84 (0.83-0.85)	0.85 (0.83-0.86)	0.333	1.91 (1.80-2.09)	1.91 (1.78-2.10)	0.345	

LDE, line domain error; DSC, Dice similarity coefficient



Pre or Post Workshop Pre Post

Figure 2.1 Box and whisker plots for the target volume/organs at risk structures for the lung cancer, pelvic bone metastasis and common iliac nodal metastasis cases. The top row represents Dice similarity coefficient (DSC) results and the bottom row represents line domain error (LDE) results. The box represents the middle 50% of the data and is bounded by the upper (Q3) and lower (Q1) quartiles and the horizontal line indicates the median value. The upper whiskers represent $Q3+1.5*IQR$ and the lower whiskers represent $Q1-1.5*IQR$. Any outliers beyond these ranges are indicated as dots.

Statistically significant improvements in DSC post-workshop were observed for each structure except for IGTVlung, Spinal_Canal, Oesophagus and BronchusProx. Only BronchusProx was associated with a worsening in median DSC post-workshop, but this difference was not statistically significant. The magnitude of increase in DSC post-workshop was often small; only GTVbone (0.08), IGTVlung (0.05) and SacralPlex (0.37) were associated with a ≥ 0.05 increase in median DSC. A median value of DSC >0.7 and >0.8 post-workshop was observed for nine (75%) and five (42%) of the 12 structures respectively; no median DSC value was >0.9 .

Statistically significant improvements in LDE post-workshop were observed for each structure except for BronchusProx, Oesophagus and Spinal_Canal. Similar to DSC results, BronchusProx was associated with a worsening in median LDE post-workshop although this difference was not statistically significant. Again, the magnitude of improvement was often small; only GTVbone (1.7 mm), CTVbone (1.2 mm) and SacralPlex (42 mm) were associated with >1 mm reduction in median LDE post-workshop.

Some post-workshop contours were unchanged from pre-workshop: GTVnode (5 participants, 24%), Bowel_Large (10 participants, 46%), GTVbone (2 participants, 10%), CTVbone (2 participants, 10%), Rectum (8 participants, 40%), IGTVlung (8 participants, 40%), Spinal_Canal (11 participants, 52%), Oesophagus (7 participants, 33%), BronchusProx (7 participants, 33%). When the data was re-analysed without these unchanged structures, no significant differences were observed.

Regarding BrachialPlex, the case instructions did not specify that only the ipsilateral structure was to be delineated and some participants contoured bilateral structures. Similarly for Femur_Head_Left, the femoral head (i.e. excluding the femoral neck) was to be delineated but several participants delineated both the femoral head and neck and/or produced bilateral structures. Therefore, these two structures were omitted from statistical comparisons.

Regarding post-workshop contours, a summary of the feedback provided to participants is shown in **Table 2.2**. Ninety-two per cent of post-workshop contours were considered to be acceptable or within acceptable variation.

Eighty-four per cent of participants provided feedback on the workshop; of these, feedback regarding the overall workshop experience and each of the individual speakers was considered to be 'good' or 'very good' in 82% and 99% of responses respectively. Ten per cent of feedback concerned technical issues during the workshop (e.g. sound quality).

Table 2.2 Summary of qualitative feedback on participants' post-workshop contours

Structure	Number of participants	Number of contours acceptable (%)	Number of contours within acceptable variation (%)	Number of contours unacceptable (%)
GTVnode	11	6 (55%)	5 (45%)	0
Bowel_Large	11	4 (36%)	6 (55%)	1 (9%)
SacralPlex	11	9 (82%)	1 (9%)	1 (9%)
GTVbone	10	2 (20%)	7 (70%)	1 (10%)
CTVbone	10	4 (40%)	5 (50%)	1 (10%)
Femur_Head_Left	10	8 (80%)	2 (20%)	0
Rectum	10	6 (60%)	2 (20%)	2 (20%)

IGTVlung	13	6 (46%)	7 (54%)	0
BrachialPlex	13	0	9 (69%)	4 (31%)
BronchusProx	13	7 (54%)	5 (38%)	1 (8%)
Oesophagus	13	4 (31%)	9 (69%)	0
Spinal_Canal	13	12 (92%)	1 (8%)	0
Total contours	138	68 (49%)	59 (43%)	11 (8%)

2.5 Discussion

This study has evaluated the impact of teaching during a SABR contouring workshop for a relatively large number of participants and multiple target volume/OARs in the thorax and pelvis. The positive feedback provided by participants about the workshop suggests that it is feasible to deliver contouring teaching in a virtual capacity. We demonstrated that median DSC/LDE values for participants who completed pre and post-workshop contours for most of the target volume/OARs were similar to the reference contour, with DSC >0.7 for 75% of structures and LDE <5 mm for 83% of structures. While statistically significant improvements post-workshop in DSC and LDE were observed for 50% and 58% of structures respectively, the magnitude of improvement was small in most cases and the clinical significance of such modest improvements remains uncertain.

Although multiple studies on the effect of teaching on contouring variation have been reported, several factors make direct comparison between these and our study challenging[16]. Heterogeneity exists between studies concerning the numbers of participants, types of teaching, the structures for which contouring variation is evaluated and the types of metrics used to evaluate this variation and the use of statistical tests[1, 2, 16]. However, systematic reviews of such studies have demonstrated that an improvement in contouring variation through teaching can be achieved[2, 20]. We did not observe a large increase in DSC/reduction in LDE post-workshop, and a number of limitations of our work may explain this. While participants were asked to review their pre-workshop contours after teaching and produce a post-workshop submission, only approximately half of participants did so which reduced the number for which an analysis of teaching impact could be performed. Furthermore, even for those who did re-submit a second set of contours in some cases no changes were made. Possible reasons for this could include satisfaction with pre-workshop contours, insufficient time to re-contour every structure and a lack of hands-on time during the workshop to practise/fully compare contours with the reference contour. The latter point may be particularly relevant since it has been previously suggested that active participation is more likely to improve learning during contouring workshops[21]. Insufficient provision of practical experience was raised as a potential explanation for failure to observe improved contouring post-teaching in a previous study of a head and neck contouring programme, although there may be time/resource challenges to effectively deliver this especially for larger audiences and during the Covid-19 pandemic where face-to-face meetings are restricted[22]. Residual differences in knowledge/ability

between participants despite teaching were also suggested as a possible reason why significant improvements in prostate/rectal contouring were not observed in a previous evaluation of the impact of teaching[23].

Low DSC/high LDE values for certain structures in our study could be related to interpretation of the case instructions, especially for BrachialPlex and Femur_Head_Left. The latter structure was also only to be delineated on a single axial CT slice at the very inferior aspect of the femoral head. Different methods for contouring BrachialPlex exist, and there remains variation in practice[24-26]. Given the high dose per fraction used with SABR and variable reliance on MRI across different treatment centres, the UK SABR Consortium Guidance recommends contouring the subclavian/axillary vessels as a surrogate for BrachialPlex[26]. National consensus is needed, and future iterations of the recently published OAR harmonisation guidance will support this[25]. For SacralPlex, some participants delineated the visible nerve using the MRI while others delineated a larger surrogate structure using the CT. Both of these may be legitimate approaches, although contouring as per the Yi et al guidance does not rely on expert MRI interpretation of nerve position and may therefore be simpler for those learning[27]. However, unfamiliarity with the contouring of certain OARs might have contributed to low DSC/high LDE results. A visual guide to delineation of BrachialPlex, BronchusProx and SacralPlex is illustrated in **Figure 2.2** while recommended contouring guidance/atlasses are collated in **Table 2.3**[25-30].

Table 2.3 A summary of resources to support target volume/organ at risk delineation

Structure	References
Standardised nomenclature guidance	AAPM TG-263 [28]
GTVnode	UK SABR Consortium guidance version 6.1, 2019 [26]
GTVbone/CTVbone	De la Pinta, 2020 [29]
Lung primary	UK SABR Consortium guidance version 6.1, 2019 [26]
OAR contouring summary resources	UK SABR Consortium guidance version 6.1, 2019 [26] Mir, 2019 [25] Wright, 2019 [30]
SacralPlex	Yi, 2012 [27]

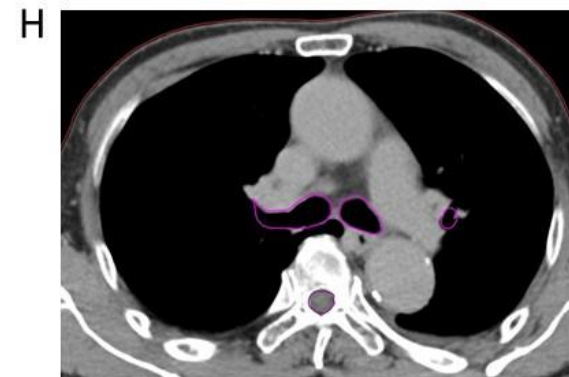
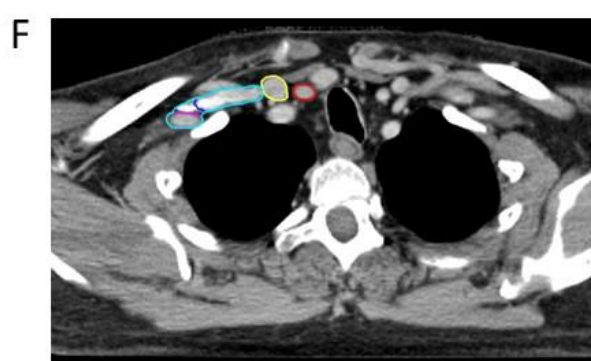
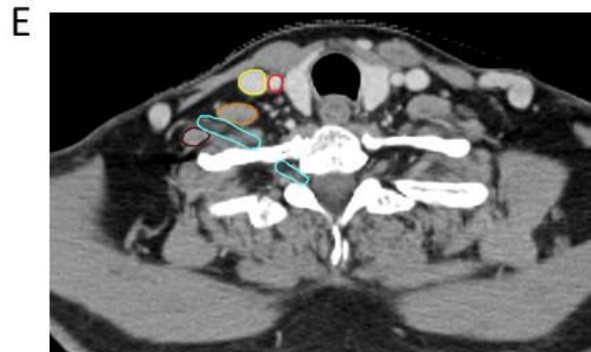
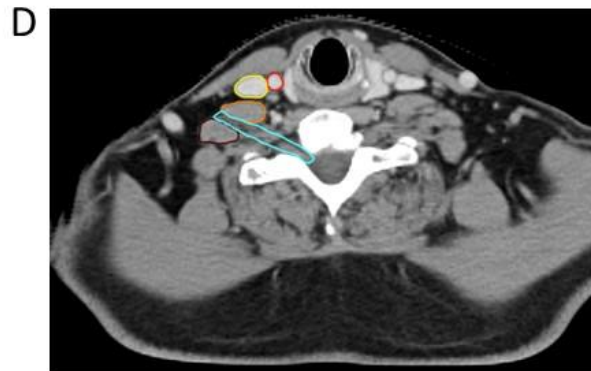
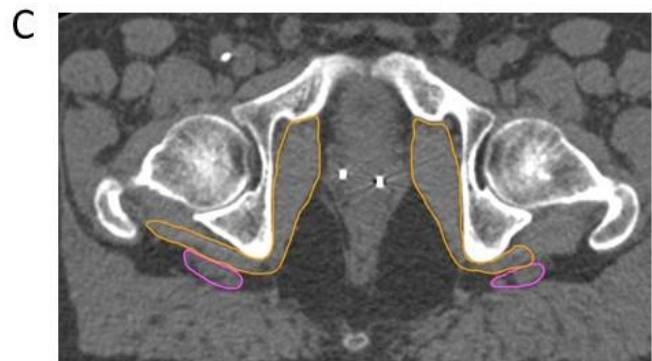
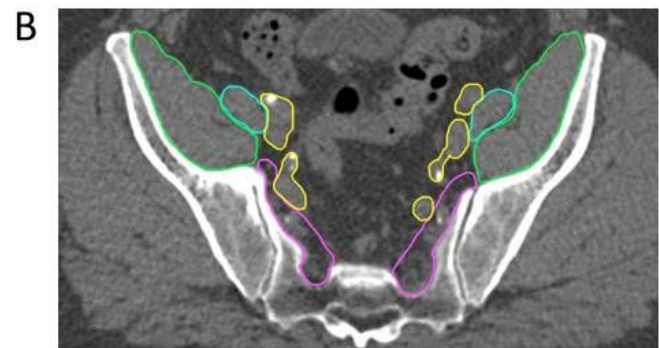
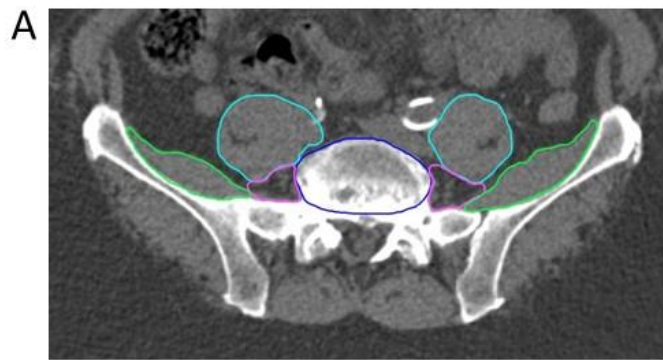


Figure 2.2 Visual guide to delineation of SacralPlex, BrachialPlex and BronchusProx. In Figure 2.2A-C, SacralPlex; iliacus muscle (green), L5 vertebral body (dark blue), obturator internus muscle (orange), psoas muscle (light blue), SacralPlex (purple), vessels (yellow) are shown. SacralPlex is contoured using a 5 mm diameter roller ball. In 2.2A, superior border of SacralPlex is shown at L4/5 vertebral interspace; SacralPlex is shown bordered by (ilio)psoas muscle anteriorly and vertebral body posteriorly. In 2.2B, at the sacro-iliac foramen, SacralPlex is shown bordered by vessels anteriorly, iliacus muscle laterally and sacral ala posteriorly. In 2.2C, inferior border of SacralPlex is shown at the level of the superior femoral neck bordered by obturator internus muscle anteriorly, gluteus maximus muscle posteriorly. In Figure 2.2D-F, BrachialPlex contoured as suggested by UK SABR Consortium Guidelines[26]; anterior scalene muscle (orange), BrachialPlex (light blue), common carotid artery (red), internal jugular vein (posterior scalene muscle (brown), subclavian artery (pink) and subclavian vein (dark blue) are shown. Intravenous contrast is helpful, and BrachialPlex is contoured using a 5 mm diameter roller ball. 2.2D shows a proximal slice: the superior border of BrachialPlex is at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries). In 2.2E, a middle section of BrachialPlex is shown; the plexus sits between anterior and middle scalene muscles. In 2.2F, the neurovascular complex including the subclavian and axillary vessels are contoured as a surrogate for the brachial plexus, ending after the neurovascular structures cross the second rib.

In Figure 2.2G-I, BronchusProx; BronchusProx (purple) is shown. In 2.2G, superior border of BronchusProx is the distal 2 cm of trachea including carina. In 2.2H, the mid-section of BronchusProx is shown and includes right/left upper lobe bronchi, bronchus intermedius, right middle lobe bronchus, lingular bronchus and right/left lower lobe bronchi. In 2.2I, contouring of lobar bronchi stops immediately at the site of a segmental bifurcation.

The metric thresholds that correlate to a minimum expected standard of contouring are uncertain but it has been previously suggested that DSC >0.7 indicates a good level of agreement[2]. However, previous studies have demonstrated discrepancies between contours considered to be acceptable based on expert review and the results of overlap measure comparisons[31]. In this study, 92% of the post-workshop contours were considered to be acceptable/within acceptable variation while 75% of structures had a DSC >0.7. A range of comparison metrics exists and each provides different information about the relationship between two contours and each has its limitations[16]. A summary of commonly used metrics for contour comparison is shown in **Table 2.4**; it is unclear which is the optimum metric to use[1, 2, 16, 18, 32-37]. For this reason, it has previously been recommended that multiple metrics ideally be reported including measures of volume, overlap and distance[1, 16]. In this study, we only reported DSC and LDE since we did not have volumetric contouring data. It should be emphasised that DSC may provide less reliable results when applied to very small contours and it may lack discrimination for very large volumes[18]. However, it does provide some insight into both the volumetric and spatial relationship between two contours and it is frequently reported in contouring studies[1, 11].

Quantitative concordance in target volume/OAR delineation does not necessarily equate to a clinically acceptable contour; incorrect delineation of even a small proportion of a target volume or an OAR could have profound clinical consequences, especially for SABR where tight margins, steep dose gradients and ablative doses are used[2, 38, 39]. This risk means that quantitative metrics should ideally be accompanied by visual review of contours and provision of qualitative feedback, analogous to the peer review process used in clinical practice and recommended by the RCR[7]. This approach is used in clinical trials for pre-trial approval for participation or on-trial individual case evaluation. Qualitative feedback can be provided detailing acceptable/unacceptable variation from the protocol and a similar process was used in this study for feedback on post-workshop contours[3, 40-42]. However, this approach may be time consuming and an efficient/reliable method of assessment which can identify clinically relevant discrepancies is needed[1, 16, 31].

Table 2.4 Summary of metrics for contour comparison

<i>Metric type</i>	<i>Example</i>	<i>Description</i>	<i>Advantages</i>	<i>Disadvantages</i>
Volume-based metrics	Volume [1, 16, 32, 34-35]	Commonly calculated by multiplying the number of voxels within a contour by the size of the voxel	Easy to calculate	No information provided on location of contours
	Centre of volume/mass [1-2, 16, 34-35]	Provides a single point representing the location of a contour	Provides information on differences in volume location	Contours with different volumes may have the same centre of volume Centre of volume may lie outside of the volume for curved structures
Volume overlap metrics	Conformity/concordance index [1-2, 16, 34-35] DICE similarity coefficient [2, 16, 18, 34-35, 37] Jaccard similarity coefficient [34-35, 37]	Measure of the relative overlap of contours, taking into account their intersection and union Presented as a ratio	Provide a single measurement with a description of both volume and position Comparisons can be made against a reference contour	No information provided on how contours vary in size, shape or location in absolute terms No information provided on location of variation between contours May be less reliable or lack discrimination for very small or large volumes

				respectively
Distance-based metrics	Maurer distance [36]	Euclidian (straight line) distance between points on two contours	Provides a measure of the maximum and minimum distance between contours	No information provided on how contours vary by volume, size, shape or location
	Hausdorff distance [16, 37]	Maximum distance between points on contours (equivalent to the maximum Maurer distance)	Provides a quantitative measure of the maximum distance between contours	As for Maurer distance plus: Sensitive to outliers- calculation of an average Hausdorff distance may mitigate this
	Average surface distance [16, 35]	Average distance between points on contours are determined	Provides a single measure of the average distance between contours	Use of an average value may mask areas of incorrect contouring
	Percentage of surface area differing (PSAD) [33]	The percentage of a contour which varies	Provides information on how much a contour	No information provided on the magnitude of

		beyond a defined extent	would need to be modified compared to another	contouring errors, only whether they are smaller/larger than the defined extent
Dimension	Dimension derived from encompassing dimension or from the centre of volume [1, 16]	Dimension of a structure determined along X, Y and Z axes	Provides information on size and approximate shape of a contour	May be misleading for irregularly shaped contours
Shape/surface-based metrics	Nearest point method [1]	Comparison of the surface/shape of 3 dimensional structures	Provides topological information in addition to distance between contours	No information provided on contour volume Challenges exist with analysis of asymmetrical shapes
Statistical measures of agreement	Cohen's kappa [34, 37] Inter/intra-observer reliability coefficients [34,	Measure of chance-corrected agreement between two or more observers	Cohen's kappa provides a measure of agreement robust to that caused by chance	Cohen's kappa designed for use with ordinal or nominal types of data

	37]		Inter/intra-observer reliability coefficients provide measures of inter/intra-observer agreement, reliability of results and minimum number of observers required	
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The practice of clinical oncology takes place against an increasingly complex backdrop of developments in imaging and novel methods of treatment delivery. Alongside ever increasing pressures in healthcare services, considerable challenges exist for training and continuous professional development of trainees and consultants respectively[9]. Formal training initiatives have been established to deliver the acquisition, and maintenance, of contouring competences in an attempt to improve target volume/OAR delineation beyond what could be achieved by a single workshop in isolation. The Fellowship in Anatomic deLineation and CONtouring (FALCON) programme is a European Society of Radiation Oncology (ESTRO) initiative that provides access to e-learning contouring resources in addition to its use within dedicated workshops[18, 21]. The RCR ARENA and Clinical Oncology Planning Project (COPP) are some example of initiatives to increase access to expert/peer-led structured outlining training to promote consistency in target volume and OAR outlining, and facilitate robust assessment of outlining practice for all grades of Clinical Oncologists[43].

This study has a number of additional limitations. The workshop was limited in its time/level of interactivity because of restrictions imposed during the pandemic and this could have impacted on the educational experience/DSC and LDE results that we observed (although participant feedback for the workshop remained positive). The same cases were used for both pre and post-workshop contouring; while this enabled the analysis of paired data, it meant that post-workshop contour performance could have been influenced by familiarity with the case and thus extrapolation of similar levels of performance to other cases would not necessarily be guaranteed. We did not stratify by prior experience when undertaking our analysis; this was because this information was not available to the authors but it could have influenced the results that were obtained. The workshop was aimed at those without prior experience in SABR but experience with OAR delineation would have varied depending on disease site expertise. We also did not evaluate longer-term maintenance of contouring competences by provision of further cases for contouring, although response rates for such interventions may be limited[20]. Finally, feedback on post-workshop contours was only available for approximately half of participants included in our analyses; this affected the conclusions that can be drawn regarding the qualitative feedback but does reflect the challenge of providing such information in a timely manner.

When planning a contouring workshop, the following considerations may be relevant based on prior recommendations/the authors' experience[3, 16, 20, 31, 44]:

- Workshop format; incorporation of time to practise contouring/re-contouring is recommended in addition to didactic teaching (the duration of the workshop should be considered in relation to this)
- Clarity of instructions for cases to be contoured including detailed delineation guidance and specification of laterality, where relevant
- Timely access to relevant target volume/OAR guidance/atlasses
- Provision of co-registered imaging
- Target audience; disease sites, numbers of target volume/OARs, number/complexity of cases
- Choice of assessment; quantitative metrics (such as volume, distance and overlap metrics) should ideally be used in conjunction with qualitative feedback. Be realistic about how much qualitative feedback can be provided in a timely manner to each participant
- Post workshop, provision of expert contour (where available) for participant comparison
- Where a reference contour is used; discussion regarding variation that may occur between even 'expert' outliners. One approach could be to use three expert contours and demonstrate the union and overlap as the maximum and minimum acceptable contours
- Identification of common errors/sources of variation for particular target volume/OARs
- Highlight available e-learning resources for self-directed learning
- Design of workshop feedback to evaluate participant confidence in contouring before/after the workshop
- Audiovisual/technological considerations; including method of quality assurance for displayed imaging and provision for participants with disabilities

2.6 Conclusion

This study has demonstrated that virtual contouring training is feasible and that teaching during a virtual SABR contouring workshop for multiple target volumes/OARs was associated with some improvements in contouring variation. Virtual contouring workshops could play an important role in aiding the acquisition of contouring competences alongside formal training initiatives.

2.7 Acknowledgements

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Chapter 3 Ultra Hypofractionated Extended Nodal Irradiation Using Volumetric Modulated Arc Therapy for Oligorecurrent Pelvic Nodal Prostate Cancer

3.1 Abstract

3.1.1 Background

Prostate cancer (PCa) may recur after primary treatment but no standard of care exists for patients with pelvic nodal relapse. Based on observational data, Extended Nodal Irradiation (ENI) might be associated with fewer treatment failures than Stereotactic Ablative Radiotherapy (SABR) to the involved node(s) alone. Ultra hypofractionated ENI is yet to be evaluated in this setting, but it could provide a therapeutic advantage if PCa has a low α/β ratio in addition to patient convenience/resource benefits. This volumetric modulated arc therapy (VMAT) planning study developed a class solution for 5-fraction Extended Nodal Irradiation (ENI) plus a simultaneous integrated boost (SIB) to involved node(s).

3.1.2 Material and methods

Ten patients with oligorecurrent nodal disease after radical prostatectomy/post-operative prostate bed radiotherapy were selected. Three plans were produced for each dataset to deliver 25 Gy in 5 fractions ENI plus SIBs of 40, 35 and 30 Gy. The biologically effective dose (BED) formula was used to determine the remaining dose in 5 fractions that could be delivered to re-irradiated segments of organs at risk (OARs). Tumour control probability (TCP) and normal tissue complication probability (NTCP) were calculated using the LQ-Poisson Marsden and Lyman-Kutcher-Burman models respectively.

3.1.3 Results

Six patients had an OAR positioned within planning target volume node (PTVn), which resulted in reduced target coverage to PTV node in six, five and four instances for 40, 35 and 30 Gy SIB plans respectively. In these instances, only 30 Gy SIB plans had a median PTV coverage >90% (inter-quartile range 90-95). No OAR constraint was exceeded for 30 Gy SIB plans, including where segments of OARs were re-irradiated. Gross tumour volume node (GTVn) median TCP was 95.7% (94.4-96), 90.7% (87.1-91.2) and 78.6% (75.8-81.1) for

40, 35 and 30 Gy SIB plans respectively, where an α/β ratio of 1.5 was assumed. SacralPlex median NTCP was 43.2% (0.7-61.2), 12.1% (0.6-29.7) and 2.5% (0.5-5.1) for 40, 35 and 30 Gy SIB plans respectively. NTCP for Bowel_Small was <0.3% and zero for other OARs for all three plan types.

3.1.4 Conclusions

Ultra hypofractionated ENI planning for pelvic nodal relapsed PCa appears feasible with encouraging estimates of nodal TCP and low estimates of NTCP, especially where a low α/β ratio is assumed and a 30 Gy SIB is delivered. This solution should be further evaluated within a clinical trial and compared against SABR to involved node(s) alone.

3.2 Introduction

Prostate cancer (PCa) is the commonest cancer in men and localised disease can be treated by radical prostatectomy (RP) with/without post-operative prostate bed radiotherapy, external beam radiotherapy or brachytherapy[1]. Up to half of patients may experience treatment failure, indicated by a rise in prostate specific antigen (PSA).

No clear standard of care exists for patients with recurrent pelvic nodal disease but an increasingly popular treatment where limited sites of pelvic nodal recurrence (oligorecurrence) are identified is Stereotactic Ablative Radiotherapy (SABR) to the involved node(s)[2-4].

An alternative approach is Extended Nodal Irradiation (ENI), where sites of potential micrometastatic disease are treated with/without a boost to macroscopically involved node(s). ENI might be associated with fewer treatment failures compared with SABR to the involved node alone based on observational studies, and it is currently being investigated in phase II trials using conventional dose fractionation schedules[5-8]. Ultra hypofractionated ENI has been investigated for the treatment of primary disease, although this approach is yet to be evaluated in the recurrent disease setting[9-12].

There has been a trend towards hypofractionation in PCa, supported by analyses suggesting that the disease has a lower α/β ratio of approximately 1.5 Gy relative to the 3 Gy reported for the late normal tissue reactions of most pelvic organs at risk (OARs)[13-16]. This would predict for an improved therapeutic ratio for hypofractionated schedules, and these would also provide patient convenience and resource benefits[17].

This planning study developed a volumetric modulated arc therapy (VMAT) class solution for 5-fraction ultra hypofractionated ENI with a simultaneous integrated boost (SIB) to macroscopically involved pelvic lymph nodes for patients with oligorecurrent nodal disease following RP and post-operative prostate bed radiotherapy. The impact on tumour control probability (TCP) and normal tissue complication probability (NTCP) of plans with SIB doses of 30, 35 and 40 Gy was also examined.

3.3 Material and methods

3.3.1 Patients and imaging

Planning computed tomography (CT) datasets were used from 10 patients who had previously undergone SABR for oligorecurrent pelvic nodal PCa post RP/post-operative prostate bed radiotherapy. Clinical characteristics are shown in **Supplementary Table 3.1**. Planning CT images were acquired using a Siemens Sensation Open CT scanner (Siemens Healthineers, Erlangen, Germany) with intravenous contrast and 2 mm thick axial slices. Patients were positioned head first supine and immobilised within a vacuum bag (BodyFIX®, Elekta AB, Stockholm, Sweden). Scanning was undertaken with empty bladder and rectum.

3.3.2 Target volume and organ at risk delineation

Gross Tumour Volume node (GTVn) was delineated with reference to the diagnostic positron emission tomography-computed tomography (PET-CT) and a 0 mm isometric margin applied to create Clinical Target Volume node (CTVn). No image co-registration between planning CT and PET-CT was performed. A 5 mm isometric margin was applied to CTVn to create Planning Target Volume node (PTVn), since it was envisaged that daily online volumetric image treatment verification would be used[18, 19].

Clinical Target Volume elective (CTV_Elective) was delineated as per the Prostate and pelvis Versus proState Alone Treatment for Locally Advanced Prostate Cancer boost (PIVOTALboost) trial, modified to improve coverage of the common/external iliac regions as per recent recommendations[5, 8, 20-22]. The following nodal regions were included: Common Iliac, External Iliac, Internal Iliac (including Obturator) and Pre-Sacral (S1-3). The boundaries of the included nodal regions are shown in **Supplementary Table 3.2**. A 3 mm isometric expansion of bowel structures was subtracted from CTV_Elective. A 5 mm isometric margin was applied to CTV_Elective to create Planning Target Volume elective (PTV_Elective). Since it was assumed that post-operative prostate bed radiotherapy had previously been delivered, only the above nodal regions were encompassed and a 1 cm gap between the superior border of the post-operative radiotherapy volume and the inferior border of PTV_Elective was applied.

OARs were delineated with reference to PIVOTALboost, Radiation Therapy Oncology Group (RTOG) Pelvic Normal Tissue Contouring Guidelines and other specific contouring guidance/atlasses[18, 23, 24]. The following OARs

were delineated: Bladder, Bowel_Small, CaudaEquina, Colon, Colon_Sigmoid, Femur_Head_L/R, Rectum and SacralPlex. It was considered that point doses in 5 fractions would be most relevant to ultra hypofractionated treatments[25]. The boundaries of OARs are shown in **Supplementary Table 3.3**. The remaining dose in 5 fractions that could be delivered to sub-divisions of OARs (Bladder_Reirrad, Bowel_Small_Reirrad, Colon_Sigmoid_Reirrad, Rectum_Reirrad and SacralPlex_Reirrad) within the post-operative radiotherapy volume and the 1 cm gap superior to it based on the American Association of Physicists in Medicine (AAPM) Report 101 constraints was calculated using biologically effective dose (BED) remaining calculations (shown in **Supplementary Material, section 3.8.2**). No recovery of OARs was assumed for the purposes of these calculations, aside from for SacralPlex_Reirrad where it was necessary to assume 25% recovery from the previously delivered dose.

3.3.3 Treatment planning and development of a class solution

VMAT plans were produced in RayStation Research version 9B (RaySearch Laboratories AB, Stockholm, Sweden) using a collapsed cone algorithm and a clinical 6 MV flattening filter free beam model for an Elekta Agility linear accelerator (Elekta AB, Stockholm, Sweden). A 3 mm dose grid was used for planning. A single 360° arc (rotating anticlockwise from 179° to 180°) was used with the collimator and couch set at zero degrees. The plans were monitor unit limited and a maximum delivery time of 180 seconds was allowed. The isocentre was set at the inferior border of PTV_Elective to produce a sharper fall off in dose inferior to the volume. The clinical goals/plan parameters recorded are shown in **Table 3.1**. OAR constraints were prioritised over target volume coverage for clinical goals.

Table 3.1 Clinical goals

Structure	Clinical goal*	40 Gy SIB parameter (Gy)	35 Gy SIB parameter (Gy)	30 Gy SIB parameter (Gy)
PTVn	Minimum coverage D98%	≥38	≥33.25	≥28.5
	Maximum coverage D2%	≤42	≤36.75	≤31.5
	Median dose D50%	40 ±2% (39.2-40.8)	35 ±2% (34.3-35.7)	30 ±2% (29.4- 30.6)
PTV_Elective	Minimum coverage D98%	≥23.75	≥23.75	≥23.75
	Maximum coverage D2%	≤26.25	≤26.25	≤26.25
	Median dose D50%	25 ±2% (24.5-25.5)	25 ±2% (24.5-25.5)	25 ±2% (24.5- 25.5)
Bladder	Dmax 0.5cc	≤38	≤38	≤38
Bowel_Small	Dmax 0.5cc	≤35	≤35	≤35
	D10cc	≤25	≤25	≤25
Colon	Dmax 0.5cc	≤38	≤38	≤38
Colon_Sigmoid	Dmax 0.5cc	≤38	≤38	≤38

CaudaEquina	Dmax 0.1cc	≤32	≤32	≤32
Femur_Head_L/R	D10cc	≤30	≤30	≤30
PenileBulb	Dmax 0.5cc	≤50	≤50	≤50
	D3cc	≤30	≤30	≤30
Rectum	Dmax 0.5cc	≤38	≤38	≤38
SacralPlex	Dmax 0.1cc	≤32	≤32	≤32
Bladder_Reirrad	Dmax 0.5cc	≤14.5	≤14.5	≤14.5
Bowel_Small_Reirrad	Dmax 0.5cc	≤7.3	≤7.3	≤7.3
Colon_Sigmoid_Reirrad	Dmax 0.5cc	≤14.5	≤14.5	≤14.5
Rectum_Reirrad	Dmax 0.5cc	≤14.5	≤14.5	≤14.5
SacralPlex_Reirrad	Dmax 0.1cc	≤14.75	≤14.75	≤14.75

D2%, dose to 2% of the volume; D50%, median dose (dose to 50% of the volume); D98%, dose to 98% of the volume; D3cc, dose to 3cc; D10cc, dose to 10cc; Dmax 0.1cc, maximum dose to 0.1cc; Dmax 0.5cc, maximum dose to 0.5cc; PTV_Elective, Planning Target Volume elective volume; PTVn, Planning Target Volume node; SIB, simultaneous integrated boost

*OAR constraints were prioritised over target volume coverage, therefore volume parameters should be considered to represent optimal rather than mandatory clinical goals

The aim was to cover 98% of PTVn/PTV_Elective with 95% of the prescription dose (D98%). Where the minimum target volume coverage was not achieved (for example, where coverage was compromised by an adjacent OAR), the volume of PTVn or PTV_Elective that did achieve coverage by that minimum dose was reported (for example, 95% instead of 98% coverage by 95% of the prescribed dose). Conformity index (CI) was calculated for PTV_Elective using the following formula:

$$CI = \frac{\text{Volume receiving 95\% of the prescribed dose}}{\text{Volume of PTV_Elective}}$$

Equation 3.1
Conformity index

The following dose fractionation schedules were used: 25 Gy in 5 fractions was delivered to PTV_Elective, to be treated once a day on alternate days over 10 days with SIBs to PTVn of 40, 35 and 30 Gy. Each plan was prescribed to the median dose (D50%) of PTVn. Each patient therefore had three treatment plans.

3.3.4 TCP/NTCP modelling

For TCP/NTCP modelling, the cumulative dose volume histogram (DVH) for each target volume/OAR from each plan was converted to a differential DVH with 0.1 Gy bin width and a 1 mm dose grid. These DVHs were imported into BioSuite version 12.2 (Clatterbridge Cancer Centre, Liverpool, UK) for calculation of TCP and NTCP. TCP was calculated for GTVn, since established TCP parameters exist for macroscopic PCa[26]. TCP was not calculated for CTV_Elective since the most appropriate TCP parameters for elective treatment of potential microscopic disease within nodal regions are uncertain.

TCP was calculated using the LQ-Poisson Marsden TCP model, originally described by Nahum and Sanchez-Nieto[27]. This use of this model is discussed in **Supplementary Material, section 3.8.3**. The parameters for the model are: $\bar{\alpha}$ (mean population sensitivity), σ_{α} (standard deviation of population radiosensitivity), α/β ratio and ρ_{clon} (initial clonogenic cell density) and the values used are shown in **Table 2**. Since there remains debate regarding the α/β ratio of PCa, three sets of TCP parameters were used to estimate TCP for high (10 Gy), low (3 Gy) and very low (1.5 Gy) values of α/β , which were derived by Uzan and Nahum based on RT01 trial data[26, 28].

NTCP was calculated using the Lyman-Kutcher-Burman (LKB) model, as discussed in **Supplementary Material, section 3.8.4**[29, 30]. NTCP was calculated for the following OARs: Bladder, Bowel_Small, CaudaEquina, Colon, Colon_Sigmoid, Femur_Head_L/R, Rectum and SacralPlex. The LKB model uses the following parameters: TD_{50} (dose that will result in a 50% probability of the complication), m (inversely related to the slope at the steepest point of the NTCP curve) and n (volume effect parameter). The parameters used are shown in **Table 2**. Aside from the Quantitative Effects of Normal Tissue Effects in the Clinic (QUANTEC) rectal NTCP parameters, there are limited recent parameters available in the literature and therefore the traditional Burman parameters were used for other OARs[31, 32].

Table 3.2 TCP and NTCP parameters

Structure	Endpoint	Parameter:	α/β (Gy)	α^- (Gy⁻¹)	σ_α (Gy⁻¹)	ρ_{clon} (cm⁻³)	Reference
GTVn	TCP		10	0.301	0.114	1x10 ⁷	Uzan[26]
	TCP		3	0.217	0.082	1x10 ⁷	Uzan[26]
	TCP		1.5	0.155	0.058	1x10 ⁷	Uzan[26]
Structure	Endpoint	Parameter:	TD₅₀ (Gy)	<i>m</i>	<i>n</i>		Reference
Bladder	NTCP (contracture/volume loss)		80	0.11	0.5		Burman[31]
Bowel_Small	NTCP (obstruction/perforation)		55	0.16	0.15		Burman[31]
Colon	NTCP (obstruction/perforation/ulceration/fistula)		55	0.11	0.17		Burman[31]
Colon_Sigmoid	NTCP (obstruction/perforation/ulceration/fistula)		55	0.11	0.17		Burman[31]
CaudaEquina	NTCP (neuropathy)		75	0.12	0.03		Burman[31]

Femur_Head_L/R	NTCP (necrosis)	65	0.12	0.25	Burman[31]
Rectum	NTCP (\geq Grade 2 late toxicity/bleeding)	76.9	0.13	0.09	Michalski[32]
SacralPlex	NTCP (neuropathy)	75	0.12	0.03	Burman[31]

$\bar{\alpha}$, mean population sensitivity; α/β , alpha beta ratio; m , inversely related to the slope at the steepest point of the NTCP curve; n , volume effect parameter; NTCP, normal tissue complication probability; ρ_{clon} , initial clonogenic cell density; σ_{α} , standard deviation of population radiosensitivity; TCP, tumour control probability; TD_{50} , dose that will result in a 50% probability of the complication

3.3.5 Statistics

Descriptive statistics were used for target volume and OAR dosimetry and TCP/NTCP from each plan. Statistical comparisons of dosimetry between the different plan types were not performed, since different SIB doses were deliberately used. The Friedman Analysis of Variance by Ranks test was used to compare GTVn TCP for each plan type (30, 35, 40 Gy SIB plans) for α/β of 10, 3 and 1.5 Gy. NTCP results between plan types were also compared using Friedman's test. Tests were performed pair-wise and were 2-tailed. A Bonferroni correction was applied for multiple comparisons, which reduced the P value which was considered statistically significant (for example, for three comparisons the P value would reduce from 0.05 to 0.0167). All analyses were performed in IBM SPSS Statistics for Windows version 26 (IBM Corp, Armonk, NY, USA).

3.4 Results

Of the 10 patients in the study, eight had a single pelvic lymph node, one had two nodes and one had three nodes. Lymph nodes were located within the left/right common iliac (n=2), external iliac (n=6), internal iliac (n=4) and pre-sacral (n=1) regions. The median volume of nodes was 1.12 cm³ (range 0.43-7.96). At least one OAR was positioned within PTVn in six of the 10 plans (60%): Bowel_Small (n=6), Colon_Sigmoid (n=1) and SacralPlex (n=2).

3.4.1 PTVn and PTV_Elective dosimetry

Target volume and OAR dosimetry for PTVn and PTV_Elective are summarised in **Table 3.3**. An example plan is illustrated in **Figure 3.1**. Target coverage of PTVn (D98%) was achieved in four (40%), five (50%) and six (60%) instances for 40, 35 and 30 Gy SIB plans respectively. Where PTVn coverage was not achieved, the median percentage volume (IQR) covered by 95% of the prescribed dose was 75% (70-86.3), 85% (80-90) and 92.3% (90-95) for 40, 35 and 30 Gy SIB plans respectively. D98% to PTV_Elective was achieved in one (10%), two (20%) and three (30%) instances for 40, 35 and 30 Gy SIB plans respectively. Where minimum PTV_Elective coverage was not achieved, the median percentage volume (IQR) covered by 95% of the prescribed dose was 95% (95-95), 95% (93.8-95) and 95% (93.8-95) for 40, 35 and 30 Gy SIB plans respectively.

Table 3.3 Target volume and organ at risk dosimetry

<i>Structure</i>	<i>Parameter</i>	<i>40 Gy SIB plans Median Gy (IQR)</i>	<i>35 Gy SIB plans Median Gy (IQR)</i>	<i>30 Gy SIB plans Median Gy (IQR)</i>
PTVn	D50%	40.5 (40.1-40.7)	35.3 (35.1-35.5)	30.6 (30.4-30.7)
	D98%	34.4 (31.0-38.0)	32.9 (29.9-34.2)	29.2 (28.2-29.9)
	D2%	41.7 (41.3-41.8)	36.4 (35.6-36.5)	31.2 (31.1-31.3)
PTV_Elective	D50%	25.1 (25.1-25.1)	25.1 (25.1-25.1)	25.5 (25.1-25.6)
	D98%	23.2 (22.5-23.5)	23.4 (22.4-23.7)	23.1 (22.1-23.7)
	D2%	26.1 (25.9-26.2)	26.0 (25.9-26.1)	26.3 (26.0-26.4)
	CI	1.1 (1.1-1.2)	1.2 (1.1-1.2)	1.1 (1.1-1.2)
Bladder	D0.5cc <38 Gy	5.6 (2.2-12.7)	5.5 (2.1-12.6)	5.3 (2.0-13.7)
Bladder_Reirrad	D0.5cc <14.5 Gy	12.3 (7.7-13.9)	12.1 (9.9-14.5)	12.4 (7.5-14.1)

Bowel_Small	D0.5cc <35 Gy	27.6 (25.3-33.1)	25.7 (25.2-31.0)	25.7 (25.2-28.4)
	D10cc <25 Gy	24.7 (22.9-25.0)	24.6 (22.9-24.9)	24.7 (22.9-24.8)
Bowel_Small_Reirrad	D0.5cc <7.3 Gy	7.4 (6.6-7.5)	7.2 (6.6-7.4)	7.1 (6.7-7.3)
CaudaEquina	D0.1cc <32 Gy	19.1 (16.6-20.2)	18.0 (16.7-20.6)	17.0 (15.9-20.7)
Colon	D0.5cc <38 Gy	19.4 (14.9-24.5)	18.8 (14.9-24.6)	18.7 (14.7-24.5)
Colon_Sigmoid	D0.5cc <38 Gy	25.3 (25.2-26.3)	25.5 (25.0-25.9)	25.4 (25.1-26.0)
Colon_Sigmoid_Reirrad	D0.5cc <14.5 Gy	13.4 (11.9-14.0)	13.2 (11.9-14.0)	13.1 (12.4-13.3)
Femur_Head_L	D10cc <30 Gy	2.5 (2.0-12.3)	2.4 (2.0-11.7)	2.3 (2.0-11.5)
Femur_Head_R	D10cc <30 Gy	2.7 (1.5-8.7)	2.7 (1.5-8.5)	3.1 (1.5-8.5)

PenileBulb	D0.5cc <50 Gy	0	0	0
	D3cc <30 Gy	0	0	0
Rectum	D0.5cc <38 Gy	20.7 (18.0-24.9)	20.6 (18.4-25.1)	20.3 (17.8-24.9)
Rectum_Reirrad	D0.5cc <14.5 Gy	12.4 (10.2-13.1)	12.8 (10.6-13.2)	12.2 (10.8-13.3)
SacralPlex	D0.1cc <32 Gy	29.0 (26.2-30.5)	29.4 (26.9-30.3)	27.9 (27.0-29.4)
SacralPlex_Reirrad	D0.1cc <14.6 Gy	13.6 (12.4-14.1)	13.7 (12.7-14.3)	13.7 (12.6-14.0)

CI, conformity index; D2%, dose to 2% of the volume; D50%, median dose (dose to 50% of the volume); D98%, dose to 98% of the volume; D3cc, dose to 3cc; D10cc, dose to 10cc; Dmax 0.1cc, maximum dose to 0.1cc; Dmax 0.5cc, maximum dose to 0.5cc; IQR, inter-quartile range; SIB, simultaneous integrated boost

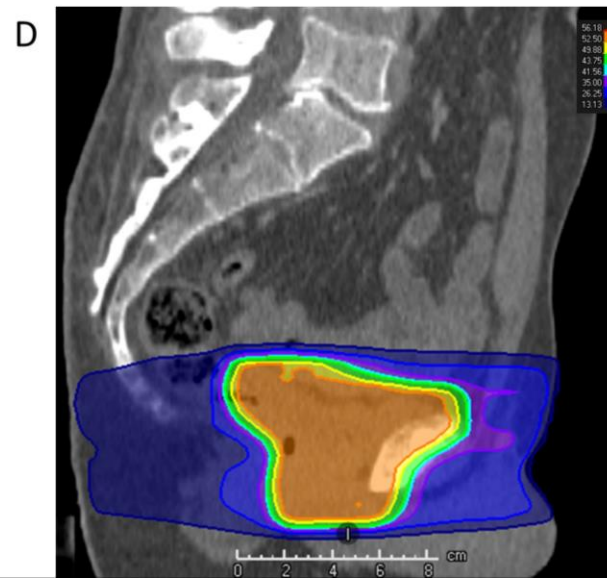
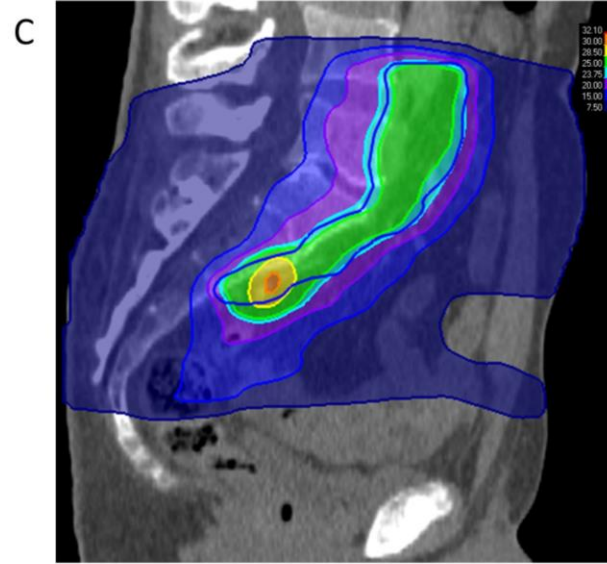
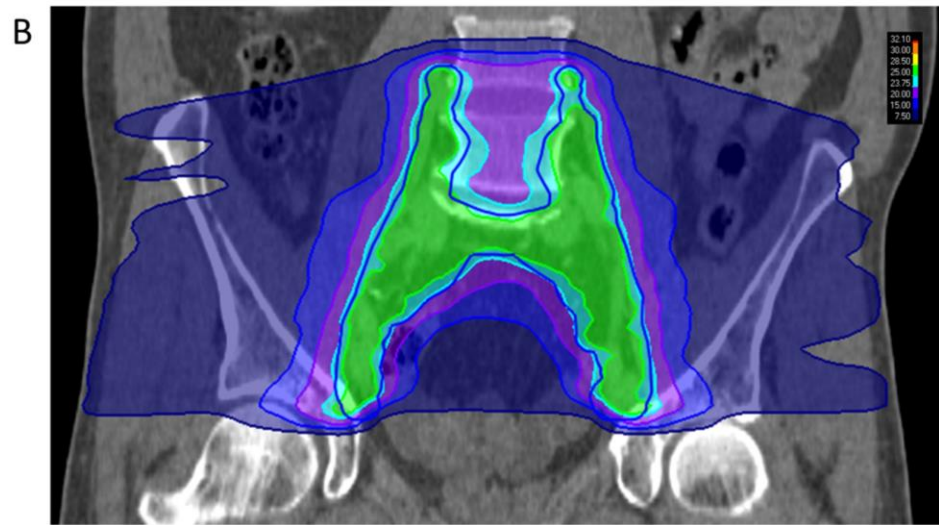
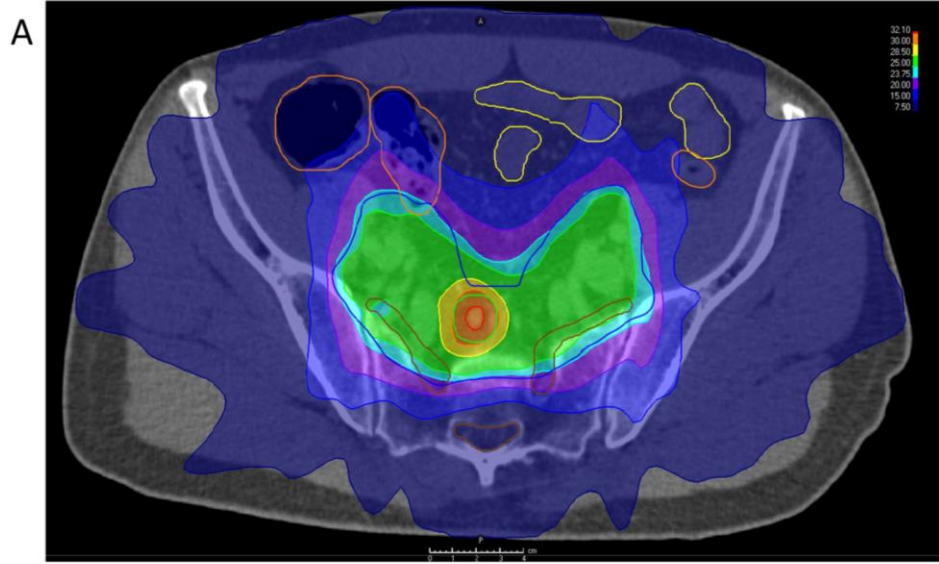


Figure 3.1 Example Extended Nodal Irradiation plan.

Figure 3.1A. Axial representation of the isodose distribution for a 30 Gy SIB plan to a pre-sacral nodal recurrence. The isodoses are displayed in absolute values of dose (Gy), as per the key in the top right of each image. GTVn (red), PTVn (green), PTV_Elective (blue), Bowel_Small (yellow), Colon/Colon_Sigmoid (orange) and SacralPlex (brown) are shown.

Figure 3.1B. Coronal representation of the same plan.

Figure 3.1C. Sagittal representation of the same plan. The fall-off in dose superior to the post-operative radiotherapy isodose distribution in Figure 1.1D can be visualised.

Figure 3.1D. Sagittal representation of the isodose distribution for a post-operative radiotherapy plan (52.5 Gy in 20 fractions).

In all cases, D50% to PTVn was within 3% of the prescribed dose. Maximum of 105% of the prescribed dose (D2%) to PTVn was exceeded in two (20%), one (10%) and two (20%) instances for 40, 35 and 30 Gy SIB plans respectively; in all instances, D2% was <107% of the prescribed dose. In all cases, D50% to PTV_Elective was within 3% of the prescribed dose. D2% to PTV_Elective was exceeded in one (10%), one (10%) and five (50%) instances for 40, 35 and 30 Gy SIB plans respectively; in all cases, D2% was <107% of the prescribed dose.

The median (IQR) CI for PTV_Elective was 1.14 (1.12-1.18), 1.16 (1.13-1.19) and 1.11 (1.10-1.15) for 40, 35 and 30 Gy SIB plans respectively. CI was not calculated for PTVn since this metric was not designed for a SIB within an elective volume.

Regarding fully segmented OARs, no constraint was exceeded for 40, 35 and 30 Gy SIB PTV_Elective plans. Concerning re-irradiation sub-divisions of OARs, constraints were exceeded in three patients; Bladder_Reirrad, Bowel_Small_Reirrad, Colon_Sigmoid_Reirrad and SacralPlex_Reirrad were exceeded in one (10%), two (20%), one (10%) and one (10%) instances each for both 40 and 35 Gy SIB plans. The maximum percentage the constraint was exceeded for 40 Gy and 35 Gy SIB plans for Bladder_Reirrad, Bowel_Small_Reirrad, Colon_Sigmoid_Reirrad and SacralPlex_Reirrad was 6%, 4%, 4% and 2% respectively. No OAR sub-division constraint was exceeded for 30 Gy SIB plans.

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3.4.2 TCP and NTCP

TCP and NTCP are shown in **Table 3.4**.

For 40, 35 and 30 Gy SIB plans, GTVn TCP was significantly improved where an α/β of 1.5Gy or 3Gy were used compared with 10 Gy ($P<0.0001$ and 0.032 respectively) and where 1.5 Gy was used compared with 3 Gy ($P=0.032$). NTCP for SacralPlex was significantly lower for 30 Gy compared with 40 Gy SIB plans (median 2.5% versus 43.2%, $P=0.016$). NTCP for Bowel_Small (median 0.1% for 40, 35 and 30 Gy SIB plans) was not significantly different once a Bonferroni correction was applied. NTCP for all other OARs was zero.

Table 3.4 Tumour control probability (TCP) and normal tissue complication probability (NTCP)

<i>Structure</i>	<i>Alpha/beta ratio (Gy)</i>	<i>$\rho_{clon} cm^3$</i>	<i>40 Gy SIB plans Median % (IQR)</i>	<i>P value for plan comparison where significant</i>	<i>35 Gy SIB plans Median % (IQR)</i>	<i>P value for plan comparison where significant</i>	<i>30 Gy SIB plans Median % (IQR)</i>	<i>P value for plan comparison where significant</i>
TCP GTVn	10	10^7	74.7 (68.0-75.8)		58.3 (47.2-60.4)		33.6 (28.2-38.7)	
				α/β 3>10: P=0.032*		α/β 3>10: P=0.032*		α/β 3>10: P=0.032*
	3	10^7	91.5 (89.1-91.9)		83.3 (77.5-84.3)		65.5 (61.5-69.4)	
				α/β 1.5>10: P<0.0001*		α/β 1.5>10: P<0.0001*		α/β 1.5>10: P<0.0001*
	1.5	10^7	95.7 (94.4-96.0)		90.7 (87.1-91.2)		78.6 (75.8-81.1)	
NTCP Bladder			0		0		0	

NTCP Bowel_Small	0.1 (0-0.3)	0.1 (0-0.2)	0.1 (0-0.1)	P=0.024**
NTCP CaudaEquina	0	0	0	
NTCP Colon	0	0	0	
NTCP Colon_Sigmoid	0	0	0	
NTCP Femur_Head_L	0	0	0	
NTCP Femur_Head_R	0	0	0	
NTCP Rectum	0	0	0	
NTCP SacralPlex	43.2 (0.7-61.2)	12.1 (0.6-29.7)	2.5 (0.5-5.1)	30 Gy SIB

plan<40 Gy
SIB plan:
P=0.016*

IQR, inter-quartile range; NTCP, normal tissue complication probability; ρ_{clon} , initial clonogenic cell density; SIB, simultaneous integrated boost; TCP, tumour control probability

*Indicates statistically significant result on pair-wise analysis using Friedman's Two Way Analysis of Variance by Ranks test (significance level adjusted by the Bonferroni correction for multiple tests)

**Indicates result not statistically significant following pair-wise analysis using Friedman's Two Way Analysis of Variance by Ranks test and once significance level adjusted by the Bonferroni correction for multiple tests

3.5 Discussion

Our study is the first to evaluate the feasibility of planning ultra hypofractionated ENI with a SIB of 30, 35 or 40 Gy for patients with pelvic nodal relapse following RP and post-operative prostate bed radiotherapy. Estimates of high GTVn TCP of 75-80% were obtained, especially where either a higher SIB dose was used or where a lower α/β ratio was assumed. OAR constraints for fully segmented structures were met and, in most cases, it was also possible to deliver ENI within cumulative constraints taking into account dose previously delivered during post-operative prostate bed radiotherapy to the more inferior portions of OARs (i.e. those in closest proximity to the previous treatment). NTCP estimates were very low, except for SacralPlex at higher SIB doses.

In general, PTVn and PTV_Elective minimum coverage appeared acceptable with excess dose within/outside of target volumes constrained. Sixty per cent of the cases had an OAR within the PTVn which meant that the minimum PTVn coverage had to be compromised in some cases, especially as SIB dose was increased from 30 to 35/40 Gy. Where PTVn coverage was compromised, median coverage by 95% of the prescribed dose was >90% only for plans with a 30 Gy SIB. Where minimum coverage of PTV_Elective was not met, 95% of the volume was still covered by 95% of the prescribed dose.

Data from early phase trials and prospective observational studies of SABR for pelvic nodal relapse in PCa using doses ranging from 20-48 Gy in 3-5 fractions suggest rates of local control >90% at 1 year and that the time to commencing androgen deprivation therapy (ADT) can be delayed, but that by 1-2 years the majority of patients will develop further sites of relapse [2, 3, 33, 34]. These relapses may occur within the pelvis including along the adjacent nodal chain where the delivery of further SABR could be compromised[35]. There are few studies of ENI in the setting of pelvic nodal relapse post RP/post-operative prostate bed radiotherapy[6-8, 36-38]. Pelvic nodal irradiation for relapsed disease has been evaluated in single arm phase II studies, although outcome data are awaited for the Oligometastatic Pelvic Node Relapses of Prostate Cancer Genitourinary Group P07 (OLIGOPELVIS GETUG P07) phase II trial and, in a study by Fodor et al, few patients specifically received ENI to the pelvis alone after RP/post-operative prostate bed radiotherapy [8, 36]. There are also limited comparative clinical data between ENI and SABR to the involved node alone[6, 7]. A recent multicentre retrospective study by De Bleser et al observed that ENI was associated with approximately a 10% improvement in metastasis-free survival at 3 years compared with SABR (77% versus 68%)

with superior outcomes for patients with a single pelvic node (95% versus 85%); other authors have also observed similar 3-year findings[6, 7]. Accepting the difference in methods of measurement, these results appear similar to the TCP findings in our study where an α/β ratio of 1.5 Gy is assumed. Previous studies have also observed that the number of metastatic lesions influences survival, although the maximum number of pelvic lesions that should be treated by ENI while maintaining clinical/dosimetric utility remains uncertain[39]. In our study, 80% of patients had a single node although two patients had two/three nodes respectively. A randomised comparison of ENI and SABR is currently being evaluated in the phase II Salvage Treatment of OligoRecurrent nodal prostate cancer Metastases (STORM) trial[5].

Concerning toxicity, conventionally fractionated ENI appears to be well tolerated, with no grade 3+ genitourinary (GU)/gastrointestinal (GI) toxicity by 1 year in the early results of OLIGOPELVIS GETUG P07 which used 54 Gy in 30 fractions ENI plus a SIB of 66 Gy to involved nodes[40]. In observational studies, rates of grade 3+ GU/GI toxicity of 2-4% have been observed[6, 7]. There are preliminary data to support the safety of 5-fraction ENI from the primary PCa disease setting[10-12]. Rates of grade 3+ late GU toxicity of up to 5% were observed in these studies, although they examined patients treated with ENI plus a SIB of up to 40 Gy to the prostate/seminal vesicles. More relevant to this planning study, where limited dose is delivered to the bladder, no grade 3+ GI toxicities were observed (although these studies did not deliver a SIB to macroscopically involved nodes and included small numbers of patients and modest durations of follow up). In this current study, OAR constraints were not exceeded (aside from re-irradiation sub-divisions of OARs, see below) and Bowel_Small/Colon/Colon_Sigmoid/Rectum NTCP estimates were very low/zero, which suggests that it could be feasible to safely deliver ultra hypofractionated ENI. A cautionary note is that the NTCP parameters for these structures were fitted to data from patients treated with conventionally fractionated radiotherapy rather than ultra hypofractionated treatments[31, 32]. The volume effect parameter (measuring the seriality of the OAR) therefore may not be relevant to ultra hypofractionated treatments where point doses are likely of greater relevance in terms of the risk of severe toxicity. The NTCP values could therefore underestimate the true risk. NTCP for SacralPlex was high despite OAR constraints being met, especially for 40 and 35 Gy SIB (although it fell to a median of 2.5% with 30 Gy SIB). The high seriality of this structure means that only a small volume of the structure would need to receive excess dose to increase NTCP[31]. The position of GTVn in relation to SacralPlex appears to be important, as evidenced by NTCP <1% for three 40 Gy SIB plans

where PTVn was >2 cm to SacralPlex. Nevertheless, acute sacral plexopathy and late low back pain has been observed in patients undergoing 25 Gy in 5 fractions pre-operative radiotherapy for rectal cancer[41, 42]. Where there is concern regarding the proximity of SacralPlex (and luminal OARs), the use of 30 Gy SIB may be more appropriate. NTCP was not calculated for re-irradiation sub-divisions of OARs since the complexities of accurately establishing a combined NTCP from both radiotherapy treatments was beyond the scope of this project.

The use of a 1 cm gap between the superior border of a previously delivered RT volume and the inferior border of the PTV_Elective volume and placement of the isocentre at the inferior aspect of the PTV_Elective appears to minimise delivery of excess dose to previously irradiated OARs. A 1 cm gap was also used in the OLIGOPELVIS GETUG P07 trial[8]. No fully segmented OAR constraint was exceeded for any of the plans in our study and, while re-irradiation volumes of Bladder_Reirrad, Bowel_Small_Reirrad, Colon_Sigmoid_Reirrad and SacralPlex_Reirrad were exceeded in three patients for 40 and 35 Gy SIB plans, this was only by $\leq 6\%$ and no constraints were exceeded for 30 Gy SIB plans. When it is considered that a conservative approach was taken (i.e. it was assumed that the whole of the sub-division of each OAR received 105% of the prescribed dose of 52.5 Gy in 20 fractions) with regards to the constraint used, this is likely acceptable. In addition, no recovery was assumed apart from SacralPlex_Reirrad (where it was necessary to allow 25% recovery in order to obtain a realistic constraint). This approach would appear to be acceptable when extrapolated from the data to support evidence of recovery of spinal cord after a 6 month interval following irradiation[43].

There is an absence of consensus regarding dose constraints for re-irradiation in the pelvis[44]. A number of approaches have been suggested including the use of cumulative maximum constraints with subtraction of previously delivered dose from a traditional constraint, with/without an allowance for recovery[45-48]. While from a radiobiological point of view, large doses per fraction could risk excess late toxicity the clinical evidence suggests that the use of highly conformal ultra hypofractionated/SABR re-irradiation can be safely delivered with the use of tight PTV margins, reproducible patient positioning and high quality image guided radiotherapy[48]. There were few grade 3+ toxicities observed following SABR re-irradiation in series by Abusaris et al and Smith et al where the use of maximum cumulative OAR doses was described[45, 48]. The degree of recovery after irradiation of most pelvic OARs is uncertain but after a reasonable time interval (for example, 6-12 months) it may be

acceptable to assume some recovery based on traditional constraints and on the practice in high volume centres with well-established programmes for re-irradiation as well as the maximum constraints allowed by Abusaris et al and Smith et al[45, 47, 48]. If 25% recovery were to be permitted for Bladder_Reirrad, Bowel_Small_Reirrad and Colon_Sigmoid_Reirrad in our study, no OAR constraint would have been exceeded.

Our study has certain limitations. Multiple nodes were only planned in two patients, meaning that our class solution may not always work for patients with multiple nodes especially where these are in close proximity to OARs. In this case, use of a 30 Gy SIB is likely to be more appropriate. We used a well-recognised CI formula to measure the conformity of the 95% isodose to PTV_Elective. However, this could result in high CI values where the 95% isodose does not conform closely to PTV_Elective. A post-operative prostate bed radiotherapy PTV was delineated to determine the position of the 1 cm gap on the same planning CT as the ENI plans as a pragmatic solution, whereas the optimal approach would be to co-register the two planning CT scans and dose distributions to determine the actual dose received by each OAR. This was not done since there are challenges in accounting for changes in anatomy and methods of deformable image registration in the pelvis remain under investigation[49]. Our estimates for the remaining dose that could be safely delivered to OARs within the 1 cm gap were based on an assumption that all of that segment received 105% of the previous dose and was therefore conservative and considered to be safe. On the other hand, the NTCP parameters used were based on historical data derived from patients treated with conventionally fractionated radiotherapy and may not therefore be applicable to ultra hypofractionated schedules; alternative parameters remain to be determined however, and previous studies of primary prostate SABR have used similar values[50].

3.6 Conclusions

Ultra hypofractionated ENI planning for pelvic nodal relapsed PCa appears feasible with encouraging estimates of nodal TCP and low estimates of NTCP, especially where a low α/β ratio is assumed and a 30 Gy SIB is delivered. We propose that this solution be taken forward for evaluation within a clinical trial and compared against SABR to involved node(s) alone.

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3.8 Supplementary Material

3.8.1 Supplementary Tables

Supplementary Table 3.1 Clinical characteristics of included patients

<i>Patien nt</i>	<i>Presenti ng PSA (ng/ml)</i>	<i>Pathologi cal T stage (RP)</i>	<i>Pathologi cal N Stage</i>	<i>Pathologi cal Gleason score (RP)</i>	<i>NCCN risk category</i>	<i>Interva l betwe en SRT and nodal relaps e (mont hs)</i>	<i>PSA at diagno sis of relapse (ng/ml)</i>	<i>Imaging used to diagnos e relapse</i>	<i>Age at time of SAB R</i>	<i>Number of nodal metasta ses</i>	<i>Nodal region (s)</i>	<i>Volu me of GTVn (cm³)</i>	<i>Closest OAR(s)</i>	<i>Distan ce from PTVn edge to closest OAR (negati ve if within PTVn) (mm)*</i>
1	8.4	pT2	pN0	3+4	Intermedi ate	41	0.8	Choline PET-CT	64	2	Right commo n iliac	5.89	Bowel_Sm all	-2.3

												Right internal iliac	4.74	Bowel_Sm all	-1.4
2	11.8	pT3a	pN0	4+3	High	47	2.3	Choline PET-CT	65	1	Right externa l iliac	0.75	Bowel_Sm all	1.5	
3	5.7	pT3b	pN0	3+4+5	High	77	3.9	CT	67	1	Right externa l iliac	7.96	Bowel_Sm all	-5	
4	72.5	pT3a	pN0	4+3	High	99	1.9	PSMA PET-CT	66	1	Left internal iliac	1.68	SacralPlex	5	
5	7.8	pT3b	pN0	3+4	High	46	14	CT	74	1	Left externa l iliac	0.65	Bladder	99	
6	14	pT3a	pN0	4+3+5	High	47	2.8	Choline PET-CT	63	1	Left internal iliac	0.78	SacralPlex	-2.5	
7	3.6	pT3a	pN0	3+4	High	10	1.2	MRI	63	1	Pre-	0.43	SacralPlex	3.9	

						(note, did not receive post-op RT)		pelvis Choline PET-CT			sacral					
8	8.9	pT3b	pN0	4+3	High	76	6.8	CT	73	1	Left commo n iliac	3.13	SacralPlex	-7.6		
9	10.8	pT3b	pN0	3+4	High	29	0.97	Fluciclov ine PET- CT	63	1	Left externa I iliac	0.55	Bowel_Sm all	-5.9		
10	6.8	pT3b	pN0	3+5	High	42	1.23	Choline PET-CT	56	3	Left externa I iliac	1.12	Bowel_Sm all	-2.1		
											Left externa I iliac	0.51			Colon_Sig moid	-2.4
											Right internal					

											iliac	1.28	Bowel_Sm all	-1.2
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CT, computed tomography; GTVn, gross tumour volume node; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; OAR, organ at risk; PET-CT, positron-emission tomography-computed tomography; PSA, prostate specific antigen; PTVn, planning target volume node; RP, radical prostatectomy; RT, radiotherapy

*Distance was taken to be the closest measurement between the edge of PTVn and the most proximal OAR, measured on axial CT

Supplementary Table 3.2 CTV_Elective boundaries

<i>Nodal region</i>	<i>Superior</i>	<i>Inferior</i>	<i>Lateral</i>	<i>Medial</i>	<i>Anterior</i>	<i>Posterior</i>
Common iliac	Aortic bifurcation	Common iliac vessel bifurcation	7 mm lateral to common iliac vessels, excluding muscle	7 mm medial to internal iliac vessels, excluding bowel	7 mm anterior to common iliac vessels, excluding bowel	Bony pelvis
External iliac	Common iliac vessel bifurcation	Midpoint of femoral head	7 mm lateral to external iliac vessels, excluding muscle	7 mm medial to internal iliac vessels, excluding bowel	7 mm anterior to external iliac vessels, excluding bowel	Internal iliac nodal region
Internal iliac	Common iliac vessel bifurcation	Levator ani insertion into obturator fascia/obturator internus muscle	7 mm lateral to internal iliac vessels, excluding muscle	7 mm medial to internal iliac vessels, excluding bowel	External iliac nodal region	7 mm posterior to internal iliac vessels, excluding bowel/bladder/bone
Obturator	Superior aspect of obturator internus	Obturator canal, where obturator artery moves lateral to obturator	Obturator internus muscle	7 mm medial to internal iliac vessels/18 mm	Anterior border of obturator	Internal iliac nodal region

	muscle	internus muscle		medial to obturator internus, excluding bowel/bladder	internus muscle
Pre-sacral	Superior aspect of S1 vertebrae	Inferior aspect of S3 vertebrae	Internal iliac nodal region		12 mm anterior to sacrum, excluding bowel
					Bony pelvis, excluding sciatic notches

Supplementary Table 3.3 Organs at risk definitions and boundaries

<i>Organ at risk</i>	<i>Definition</i>	<i>Superior</i>	<i>Inferior</i>	<i>Lateral</i>	<i>Medial</i>	<i>Anterior</i>	<i>Posterior</i>
Bladder	Outer wall of bladder	Dome of bladder	Base of bladder	Lateral wall of bladder	N/A	Anterior wall of bladder	Posterior wall of bladder
Bowel_Small	Individual small bowel loops excluding spaces between loops	2 cm superior to PTV	Axial image demonstrating most inferior loop of small bowel	Lateral extent of small bowel loops	N/A	Anterior extent of small bowel loops	Posterior extent of small bowel loops
CaudaEquina	Spinal canal	L1/2 vertebral interspace	Inferior aspect of spinal canal, continuing as SacralPlex	Lateral spinal canal	N/A	Anterior spinal canal	Posterior spinal canal
Colon	Outer wall of caecum, ascending, transverse	2cm superior to PTV	Junction with Colon_Sigmoid	Lateral extent of colon	N/A	Anterior extent of colon	Posterior extent of colon

	and descending colon						
Colon_Sigmoid	Contour outer wall of sigmoid colon	Junction with inferior aspect of descending colon	Rectosigmoid junction, best appreciated as axial image where rectum loses round/oval shape and turns anteriorly to connect with sigmoid colon	Lateral extent of sigmoid colon	N/A	Anterior extent of sigmoid colon	Posterior extent of sigmoid colon
Femur_Head_L/R	Femoral ball excluding neck	Superior aspect of femoral ball	Inferior aspect of femoral ball	Lateral aspect of femoral ball	Medial aspect of femoral ball	Anterior aspect of femoral ball	Posterior aspect of femoral ball
Penile bulb	Oval structure of penile bulb	Superior aspect of penile bulb	Inferior aspect of penile bulb (continues as corpus spongiosum)	Lateral aspect of penile bulb, bounded by crura of penis	N/A	Anterior aspect of penile bulb, bounded by corpus cavernosum	Posterior aspect of penile bulb, bounded by levator ani

Rectum	Outer wall of rectum	Rectosigmoid junction, where rectum loses round/oval shape and turns anteriorly to connect with sigmoid	Anorectal junction, where insertion of levator ani/puborectalis sling is visualised	Lateral wall of rectum	N/A	Anterior wall of rectum	Posterior wall of rectum
SacralPlex	As per [24]						

3.8.2 Biologically effective dose remaining calculations

Biologically effective dose (BED) remaining calculations were performed to determine constraints for OAR sub-divisions within/1 cm superior to the prior SRT volume. For each of the structures (1. Bladder/Colon_Sigmoid/Rectum, 2. SacralPlex, 3. Bowel_Small), the remaining dose in 5 fractions that can be delivered to the OAR sub-divisions is calculated. Of note, it was necessary to allow 25% recovery of SacralPlex in order to achieve a meaningful constraint (see Discussion).

The BED formula is:

$$BED = D\left(1 + \frac{d}{\alpha/\beta}\right) \quad \text{Equation 3.2 BED formula}$$

D=total dose; d=dose per fraction; α/β = alpha/beta ratio (an α/β ratio of 3 is assumed for Bladder/Bowel_Small/Colon_Sigmoid/Rectum and 2 for SacralPlex)

1. Bladder/Colon_Sigmoid/Rectum

Constraint: at most 38 Gy to 0.5cm³ delivered in 5 fractions (38 Gy in 5 fractions)

Total BED

38 Gy in 5 fractions (7.6 Gy per fraction)

$$BED = 38\left(1 + \frac{7.6}{3}\right)$$

$$BED = 134.3 \text{ Gy}$$

Calculating BED delivered during first treatment:

Prescription dose to prostatic fossa PTV from first treatment was 55.2 in 20 fractions. A maximum total dose of 105% of the prescription dose is assumed

$$\text{Total dose} = 52.5 \times 105\%$$

$$\text{Total dose} = 55.13 \text{ Gy in 20 fractions (2.76 Gy per fraction)}$$

$$BED = 55.13\left(1 + \frac{2.76}{3}\right)$$

$$BED = 105.78 \text{ Gy}$$

Calculation potential BED remaining

$$BED \text{ remaining} = 134.3 - 105.78$$

$$BED \text{ remaining} = 28.52 \text{ Gy}$$

Converting BED remaining into maximum deliverable total dose during second treatment

$$BED = D(1 + \frac{d}{\alpha/\beta})$$

$$BED = 5 \times d \left(1 + \frac{d}{3}\right)$$

$$BED = 5d + \frac{5d^2}{3}$$

$$28.52 = 5d + \frac{5}{3}d^2$$

$$0 = \frac{5}{3}d^2 + 5d - 28.52$$

This must be solved as a linear-quadratic equation

$$d = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} \quad \text{Equation 3.3 Linear quadratic formula}$$

Where $a = \frac{5}{3}$ (1.67), $b = 5$ and $c = -28.6$

$$d = \frac{-5 \pm \sqrt{5^2 - 4 \times (1.67 \times -28.52)}}{2 \times 1.67}$$

$$d = \frac{-5 \pm \sqrt{25 - (-191.51)}}{3.34}$$

$$d = \frac{-5 \pm 14.71}{3.34}$$

$$d = \frac{9.71}{3.34} \text{ or } \frac{-19.71}{3.34}$$

$$d = 2.91 \text{ or } -5.90$$

Since delivered dose cannot be negative, d is assumed to be 2.9 Gy

$$D = d \times \text{number of fractions}$$

$$D = 2.91 \times 5$$

$$D = 14.54 \text{ Gy}$$

Therefore, the maximum remaining total dose that may be delivered to Bladder/Colon_Sigmoid/Rectum during the second course of radiotherapy is 14.5 Gy in 5 fractions

2. SacralPlex

Constraint: At most 32 Gy to 0.1 cm³ delivered in 5 fractions (32 Gy in 5 fractions)

Total BED

32 Gy in 5 fractions (6.4 Gy per fraction)

$$BED = 32 \left(1 + \frac{6.4}{2} \right)$$

$$BED = 134.4 \text{ Gy}$$

Calculating BED delivered during first treatment

Prescription dose to prostatic fossa PTV from first treatment was 55.2 in 20 fractions. A maximum total dose of 105% of the prescription dose is assumed. If a minimum time period of 6 months between treatments is allowed, a 25% recovery from the first treatment is assumed.

$$\text{Total dose} = 55.2 \times 105\%$$

Total dose = 55.13 Gy in 20 fractions (2.76 Gy per fraction)

$$BED = 55.13 \left(1 + \frac{2.76}{2} \right)$$

$$BED = 131.21 \text{ Gy}$$

$$BED \text{ allowing for recovery} = 131.21 \times 75\%$$

$$BED \text{ allowing for recovery} = 98.41$$

Calculation potential BED remaining

$$BED \text{ remaining} = 134.4 - 98.41$$

$$BED \text{ remaining} = 35.99 \text{ Gy}$$

Converting BED remaining into maximum deliverable total dose during second treatment. BED equation rearranged as a quadratic equation in order to discover the value of d

$$BED = D \left(1 + \frac{d}{\alpha/\beta} \right)$$

$$BED = 5 \times d \left(1 + \frac{d}{2} \right)$$

$$BED = 5d + \frac{5d^2}{2}$$

$$50.31 = 5d + \frac{5}{2}d^2$$

$$0 = \frac{5}{2}d^2 + 5d - 35.99$$

This must be solved as a linear-quadratic equation

$$d = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

Where the known values are: $a = \frac{5}{2}$ (2.5), $b = 5$ (number of fractions), $c = -35.99$ (BED remaining) and d is the unknown value

$$d = \frac{-5 \pm \sqrt{5^2 - 4 \times (2.5 \times -35.99)}}{2 \times 2.5}$$

$$d = \frac{-5 \pm \sqrt{25 - (-359.9)}}{5}$$

$$d = \frac{-5 \pm 19.62}{5}$$

$$d = \frac{14.62}{5} \text{ or } \frac{-24.62}{5}$$

$$d = 2.92 \text{ or } -4.92$$

Since delivered dose cannot be negative, d is assumed to be 2.92 Gy

$$D = d \times \text{number of fractions}$$

$$D = 2.92 \times 5$$

$$D = 14.6 \text{ Gy}$$

Therefore, the maximum remaining total dose that may be delivered to SacralPlex during the second course of radiotherapy is 14.75 Gy in 5 fractions

3. Bowel_Small

Constraint: at most 35 Gy to 0.5cm³ delivered in 5 fractions (35 Gy in 5 fractions)

Total BED

35 Gy in 5 fractions (7 Gy per fraction)

$$BED = 35 \left(1 + \frac{7}{3}\right)$$

$$BED = 116.67 \text{ Gy}$$

Calculating BED delivered during first treatment

Prescription dose to prostatic fossa PTV from first treatment was 55.2 in 20 fractions. A maximum total dose of 105% of the prescription dose is assumed

$$\text{Total dose} = 52.5 \times 105\%$$

$$\text{Total dose} = 55.13 \text{ Gy in 20 fractions (2.76 Gy per fraction)}$$

$$BED = 55.13 \left(1 + \frac{2.76}{3}\right)$$

$$BED = 105.78 \text{ Gy}$$

Calculation potential BED remaining

$$BED \text{ remaining} = 116.67 - 105.78$$

$$BED \text{ remaining} = 10.89 \text{ Gy}$$

Converting BED remaining into maximum deliverable total dose during second treatment

$$BED = D\left(1 + \frac{d}{\alpha/\beta}\right)$$

$$BED = 5 \times d \left(1 + \frac{d}{3}\right)$$

$$BED = 5d + \frac{5d^2}{3}$$

$$10.89 = 5d + \frac{5}{3}d^2$$

$$0 = \frac{5}{3}d^2 + 5d - 10.89$$

This must be solved as a linear-quadratic equation

$$d = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

Where $a = \frac{5}{3}$ (1.67), $b=5$ and $c=-10.89$

$$d = \frac{-5 \pm \sqrt{5^2 - 4 \times (1.67 \times -10.89)}}{2 \times 1.67}$$

$$d = \frac{-5 \pm \sqrt{25 - (-72.75)}}{3.34}$$

$$d = \frac{-5 \pm 9.89}{3.34}$$

$$d = \frac{4.89}{3.34} \text{ or } \frac{-14.89}{3.34}$$

$$d = 1.46 \text{ or } -4.46$$

Since delivered dose cannot be negative, d is assumed to be 1.46 Gy

$$D = d \times \text{number of fractions}$$

$$D = 1.46 \times 5$$

$$D = 7.32 \text{ Gy}$$

Therefore, the maximum remaining total dose that may be delivered to Bowel_Small during the second course of radiotherapy is 7.32 Gy in 5 fractions

3.8.3 Tumour control probability

Tumour control probability (TCP) was calculated using the LQ Poisson Marsden TCP model, originally described by Nahum and Sanchez-Nieto [27]. TCP, in response to dose D delivered in n fractions of dose d and for an initial clonogenic cell number N_0 , is determined according to the equation:

$$\overline{TCP}(D, \sigma_\alpha, N_0) = \sum_i g_i \cdot TCP(\alpha, \beta, D, N_0), \text{ where}$$

$$TCP(\alpha, \beta, D, N_0) = \exp\left(-N_0 \exp\left[-\alpha D \left(1 + \frac{\beta}{\alpha} d\right)\right]\right), \text{ and}$$

$$g_i \propto \left(\frac{1}{\sigma_\alpha \cdot \sqrt{2\pi}}\right) \cdot \exp\left[\frac{-\left(\alpha_i - \bar{\alpha}\right)^2}{2 \cdot \sigma_\alpha^2}\right]$$

Whereby the calculated TCP is averaged for a population in which radiosensitivity varies according to a Gaussian distribution over α_i values with mean, $\bar{\alpha}$, and standard deviation, σ_α . Within this population, a fraction of patients, g_i , have radiosensitivity $\alpha = \alpha_i$, and $\sum_i g_i = 1$. For a patient with radiosensitivity α receiving a non-uniform dose distribution represented by a differential DVH containing j bins of volume v_j each of which receives dose d_j for n fractions, to total dose D_j , the final expression is combined to become:

$$TCP = \frac{1}{\sigma_\alpha \cdot \sqrt{2\pi}} \int_0^\infty \left(\prod_j \exp\left[-\rho_{clon} \cdot v_j \cdot \exp\left(-\alpha \cdot D_j \cdot \left(1 + \frac{\beta}{\alpha} \cdot d_j\right)\right)\right] \right) \cdot \exp\left[\frac{-\left(\alpha - \bar{\alpha}\right)^2}{2 \cdot \sigma_\alpha^2}\right] d\alpha$$

where ρ_{clon} represents the initial clonogenic cell density.

A correction for cell proliferation during the course of treatment was not incorporated into TCP calculations since it was assumed that the overall treatment time (10 days) would be shorter than the time taken for repopulation to commence.

3.8.4 Normal tissue complication probability

Normal tissue complication probability (NTCP) was calculated for Bladder, Bowel_Small, CaudaEquina, Colon, Colon_Sigmoid, Femur_Head_L/R, Rectum and SacralPlex using the Lyman-Kutcher-Burman (LKB) model [29-30].

Initially each DVH bin was converted to the equivalent dose in 2 Gy fractions (EQD2) according to:

$$EDQ2 = D \cdot \frac{(\alpha / \beta + d)}{(\alpha / \beta + 2)} \quad \text{Equation 3.4 Equivalent dose in 2 Gy fractions}$$

As a conservative approach, an α/β ratio of 3Gy was used for equivalent dose conversion.

EUD was then calculated: this reduces a non-uniform dose distribution to a single dose which in a uniformly irradiated tissue would result in the same level of cell kill (and NTCP) as in the non-uniform dose:

$$EUD = \sum_i \left(D_i^n \frac{V_i}{V_{total}} \right)^n$$

Where D_i is the dose to dose bin i , V_i is the volume of dose bin i , V_{total} is the total volume of the tissue and n is a volume effect parameter. Large values of n (i.e. close to 1) represent a large volume effect as in parallel structures, and so EUD is approximately equal to the mean dose) and small values of n (i.e. approaching zero) represent a small volume effect as in serial structures where EUD approaches the maximum dose).

NTCP is then calculated according to:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t \exp\left(-\frac{x^2}{2}\right) dx$$

And

$$t = \frac{EUD - TD_{50}}{m \cdot TD_{50}}$$

TD_{50} is the dose that will result in 50% probability of complication in a uniformly irradiated tissue and m is inversely proportional to the slope of the steepest point on the NTCP versus dose response curve (thus larger values of m represent more shallow dose-complication slopes)

Chapter 4 A feasibility study of hyoscine butylbromide (buscopan) to improve image quality of cone beam computed tomography during abdominal/pelvic Stereotactic Ablative Radiotherapy

4.1 Abstract

4.1.1 Background

Cone beam computed tomography (CBCT) is used for image guidance of Stereotactic Ablative Radiotherapy (SABR), but it is susceptible to bowel motion artefacts. This trial evaluated the impact of hyoscine butylbromide (buscopan) on CBCT image quality and its feasibility within a radiotherapy workflow.

4.1.2 Methods

A single-centre feasibility trial (ISRCTN24362767) was performed in patients treated with SABR for abdominal/pelvic oligorecurrence. Buscopan was administered to separate cohorts by intramuscular (IM) or intravenous (IV) injection on alternate fractions, providing within-patient control data. Four-point Likert scales were used to assess overall image quality (ranging from excellent to impossible to use) and bowel motion artefact (ranging from none to severe). Feasibility was determined by patient/radiographer questionnaires and toxicity assessment. Descriptive statistics are presented.

4.1.3 Results

Sixteen patients were treated (8 by IM and 8 by IV buscopan). The percentage of images of excellent quality with/without buscopan was 47% versus 29% for IM buscopan and 65% versus 40% for IV buscopan. The percentage of images with no bowel motion artefact with/without buscopan was 24.6% versus 8.9% for IM buscopan and 25.8% versus 7% for IV buscopan. Four patients (25%) reported dry mouth. Fourteen patients (93%) would accept buscopan as routine. Eleven radiographers (92%) reported no delay in treatments.

4.1.4 Conclusions

A trend towards improved image quality/reduced bowel motion artefact was observed with IM/IV buscopan. Buscopan was well tolerated with limited impact on workflow.

4.2 Introduction

Stereotactic Ablative Radiotherapy (SABR) is increasingly used to treat limited sites of metastatic relapse (so-called oligorecurrence) in the abdomen/pelvis after primary treatment for malignancy[1-3]. SABR is ultra hypofractionated radiation, delivering large doses per fraction to a highly conformal target volume using steep dose gradients in a small number of fractions. To safely deliver SABR, effective immobilisation and accurate target localisation within millimetre tolerances using image guidance and online correction for inter-fraction motion and set up errors are required[4, 5].

For linear accelerator-delivered SABR, volumetric image guidance is commonly acquired using cone beam computed tomography (CBCT)[6]. In contrast to diagnostic helical computed tomography (CT), CBCT image projections are typically acquired over at least 1-2 minutes and are susceptible to motion artefacts (including from bowel) that manifest after reconstruction into volumetric images[7, 8].

In radiology, hyoscine butylbromide (Buscopan[®] [Sanofi, Reading, UK], herein referred to as buscopan) is routinely used to reduce motion artefacts during magnetic resonance imaging (MRI) of the abdomen and pelvis (among other examinations)[9].

However, administration of anti-peristaltic agents to reduce bowel motion artefacts during radiotherapy has not been previously investigated. In this prospective trial, we evaluated the impact of intramuscular (IM) and intravenous (IV) buscopan on CBCT image quality and feasibility of its delivery during an abdominal/pelvic SABR workflow.

4.3 Materials and Methods

4.3.1 Trial design

A single-centre, non-randomised feasibility study was undertaken in Leeds Teaching Hospitals NHS Trust in patients treated with abdominal/pelvic SABR. The trial was registered on the National Institute for Health Research (NIHR) Clinical Research Network Portfolio (ID 40521) and International Standard Randomised Controlled Trial Number (ISRCTN) registry (ISRCTN24362767). An application for ethical approval was made using the Integrated Research Application System (IRAS) (ID 252816) 13th February 2019. Ethical approval

was granted 28th May 2019 by NHS Health Research Authority Yorkshire & The Humber- Leeds West Research Ethics Committee (reference 19/YH/0074). A copy of the study protocol is shown in **Appendix A**. A Consolidated Standards of Reporting Trials (CONSORT) trials checklist is shown in **Appendix B**.

4.3.2 Participants

Participants were identified through Leeds Cancer Centre SABR multidisciplinary meetings. Eligible patients were treated with SABR for oligorecurrent soft tissue/bone metastatic disease in the abdomen/pelvis. Ineligible patients had contraindications to buscopan: severe/recent cardiac disease, tachyarrhythmias, narrow angle glaucoma, myasthenia gravis, mechanical/functional bowel obstruction, obstructive uropathy, porphyria, allergy to buscopan and concomitant administration of anticoagulants (IM buscopan cohort)[9, 10]. All participants provided written informed consent.

4.3.3 Interventions

Buscopan was administered to separate cohorts by IM or IV injection on alternate fractions. Each patient therefore provided data without buscopan, acting as a within-person control regarding their individual bowel appearance/motion. Initially, IM buscopan was used since it was considered that this would be more feasible to deliver within a radiotherapy workflow. After review of the first three patients treated with IM buscopan and concern for limited impact on image quality, a substantial amendment to the protocol was made to administer IV buscopan and which received approval 5th March 2020. IM buscopan (20 mg/ml) was administered into the buttock immediately before the patient entered the treatment room. IV buscopan (20 mg/ml) was diluted in 10 ml 0.9% sodium chloride and administered over 1 minute via a peripherally-sited venous cannula, as per institutional protocol. IV buscopan was administered once the patient was positioned on the treatment table prior to set-up. The ratio of fractions with/without buscopan was 2:1 and 3:2 for 3 and 5 fraction SABR respectively. Patient involvement in the study finished after their final SABR fraction.

SABR was delivered using a Versa HD™ linear accelerator (Elekta AB, Stockholm, Sweden) as 30 Gy in 3-5 fractions on alternate days for soft tissue/non-spinal bone lesions and 24 Gy in 3 fractions for spinal lesions. Patients were positioned supine and immobilised in a BodyFix® vacuum bag (Elekta). CBCTs were acquired using XVI version 5.04 (Elekta) at baseline (after patient set up), pre-treatment (after target matching and application of shifts in treatment table position) and post-treatment. The following acquisition

parameters were used: 120 kV, 20-32 mA, 20-40 ms, 660-1320 projections. Time from injection to each CBCT was recorded. Dietary advice was not provided. For pelvic lesions, scanning was undertaken with empty bladder and rectum.

4.3.4 Outcomes

The primary endpoint was improvement in image quality when buscopan was given compared with when it was not given and was assessed using two 4-point Likert scales; an overall image quality scale and a bowel motion artefact scale. The overall image quality scale had the following points: 4 (excellent quality), 3 (satisfactory quality), 2 (poor quality) and 1 (impossible to use). The scale was task-orientated; image quality was scored in the context of matching to the target. The bowel motion artefact scale had the following points: 0 (no artefact), 1 (mild artefact), 2 (moderate artefact) and 3 (severe artefact). Each scale had been internally validated in a retrospective study in which the image quality of CBCT was evaluated in patients previously treated with abdominal/pelvic SABR[11].

Image quality was evaluated concurrently by Finbar Slevin (clinical research fellow) and Matthew Beasley (senior radiographer) as a consensus score. It was considered that this approach was analogous to the use of image guidance in clinical practice, where pairs of radiographers agree on target matching prior to treatment delivery. Training was performed using images from the previously treated cohort corresponding to each point on the respective Likert scales. Images were viewed in X-ray Volume Imaging (XVI, Elekta) using the following procedure: a random sequence of images per patient was generated using Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington, USA) and a third person (not scoring the images) loaded each image as per the random sequence. Dates/times were concealed from images to ensure scorers were blinded to whether buscopan was administered. Exploratory analyses of image quality were undertaken for timing of CBCT and whether the treated lesion was pelvic (below level of aortic bifurcation) versus abdominal and soft tissue versus bone.

Secondary endpoints were to demonstrate that administration of IM/IV buscopan was feasible within an abdominal/pelvic SABR workflow and was tolerated by patients. These were assessed on the final fraction using a combination of clinician-assessed toxicity (using Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0) and patient/radiographer questionnaires[12]. The questionnaires used a 4-point Likert scale with the following points: 1 (not at all), 2 (somewhat), 3 (moderately) and 4 (very much

so). For patients, questions primarily concerned their experience of treatment with buscopan and can be seen in **Table 3**. One radiographer per patient was approached to complete a questionnaire. These questions primarily concerned the impact of buscopan on workflow and can be seen in **Table 4**. Questionnaire design was based on previously published radiotherapy/MRI patient questionnaires[13, 14].

4.3.5 Statistics

This feasibility study was not designed to demonstrate statistical significance; therefore, there was no formal sample size calculation[15]. Given each patient received three scans per 3/5 fractions, a sample of 16 patients provided between 144 to 240 images and was considered sufficient information. Each patient provided data with/without buscopan, acting as a within-person control. However, pairing of data to utilise standard statistical paired tests was infeasible, with no clear pairing and violation of the assumption of independent samples due to pairing across multiple scan/time points for the same patient. More sophisticated approaches, that account for the complex data structure, such as mixed modelling, were considered unsuitable for the number of patients. Therefore, descriptive statistics are presented including median and inter-quartile range (IQR). To account for differences in numbers of images with/without buscopan and intra-patient correlation in bowel motion, image quality scores were summarised per patient prior to being summarised for the whole cohort[16, 17].

4.4 Results

4.4.1 Participants

The trial schema is shown in **Figure 4.1**. Of 26 patients approached about the trial, 10 were excluded because of ineligibility or because they declined to participate. Sixteen patients commenced treatment (eight in the IM cohort and eight in the IV cohort); of these, one patient in the IV cohort experienced vertebral collapse and SABR was stopped early. The first patient was recruited September 2019 and the final patient completed treatment January 2021. Study recruitment was paused for 6 months from March-July 2020 during the Covid-19 pandemic.

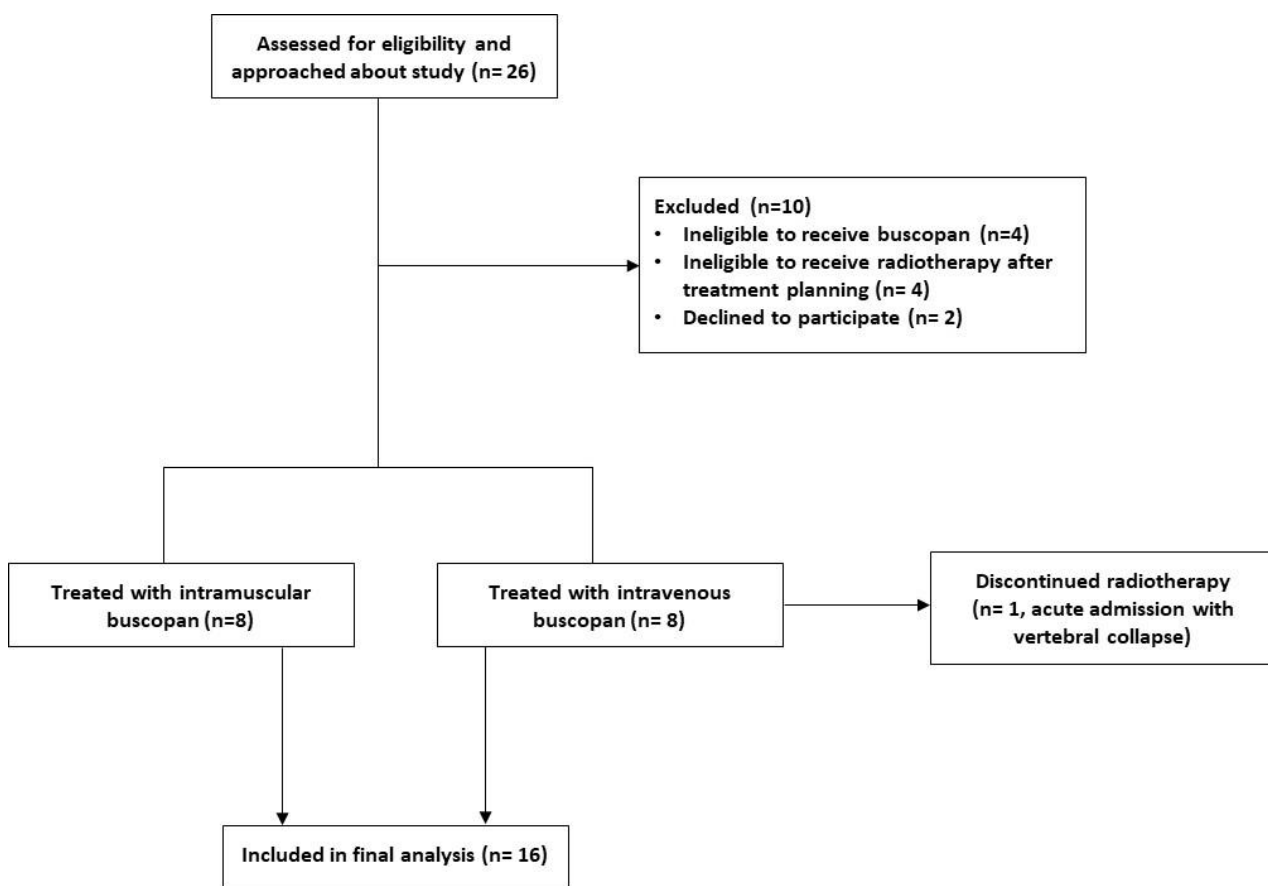


Figure 4.1 Flow diagram showing numbers of participants approached for the study, numbers of patients excluded/recruited and numbers of patients who completed the study.

Baseline demographic and clinical characteristics of the patients are shown in **Supplementary Table 4.1**. Eleven patients received 5-fraction SABR and five received 3 fractions. Eight lesions were in soft tissue and eight were in bone. Ten lesions were pelvic and six were abdominal.

4.4.2 Primary endpoint

Figure 4.2 illustrates the impact of IM and IV buscopan on bowel motion artefact in CBCT images.

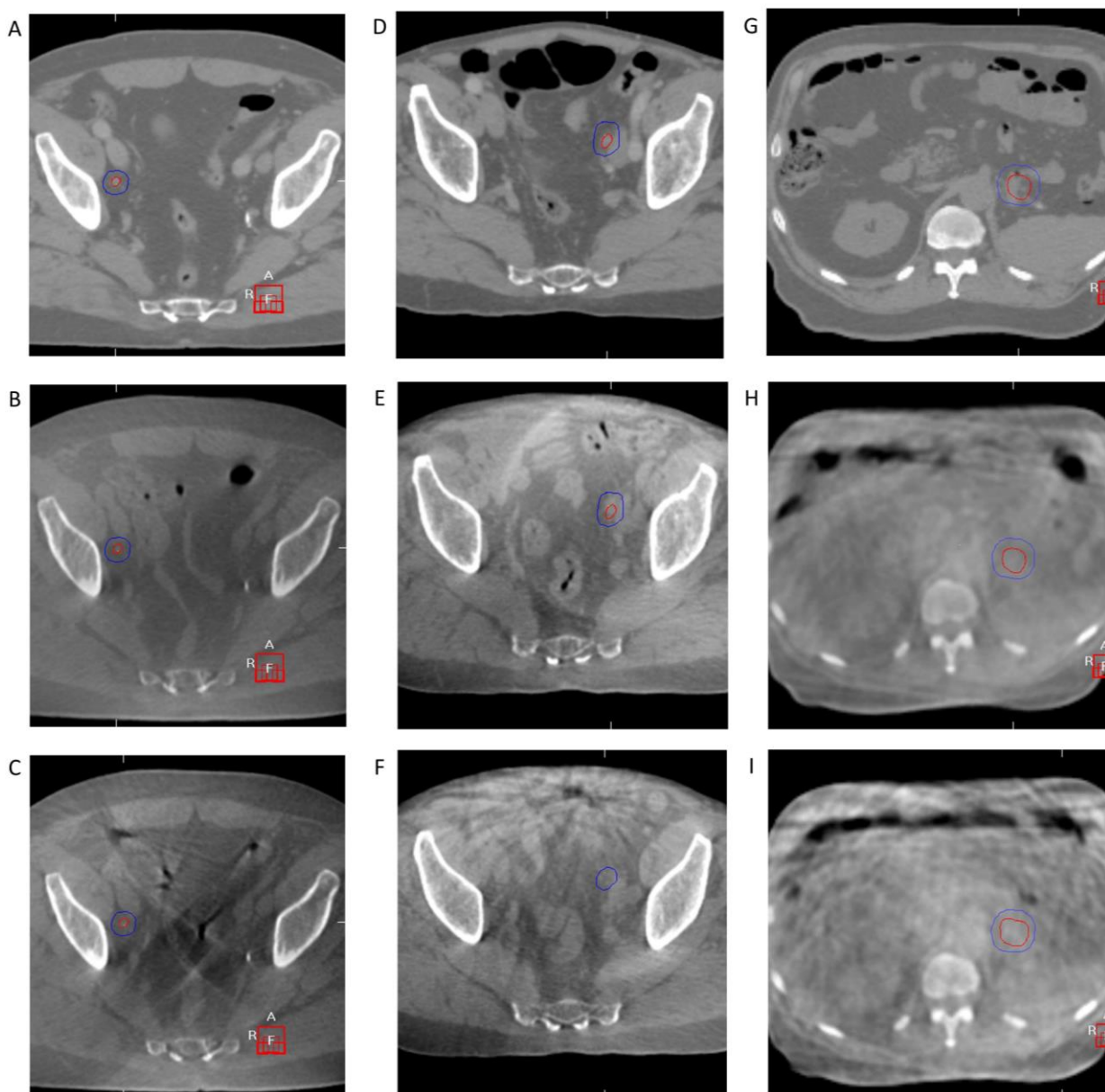


Figure 4.2 Planning CT and CBCT images with/without IM and IV buscopan for three patients. GTV and PTV are shown in each image. In Figure 4.2A-C, a planning CT for a right external iliac nodal metastasis is shown in A, CBCT with IM buscopan in B and CBCT without IM buscopan in C. Reduced streak artefact from bowel gas is apparent in B compared with C.

In Figure 4.2D-F, a planning CT for a left external iliac nodal metastasis is shown in D, CBCT with IV buscopan in E and CBCT without IV buscopan in F. Reduced streak artefact from bowel gas is apparent in E compared with F.

In Figure 4.2G-I, a planning CT for a pancreatic tail metastasis is shown in G, CBCT with IV buscopan is shown in H and CBCT without IV buscopan is shown in I. Despite some apparent reduction in bowel motion artefact in H compared with I, persistent artefact is shown in H and is likely related to respiratory motion.

Sixteen patients were included in the image quality analyses (eight in IM cohort and eight in IV cohort); 127 images with buscopan (65 and 62 in IM and IV cohorts respectively) and 88 without buscopan (45 and 43 in IM and IV cohorts respectively). One image (without buscopan) in the IV cohort was excluded because of scan failure.

For patients who received IM buscopan, the percentage of images of excellent quality with/without buscopan was 47% versus 29%. For patients who received IV buscopan, the percentage of images of excellent quality with/without buscopan was 65% versus 40%. A summary of overall image quality and the proportion of images corresponding to each point on the scale is shown in **Table 4.1**. The proportion of scores per patient is illustrated in **Figure 4.3**. Individual patient data is shown in **Supplementary Table 4.2**.

Table 4.1 Summary of overall image quality scores and proportion of individual scores by receipt of buscopan

<i>Image type</i>	<i>Number of patients</i>	<i>Number of images</i>	<i>Median Likert scale score* (IQR)</i>	<i>Absolute number of images with score of 4 (%)</i>	<i>Absolute number of images with score of 3 (%)</i>	<i>Absolute number of images with score of 2 (%)</i>	<i>Absolute number of images with score of 1 (%)</i>
Images with IM buscopan	8	65	3.0 (3.0-4.0)	29 (44.6%)	35 (53.8%)	1 (1.5%)	0
Images without IM buscopan	8	45	3.0 (3.0-3.3)	13 (28.9%)	29 (64.4%)	3 (6.7%)	0
Images with IV buscopan	8	62	4.0 (3.0-4.0)	40 (64.5%)	14 (22.6%)	8 (12.9%)	0
Images without IV buscopan	8	43	3.5 (3.0-4.0)	17 (39.5%)	17 (39.5%)	9 (20.9%)	0
All images with buscopan	16	127	3.5 (3.0-4.0)	70 (55.1%)	49 (38.6%)	9 (7.1%)	0
All images without buscopan	16	88	3.0 (3.0-4.0)	30 (34.1%)	46 (52.3%)	12 (13.6%)	0

*4=excellent quality, 3=satisfactory, 2=poor, 1=impossible to use

IM, intra-muscular; IQR, inter-quartile range; IV, intravenous; min, minimum; max, maximum

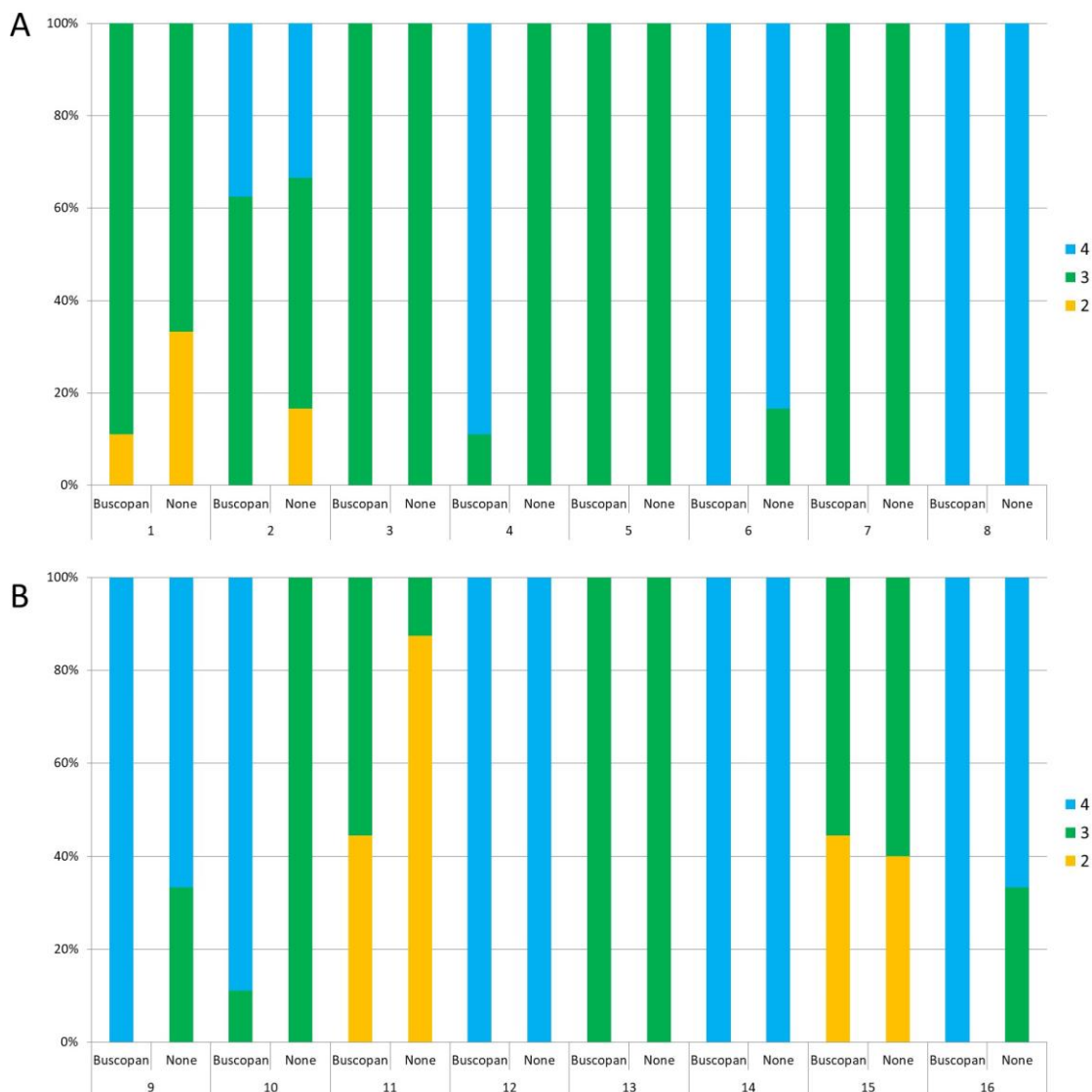


Figure 4.3 Proportions of overall image quality scores per patient. In Figures 4.3A-B, overall image quality scores are shown with/without buscopan for each patient treated with IM buscopan (A, patients 1-8) and IV buscopan (B, patients 9-16). 4=excellent image quality, 3=satisfactory image quality and 2=poor image quality

For patients who received IM buscopan, the percentage of images with no bowel motion artefact with/without buscopan was 24.6% versus 8.9%. For patients who received IV buscopan, the percentage of images of excellent quality with/without buscopan was 25.8% versus 7%. A summary of bowel motion artefact and the proportion of images corresponding to each point on the scale is shown in **Table 4.2**. The proportion of scores per patient is illustrated in **Figure 4.4**. Individual patient data is shown in **Supplementary Table 4.3**.

Table 4.2 Summary of bowel motion artefact scores and proportion of individual scores by receipt of buscopan

<i>Image type</i>	<i>Number of patients</i>	<i>Number of images</i>	<i>Median bowel motion artefact scale score* (IQR)</i>	<i>Absolute number of images with score of 0 (%)</i>	<i>Absolute number of images with score of 1 (%)</i>	<i>Absolute number of images with score of 2 (%)</i>	<i>Absolute number of images with score of 3 (%)</i>
Images with IM buscopan	8	65	1.0 (0.8-1.5)	16 (24.6%)	27 (41.5%)	13 (20%)	9 (13.8%)
Images without IM buscopan	8	45	2.0 (1.0-2.6)	4 (8.9%)	15 (33.3%)	11 (24.4%)	15 (33.3%)
Images with IV buscopan	8	62	1.0 (0.8-2.3)	16 (25.8%)	22 (35.5%)	8 (12.9%)	16 (25.8%)
Images without IV buscopan	8	43	2.3 (1.0-3.0)	3 (7%)	16 (37.2%)	5 (11.6%)	19 (44.2%)
All images with buscopan	16	127	1.0 (0.8-2.3)	32 (25.2%)	50 (39.4%)	21 (16.5%)	25 (19.7%)
All images without buscopan	16	88	2.0 (1.0-3.0)	7 (8%)	31 (35.2%)	16 (18.2%)	34 (38.6%)

*0=no bowel motion artefact, 1=mild bowel motion artefact, 2=moderate bowel motion artefact, 3=severe bowel motion artefact

IM, intramuscular; IQR, inter-quartile range; IV, intravenous

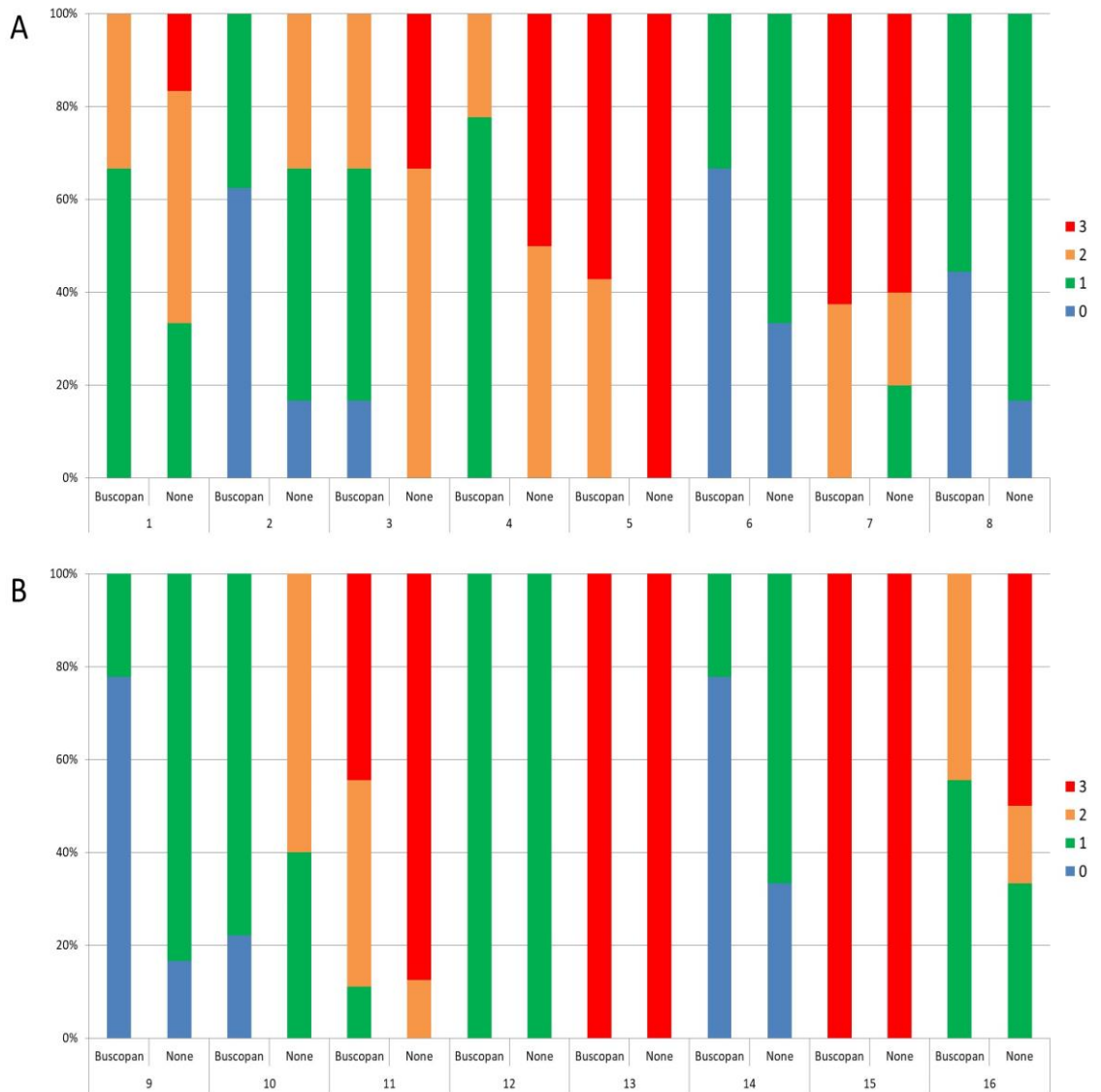


Figure 4.4 Proportions of bowel motion artefact scores per patient. In Figures 4.4A-B, bowel motion artefact scores are shown with/without buscopan for each patient treated with IM buscopan (A, patients 1-8) and IV buscopan (B, patients 9-16). 0=no artefact, 1=mild artefact, 2=moderate artefact and 3=severe artefact.

Summaries of image quality by timing of CBCT and for pelvic versus abdominal and soft tissue versus bone lesions are shown in **Supplementary Tables 4.4-4.6**.

Median time (IQR) from injection to baseline, pre-treatment and post-treatment imaging was 10 minutes (7-11) and 7 minutes (5-8), 14 minutes (13-17) and 12 minutes (11-15) and 21 minutes (17-26) and 20 minutes (17-26) for IM and IV buscopan respectively.

4.4.3 Secondary endpoints

A summary of patient questionnaire data for 15 patients is shown in **Table 4.3**. Questionnaire data was not available for the patient who did not complete SABR as planned. Fourteen patients (93%) who completed questionnaires would accept buscopan prior to routine SABR treatment.

A summary of radiographer questionnaire data for 12 radiographers is shown in **Table 4.4**. Questionnaires were offered to 16 radiographers and 12 accepted. Eleven radiographers (92%) reported no delay in patients' treatments as a result of buscopan.

4.4.4 Toxicity

A summary of acute toxicities is shown in **Table 4.5**. No \geq grade 3 toxicities were observed.

Table 4.3 Summary of end of treatment patient questionnaire data

Question	Buscopan route of administration	Median score** (IQR)	Absolute number of patients indicating a score of 1 (%)	Absolute number of patients indicating a score of 2 (%)	Absolute number of patients indicating a score of 3 (%)	Absolute number of patients indicating a score of 4 (%)
I understood why the injection was being given	All patients (n=15)	4.0 (4.0-4.0)				15 (100.0%)
	IM buscopan (n=8)	4.0 (4.0-4.0)				8 (100.0%)
	IV buscopan (n=7)*	4.0 (4.0-4.0)				7 (100.0%)
Before it was given, I was anxious about having the injection	All patients	1.0 (1.0-2.0)	9 (60.0%)	4 (26.7%)	1 (6.7%)	1 (6.7%)
	IM buscopan	1.5 (1.0-2.3)	4 (50.0%)	2 (25.0%)	1 (12.5%)	1 (12.5%)
	IV buscopan	1.0 (1-1.5)	5 (71.4%)	6 (85.7%)		
I found having the injection frightening	All patients	1.0 (1.0-1.0)	14 (93.3%)			1 (6.7%)
	IM buscopan	1.0 (1.0-1.0)	7 (87.5%)			1 (12.5%)
	IV buscopan	1.0 (1.0-1.0)	7 (100.0%)			
I found the injection painful	All patients	1.0 (1.0-2.0)	9 (60.0%)	5 (33.3%)		1 (6.7%)
	IM buscopan	1.0 (1.0-2.0)	5 (62.5%)	2 (25.0%)		1 (12.5%)

	IV buscopan	1.0 (1.0-2.0)	4 (57.1%)	3 (42.9%)		
I found the injection delayed my treatment	All patients	1.0 (1.0-1.0)	12 (80.0%)	2 (13.3%)		1 (6.7%)
	IM buscopan	1.0 (1.0-1.0)	7 (87.5%)			1 (12.5%)
	IV buscopan	1.0 (1.0-1.5)	5 (71.4%)	2 (28.6%)		
I found the injection gave me side effects	All patients	1.0 (1.0-2.0)	10 (66.7%)	4 (26.7%)		1 (6.7%)
	IM buscopan	1.0 (1.0-2.0)	5 (62.5%)	2 (25.0%)		1 (12.5%)
	IV buscopan	1.0 (1.0-1.5)	5 (71.4%)	2 (28.6%)		
If I needed treatment again, I would be prepared to have the injection before each fraction	All patients	4.0 (4.0-4.0)			1 (6.7%)	14 (93.3%)
	IM buscopan	4.0 (4.0-4.0)			1 (12.5%)	7 (87.5%)
	IV buscopan	4.0 (4.0-4.0)				7 (100.0%)

*0=no bowel motion artefact, 1=mild bowel motion artefact, 2=moderate bowel motion artefact, 3=severe bowel motion artefact

IM, intramuscular; IQR, inter-quartile range; IV, intravenous

Table 4.4 Summary of end of treatment radiographer questionnaire data

<i>Question</i>	<i>Buscopan route of administration</i>	<i>Median score** (IQR)</i>	<i>Absolute number of radiographers indicating a score of 1 (%)</i>	<i>Absolute number of radiographers indicating a score of 2 (%)</i>	<i>Absolute number of radiographers indicating a score of 3 (%)</i>	<i>Absolute number of radiographers indicating a score of 4 (%)</i>
I understood why buscopan was being given	All patients (n=12) *	3.3 (3.0-4.0)			6 (50.0%)	6 (50.0%)
	IM buscopan (n=6)	3.8 (3.1-4.0)			3 (50.0%)	4 (66.7%)
	IV buscopan (n=6)	3.0 (3.0-3.8)			3 (50.0%)	2 (33.3%)
I had to wait for someone to attend to administer buscopan	All patients	1.0 (1.0-2.1)	8 (66.7%)	1 (8.3%)	2 (16.7%)	1 (8.3%)
	IM buscopan	1.0 (1.0-1.0)	5 (83.3%)		1 (16.7%)	
	IV buscopan	1.5 (1.0-2.8)	3 (50.0%)	1 (16.7%)	1 (16.7%)	1 (16.7%)
Administration of buscopan delayed the patient's treatment	All patients	1.0 (1.0-1.0)	11 (91.7%)		1 (8.3%)	
	IM buscopan	1.0 (1.0-1.0)	6 (100.0%)			
	IV buscopan	1.0 (1.0-1.0)	5 (83.3%)		1 (16.7%)	
Administration of buscopan appeared	All patients	1.0 (1.0-1.0)	12 (100.0%)			

to be painful for the patient	IM buscopan	1.0 (1.0-1.0)	6 (100.0%)			
	IV buscopan	1.0 (1.0-1.0)	6 (100.0%)			
Buscopan appeared to give the patient side effects	All patients	1.0 (1.0-1.0)	12 (100.0%)			
	IM buscopan	1.0 (1.0-1.0)	6 (100.0%)			
	IV buscopan	1.0 (1.0-1.0)	6 (100.0%)			
I thought that image quality was better when buscopan was given	All patients	2.3 (2.0-3.0)	1 (8.3%)	5 (41.7%)	4 (33.3%)	1 (8.3%)
	IM buscopan	2.3 (2.0-2.9)		3 (50.0%)	2 (33.3%)	
	IV buscopan	2.5 (2.0-3.0)	1 (16.7%)	2 (33.3%)	1 (16.7%)	1 (16.7%)
I would be prepared for buscopan to be given routinely for abdominal/pelvic SABR treatments	All patients	4.0 (3.0-4.0)			5 (41.7%)	7 58.3%
	IM buscopan	3.5 (3.0-4.0)			3 (50.0%)	3 (50.0%)
	IV buscopan	4.0 (3.3-4.0)			2 (33.3%)	4 (66.7%)

*Radiographer questionnaire data not available for four patients, **1='not at all', 2='somewhat', 3='moderately', 4='very much so'

SABR, stereotactic ablative radiotherapy

Table 4.5 Summary of acute toxicity data

<i>Acute toxicity</i>	<i>CTCAE grade*</i>	<i>Total number of patients (% of 16)**</i>	<i>Number of patients treated with IM buscopan (% of 8)</i>	<i>Number of patients treated with IV buscopan (% of 8)</i>
None		6 (37.5%)	4 (50.0%)	2 (25.0%)
Dry mouth	1	3 (18.8%)	1 (12.5%)	2 (25.0%)
	2	1 (6.3%)	1 (12.5%)	
Injection site discomfort/bruising	1	2 (12.5%)	1 (12.5%)	1 (12.5%)
Cannula removal discomfort	1	1 (6.3%)		1 (12.5%)
Abdominal pain	1	1 (6.3%)		1 (12.5%)
Diarrhoea	1	4 (25.0%)	2 (25.0%)	2 (25.0%)

*Toxicity graded as per Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0

**Total exceeds 100% since some patients reported more than one toxicity

CTCAE, Common Toxicity Criteria for Adverse Events; IM, intramuscular; IV, intravenous

4.5 Discussion

This is the first study to evaluate the impact of anti-peristaltic agents in radiotherapy/on CBCT image quality. We observed a trend to improved overall image quality when buscopan was given. The percentage difference in image quality without buscopan between the IM and IV cohorts demonstrates considerable inter-patient variation, possibly as a result of individual bowel appearance/motion and this validates the approach of using patients as their own control. There was also a trend to reduced bowel motion artefacts with buscopan. Since the study was not powered to detect a statistically significant improvement in image quality, these findings should be considered as a signal of the anti-peristaltic effect of buscopan.

The administration of buscopan appeared to be feasible. In general, IM and IV buscopan was well tolerated by patients as evidenced by toxicity assessment/questionnaire responses. Dry mouth and injection site discomfort were related to buscopan, with abdominal discomfort/diarrhoea more likely due to SABR. Previous prospective/randomised studies of buscopan during abdominal/pelvic MRI differ in the toxicities reported. Some reported blurred vision in up to 20% of participants, with dry mouth (63%), warmth (20%), dizziness (11%) and palpitations (6%) also described in a study by Johnson et al[18-21]. Rate of administration of IV buscopan was not described in Johnson et al, but it is possible that administration over 1 minute minimised toxicity in our IV cohort[22]. Other studies reported no toxicity, although Johnson et al used patient questionnaires to assess toxicity[20, 23-26]. Radiographer questionnaire responses suggested that buscopan did not negatively impact on workflow. This is despite no specific slot for cannulation/administration of buscopan having been booked for patients, which would likely aid patient flow in routine practice.

Several previous prospective and two randomised radiology studies have evaluated the impact of buscopan on image quality for MRI of the abdomen and pelvis[21, 23-29]. Heterogeneity exists between these studies for the route of buscopan administration, the method of image analysis (qualitative Likert-type scales versus measurement of image noise) and whether bowel is evaluated or another organ/lesion. Nevertheless, in prospective studies administration of IM/IV buscopan was associated with significantly improved image quality, reduced bowel motion artefacts and improved organ/lesion identification[21, 25-29]. In two randomised studies (which quantified image noise with/without buscopan), a significant reduction in bowel artefact noise was observed when buscopan was administered[23, 24].

The magnitude of improvement in image quality in our study was modest. However, accepting differences in measurement between studies the improvements we observed are comparable to the differences in overall image quality/bowel motion artefact of approximately 0.5-1.0 on five-point scales reported in prospective studies of buscopan in MRI abdomen/pelvis[21, 26, 27]. In contrast to radiology where the clarity of lesion visualisation may be of critical diagnostic importance, the clinical benefits of the improvements in image quality/reduced bowel motion artefacts on CBCT that we observed are less easy to define. The percentage of images scored as poor for overall quality with buscopan was almost half that without. However, all of the patients in the study proceeded with treatment regardless of the quality of their images and no image was scored as impossible to use, which suggests that for CBCT-guided SABR poor quality may be good enough. The published MRI data, combined with the feasibility that we demonstrated of delivering buscopan within a SABR workflow, suggest that a useful application of buscopan could be for MR linac-delivered SABR. A concern with the delivery of ablative doses in the abdomen and pelvis is the risk of toxicity, especially concerning bowel. The greater soft tissue visualisation afforded by MRI compared with CBCT and online re-optimisation may provide the opportunity to adapt the delivered dose based on the daily position of adjacent OARs such as bowel[30, 31]. This approach would require confidence in clearly delineating both the target and OARs. Buscopan could therefore be an important adjunct to improve the quality of images for bowel delineation, for which deformable image registration/autocontouring strategies remain under investigation[32]. Ease of target/bowel visualisation, time taken for delineation and the extent/dosimetric consequences of intra-fraction bowel motion with/without buscopan could be endpoints measured within a future trial.

Although our study was not designed to compare IM and IV buscopan, we observed similar image quality scores by both administration routes, with slightly improved summary data for IV buscopan. We did not observe any trends in image quality based on the timing of CBCT. Limited data exist concerning the onset and duration of anti-peristaltic effects by different routes of administration, but they approximately support action of buscopan within our time window between first and last CBCT. Previous studies of buscopan in small bowel cine MRI reported approximate onset of action of IV buscopan and IM buscopan of <90 seconds and 5 minutes respectively[19, 33]. Mean duration of action was reported to be 21-23 minutes and approximately 18 minutes for IV and IM buscopan respectively. Large variations between participants in the onset, extent and duration of response were observed in these small studies, especially concerning IM buscopan. It was speculated that this could be due to slower/less reliable absorption of drug via the IM route[33]. However, other

studies that evaluated the impact of buscopan on image quality of abdominal MRI administered IM buscopan around 20 minutes prior to the examination with persisting anti-peristaltic effects[34, 35]. All of this means that, while the MRI data supports greater rapidity/reliability of anti-peristaltic effect with IV buscopan, it might still be possible to observe a benefit in reduction in CBCT bowel motion artefact with IM buscopan if cannulation/administration of IV buscopan is not practical.

A further consideration concerns the location of the treated lesion. In this study, 39% of images without buscopan were scored as containing severe bowel motion artefacts, although only 14% of images were considered to be of overall poor quality. This discrepancy may be related to the scoring process we used, where overall image quality was assessed in the context of the ability to match to the target. Fifty per cent of lesions occurred in bone, where the automatic registration between planning CT and CBCT typically works well[36]. These patients were included where bowel was close to the lesion but it meant that an image could be scored as being of overall satisfactory quality despite the presence of severe bowel motion artefact, and therefore buscopan may have less impact on matching for bone lesions. We also observed inferior image quality with/without buscopan for abdominal lesions compared with pelvic lesions (median bowel motion artefact score 3 versus 1), which is likely secondary to the influence of respiratory motion. Few upper abdominal soft tissue lesions were treated during the study period but, for these, the application of motion management strategies such as breath hold/respiratory gating in combination with buscopan could be investigated[37, 38].

This study has several limitations. The number of patients was small and there was no statistical comparison of image quality with/without buscopan. Our methods of image assessment were inherently subjective and our use of a consensus score meant that the results could have been over-influenced by one of the scorers. However, we used example images for training and similar Likert scales were used in many of the prospective radiology studies of buscopan in MRI abdomen/pelvis. An alternative approach of quantitative assessment of image noise may be influenced by patient motion/variations in acquisition of regions of interest for measurement[20, 21, 23, 25-27, 29]. Other factors, such as soft tissue contrast, may influence CBCT image quality but we did not attempt to incorporate this into our qualitative image assessment[39]. Other methods of improving CBCT image quality by reduction of image noise and motion artefacts exist, such as dual-energy CT, anti-scatter grids, beam filters and reconstruction algorithms⁴⁰⁻⁴¹. However, CBCT systems with advanced capabilities may not yet be widely implemented in radiotherapy

departments, meaning that there remains a value in investigating the impact of anti-peristaltic agents on bowel motion artefacts. Some data was missing, which may have influenced our conclusions regarding the feasibility of IM/IV buscopan; toxicity assessment/patient questionnaires from one patient who did not complete SABR and radiographer questionnaires from four patients.

4.6 Conclusion

A trend to improved image quality was observed with buscopan and its use in a SABR workflow appears to be feasible. The clinical benefits of buscopan should be investigated and might be best evaluated as part of an MR-guided adaptive SABR workflow.

4.7 Acknowledgements

The trial design received input from the Clinical and Translational Radiotherapy Research Working Group (CTRad) Proposals Guidance Meeting in July 2018 and Leeds Radiotherapy Patient and Public Involvement Group. The patient/radiographer questionnaire design received input from Helen McNair (Lead Research Radiographer, The Royal Marsden Hospital, London). The authors would like to acknowledge Katherine O'Mahoney and Sharon Fernandez for their assistance with image analysis.

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4.9 Supplementary Material

4.9.1 Supplementary Tables

Supplementary Table 4.1 Patient characteristics

<i>Patient number</i>	<i>Patient age</i>	<i>Primary disease</i>	<i>Location of lesion treated by SABR</i>	<i>SABR total dose (Gy)</i>	<i>Number of SABR fractions</i>	<i>Comments including non-bowel sources of artefact</i>
1	81	Colon cancer	Mesenteric nodule (level of aortic bifurcation)	30	5	
2	70	Prostate cancer	Right external iliac lymph node	30	5	
3	66	Prostate cancer	Left 11th rib metastasis	30	3	
4	77	Prostate cancer	Left iliac blade metastasis	30	5	Abdominal aortic aneurysm (EVAR) Bilateral total hip replacements
5	73	Prostate cancer	L1 vertebral metastasis	24	3	
6	43	Breast cancer	Left sacral metastasis	30	5	
7	76	Breast cancer	L3 vertebral metastasis	24	3	

8	69	Colon cancer	Mesenteric nodule (level of iliac vessels)	30	5	
9	75	Prostate cancer	Right inferior pubic ramus metastasis	30	5	
10	62	Prostate cancer	Left external iliac lymph node	30	5	
11	68	Renal cancer	Tail of pancreas metastasis	30	5	Severe respiratory motion artefact
12	54	Rectal neuroendocrine tumour	Left internal iliac lymph node	30	3	
13	67	Medullary thyroid cancer	L2 vertebral metastasis	24	3	SABR stopped early after vertebral collapse
14	55	Breast cancer	Right acetabular metastasis	30	5	
15	63	Ureteric cancer	Left renal bed metastasis	30	5	

16	75	Prostate cancer	Left external iliac lymph node	30	5	Right total hip replacement

EVAR, endovascular aneurysm repair; PTV, planning target volume; SABR, stereotactic ablative radiotherapy

Supplementary Table 4.2 Summary of individual patient data for Likert scores

<i>Patient number</i>	<i>Buscopan route</i>	<i>Total number of images</i>	<i>Number of images with buscopan</i>	<i>Number of images without buscopan</i>	<i>Median Likert score* for images with buscopan (IQR)</i>	<i>Median Likert score* for images without buscopan (IQR)</i>	<i>Number of images with score of 4 with buscopan</i>	<i>Number of images with score of 4 without buscopan</i>	<i>Number of images with score of 3 with buscopan</i>	<i>Number of images with score of 3 without buscopan</i>	<i>Number of images with score of 2 with buscopan</i>	<i>Number of images with score of 2 without buscopan</i>	<i>Number of images with score of 1 with buscopan</i>	<i>Number of images with score of 1 without buscopan</i>
1	IM	15	9	6	3.0 (3.0-3.0)	3.0 (2.3-3.0)	0	0	8	4	1	2	0	0
2	IM	14	8	6	3.0 (3.0-4.0)	3.0 (3.0-3.8)	3	2	4	3	0	1	0	0
3	IM	9	6	3	3.0 (3.0-3.0)	3.0 (3.0-3.0)	0	0	6	3	0	0	0	0
4	IM	15	9	6	4.0 (4.0-4.0)	3.0 (3.0-3.0)	8	0	1	6	0	0	0	0
5	IM	14	7	7	3.0 (3.0-3.0)	3.0 (3.0-	0	0	7	7	0	0	0	0

						3.0)								
6	IM	15	9	6	4.0 (4.0- 4.0)	4.0 (4.0- 4.0)	9	5	0	1	0	0	0	0
7	IM	13	8	5	3.0 (3.0- 3.0)	3.0 (3.0- 3.0)	0	0	8	5	0	0	0	0
8	IM	15	9	6	4.0 (4.0- 4.0)	4.0 (4.0- 4.0)	9	6	0	0	0	0	0	0
9	IV	15	9	6	4.0 (4.0- 4.0)	4.0 (3.3- 4.0)	9	4	0	2	0	0	0	0
10	IV	14	9	5	4.0 (4.0- 4.0)	3.0 (3.0- 3.0)	8	0	1	5	0	0	0	0
11	IV	17	9	8	3.0 (2.0- 3.0)	2.0 (2.0- 2.0)	0	0	5	1	4	7	0	0
12	IV	9	6	3	4.0 (4.0- 4.0)	4.0 (4.0- 4.0)	6	3	0	0	0	0	0	0
13	IV	7	3	4	3.0	3.0	0	0	3	4	0	0	0	0

					(3.0-3.0)	(3.0-3.0)								
14	IV	15	9	6	4.0 (4.0-4.0)	4.0 (4.0-4.0)	9	6	0	0	0	0	0	0
15	IV	14	9	5	3.0 (2.0-3.0)	3.0 (2.0-3.0)	0	0	5	3	4	2	0	0
16	IV	15	9	6	4.0 (4.0-4.0)	4.0 (3.3-4.0)	9	4	0	2	0	0	0	0

IM, intramuscular; IQR, inter-quartile range; IV, intravenous

*4=excellent quality, 3=satisfactory, 2=poor, 1=impossible to use

Supplementary Table 4.3 Summary of individual patient data for bowel motion artefact scores

<i>Patient number</i>	<i>Buscopan route of administration</i>	<i>Total number of images</i>	<i>Number of images with buscopan</i>	<i>Number of images without buscopan</i>	<i>Median bowel motion artefact score* for images with buscopan (IQR)</i>	<i>Median bowel motion artefact score* for images without buscopan (IQR)</i>	<i>Number of images with no artefact with buscopan</i>	<i>Number of images with no artefact without buscopan</i>	<i>Number of images with mild artefact with buscopan</i>	<i>Number of images with mild artefact without buscopan</i>	<i>Number of images with moderate artefact with buscopan</i>	<i>Number of images with moderate artefact without buscopan</i>	<i>Number of images with severe artefact with buscopan</i>	<i>Number of images with severe artefact without buscopan</i>
1	IM	15	9	6	1.0 (1.0-2.0)	2.0 (1.3-2.0)	0	0	6	2	3	3	1	1
2	IM	14	8	6	0 (0-1.0)	1.0 (1.0-1.8)	5	1	3	3	0	2	0	0
3	IM	9	6	3	1.0 (1.0-1.8)	2.0 (2.0-2.5)	0	0	1	0	3	2	2	1
4	IM	15	9	6	1.0 (1.0-1.0)	2.5 (2.0-	0	0	7	0	2	3	0	3

						3.0)									
5	IM	14	7	7	3.0 (2.0- 3.0)	3.0 (3.0- 3.0)	0	0	0	0	3	0	4	7	
6	IM	15	9	6	0 (0- 1.0)	1.0 (0.3- 1.0)	6	2	3	4	0	0	0	0	
7	IM	13	8	5	3.0 (2.0- 3.0)	3.0 (2.0- 3.0)	0	0	0	1	3	1	5	3	
8	IM	15	9	6	1.0 (0- 1.0)	1.0 (0- 1.0)	4	1	5	5	0	0	0	0	
9	IV	15	9	6	0 (0-0)	1.0 (1.0- 1.0)	7	1	2	5	0	0	0	0	
10	IV	14	9	5	1.0 (1.0- 1.0)	2.0 (1.0- 2.0)	2	0	7	2	0	3	0	0	
11	IV	17	9	8	2.0 (2.0- 3.0)	3.0 (3.0- 3.0)	0	0	1	0	4	1	4	7	
12	IV	9	6	3	1.0 (1.0-	1.0 (1.0-	0	0	6	3	0	0	0	0	

					1.0)	1.0)								
13	IV	7	3	4	3.0 (3.0- 3.0)	3.0 (3.0- 3.0)	0	0	0	0	0	0	3	4
14	IV	15	9	6	0 (0-0)	1.0 (0.3- 1.0)	7	2	2	4	0	0	0	0
15	IV	14	9	5	3.0 (3.0- 3.0)	3.0 (3.0- 3.0)	0	0	0	0	0	0	9	5
16	IV	15	9	6	1.0 (1.0- 2.0)	2.5 (1.3- 3.0)	0	0	5	2	4	1	0	3

IM, intramuscular; IQR, inter-quartile range; IV, intravenous

*0=none, 1=mild, 2=moderate, 3=severe

Supplementary Table 4.4 Summary of Likert scores and bowel motion artefact scores grouped by timing of imaging (baseline, pre-treatment and post-treatment)

<i>Image type</i>	<i>Median Likert scale score* for baseline images (IQR)</i>	<i>Median Likert scale score* for pre-treatment images (IQR)</i>	<i>Median Likert scale score* for post-treatment images (IQR)</i>	<i>Median bowel motion artefact scale score** for baseline images (IQR)</i>	<i>Median bowel motion artefact scale score** for pre-treatment images (IQR)</i>	<i>Median bowel motion artefact scale score** for post-treatment images (IQR)</i>
All images with buscopan	3.8 (3.0-4.0)	3.5 (3.0-4.0)	3.8 (3.0-4.0)	1.0 (0.8-2.3)	1.0 (0.8-2.0)	1.0 (1.0-2.3)
All images without buscopan	3.0 (3.0-4.0)	3.0 (3.0-4.0)	3.0 (3.0-3.5)	2.0 (1.0-2.6)	2.3 (1.0-3.0)	2.0 (1.0-2.6)
Images with IM buscopan	3.3 (3.0-4.0)	3.0 (3.0-4.0)	3.3 (3.0-4.0)	1.3 (0.8-2.3)	1.0 (0.8-1.3)	1.0 (1.0-1.3)
Images without IM buscopan	3.0 (3.0-3.3)	3.0 (3.0-3.3)	3.0 (3.0-3.1)	1.8 (1.0-2.5)	2.3 (1.3-3.0)	1.5 (1.0-2.1)
Images with IV buscopan	4.0 (3.0-4.0)	4.0 (3.0-4.0)	4.0 (2.8-4.0)	1.0 (0.8-2.3)	1.0 (0.8-2.3)	1.5 (0.8-3.0)
Images without IV buscopan	3.3 (3.0-4.0)	3.3 (2.9-4.0)	3.3 (2.8-3.6)	2.0 (1.0-3.0)	1.8 (1.0-3.0)	2.0 (1.0-3.0)

IM, intramuscular; IQR, inter-quartile range; IV, intravenous

*4=excellent quality, 3=satisfactory, 2=poor, 1=impossible to use, **0=none, 1=mild, 2=moderate, 3=severe

Supplementary Table 4.5 Summary of Likert scores and bowel motion artefact scores grouped by location of treated lesion (pelvis or abdomen)

<i>Image type</i>	<i>Median Likert scale score* for pelvic lesions (IQR)</i>	<i>Median Likert scale score* for abdominal lesions (IQR)</i>	<i>Median bowel motion artefact scale score** for pelvic lesions (IQR)</i>	<i>Median bowel motion artefact scale score** for abdominal lesions (IQR)</i>
All images with buscopan	4.0 (4.0-4.0)	3.0 (3.0-3.0)	1.0 (0-1.0)	3.0 (2.3-3.0)
All images without buscopan	4.0 (3.0-4.0)	3.0 (3.0-3.0)	1.0 (1.0-2.0)	3.0 (3.0-3.0)
Images with IM buscopan	4.0 (3.0-4.0)	3.0 (3.0-3.0)	1.0 (0-1.0)	3.0 (2.0-3.0)
Images without IM buscopan	3.0 (3.0-4.0)	3.0 (3.0-3.0)	1.0 (1.0-2.0)	3.0 (2.5-3.0)
Images with IV buscopan	4.0 (4.0-4.0)	3.0 (3.0-3.0)	1.0 (0-1.0)	3.0 (2.5-3.0)
Images without IV buscopan	4.0 (4.0-4.0)	3.0 (2.5-3.0)	1.0 (1.0-2.0)	3.0 (3.0-3.0)

IM, intramuscular; IQR, inter-quartile range; IV, intravenous

*4=excellent quality, 3=satisfactory, 2=poor, 1=impossible to use

**0=none, 1=mild, 2=moderate, 3=severe

Supplementary Table 4.6 Summary of Likert scores and bowel motion artefact scores grouped by type of treated lesion (soft tissue or bone)

<i>Image type</i>	<i>Median Likert scale score* for soft tissue lesions (IQR)</i>	<i>Median Likert scale score* for bone lesions (IQR)</i>	<i>Median bowel motion artefact scale score** for soft tissue lesions (IQR)</i>	<i>Median bowel motion artefact scale score** for bone lesions (IQR)</i>
All images with buscopan	3.5 (3.0-4.0)	3.5 (3.0-4.0)	1.0 (1.0-1.3)	1.0 (0-3.0)
All images without buscopan	3.0 (3.0-4.0)	3.0 (3.0-4.0)	2.0 (1.0-2.6)	2.3 (1.0-3.0)
Images with IM buscopan	3.0 (3.0-3.5)	3.0 (3.0-4.0)	1.0 (0.5-1.0)	1.0 (1.0-3.0)
Images without IM buscopan	3.0 (3.0-3.5)	3.0 (3.0-3.0)	1.0 (1.0-1.5)	2.5 (2.0-3.0)
Images with IV buscopan	4.0 (4.0-4.0)	4.0 (3.5-4.0)	1.0 (1.0-2.0)	0 (0-1.5)
Images without IV buscopan	3.0 (3.0-4.0)	4.0 (3.5-4.0)	2.5 (2.0-3.0)	1.0 (1.0-2.0)

IM, intramuscular; IQR, inter-quartile range; IV, intravenous

*4=excellent quality, 3=satisfactory, 2=poor, 1=impossible to use

**0=none, 1=mild, 2=moderate, 3=severe

Chapter 5 An international Delphi consensus for pelvic Stereotactic Ablative Radiotherapy re-irradiation

5.1 Abstract

5.1.1 Introduction

Stereotactic Ablative Radiotherapy (SABR) is increasingly used to treat oligometastatic disease and locoregional recurrences but limited evidence/guidance exists in the setting of pelvic re-irradiation. An international Delphi study was performed to develop statements to guide practice regarding patient selection, pre-treatment investigations, treatment planning, delivery and cumulative organs at risk (OARs) constraints.

5.1.2 Materials and Methods

Forty-one radiation oncologists were invited to participate in three online surveys. In Round 1, information and opinion was sought regarding participants' practice. Guidance statements were developed using this information and in Round 2 participants were asked to indicate their level of agreement with each statement. Consensus was defined as $\geq 75\%$ agreement. In Round 3, any statements without consensus were re-presented unmodified, alongside a summary of comments from Round 2.

5.1.3 Results

Twenty-three radiation oncologists participated in Round 1 and, of these, 21 (91%) and 22 (96%) completed Rounds 2 and 3 respectively. Twenty-nine of 44 statements (66%) achieved consensus in Round 2. The remaining 15 statements (34%) did not achieve further consensus in Round 3. Consensus was achieved for the majority of statements concerning patient selection and treatment planning and delivery. Lack of agreement remained regarding the minimum time interval between irradiation courses, the number/size of pelvic lesions that can be treated and the most appropriate cumulative OAR constraints.

5.1.4 Conclusions

This study has established consensus recommendations regarding patient selection, pre-treatment investigations, treatment planning and delivery for

pelvic SABR re-irradiation. Further research into this technique is required, especially regarding aspects of practice where consensus was not achieved.

5.2 Introduction

Radiotherapy is frequently used in the management of pelvic malignancies. A recurrence after primary treatment within/at the edge of a previously irradiated volume presents a potential challenge as to the optimum therapeutic approach. Decision-making depends on factors relating to the patient, primary disease, previously delivered treatment and the recurrent lesion[1, 2]. Surgery may be morbid and challenging due to post-radiation fibrosis[2-4]. Systemic anti-cancer therapies are non-curative and may provide limited symptomatic relief for localised recurrences. Re-irradiation to organs at risk (OARs) may increase or cause unexpected toxicity[2, 5].

Stereotactic Ablative Radiotherapy (SABR), also called Stereotactic Body Radiotherapy (SBRT), is increasingly used to treat limited sites of metastatic relapse after primary treatment (so-called oligorecurrence) and locoregional recurrences[2, 6, 7]. The use of SABR to maximise dose to the target and/or minimise dose to surrounding OARs could have a therapeutic advantage especially in the setting of re-irradiation. However, no high level evidence exists concerning this approach, with little formal guidance. Uncertainties remain regarding several aspects of the treatment pathway, including patient selection, planning and treatment delivery techniques and cumulative OAR constraints[2, 8, 9].

To determine current international practice, highlight areas of agreement and identify aspects of uncertainty which require further research, a Delphi study was undertaken. The purpose was to develop consensus statements to guide the practice of pelvic SABR re-irradiation. The Delphi was restricted to SABR re-irradiation, since the intention was to develop specific statements which would provide a framework for SABR re-irradiation implementation by centres not currently delivering this and support its development by those already using it.

5.3 Materials and Methods

5.3.1 Organising group

The study was led by Finbar Slevin, John Lilley, Peter Dickinson, Maria A Hawkins, Ann M Henry and Louise J Murray, all of whom have clinical experience of pelvic SABR re-irradiation in the UK. The study protocol, invitation letter and participant information sheet is in **Appendix C**.

5.3.2 Participants

Radiation/clinical oncologists who had published articles about pelvic SABR re-irradiation, or who were considered by the organisers to be international experts in the field, were approached by e-mail. If unable to participate, they were asked to nominate another appropriate individual. Only one oncologist from any research group was included. Forty-one invitations were made for the first round and participants who completed this were invited to complete subsequent rounds. All participants consented to participate prior to each round.

5.3.3 Questionnaires

A modified Delphi technique employing online questionnaires was used as a structured, transparent and iterative approach to obtain anonymous feedback and to allow participants to reassess their own judgements based on the feedback provided[10, 11]. A web-based survey platform was used (Online surveys, Jisc, Bristol, UK). The organisers were blinded to participant responses and did not complete any questionnaires. Three rounds took place.

Round 1 used mainly open-ended questions to gather information regarding participants' practice. A copy of the Round 1 questionnaire is shown in **Appendix D**. Data were reviewed to identify themes and assemble statements to guide practice including: definition of pelvic SABR re-irradiation, patient selection, pre-treatment investigations, target volume/OAR delineation, treatment planning and delivery and cumulative OAR constraints.

In Round 2, statements were presented alongside summary data from Round 1. A copy of the Round 2 questionnaire is shown in **Appendix E**. Participants were asked to indicate their level of agreement with each statement using a 5-point Likert scale (strongly agree, agree, neither agree/disagree, disagree, strongly disagree). Where participants did not agree/strongly agree, they were asked to provide an explanation in an accompanying free text box. Consensus was defined *a priori* where $\geq 75\%$ of participants indicated that they either agreed/strongly agreed with the statement[11]. For cumulative OAR constraints,

a table was provided which summarised published constraints (approaches include either relatively large cumulative maximum constraints or the subtraction of previously delivered dose from a traditional constraint with/without allowance for recovery), alongside participant information provided in Round 1[12-15].

In Round 3, statements without consensus in Round 2 were re-presented unmodified alongside the level of agreement of the whole group and a summary of free text comments from Round 2. A copy of the Round 3 questionnaire is shown in **Appendix F**. Participants were asked to indicate their level of agreement for these re-presented statements, taking into account Round 2 results. Statements with <75% agreement after Round 3 were considered not to have achieved consensus.

5.4 Results

Twenty-three radiation oncologists (56% of 41 initial invitations) participated in Round 1. Of these, 21 (91% of 23 Round 1 participants) and 22 (96%) participated in Rounds 2 and 3 respectively. Countries represented were: Canada (2 participants), France (1), Italy (6), South Korea (1), Switzerland (2), UK (4) and USA (5). Sub-specialty interests were: genitourinary (19, 83%), lower gastrointestinal (11, 48%) and gynaecological (8, 35%). Some experts practice in >1 sub-specialty.

Round 1 opened 27/10/2020 and Round 3 closed 22/03/2021. A study schema is shown in **Figure 5.1**. After Round 1, 44 practice statements were produced. In Round 2, 29 of these achieved consensus and 15 statements without consensus were re-presented in Round 3. Of these, none achieved consensus in Round 3. Final lists of statements with and without consensus are shown in **Supplementary Material, sections 5.9.1** and **5.9.2** respectively.

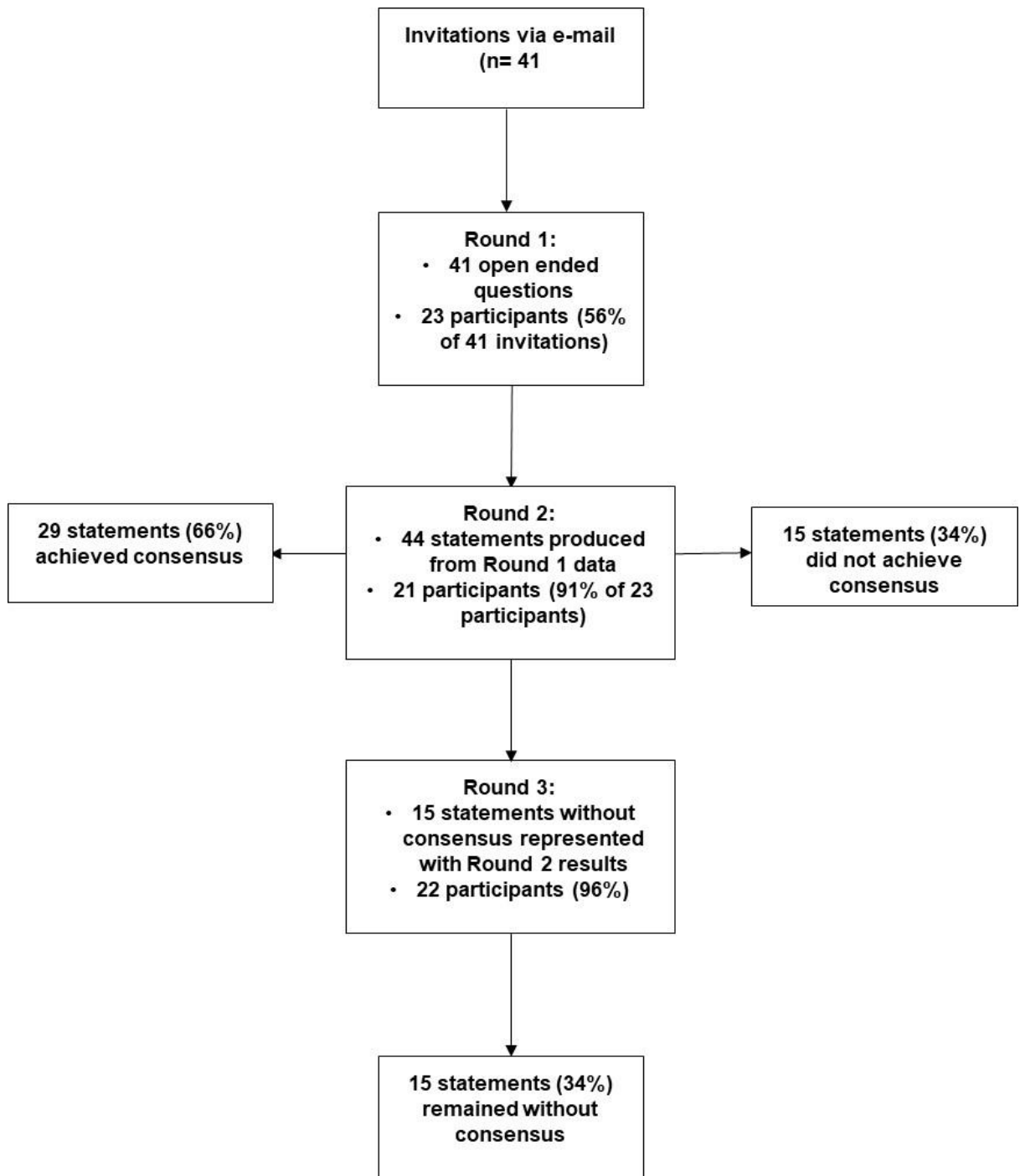


Figure 5.1 Study schema.

5.4.1 Definition of pelvic SABR re-irradiation, patient selection and pre-treatment investigations

Statements in this section and corresponding levels of agreement are shown in **Table 5.1**. After Round 3, absence of consensus remained for 7/17 statements. This included statements concerning number (statement 5) and size (statement 6) of lesions appropriate for treatment. Location of lesions/proximity to OARs was considered more relevant than number/size of lesions for 9 and 6 participants respectively. Despite this lack of agreement, statement 4 (which recommended that these each of these factors be considered as part of clinical decision making) did achieve consensus (86%). There was no consensus regarding a lesion in contact with a critical/luminal OAR (statement 8): despite 90% agreeing that SABR was inappropriate where there was direct invasion of such an OAR (statement 7), only 50% agreed it may not be appropriate where there was contact rather than invasion. In such a scenario, delivery of a lower total dose/compromise of PTV coverage and close intra/inter-fraction monitoring were alternative approaches suggested by 3 and 2 participants respectively. A number of related objections were made for statements 16 and 17, which described scenarios where non-SABR re-irradiation might be preferred, and which failed to achieve consensus.

No consensus was reached regarding a minimum time interval of 12 months from prior radiation (statement 9). Only 43% of participants agreed with this interval; comments included that previously delivered OAR doses (3 participants) and primary disease type (2 participants) were of greater importance or suggested alternative time intervals (3 participants). Regarding diagnostic imaging (statement 14), 19 participants (83%) agreed that positron emission tomography-computed tomography was recommended but, among those who disagreed, 3 (13%) considered that magnetic resonance imaging might be unnecessary for nodal staging.

Table 5.1 Consensus for statements regarding definition of SABR re-irradiation in the pelvis, patient selection and pre-treatment investigations. Statements which achieved consensus are highlighted in bold

<i>Statement</i>	<i>Number of participants</i>	<i>Round</i>	<i>Strongly agree</i>	<i>Agree</i>	<i>Neither agree/disagree</i>	<i>Disagree</i>	<i>Strongly disagree</i>	<i>Percentage agreement</i>
1. Definition of SABR re-irradiation in the pelvis: Delivery of SABR, after initial radiotherapy to the pelvis, and where there is overlap of previously delivered dose with the new treatment that could result in excess dose to an OAR and/or significant toxicity	21	2	38%	52%	5%	0	5%	91%
2. SABR re-irradiation in the pelvis can be considered as an alternative to surgical exenteration following an appropriate	21	2	29%	62%	5%	0	5%	91%

<p>multidisciplinary team discussion which takes into account individual patient and disease factors and the respective feasibility/risks of SABR and surgery</p>								
<p>3. SABR re-irradiation in the pelvis may be considered in the presence of extra-pelvic oligometastatic disease where this extra-pelvic disease can be controlled with metastasis-directed therapy</p>	21	2	33%	57%	5%	0	5%	90%
<p>4. When considering the feasibility of SABR re-</p>	21	2	57%	29%	10%	0	5%	86%

irradiation in the pelvis it is necessary to take into account the number of lesions, the size of the target, and the target's location and proximity to OARs								
5. The maximum number of pelvic lesions treated by SABR re-irradiation should not exceed 3	21	2	5%	38%	14%	43%	0	43%
	22	3	0	27%	5%	64%	5%	27%
6. The maximum size of an individual pelvic lesion treated by SABR re-irradiation should not exceed 6 cm in maximum dimension	20	2	15%	45%	10%	30%	0	60%
	22	3	9%	46%	9%	32%	5%	55%
7. SABR re-irradiation in	21	2	33%	57%	5%	5%	0	90%

the pelvis is not usually appropriate where there is direct invasion of a luminal OAR								
8. SABR re-irradiation in the pelvis may not be appropriate where the lesion is in contact with a luminal/critical OAR	21	2	9.5%	38%	19%	33%	0	48%
	22	3	5%	46%	14%	32%	5%	50%
9. A minimum time interval of 12 months should have elapsed between a previous course of radiotherapy in the pelvis and SABR re-irradiation in the pelvis	21	2	0	38%	24%	33%	5%	38%
	21	3	10%	33%	19%	38%	0	43%
10. Patients otherwise eligible for SABR re-	21	2	24%	62%	5%	5%	5%	86%

irradiation in the pelvis should, in general, have a minimum WHO performance status score of 2 (or equivalent)								
11. Previous acute radiotherapy toxicity that was expected/transient should not in itself preclude SABR re-irradiation in the pelvis, unless it was particularly severe or unexpected	21	2	19%	81%	0	0	0	100%
12. SABR re-irradiation in the pelvis should be used with caution in the presence of moderate (e.g. CTCAE grade 2) previous/persistent late	21	2	33%	62%	0	5%	0	95%

radiotherapy toxicity								
13. SABR re-irradiation in the pelvis should be avoided in the presence of severe (e.g. CTCAE grade 3 or greater) previous/persistent late radiotherapy toxicity	21	2	35%	55%	0	10%	0	90%
14. Diagnostic staging imaging prior to SABR re-irradiation in the pelvis should include MRI pelvis and PET-CT	21	2	24%	48%	5%	14%	10%	71%
	22	3	18%	55%	5%	18%	5%	73%
15. Histological confirmation of recurrence prior to SABR re-irradiation in the pelvis may not	21	2	33%	48%	10%	0	10%	81%

always be possible or necessary and treatment may be appropriate based on a clinical and radiological diagnosis of recurrence								
16. Non-SABR re-irradiation in the pelvis (e.g. using conventionally or hyperfractionated radiotherapy) is preferred for lesions >6 cm	21	2	14%	33%	29%	24%	0	48%
	22	3	9%	55%	14%	23%	0	64%
17. Non-SABR re-irradiation in the pelvis is preferred for lesions infiltrating or in contact with a luminal/critical OAR	21	2	10%	43%	29%	19%	0	52%
	22	3	5%	50%	18%	27%	0	55%

CTCAE, Common Toxicity Criteria for Adverse Events; MRI, magnetic resonance imaging; OAR, organ at risk; PET-CT, positron emission tomography-computed tomography; SABR, Stereotactic Ablative Radiotherapy; WHO, World Health Organisation

5.4.2 Target volume/OAR delineation and treatment planning and delivery

Statements in this section and corresponding levels of agreement are shown in **Table 5.2**. After Round 3, absence of consensus remained for 1/13 statements. Although 73% of participants agreed that the point maximum dose within the PTV should not exceed 140%, 2 participants indicated that proximity to OARs would determine the maximum acceptable dose and 1 participant considered that a lower maximum (115-125%) more appropriate. There was agreement for statements which concerned aspects of multidisciplinary team decision-making (statement 30), patient set-up (statements 18-19), target volume/OAR delineation (statements 20-21 and 24-25), treatment planning and delivery (statements 22 and 26-27) and documentation of disease/toxicity outcomes (statement 29).

Table 5.2 Consensus for statements regarding SABR re-irradiation planning and treatment delivery. Statements which achieved consensus are highlighted in bold

<i>Statement</i>	<i>Number of participants</i>	<i>Round</i>	<i>Strongly agree</i>	<i>Agree</i>	<i>Neither agree/disagree</i>	<i>Disagree</i>	<i>Strongly disagree</i>	<i>Percentage agreement</i>
18. For SABR re-irradiation in the pelvis, patients should be positioned supine with the use of a device offering reproducible immobilisation (such as a vacuum bag or equivalent)	21	2	29%	57%	10%	5%	0	86%
19. During SABR re-irradiation in the pelvis, bladder preparation (filling/emptying) and rectal emptying should be determined on an individual patient basis, taking into account the	21	2	48%	48%	0	0	5%	95%

position of the OAR during the prior treatment and the proximity of the OAR to the new target volume								
20. Image co-registration with MRI or PET-CT to the planning CT should be used where it will improve target or OAR delineation	21	2	48%	48%	0	0	5%	95%
21. Intravenous contrast should be used (unless contra-indicated) where it would improve target volume or OAR delineation	21	2	40%	55%	5%	0	0	95%
22. Acceptable dose	21	2	19%	57%	5%	14%	5%	76%

<p>fractionation schedules for SABR re-irradiation in the pelvis are 30-37.5 Gy in 5-6 fractions or 21-27 Gy in 3 fractions with treatment delivered on alternate days</p>								
<p>23. For conventional linear accelerator-based SABR, the maximum allowable dose within the target volume for SABR re-irradiation in the pelvis should not exceed 140% of the prescribed dose</p>	21	2	0	71%	5%	19%	5%	71%
	22	3	0	73%	14%	9%	5%	73%
<p>24. Target volume and OAR nomenclature should be based on the recommendations in American Association of</p>	21	2	19%	71%	5%	5%	0	90%

Physicists in Medicine (AAPM) report TG-263								
25. As a minimum, the following OARs should be delineated for SABR re-irradiation in the pelvis: Bladder, CaudaEquina, Femur_Head_L/R (with/without neck), Rectum, SacralPlex and a small and large bowel structure (e.g. Bowel_Small, Colon, Colon_Sigmoid)	21	2	19%	57%	5%	19%	0	76%
26. SABR re-irradiation in the pelvis should use IMRT (or similar high conformity techniques)	21	2	52%	43%	0	5%	0	95%

27. Daily online treatment verification using volumetric imaging or fiducial markers should be used for SABR re-irradiation in the pelvis	21	2	48%	48%	0	5%	0	95%
28. The concurrent administration of systemic anticancer therapies with SABR re-irradiation in the pelvis, aside from hormone therapy, is not recommended	21	2	10%	81%	0	10%	0	91%
29. Long term disease outcomes and toxicity data should be	21	2	33%	52%	10%	5%	0	86%

<p>prospectively recorded for patients treated with SABR re-irradiation in the pelvis</p>								
<p>30. A multidisciplinary team including a radiation/clinical oncologist, medical physicist and radiographer/RTT, experienced in the practice of SABR re-irradiation in the pelvis, should be involved in determining the technical suitability of SABR re-irradiation cases and in the review of the treatment plan</p>	21	2	29%	62%	5%	5%	0	91%

CT, computed tomography; IMRT, intensity modulated radiotherapy; MRI, magnetic resonance imaging; OAR, organ at risk; PET-CT, positron emission tomography-computed tomography; RTT, radiation therapist; SABR, Stereotactic Ablative Radiotherapy

5.4.3 Proposed cumulative OAR dose constraints

Statements in this section and corresponding levels of agreement are shown in **Table 5.3**. After Round 3, absence of consensus remained for 7/14 statements and these primarily described cumulative OAR constraints. Based on the information from Round 1 (with the exception of CaudaEquina/SacralPlex where most participants did allow recovery), approximately half of participants did not allow recovery from prior radiation, while the remainder did (by varying amounts/after varying time intervals). Therefore, 2 statements were produced per OAR: an optimal constraint in equivalent dose in 2 Gy fractions (EQD2) (without recovery) and a higher mandatory maximum cumulative constraint that might be appropriate once 12 months had elapsed from prior radiation. A summary of published data used to develop these is shown in **Table 5.4**. Optimal constraints were based on traditional de novo SABR American Association of Physicists in Medicine (AAPM) report 101 constraints in 5 fractions used cumulatively[13]. Mandatory cumulative maximum constraints were based on the mean value of constraints derived from published literature and which either used a large cumulative constraint (without recovery) or a traditional constraint incorporating recovery[12-15].

Only statements for mandatory maximum cumulative dose to bladder of 110 Gy₃ (statement 35) and optimal dose to CaudaEquina/SacralPlex of 67 Gy₂ (statement 38) achieved consensus. The percentage agreement for each of the remaining OAR constraint statements after Round 3 was $\geq 50\%$, except for maximum cumulative dose to Bowel_Small (statement 37, 40.9%). Where consensus was not achieved for OAR constraint statements, small but broadly comparable numbers of participants indicated that they considered the constraint to be too high or too low (see **Appendix F**). Despite absence of consensus for most constraints, there was agreement both that published constraints should be used and that the previously delivered dose should be reviewed and a calculation of the maximum allowable dose for SABR re-irradiation (either in EQD2 or biologically effective dose (BED)) should be performed. Consensus was also obtained that OAR constraints should be prioritised over target volume coverage; participants would accept compromise in PTV dose and proceed with a minimum of 70% coverage by the prescribed dose.

Table 5.3 Consensus for statements regarding cumulative organ at risk constraints. Statements which achieved consensus are highlighted in bold

<i>Statement</i>	<i>Number of participants</i>	<i>Round</i>	<i>Strongly agree</i>	<i>Agree</i>	<i>Neither agree/disagree</i>	<i>Disagree</i>	<i>Strongly disagree</i>	<i>Percentage agreement</i>
31. Treatment planning for SABR re-irradiation in the pelvis should include a review of the previously delivered dose to each OAR and calculation of the maximum allowable dose to each OAR during the new treatment (in EQD2 or BED)	21	2	48%	38%	14%	0	0	86%
32. Where there has been previous delivery of gynaecological brachytherapy, SABR re-irradiation is not recommended where there would be overlap of the	21	2	10%	52%	5%	33%	0	62%
	22	3	9%	41%	18%	32%	0	50%

planning target volumes								
33. External peer-reviewed guidance/literature should be used to guide cumulative OAR constraints for SABR re-irradiation in the pelvis	21	2	10%	71%	10%	5%	5%	81%
34. Optimally, the Bladder should receive no more than a cumulative dose of 80 Gy ₃ EQD2 to 0.5 cc (assuming no recovery)	21	2	10%	62%	10%	19%	0	71%
	22	3	0	50%	14%	27%	9%	50%
35. The degree of recovery of Bladder after radiotherapy is uncertain but if 12 months or more have elapsed it is reasonable to assume some	21	2	5%	76%	14%	5%	0	81%

<p>recovery and the Bladder may receive up to a maximum cumulative EQD2 of 110 Gy₃ to 0.5 cc</p>								
<p>36. Optimally, Bowel_Small should receive no more than a cumulative dose of 70 Gy₃ EQD2 to 0.5 cc (assuming no recovery)</p>	<p>19 22</p>	<p>2 3</p>	<p>5% 0</p>	<p>47% 55%</p>	<p>11% 5%</p>	<p>26% 41%</p>	<p>11% 0</p>	<p>53% 55%</p>
<p>37. The degree of recovery of Bowel_Small after radiotherapy is uncertain but if 12 months or more has elapsed it is reasonable to assume some recovery and Bowel_Small may receive up to a maximum cumulative EQD2 of 90 Gy₃ to 0.5 cc</p>	<p>21 22</p>	<p>2 3</p>	<p>5% 0</p>	<p>48% 41%</p>	<p>29% 23%</p>	<p>10% 36%</p>	<p>10% 0</p>	<p>52% 41%</p>

<p>38. Optimally, the CaudaEquina/SacralPlex should receive no more than a cumulative dose of 67 Gy₂ EQD2 to 0.1 cc (assuming no recovery)</p>	19	2	11%	68%	16%	5%	0	79%
<p>39. The degree of recovery of CaudaEquina/SacralPlex after radiotherapy is uncertain but once 12 months or more have elapsed it is reasonable to assume some recovery and CaudaEquina/SacralPlex may receive up to a maximum cumulative EQD2 of 85 Gy₂ to 0.1 cc</p>	19	2	11%	58%	16%	11%	5%	68%
	22	3	0	64%	14%	23%	0	64%
<p>40. Optimally, the Colon/Colon_Sigmoid/Rectum should receive no more than a cumulative dose of 80 Gy₃</p>	21	2	0	62%	10%	19%	10%	62%
	22	3	0	59%	5%	27%	9%	59%

EQD2 to 0.5 cc (assuming no recovery)								
41. The degree of recovery of Colon/Colon_Sigmoid/Rectum after radiotherapy is uncertain but once 12 months or more have elapsed it is reasonable to assume some recovery and Colon/Colon_Sigmoid/Rectum may receive up to a maximum cumulative EQD2 of 100 Gy ₃ to 0.5 cc	21	2	5%	48%	14%	29%	5%	52%
	22	3	0	55%	9%	36%	0	55%
42. OAR constraints should usually take priority over target volume coverage for SABR re-irradiation in the pelvis	21	2	19%	71%	0	5%	5%	90%
43. If PTV coverage is	21	2	0	81%	5%	14%	0	81%

<p>compromised in order to meet an OAR constraint, a minimum of 70% of the PTV should receive the prescribed dose in order to proceed with SABR re-irradiation in the pelvis</p>								
<p>44. The accepted risk of toxicity associated with SABR re-irradiation in the pelvis will depend on the prognosis and availability of effective alternative treatments and should be a shared decision with the patient</p>	21	2	67%	29%	0	0	5%	95%

BED, biologically effective dose; EQD2, equivalent dose in 2 Gy fractions; OAR, organ at risk; SABR, PTV, planning target volume; Stereotactic Ablative Radiotherapy

Table 5.4 A summary of published OAR constraints: maximum cumulative dose in EQD2 to 0.5 cc for each OAR is shown based on first treatment of 45 Gy in 25 fractions (EQD2 43.2 Gy₃) with/without allowance for recovery

OAR		Abusaris [14]	Smith [17]	Paradis* [16]	AAPM* [15]	
Conservative approach, based on use of a traditional constraint in a cumulative manner (may prevent delivery of meaningful re-irradiation dose in some circumstances)						
Bladder	Constraint (no recovery; used cumulatively)	-	-	85 Gy	80 Gy	AAPM constraints used as suggested optimal constraints in above statements
Bowel_Small	Constraint (no recovery; used cumulatively)	-	-	54 Gy	70 Gy	
CaudaEquina/SacralPlex	Constraint (no recovery; used cumulatively)	-	-	70 Gy	67 Gy	
Colon/Colon_Sigmoid/Rectum	Constraint (no recovery; used	-	-	70 Gy	80 Gy	

	cumulatively)						
Less conservative approach, allowing larger cumulative dose and/or incorporating recovery into traditional constraint							
		Abusaris*†‡ [14]	Smith*†‡ [17]	Paradis*§ (50% recovery after 12 months) [16]	AAPM*# (25% recovery after 12 months) [15]	AAPM*# (50% recovery after 12 months) [15]	Mean cumulative EQD2 when recovery incorporated (used to guide suggested mandatory constraints for use after at least 12 month interval in statements above)
Bladder	Cumulative constraint (includes additional recovery where appropriate)	120 Gy	120 Gy	106.6 Gy	91.4 Gy	102.2 Gy	108 Gy
Bowel_Small	Cumulative constraint (includes additional recovery	110 Gy	98 Gy	64.8 Gy	80.8 Gy	91.6 Gy	89 Gy

	where appropriate)						
CaudaEquina/SacralPlex	Cumulative constraint (includes additional recovery where appropriate)		74.4 Gy	91.5 Gy	77.9 Gy	88.6 Gy	83.1 Gy
Colon/Colon_Sigmoid/Rectum	Cumulative constraint (includes additional recovery where appropriate)	110 Gy	110 Gy	91.5 Gy	91.4 Gy	102.2 Gy	101 Gy

* α/β ratio for all OARs of 3 used except for CaudaEquina/SacralPlex (α/β of 2) and Paradis et al (α/β of 2.5)

†Larger cumulative constraints used in Abusaris et al and Smith et al for Bladder, Bowel_Small and Colon/Colon_Sigmoid/Rectum, with no additional recovery permitted

‡No grade 3+ toxicity reported in Abusaris et al after a median follow up duration of 15 months (range 2-52 months). One patient experienced grade 3 pain but no other grade 3+ toxicity was reported in Smith et al after a median follow up duration of 24.5 months (IQR 17.8-28.8 months)

§50% recovery for all OARs for Paradis et al except Bowel_Small (25% recovery)

#Recovery not specified by AAPM but included as illustrative of practice

5.5 Discussion

This study has developed statements to guide pelvic SABR re-irradiation practice; 66% of these achieved consensus from an international group of radiation oncologists. Agreement was reached for statements about patient selection, treatment planning and delivery. Consensus was not reached for statements about minimum time interval between irradiation courses, maximum number/size of lesions and cumulative OAR constraints. Statements which achieved agreement form a useful guide for practice. In particular, statements that did not reach consensus highlight the lack of robust evidence, variation in practice and areas that require further research.

Of note, this study was based on expert opinion and was not necessarily evidence-based. Limited published literature exists concerning pelvic SABR re-irradiation. Most studies are small, single centre, retrospective and non-comparative, with modest follow up[2]. Many examined multiple tumour types with variation in dose-fractionation schedules, treatment techniques and endpoints. Reported rates of local control and survival outcomes vary considerably and histological subtypes (e.g. 1-year local control and overall survival range from 51-100% and 46-100% respectively[2, 15-17]). It remains uncertain whether control of the re-irradiated lesion influences patterns of further metastatic spread and survival.

5.5.1 Definition of pelvic SABR re-irradiation

Agreement was reached regarding a definition, although there was no consensus regarding a statement which quantified a pre-specified overlap (e.g. a defined isodose or dose) to qualify a treatment as re-irradiation. Similar challenges in agreeing a definition which quantified overlap were encountered in a thoracic re-irradiation Delphi study[18]. This was considered to be due to heterogeneity between patients and a lack of data to support a pre-specified overlap in OARs, and these same factors may well apply here.

5.5.2 Patient selection

Despite the majority of participants indicating that the number/size of pelvic lesions influenced decision making, consensus was not gained for specific statements relating to these factors. This likely reflects uncertainty regarding the most appropriate limits which maintain clinical utility but also the intent of treatment. In the non-re-irradiation oligorecurrence setting, often up to 3 or 5 lesions have been considered appropriate for SABR[6, 19]. Ongoing studies, such as SABR-COMET 10, will investigate the value of treating a greater

number of lesions[20]. Of note, locoregional recurrence is a separate entity to oligorecurrence and, in the setting of isolated locoregional recurrence, equivalent limits on numbers of treated lesions may not apply[21]. Indeed, for both scenarios (i.e. local recurrence or oligorecurrence), several participants indicated that OAR dosimetry was of greater relevance or highlighted the potential for the statement to exclude a patient with >3 small closely-related lesions. However, there is likely to be a technical limit to the number/size of pelvic treatment volumes for which acceptable target coverage can be achieved while conformality is maintained/OAR constraints are respected. In addition, the complexity of treatment delivery including internal motion management also increases with each additional volume treated[22].

Consensus was not achieved concerning the time between prior radiation and SABR, which likely reflects uncertainty regarding what the acceptable minimum interval should be. Indeed, among participants who did not agree with a 12 month minimum interval, there was no majority view as to whether this should be shorter or longer. Similar to a smaller number of lesions, a longer interval might suggest less aggressive disease and a potentially better outcome from SABR re-irradiation[2]. On the other hand, the clinical need to obtain disease control/improve symptoms for a patient with, for example, an aggressive rectal cancer recurrence with associated poor prognosis, differs to a patient with a small volume prostate cancer recurrence[23-27]. The time interval could also influence whether an allowance for normal tissue recovery is made from prior radiation, although the extent to which this occurs and time intervals required are uncertain for most OARs[28, 29]. While individual case assessment should be made regarding the appropriate time interval from prior irradiation, a conservative approach for patients with a better prognosis may be to use a 12-month minimum interval (especially where allowance for recovery is to be made).

5.5.3 Proposed cumulative OAR constraints

Considerable uncertainty remains regarding the most appropriate constraints for SABR re-irradiation and whether any recovery should be incorporated.

Reported rates of grade 3+ toxicity following SABR re-irradiation are typically <15%, although the observational nature of many of existing studies and limited use of patient-reported outcome measures (PROMs) restricts interpretation[2, 15-17]. When severe toxicity is reported, this may include potentially life-threatening conditions such as bowel obstruction or fistulae[2]. Few studies clearly report the use of cumulative dose constraints but there was clear

consensus in this Delphi that previously delivered dose should be reviewed and the maximum permissible dose to each OAR calculated[12, 15].

Although few statements relating to optimal constraints gained consensus, it is likely that combined treatment plans which meet these, without an allowance for recovery, are safe, since the use of these traditional constraints (intended for first SABR irradiation) in a cumulative fashion is likely conservative. This approach may necessitate lower total doses (e.g. ~30 Gy in 5 fractions), especially in order to meet bowel constraints. It may be particularly appropriate for patients with better prognosis, other established treatment options and potential to survive to develop significant late toxicity, such as in prostate cancer. In addition, regarding prostate cancer, if the α/β ratio is as low as thought, relatively 'low' SABR doses (e.g. 30 Gy in 5 fractions) deliver relatively high (>100 Gy) BEDs, although no high-level evidence exists to support a minimum acceptable BED[30-32].

Conversely, using traditional constraints cumulatively, without repair, may restrict the delivery of meaningful dose, especially for other histological subtypes or where the target is in close proximity to an OAR. This may be unnecessarily conservative and ignores potential for some recovery. Where a higher dose is considered necessary, maximum cumulative constraints, such as those reported by Abusaris et al and Smith et al, or incorporation of increasing amounts of recovery with time to traditional constraints, as described by Paradis et al, may need to be adopted, accepting the limited data to support this approach[12, 14, 15]. It should be noted that the cumulative constraints reported by Abusaris might be considered considerably lenient, given that they tend to be less restrictive than traditional constraints, even when 50% recovery is incorporated and also, in practice, may greatly exceed more accepted de novo SABR constraints, such as those of the AAPM (see **Table 5.4**)[12, 13]. Regardless of the approach, there was clear consensus that SABR re-irradiation should use highly conformal techniques and daily online image guidance and that SABR re-irradiation should be a shared decision between clinician and patient. This discussion should emphasise current uncertainties regarding OAR constraints and need for further research.

5.5.4 Future directions

The promising data associated with SABR for oligometastatic disease, particularly related to local control, are justification for further investigation specifically concerning SABR in the re-irradiation setting[6]. High-quality prospective studies of pelvic SABR re-irradiation are needed to evaluate disease outcomes alongside robust methods of toxicity assessment (including

PROMs). Radiotherapy quality assurance should include standardised methods of dose prescription, as per ICRU 91[33]. Priorities for studies are to determine appropriate time intervals to re-irradiation/magnitude of normal tissue recovery, maximum number/size of treated lesions and cumulative OAR constraints. Clinical trials in such a heterogeneous population are likely to be challenging. An alternative approach is to define a minimum dataset for pelvic SABR re-irradiation to standardise data collection across multiple centres or from cancer registries[2]. Indeed, the ReCare registry study, currently in the design stage, aims to gather real-world data from re-irradiated patients[34]. There could, however, still be an advantage to obtaining multicentre data specifically relating to pelvic SABR re-irradiation. The statements developed in this study could be a helpful starting point in determining the patient, disease and treatment parameters to be investigated.

5.5.5 Limitations

We focused on SABR re-irradiation to develop statements with specific recommendations. This approach excludes non-SABR re-irradiation and therefore limits the generalisability of our statements. Our selection criteria for the Delphi focussed primarily on radiation oncologists who had published articles on pelvic SABR re-irradiation. We considered this approach to be pragmatic but it could have excluded those who are unpublished but have extensive clinical experience. Not everyone who was invited participated, but we consider that we obtained a good response rate, especially given the current Covid-19 pandemic. We were not disease-specific in our inclusion criteria, meaning that some statements may not be applicable to all disease sites. The maximum allowable dose with the PTV (for which no consensus could be obtained) would depend on the prescribed dose and so perhaps this statement is open to interpretation.

5.6 Conclusion

This study has established recommendations regarding patient selection, pre-treatment investigations, treatment planning and delivery for pelvic SABR re-irradiation. Important areas for future research include the minimum time interval between irradiation, number/size of pelvic lesions that can be treated and the most appropriate cumulative normal tissue constraints.

5.7 Acknowledgements

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5.9 Supplementary Material

5.9.1 Final list of statements with consensus

Supplementary Table 5.1 Statements which achieved consensus regarding definition of SABR re-irradiation in the pelvis, patient selection and pre-treatment investigations

1. Definition of SABR re-irradiation in the pelvis: Delivery of SABR, after initial radiotherapy to the pelvis, and where there is overlap of previously delivered dose with the new treatment that could result in excess dose to an OAR and/or significant toxicity

2. SABR re-irradiation in the pelvis can be considered as an alternative to surgical exenteration

following an appropriate multidisciplinary team discussion which takes into account individual patient and disease factors and the respective feasibility/risks of SABR and surgery

3. SABR re-irradiation in the pelvis may be considered in the presence of extra-pelvic oligometastatic disease where this extra-pelvic disease can be controlled with metastasis-directed therapy

4. When considering the feasibility of SABR re-irradiation in the pelvis it is necessary to take into account the number of lesions, the size of the target, and the target's location and proximity to OARs

7. SABR re-irradiation in the pelvis is not usually appropriate where there is direct invasion of a luminal OAR

10. Patients otherwise eligible for SABR re-irradiation in the pelvis should, in general, have a minimum WHO performance status score of 2 (or equivalent)

11. Previous acute radiotherapy toxicity that was expected/transient should not in itself preclude SABR re-irradiation in the pelvis, unless it was particularly severe or unexpected

12. SABR re-irradiation in the pelvis should be used with caution in the presence of moderate (e.g. CTCAE grade 2) previous/persistent late radiotherapy toxicity

13. SABR re-irradiation in the pelvis should be avoided in the presence of severe (e.g. CTCAE grade 3 or greater) previous/persistent late radiotherapy toxicity

15. Histological confirmation of recurrence prior to SABR re-irradiation in the pelvis may not always be possible or necessary and treatment may be appropriate based on a clinical and radiological diagnosis of recurrence

CTCAE, Common Toxicity Criteria for Adverse Events; OAR, organ at risk; SABR, Stereotactic Ablative Radiotherapy; WHO, World Health Organisation

Supplementary Table 5.2 Statements which achieved consensus regarding SABR re-irradiation planning and treatment delivery

18. For SABR re-irradiation in the pelvis, patients should be positioned supine with the use of a device offering reproducible immobilisation (such as a vacuum bag or equivalent)
19. During SABR re-irradiation in the pelvis, bladder preparation (filling/emptying) and rectal emptying should be determined on an individual patient basis, taking into account the position of the OAR during the prior treatment and the proximity of the OAR to the new target volume
20. Image co-registration with MRI or PET-CT to the planning CT should be used where it will improve target or OAR delineation
21. Intravenous contrast should be used (unless contra-indicated) where it would improve target volume or OAR delineation
22. Acceptable dose fractionation schedules for SABR re-irradiation in the pelvis are 30-37.5 Gy in 5-6 fractions or 21-27 Gy in 3 fractions with treatment delivered on alternate days
24. Target volume and OAR nomenclature should be based on the recommendations in American Association of Physicists in Medicine (AAPM) report TG-263
25. As a minimum, the following OARs should be delineated for SABR re-irradiation in the pelvis: Bladder, CaudaEquina, Femur_Head_L/R (with/without neck), Rectum, SacralPlex and a small and large bowel structure (e.g. Bowel_Small, Colon, Colon_Sigmoid)
26. SABR re-irradiation in the pelvis should use IMRT (or similar high conformity techniques)
27. Daily online treatment verification using volumetric imaging or fiducial markers should be used for SABR re-irradiation in the pelvis
28. The concurrent administration of systemic anticancer therapies with SABR re-irradiation in the pelvis, aside from hormone therapy, is not recommended

29. Long term disease outcomes and toxicity data should be prospectively recorded for patients treated with SABR re-irradiation in the pelvis

30. A multidisciplinary team including a radiation/clinical oncologist, medical physicist and radiographer/RTT, experienced in the practice of SABR re-irradiation in the pelvis, should be involved in determining the technical suitability of SABR re-irradiation cases and in the review of the treatment plan

CT, computed tomography; IMRT, intensity modulated radiotherapy; MRI, magnetic resonance imaging; OAR, organ at risk; PET-CT, positron emission tomography-computed tomography; RTT, radiation therapist; SABR, Stereotactic Ablative Radiotherapy

Supplementary Table 5.3 Statements which achieved consensus regarding cumulative organ at risk constraints

31. Treatment planning for SABR re-irradiation in the pelvis should include a review of the previously delivered dose to each OAR and calculation of the maximum allowable dose to each OAR during the new treatment (in EQD2 or BED)

33. External peer-reviewed guidance/literature should be used to guide cumulative OAR constraints for SABR re-irradiation in the pelvis

35. The degree of recovery of Bladder after radiotherapy is uncertain but if 12 months or more have elapsed it is reasonable to assume some recovery and the Bladder may receive up to a maximum cumulative EQD2 of 110 Gy₃ to 0.5 cc

38. Optimally, the CaudaEquina/SacralPlex should receive no more than a cumulative dose of 67 Gy₂ EQD2 to 0.1 cc (assuming no recovery)

42. OAR constraints should usually take priority over target volume coverage for SABR re-irradiation in the pelvis

43. If PTV coverage is compromised in order to meet an OAR constraint, a minimum of 70% of the PTV should receive the prescribed dose in order to proceed with SABR re-irradiation in the

pelvis

44. The accepted risk of toxicity associated with SABR re-irradiation in the pelvis will depend on the prognosis and availability of effective alternative treatments and should be a shared decision with the patient

BED, biologically effective dose; EQD2, equivalent dose in 2 Gy fractions; OAR, organ at risk; SABR, PTV, planning target volume; Stereotactic Ablative Radiotherapy

5.9.2 Final list of statements without consensus

Supplementary Table 5.4 Statements without consensus regarding definition of SABR re-irradiation in the pelvis, patient selection and pre-treatment investigations

5. The maximum number of pelvic lesions treated by SABR re-irradiation should not exceed 3
6. The maximum size of an individual pelvic lesion treated by SABR re-irradiation should not exceed 6 cm in maximum dimension
8. SABR re-irradiation in the pelvis may not be appropriate where the lesion is in contact with a luminal/critical OAR
9. A minimum time interval of 12 months should have elapsed between a previous course of radiotherapy in the pelvis and SABR re-irradiation in the pelvis
14. Diagnostic staging imaging prior to SABR re-irradiation in the pelvis should include MRI pelvis and PET-CT
16. Non-SABR re-irradiation in the pelvis (e.g. using conventionally or hyperfractionated radiotherapy) is preferred for lesions >6 cm
17. Non-SABR re-irradiation in the pelvis is preferred for lesions infiltrating or in contact with a luminal/critical OAR

MRI, magnetic resonance imaging; OAR, organ at risk; PET-CT, positron emission tomography-computed tomography; SABR, Stereotactic Ablative Radiotherapy

Supplementary Table 5.5 Statements without consensus regarding SABR re-irradiation planning and treatment delivery

23. For conventional linear accelerator-based SABR, the maximum allowable dose within the target volume for SABR re-irradiation in the pelvis should not exceed 140% of the prescribed dose

SABR, Stereotactic Ablative Radiotherapy

Supplementary Table 5.6 Statements without consensus regarding cumulative organ at risk constraints

32. Where there has been previous delivery of gynaecological brachytherapy, SABR re-irradiation is not recommended where there would be overlap of the planning target volumes

34. Optimally, the Bladder should receive no more than a cumulative dose of 80 Gy₃ EQD2 to 0.5 cc (assuming no recovery)

36. Optimally, Bowel_Small should receive no more than a cumulative dose of 70 Gy₃ EQD2 to 0.5 cc (assuming no recovery)

37. The degree of recovery of Bowel_Small after radiotherapy is uncertain but if 12 months or more has elapsed it is reasonable to assume some recovery and Bowel_Small may receive up to a maximum cumulative EQD2 of 90 Gy₃ to 0.5 cc

39. The degree of recovery of CaudaEquina/SacralPlex after radiotherapy is uncertain but once 12 months or more have elapsed it is reasonable to assume some recovery and CaudaEquina/SacralPlex may receive up to a maximum cumulative EQD2 of 85 Gy₂ to 0.1 cc

40. Optimally, the Colon/Colon_Sigmoid/Rectum should receive no more than a cumulative dose of 80 Gy₃ EQD2 to 0.5 cc (assuming no recovery)

41. The degree of recovery of Colon/Colon_Sigmoid/Rectum after radiotherapy is uncertain but once 12 months or more have elapsed it is reasonable to assume some recovery and Colon/Colon_Sigmoid/Rectum may receive up to a maximum cumulative EQD2 of 100 Gy₃ to 0.5 cc

EQD2, equivalent dose in 2 Gy fractions; SABR, Stereotactic Ablative Radiotherapy

Chapter 6 Discussion

6.1 Summary of aims

This thesis investigated several aspects of the treatment pathway for pelvic SABR, including impact of teaching on target volume/OAR delineation (Chapter 2), optimising target volume and dose fractionation schedules during treatment planning for ultra hypofractionated ENI in PCa (Chapter 3), motion management of bowel motion artefacts during IGRT using an anti-peristaltic agent (Chapter 4) and establishing consensus for practice of pelvic SABR re-irradiation in the absence of clinical trial evidence (Chapter 5).

In the following sections, a summary of each study, its limitations and potential future work are discussed.

6.2 Evaluation of the impact of teaching on delineation variation during a virtual Stereotactic Ablative Radiotherapy contouring workshop (Chapter 2)

6.2.1 Summary

Clinician delineation variability remains one of the greatest sources of error in radiotherapy planning. National teaching during a virtual contouring workshop aimed at clinical oncologists not familiar with SABR, and which occurred during the Covid-19 pandemic, was feasible. It was associated with quantitative improvements in contouring variation for approximately half of contoured structures compared with contours produced pre-workshop. Statistically significant improvements in median DSC and reductions in median LDE for the whole cohort of participants were observed for 6 (50%) and 7 (58%) of 12 evaluated structures respectively. However, the magnitude of improvements was modest. An increase in median DSC post-workshop ≥ 0.05 was only observed for GTV bone, IGTV lung and sacral plexus and reduction in median LDE > 1 mm was only observed for GTV bone, CTV bone and sacral plexus. In qualitative feedback on post-workshop contours provided by the workshop faculty, 92% of contours were considered to be acceptable or within acceptable variation (as determined by the reviewing faculty member).

6.2.2 Limitations

Several limitations with regards to this study are described in Chapter 2, and mainly relate to restrictions in the format/conduct of the workshop and the retrospective design of this study to evaluate data provided during the workshop.

6.2.3 Future work

Several recommendations for future contouring workshops are highlighted in Chapter 2, and further studies of the impact of teaching on contouring variation would benefit from a workshop designed in parallel with these. At a basic level, this could improve the reliability of the study by maximising the number of participants for whom paired data pre and post-workshop are available and reduce the amount of missing data, for example where contours for certain structures were not repeated post-workshop. A more detailed assessment of the value of quantitative metrics versus qualitative feedback could be performed, to get a better understanding of the optimum combination of metrics and their limitations compared to qualitative assessment. Few contouring studies evaluate the dosimetric impact of variation in contouring, meaning that there is an opportunity to investigate this, perhaps in combination with its impact on estimates of TCP/NTCP[1]. In addition to optimising the evaluation of contouring performance after teaching, a better understanding of the most appropriate method of contouring assessment and the dosimetric/biological implications of errors in contouring would potentially be of use in the quality assurance of clinical trials, e-learning contouring programme such as ESTRO FALCON and the RCR ARENA and COPP initiatives[2, 3].

6.3 Ultra hypofractionated extended nodal irradiation using volumetric modulated arc therapy for oligorecurrent pelvic nodal prostate cancer (Chapter 3)

6.3.1 Summary

This in-silico planning study in 10 patients demonstrated ultra hypofractionated ENI using VMAT in pelvic nodal recurrent prostate cancer after RP and post-operative prostatic fossa RT is feasible. A 30 Gy SIB may offer the best balance

between effectiveness (PTV node coverage) and safety (OAR constraints). Where an OAR was positioned within PTV node and a reduction in coverage was required, only 30 Gy SIB plans had a median PTV node coverage >90% (IQR 90-95). All OAR constraints were met for 30 Gy SIB plans, including for re-irradiated sub-divisions of OARs in the gap between the previously delivered prostatic fossa RT and the new ENI volume. Where a low α/β ratio of 1.5 Gy was assumed, as is likely for PCa, GTV node median estimated TCP for 30 Gy SIB plans was high at 78.6% (75.8-81.1). For 30 Gy SIB plans, sacral plexus median estimated NTCP was 2.5% (0.5-5.1) and for other OARs, including small bowel, was <0.1%. In summary, plans at this dose level provided the optimal therapeutic ratio, balancing estimated TCP and NTCP.

6.3.2 Limitations

Several limitations with this study are described in Chapter 3. An additional limitation is that, while the physicists involved in the study reviewed the plans and saw no reason as to why the dosimetry would not be acceptable, no evaluation of the feasibility of treatment delivery of the plans was undertaken. For example, a phantom study could have been performed with measurements of target volume/OAR dosimetry. Given the uncertainties regarding the correct parameter values for TCP/NTCP estimates, a sensitivity analysis of TCP calculations to small variations in TCP parameters could also have been performed[4].

6.3.3 Future work

This work provides the preliminary evidence that 25 Gy in 5 fractions ENI with a 30 Gy SIB to involved node(s) using VMAT is feasible and provides an acceptable balance between estimated TCP and NTCP. The next step is to evaluate this dose fractionation schedule within a clinical trial, to determine the disease outcomes and toxicity, and ideally, compare it against the current standard of care for patients with prostate cancer pelvic nodal recurrence.

A proposed phase III trial, with Finbar Slevin as co-investigator, has been developed and submitted for funding to Yorkshire Cancer Research in June 2021. Finbar Slevin presented the trial proposal to NCRI CTRad in January 2021 and Leeds Radiotherapy Research PPI Group in December 2020 and drafted the detailed research plan for the application. Pelvis Or Involved Node

Treatment: Eradicating Recurrence in Prostate Cancer (POINTER-PC) would be a UK multicentre open label randomised phase III trial comparing SABR to the involved node(s) alone with ENI in 20 or 5 fractions. It will recruit patients with 1-3 PET-CT defined pelvic nodal recurrences after primary PCa treatment with EBRT, brachytherapy or RP/post-operative prostatic fossa RT. The trial will address two key questions:

- i) Is MFS superior with ENI compared with SABR?
- ii) Is the late bowel toxicity of ENI in 5 fractions similar to ENI in 20 fractions?

The co-primary endpoints are MFS at 3 years (ENI versus SABR) and PROM-assessed late bowel toxicity at 3 years (ENI in 5 fractions versus ENI in 20 fractions, evaluated using the validated Expanded Prostate Cancer Index Composite (EPIC) 26-item questionnaire). Superiority of ENI (in 20 and 5 fractions) compared with SABR for MFS will be based on the estimated 10% improvement in MFS reported in the European multicentre observational study of ENI versus SABR by De Bleser et al[5]. Validated PROM instruments are recommended for assessment of treatment-related toxicity in clinical trials[6]. The minimum clinically relevant differences after treatment in bowel, urinary, hormonal and sexual domains, compared with symptoms at baseline, for EPIC 26 were established by Skolarus et al[7]. Based on this, a difference in EPIC-assessed late bowel toxicity of 5 points or fewer will be used to determine non-inferiority of ENI in 5 fractions compared with ENI in 20 fractions. In the following section, the rationale for the trial and further details will be discussed.

As discussed in Chapter 1, uncertainty remains regarding the optimum therapeutic approach to patients with PCa pelvic nodal recurrence but, despite an absence of phase III data, SABR has become a de facto standard of care[8, 9]. As discussed in Chapter 3, there is emerging clinical evidence from observational studies that ENI might be associated with fewer treatment failures than SABR in PCa pelvic nodal recurrence[5]. While this approach is currently being evaluated using conventionally fractionated ENI in the randomised phase II STORM trial, a phase III trial is needed to conclusively answer the question of whether ENI is superior to SABR and to better establish the optimum therapeutic approach for this group of patients[10]. The use of MFS as the primary endpoint for POINTER-PC is clinically relevant, given that MFS is strongly associated with overall survival in PCa[11].

Moderately hypofractionated ENI schedules (for example, 44-47 Gy in 20 fractions) are being evaluated in phase III trials in the primary disease setting (for example, PIVOTALboost and the PEARLS study, which is currently in set-up), although a direct comparison of these with ultra hypofractionated schedules is lacking[12]. Based on the data from the primary prostate-only RT setting of non-inferiority of ultra and moderately hypofractionated compared to conventionally fractionated schedules (in the HYPO-RT and CHHiP trials respectively), a more relevant (and achievable) endpoint when considering ultra versus moderately hypofractionated ENI in the recurrent disease setting might be non-inferiority of late toxicity rather than efficacy[13, 14]. Given the location of most pelvic nodal recurrences, small bowel is likely the most critical OAR with regards to a toxicity endpoint, although, as was evaluated in this planning study, consideration would be required concerning re-irradiation of other OARs including bladder, colon, rectum and sacral plexus as well as small bowel[15]. Based on the findings in Chapter 2, where poor concordance with the reference contour was observed pre and post-workshop for sacral plexus, there may be a role for a dedicated trial workshop for participating centres to ensure consistency of target volume/OAR contouring with the trial protocol.

Translational sub-studies within a phase III trial comparing ENI with SABR would maximise the opportunities provided by such a trial and generate new hypotheses for further research. Toxicity data could be correlated with radiation sensitivity genomics, for example in the RAPPER study[16]. Alongside traditional measures of disease risk in recurrent PCa, such as interval from primary treatment, burden of recurrent disease, PSA level and primary disease risk stratification, radiogenomics could provide additional information to aid clinical decision making, especially with regards to intensification of treatment[17, 18]. PET-CT radiomics, taking into account disease response and patterns of further disease relapse, could help predict which patients are most likely to benefit from ENI compared to SABR or further intensification of treatment, for example with additional systemic anticancer therapies such as docetaxel chemotherapy or androgen receptor targeted agents such as enzalutamide or abiraterone/prednisolone[19-21]. The trial could also provide an opportunity to prospectively validate measurements of circulating tumour DNA and detection of specific tumour genome mutations prior to/following treatment with ENI or SABR, which might provide prognostic and predictive

biomarkers[22]. This approach might potentially identify patients who would benefit from additional systemic therapies, such as those at higher risk of distant micrometastatic spread or early treatment failure due to rapid acquisition of resistance genomic mutations. It could also identify patients who might benefit from personalised medicine approaches, such as therapies targeted against *BRCA 1/2* or *PI3K/AKT* mutations. The trial quality assurance processes might provide an opportunity to evaluate the impact of discrepancies in contouring from the trial protocol, for example on survival or toxicity endpoints, as has been undertaken in previous clinical trials[23]. Finally, given the uncertainty regarding cumulative pelvic OAR constraints highlighted in Chapter 5, the trial could provide an opportunity to better understand what the most appropriate constraints should be, for example by correlating dosimetric data from SABR and ENI plans with toxicity outcomes.

6.4 A feasibility study of hyoscine butylbromide (buscopan) to improve image quality of cone beam computed tomography during abdominal/pelvic Stereotactic Ablative Radiotherapy (Chapter 4)

6.4.1 Summary

This prospective feasibility study is the first reported trial of an anti-peristaltic agent to reduce CBCT bowel motion artefacts during radiotherapy. The study recruited 16 patients between September 2019 and December 2020, despite a pause in recruitment for 5 months because of the Covid-19 pandemic and a substantial amendment to the trial protocol, after 8 patients were recruited, to administer buscopan by IV instead of IM injection. Trends to improved CBCT image quality and reduced bowel motion artefacts were observed where buscopan was administered by both IM and IV injection. The injection appeared to be well tolerated by patients, 93% of whom reported that they would accept it as routine. Low grade xerostomia was the most common clinician-reported toxicity (25% of patients), and no \geq grade 3 toxicities were observed. A majority of radiographers (92%) reported no delays in patient treatment from administration of buscopan. In conclusion, this single centre pilot study has

provided proof of principle to support future multi-centre studies to quantify efficacy.

6.4.2 Limitations

A number of limitations are described in Chapter 4 and additional considerations are highlighted here. Ethical approval was granted to recruit 20 participants, but, following review of images from the first three participants and apparent limited impact of IM buscopan on CBCT image quality, a decision was taken by Finbar Slevin, in liaison with Matthew Beasley, Louise J Murray and Ann M Henry, to undertake a substantial amendment to the protocol for administration of IV buscopan. This resulted in two separate cohorts of eight patients each for IM and IV buscopan. Given the impact on recruitment which resulted from Covid-19, and the timeframe for this PhD, it was decided to stop the study at this point. As discussed in Chapter 4, given that this was a feasibility study it was considered that 16 patients provided sufficient information[24].

There was a trend to reduced bowel motion artefact when buscopan was used compared to control (no buscopan). A formal comparison between the IM and IV cohorts was not possible, given the small numbers of patients and complexity of the data structure (as discussed in Chapter 4). Future studies should prospectively compare both IM and IV buscopan within each patient to better evaluate trends in impact on image quality, tolerability and feasibility by route of administration.

Buscopan had limited impact on CBCT image quality for upper abdominal lesions, which are affected by additional respiratory motion artefact, and for bone lesions, where target matching tends to be straightforward. Therefore, a greater benefit from buscopan should be observed if the eligibility criteria of future studies are restricted to patients with lower abdominal/pelvic soft tissue lesions.

6.4.3 Future work

This study provided preliminary data regarding the impact of buscopan on CBCT bowel motion artefacts. A larger study, which is appropriately powered, and for which a method for accounting for the complexity of the data structure could be incorporated (for example, a mixed methods analysis), will be required

to determine whether there is a statistically significant improvement in image quality with buscopan[25]. This trial would also act as a method for implementation of buscopan across multiple RT centres, which would mean that the findings would be also be more generalizable, including across multiple pre-treatment imaging platforms. The trial should be radiographer-led, which would improve RT departmental engagement/buy-in and foster radiographer clinical research career development.

In radiology, the additional clarity of MRI in the abdomen and pelvis obtained by suppression of bowel motion artefacts with anti-peristaltic agents is of obvious diagnostic relevance[26]. In contrast, determining the clinical benefits provided by buscopan within a RT workflow is more challenging. In addition to its use within an adaptive SABR workflow, as discussed in Chapter 4 and in particular as part of an MRI-linac pathway, there are a number of additional potential applications of buscopan which could be investigated. Discrepancies in target matching during IGRT with/without buscopan could be measured, with a hypothesis of improved visualisation of the target with a reduction in bowel motion artefacts[27]. This could be clinically relevant for SABR, where small discrepancies in matching could result in tumour undercoverage/delivery of excess dose to OARs[28].

Since the optimal anti-peristaltic agent, and its route of administration, remains uncertain, IM/IV buscopan could be compared with other agents such as glucagon or with other routes of buscopan administration[29-31]. Finally, IGRT in the upper abdomen can be particularly challenging, especially with CBCT given the multiple adjacent soft tissues and respiratory and bowel motion artefacts[32]. It is possible that, combined with a method of respiratory motion compensation (for example, abdominal compression or breath-hold), that greater improvements in image quality from suppression of gastrointestinal motion artefacts might be obtained than those observed in this study[33].

6.5 An international Delphi consensus for pelvic Stereotactic Ablative Radiotherapy re-irradiation (Chapter 5)

6.5.1 Summary

When considering pelvic SABR re-irradiation, information provided by participants highlighted the heterogeneity that exists between individual patients, different disease sub-types, previously delivered treatments and factors relating to individual recurrences. Consensus was achieved for 29 of 44 (66%) practice statements from an international group of 23 radiation oncologists concerning recommendations for patient selection, pre-treatment investigations, treatment planning and delivery for pelvic SABR re-irradiation. Given the absence of high quality evidence for pelvic SABR re-irradiation, these statements form a useful guide for practice. There remained a lack of agreement for 15 statements (34%) regarding the minimum time interval between irradiation courses, the number/size of pelvic lesions that can be treated and, in most instances, the most appropriate cumulative OAR constraints. In particular, statements without consensus highlight areas which require further research.

6.5.2 Limitations

In addition to the limitations described in Chapter 5, a number of additional considerations are discussed here. The online survey platform anonymised participant responses, which is a benefit for Delphi studies but it limited our ability to identify who had responded to the initial invitation, and therefore who to invite for round 2[34]. We did not modify statements without consensus between rounds 2 and 3. The aim of this approach was to allow participants to re-evaluate their level of agreement in round 3, taking into account the responses of other participants from round 2, but this might also have restricted our ability to achieve greater consensus for certain statements in round 3. Approaches of modification and unmodification of statements without consensus have both been used in previous radiation oncology Delphi studies and the optimum methodology remains uncertain[35-38].

6.5.3 Future work

In Chapter 5, a number of areas regarding pelvic SABR re-irradiation which require further research are highlighted, including the minimum time interval to re-irradiation, the most appropriate number/size of pelvic lesions which should be treated and the optimum cumulative OAR constraints. As discussed in Chapter 5, this consensus may be the basis for a national/international prospective registry study which standardises data collection and adheres to naming conventions. Such a study could allow comparison of dosimetry with disease and toxicity outcomes, which may help answer some of the questions highlighted above and which could inform the parameters for a clinical trial of pelvic SABR re-irradiation[39].

There is a need to understand how best to account for anatomical change and its impact on dose summation. The Support Tool for Re-Irradiation Decisions guided by Radiobiology (STRIDeR) project, developed in Leeds in collaboration with RaySearch Laboratories, is currently investigating the impact of deformable image registration of the initial and re-irradiation plans on calculation of cumulative doses, corrected for fractionation[40]. Building on STRIDeR, dose accumulation from daily online verification images could be used to better estimate the actual delivered dose during the initial treatment and during re-irradiation, and to adapt the dose which can be delivered per fraction based on this information and the daily position of the target and adjacent OARs[41].

There are a number of questions when considering a potential clinical trial in pelvic SABR re-irradiation:

i) what should the eligibility criteria be? Including multiple disease sub-types would aid recruitment but there may be considerable differences in original treatment volumes and doses and tumour biology and prognosis, which could introduce bias and limit interpretation, ii) what should the comparator arm be, if any? A randomised study might provide a better understanding of the impact of SABR, but there may be no established standard of care or one that is consistent across individual disease sub-types, iii) what should the trial endpoints be? The most clinically relevant disease-related endpoint might differ between disease sub-types and be influenced by receipt of non-SABR therapies, iv) what type of radiotherapy should be used? No consensus was obtained in Chapter 5 for scenarios where non-SABR re-irradiation might be preferred, but conventionally or hyperfractionated schedules might be more

appropriate for large recurrences or where there is direct invasion of a luminal OAR. It is also hypothesised that proton beam therapy could provide a therapeutic advantage compared with photon re-irradiation[42]. Overcoming these challenges is important to better understand the role of pelvic SABR re-irradiation in the management of pelvic recurrence after primary treatment.

6.6 Conclusion

This thesis has examined several aspects of the pelvic SABR pathway, including the impact of teaching on target volume/OAR delineation, evaluation of treatment planning for ultra hypofractionated ENI with different SIB doses, addition of buscopan to potentially improve CBCT image quality through reduction of bowel motion artefacts and development of clinical consensus regarding pelvic SABR re-irradiation. This work has contributed to a funding application for a phase III trial which will evaluate pelvic SABR versus ENI and has highlighted other potential areas for future research. It is hoped that ultimately this work will contribute to improvements in the therapeutic ratio for patients who receive SABR and ultra hypofractionated RT in the pelvis.

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Appendix A Study protocol: A feasibility study of hyoscine butylbromide (buscopan) to improve image quality of cone beam computed tomography during abdominal/pelvic Stereotactic Ablative Radiotherapy



The Leeds Teaching Hospitals NHS Trust



UNIVERSITY OF LEEDS

HBB-SABR: A feasibility study investigating the effect of hyoscine butylbromide injections on cone beam CT quality when delivering abdomino-pelvic stereotactic ablative radiotherapy (SABR)

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List of abbreviations

AE: adverse event

AR: adverse reaction

BPM: beats per minute

CBCT: cone beam computed tomography

CT: computed tomography

CTCAE: Common Toxicity Criteria for Adverse Events

Gy: Gray

HBB: hyoscine butylbromide

IMRT: intensity modulated radiotherapy

MR: magnetic resonance

MRI: magnetic resonance imaging

PET-CT: positron emission tomography-computed tomography

PTV: planning target volume

SABR: stereotactic ablative radiotherapy

SAE: serious adverse event

SAR: serious adverse reaction

SABR: stereotactic ablative body radiotherapy

SBRT: stereotactic body radiotherapy

SRS: stereotactic radiosurgery

SUSAR: serious unexpected serious adverse reaction

UAE: unexpected adverse event

VMAT: volumetric modulated arc therapy

Chapter 1 Trial summary:

1.1 Title:

HBB-SABR: A feasibility study investigating the effect of hyoscine butylbromide injections on cone beam CT quality when delivering abdomino-pelvic stereotactic ablative radiotherapy (SABR).

1.2 Background:

SABR can be used to treat oligometastatic disease in the abdomen and pelvis. Image quality of cone beam CT used for treatment verification is affected by bowel gas motion resulting in streaking artefacts. Intra-fractional bowel motion occurs close to the planning target volume (PTV) during abdomino-pelvic SABR. Diagnostic radiological studies routinely employ anti-peristaltic agents such as hyoscine butylbromide (HBB) to induce aperistalsis and improve image quality. HBB can be delivered by intravenous or intramuscular route. Intramuscular injection may be more convenient than intravenous injection in radiotherapy departments.

1.3 Objectives:

This study will investigate if administration of **intravenous** HBB is associated with better cone beam CT image quality for abdomino-pelvic SABR. It will also determine if addition of **intravenous** HBB is feasible within a clinical abdomino-pelvic SABR workflow and is tolerated by patients.

1.4 Design:

Feasibility study with patients acting as own controls.

1.5 Intervention schedule:

Intravenous HBB administered and not administered on alternate fractions to permit evaluation of image quality and bowel motion. Patients act as internal controls to reduce confounding from individual unique bowel motion. Twenty patients to be recruited.

1.6 Inclusion criteria:

- No comorbidities likely to impact on safety of administration of HBB (for example severe cardiac disease, recent cardiac event, cardiac tachyarrhythmias, angle closure glaucoma, myasthenia gravis, pyloric stenosis, severe ulcerative colitis, paralytic ileus, obstructive uropathy or allergy to HBB)
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol; those conditions should be discussed with the patient before registration in the trial
- Written informed consent

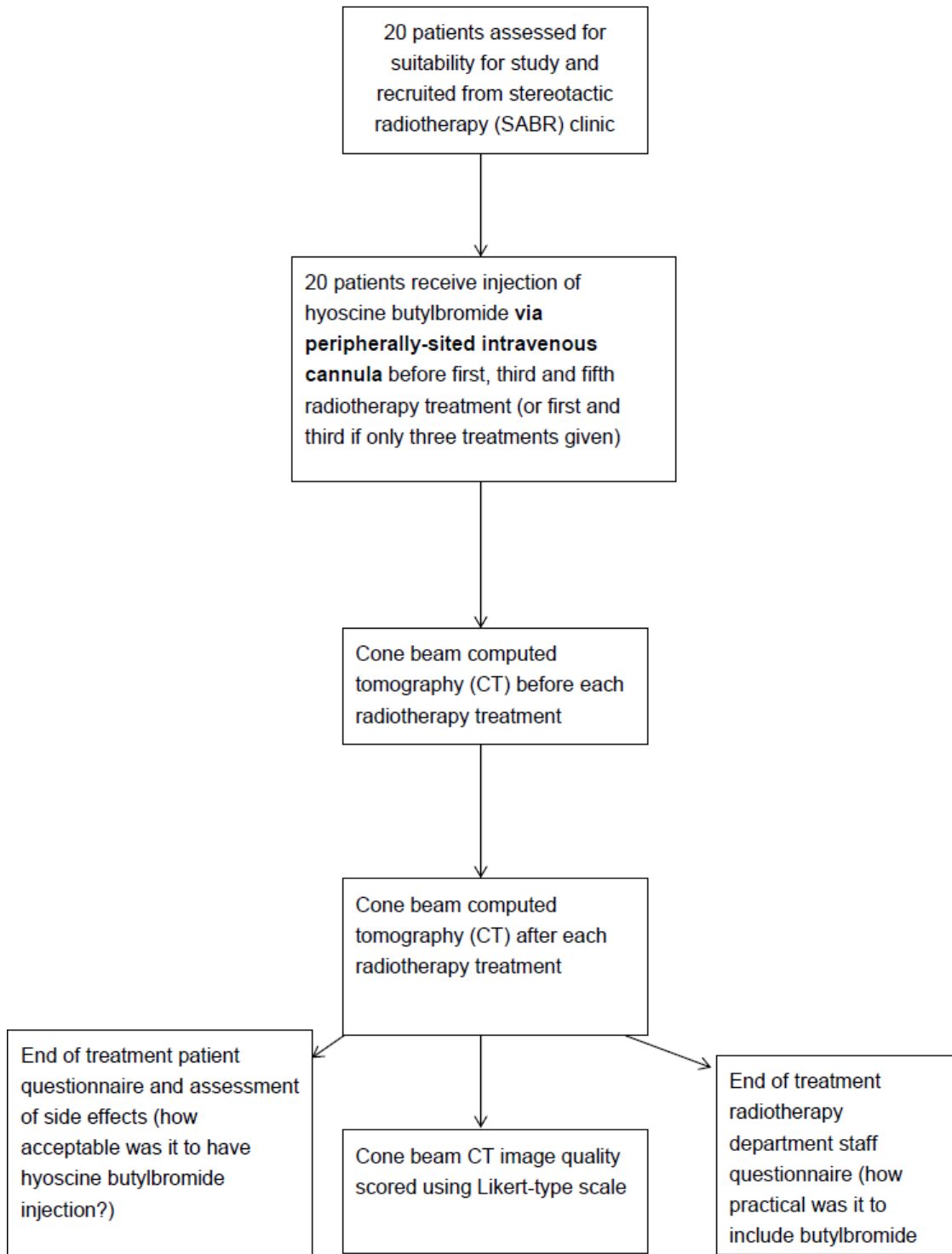
1.7 Endpoints:

Primary endpoints:

- Improvement in cone beam CT image quality when HBB administered. This will be determined by proportion of images with improved Likert-type scale results.

Secondary endpoints:

- Demonstration that administration of **intravenous** HBB is feasible within a clinical abdomino-pelvic SABR workflow.
- Demonstration of patient and radiotherapy department staff acceptability of **intravenous** HBB injection using questionnaire at time of final fraction.

1.8 Study schema:

Chapter 2 Background and introduction

2.1 Oligometastatic disease

Oligometastatic disease describes a state between a local tumour and widely disseminated metastatic disease. The implication of this diagnosis is that treating the limited sites of metastases with local metastasis-directed therapy may result in long term survival for patients previously considered incurable (Weichselbaum, 2011; Macdermed, 2008). Evidence exists for improved survival and, in some circumstances, cure of patients who undergo resection of liver metastases in colorectal cancer (Pawlik, 2005) and resection of lung metastases from a variety of primary tumour sites (Pastorino, 1997). The evidence is less clear regarding the benefits of surgical resection of lymph node metastases in some pelvic malignancies and there are high risks of post-operative side effects (Franzese, 2017; Kobayashi, 2009; Min, 2008). Systemic anticancer therapies may risk toxicity without symptomatic benefit for low volume metastatic disease and are generally not curative for solid tumours. Radiotherapy represents an alternate local therapy to surgery but metastatic lesions often regrow over time if conventional dose fractionations are used (Cheung, 2016).

2.2 Stereotactic ablative radiotherapy (SABR)

SABR is a technique of delivering high doses of therapeutic radiation with high accuracy and precision to a highly-conformal target volume (Martin, 2010). SABR can deliver an ablative dose that has equivalent or greater biological effectiveness than conventional radiotherapy. It aims to eradicate the metastatic deposit and thus provide longer term control than conventional radiotherapy, without some of the risks associated with surgery (Cheung, 2016; Martin, 2010; Sahgal, 2012; Tree, 2013). To safely deliver SABR, effective patient preparation and immobilisation as well as accurate target localisation and treatment delivery with millimetre tolerances using image guidance and online correction for inter-fraction patient internal motion and set up errors are required. Complex inverse treatment planning system software and the use of intensity modulated radiotherapy (IMRT), especially VMAT, permits the delivery of radiation to the target with steep dose gradients sparing critical normal organs and tissues (Desai, 2017; Martin, 2010; Musunuru, 2014).

2.3 SABR to treat oligometastatic disease

Much of the clinical evidence for SABR for the treatment of oligometastatic disease has been derived from retrospective observational studies with small numbers of patients. Confounding factors therefore limit interpretation of its true clinical benefit. In many centres patients may be considered for SABR where either patient or disease-related factors preclude surgical resection. Few randomised studies have been performed and many published outcomes are from single centre institutions and lack a comparator arm with other local therapies such as surgery or the standard of care for metastatic disease in the tumour site of interest (Palma, 2015).

Randomised studies are currently in progress to try to more clearly define the benefit of SABR for the treatment of oligometastatic disease including the CORE trial of SABR or standard of care for oligometastatic lung, breast and prostate cancer (ClinicalTrials.gov Identifier: NCT02759783); the SABR-COMET study of SABR or conventional palliative radiotherapy for oligometastatic cancer (Palma, 2012); the ORIOLE study of SABR versus observation in prostate cancer (Radwan, 2017); and the STORM trial of SABR or surgery for oligometastatic prostate cancer with and without whole pelvis radiotherapy (NCT03569241).

2.4 Image guidance using cone beam CT (CBCT)

Small inter and intra-fraction deviations in the patient position or position of the target or internal organs may result in a geographic miss with the potential for undercoverage of the target and overdose of critical organs at risk. Given the highly conformal volumes and high doses per fraction used for SABR, the use of 3D image guidance with correction for set up and internal organ motion discrepancies is of critical importance (Martin, 2010).

CBCT is commonly used for image-guided radiotherapy. CBCT combines an x-ray source with a flat panel detector and is mounted on a linear accelerator gantry perpendicular to the treatment head and portal image detector. As the gantry rotates images are acquired during a 180-360 degree gantry rotation over 40 seconds to two minutes. Reconstruction into volumetric images permits evaluation of bone and soft tissue structures. These images can be registered with the planning CT scan and any discrepancy in the position of the target can be observed and a match applied (Jaffray, 2002; Sykes, 2005).

2.5 Bowel organ motion

Pelvic organs are subject to changes in position, shape and volume over time and the appearance of both the target and organs at risk may differ between a radiotherapy planning scan and images obtained during treatment (Jadon, 2014). Bowel motion is under neurological and hormonal control and results in complex peristaltic waves of dilatation and relaxation (Husebye, 1999). Small bowel peristaltic waves have been shown to occur 11 times per minute with average amplitude of 7mm. In addition to this oscillating motion, large changes in bowel position and volume occur as a consequence of faeces and gas within the bowel as well as the influence of bladder volume (Froehlich, 2005). There is considerable variation in the appearance of the small bowel both within and between patients and a single CT image represents only an arbitrary shape and position of a mobile organ. The volume of bowel seen in a single scan may be larger than the average volume seen throughout a course of radiotherapy (Hysing, 2006; Kvinnsland, 2005). Bowel volume has been observed to vary by 20% compared to the planning CT scan on weekly cone beam CT images for bladder radiotherapy treatments with the volume of bowel close to the bladder correlating with bladder volume (Muren, 2003). It may be that only 20% of bowel occupies the same position throughout treatment (Hysing, 2006; Sanguineti, 2008). The position of small bowel has been seen to vary by up to 2.7cm in the anterior-posterior direction and 1.6cm in the superior-inferior direction for patients receiving adjuvant radiotherapy for rectal cancer. An increased bladder volume has also been shown to be associated with reduced amount of small bowel close to the radiotherapy target in rectal cancer (Nuyttens, 2001; Nuyttens, 2004).

2.6 Impact of bowel organ motion on CBCT quality

Image quality of CBCT is limited in comparison to diagnostic helical CT scanners for a number of reasons. Large quantities of scattered radiation reach the flat panel detector and this reduces image contrast and increases image noise, which negatively impacts on image quality (Endo, 2001; Graham, 2007; Siewerdsen, 2001).

Bowel motion negatively impacts on diagnostic image quality and anti-peristaltic agents have been used routinely for several decades, especially for abdomino-pelvic magnetic resonance imaging (MRI), CT colonography, mesenteric angiography and barium studies (Dyde, 2008; Goei, 1995; Johnson, 2007; Maher, 1999). During MRI, motion causes blurring and ghost artefacts resulting from a spreading out of the signal from an object and this causes deterioration in image quality. These artefacts

impact on MRI rather than diagnostic CT because of the long scan acquisition times (Bellon, 1986; Dosda, 2003; Martí-Bonmatí, 1996). The prolonged period of time it takes for the CBCT gantry to rotate (in comparison to a helical fan beam CT scanner where one rotation takes around one second) means any internal organ motion, including respiratory and cardiac motion, bowel peristalsis and arterial pulsation, may create significant motion artefacts during image reconstruction including blurring, streaking, doubling and distortion (Smitsmans, 2005; Xing, 2006). It is gas moving within the bowel that appears to result in streak artefacts during image reconstruction of CBCT (Nijkamp, 2008; Smitsmans, 2005).

2.7 Assessment of CBCT image quality

CT image quality can be determined by physical measurements or observer assessments. Physical measurements include spatial resolution, image uniformity and contrast to noise ratio. While these might provide an objective measure of a particular technology's performance, observer scored methods of image quality such as visual grading analysis may be more clinically relevant.

Assessments can also be performed in relation to the task for which the imaging was performed, for example identification of anatomical structures in diagnostic radiology or soft tissue matching in IGRT (Bath, 2010). Use of Likert-type rating scales for visual grading analysis has been used in diagnostic radiology studies, where observers scored the visibility of particular structure and they have also been used to assess CBCT image quality for target matching in radiotherapy studies (Johnson, 2007; Kember, 2016). An example of a scale used by Sweeney *et al* for a study comparing 4D with 3D CBCT for lung SABR was a three point score summarised as: score 1: "clearly visible tumour, no difficulty in matching"; score 2: "visible tumour but some difficulty in matching"; score 3: "tumour not visible for matching" (Sweeney, 2012). Scores with different numbers of points have been used in previous studies. Kember *et al* chose an even number scale with the points 'very clearly visible', 'clearly visible', 'unclear' and 'not visible' to avoid observers choosing the middle value by default (Kember, 2016). Measurement of intra and inter-observer agreement for several assessors of image quality can be performed to validate results (Demehri, 2015).

2.8 Use of anti-peristaltic agents in imaging

Hyoscine butylbromide (HBB) (also known as scopolamine butylbromide, butylscopolaminebromide or N-butyl scopolammonium and marketed under the trade

name Buscopan® (Boehringer Ingelheim Ltd, Germany)) is an anticholinergic quaternary ammonium compound with limited systemic absorption when administered via the enteral route. It can however be delivered by intravenous or intramuscular routes. By binding to muscarinic receptors located in smooth muscle cells of the gastrointestinal tract results it results in inhibition of bowel motility (Tytgat, 2007).

A study investigated the onset of action following administration, duration of action and effectiveness for intravenous and intramuscular HBB and glucagon for cessation of peristalsis in healthy volunteers undergoing small bowel MRI. Aperistalsis occurred on average after 85 seconds (± 25 seconds) and 65 seconds (± 25 seconds) for intravenous HBB and glucagon and 310 seconds/5.1 minutes (± 110 seconds) and 696 seconds/11.6 minutes (± 610 seconds) for intramuscular HBB and glucagon respectively. Duration of action was 1260 seconds/21 minutes (± 739 seconds) and 1397 seconds/23.3 minutes (± 842 seconds) for intravenous HBB and glucagon and 1060 seconds/17.7 minutes (± 1406 seconds) and 1690 seconds/28.2 minutes (± 1614 seconds) for intramuscular HBB and glucagon respectively. There was significant variation in the timing of onset and duration of action between individuals and the investigators reported more variability between subjects in the degree of aperistalsis after intramuscular administration of both HBB and glucagon. They speculated that this could be due to slower systemic availability of the drugs following intramuscular injection (Gutzeit, 2012).

In Europe HBB is used more frequently than glucagon for inhibition of bowel peristalsis for radiological procedures because it is less expensive and can be stored at room temperature (Dyde, 2008).

A study of intravenous HBB in pelvic MRI using Likert-type scales for qualitative image analysis found significantly improved image quality, organ identification and tumour visualisation following administration of HBB. There was a reduction in the proportion of images scored as having significant motion artefact and an increase in the proportion judged to have no motion artefact. Tumour identification post HBB was felt to be improved and fewer images permitted very limited lesion assessment. Identification of the bladder, rectum, pelvic bowel, prostate, seminal vesicles, uterus and vagina was felt to be significantly improved post HBB (Johnson, 2007).

2.9 Safety of hyoscine butylbromide (HBB)

Along with glucagon, HBB is routinely used as an anti-peristaltic agent for radiological procedures including abdomino-pelvic MRI, CT colonography, mesenteric angiography and barium studies (Dyde, 2008; Goei, 1995; Johnson, 2007; Maher, 1999). It is well tolerated, and adverse events generally appear mild and self-limiting in studies that used HBB for radiological procedures. No toxicities attributable to subcutaneous HBB were observed in a study of 25 patients undergoing abdominal MRI (Dosda, 2003).

A study of HBB in 35 patients undergoing pelvic MRI found seven patients reported blurred vision, 22 patients reported dry mouth, four patients reported dizziness and two reported palpitations. All toxicities resolved within 15 minutes except blurred vision which persisted for up to one hour (Johnson, 2007). In another study of HBB for small bowel MRI two of ten healthy volunteers experienced a short period of dizziness following administration of intravenous HBB (Froehlich, 2009). Transient visual disturbance occurred in a proportion (exact numbers not reported) of ten health volunteers administered 40mg of intravenous HBB as part of a study of bowel motility (Froehlich, 2005). Another study of intravenous HBB in abdominal MRI reported blurred vision in two of 33 patients (Laniado, 1997). Another study compared intravenous HBB, glucagon and placebo for barium enema examinations. Five of 109 (4.6%) of patients who received HBB reported blurred vision compared to no patients who received glucagon or placebo but no significant changes in visual accommodation were observed between the three groups. The authors recommended that patients who receive HBB should wait in the department until any visual disturbance has resolved before they drive home (Goei, 1995). Other authors recommended that patients should be told to expect blurred vision and not to drive for 45 minutes after the injection (Dyde, 2008).

Although anticholinergic drugs such as HBB may precipitate acute angle closure glaucoma it is undiagnosed and therefore untreated patients who are at greatest risk of this condition and therefore previous authors have recommended that all patients are advised to seek urgent medical attention if they develop painful blurred vision within 12 hours of the injection (Dyde, 2008; Fink, 1995).

Other contraindications to administration of HBB are a history of myasthenia gravis, porphyria, paralytic ileus, obstructive uropathy and a history of allergic reaction to HBB (Dyde, 2008).

A Medicines and Healthcare products Regulatory Agency (MHRA) drug safety update was published in February 2017 following reports of eight patients who died as a result of myocardial infarction or cardiac arrest following procedures that included administration of intravenous or intramuscular HBB (Medicines and

Healthcare Products Regulatory Agency, 2017). HBB may induce tachycardia as a result of anticholinergic inhibition of vagal tone and can lead to angina and cardiac ischaemia in susceptible individuals. It has been recommended not to administer HBB in patients with unstable cardiac disease such as recent acute coronary syndrome, recurrent angina especially at rest, uncontrolled left ventricular failure and cardiac tachyarrhythmias (Dyde, 2008; Joint position statement from The Royal College of Radiologists and the British Society of Gastrointestinal and Abdominal Radiologists, 2017; Maher, 1999; Medicines and Healthcare Products Regulatory Agency, 2017). Dyde et al recommended however that a small increase in pulse rate of 20 beats per minute (bpm) for around one hour and small increase in diastolic blood pressure is unlikely to be clinically significant in patients without significant cardiac disease (Dyde, 2008). There is the suggestion that pulse rate elevation may be dose-related with 40mg intravenous HBB leading to an increase of 30 bpm but the standard dose for HBB during radiological procedures is 20mg (Dyde, 2008; Mui, 2004).

2.10 Adaptive SABR workflow

Adaptive radiotherapy (ART) involves adjusting the treatment plan based on anatomical changes that are observed during pre-treatment imaging, ideally prior to that day's treatment. Previous studies in the pelvis have used different ART strategies. These include an offline replanning strategy whereby a new plan is produced after treatment is delivered, based on tumour shrinkage and pelvic internal organ motion in cervical cancer. Alternatively a library of plans can be produced to allow selection of the most appropriate 'plan of the day' based on bladder volume and daily online plan re-optimisation in bladder and prostate cancers (Ahunbay, 2010; Oh, 2014; Vestergaard, 2013). Abdomino-pelvic SABR would likely especially benefit from ART strategies. As described above there is considerable internal organ motion in the pelvis, especially for bowel, and previous studies have shown that the volume of small and large bowel receiving higher doses of radiotherapy correlates with development of gastrointestinal toxicities (Fokdal, 2005; Roeske, 2003). Given the significant hypofractionation used with SABR, ART for abdomino-pelvic SABR based on position of the target and the surrounding loops of bowel would ideally be performed daily and be performed immediately prior to delivery of treatment. However there is the potential for intrafraction bowel motion and patient discomfort during the time taken to re-optimize the plan, and bowel gas can negatively affect recontouring of bowel loops (Lim-Reinders, 2017; Vestergaard, 2013). Deformable image registration has the potential to rapidly facilitate

recontouring of relevant structures on pre-treatment CBCT, but artefacts generated during acquisition of the CBCT images may introduce significant error into the process. In addition, deformable image registration strategies for small and large bowel loops are not well developed (Lim-Reinders, 2017; Perna, 2016; Schulze, 2011). Our study aims to investigate whether administration of intramuscular HBB could reduce the streak artefacts seen on CBCT images associated with moving gas. If successful this would help contribute towards development of an adaptive workflow for abdomino-pelvic SABR. The future of ART may be in MR-guided radiotherapy, for example utilising an MR linear accelerator or cobalt machine, with deformable image registration of the MR images to the planning scan and automatic recontouring of targets and organs at risk (Acharya, 2016; Bohoudi, 2017; Kupelian, 2014). Potential for intrafraction bowel motion would exist during both the acquisition of MR sequences and replanning process, and therefore a wider application of HBB could be used to both reduce bowel motion MR artefacts and stabilise bowel position prior to delivery of an adapted radiotherapy treatment.

2.11 Conclusions

Streak artefacts from moving bowel gas negatively impact image quality of CBCT images used for abdomino-pelvic SABR. HBB is routinely used in diagnostic radiology, especially for abdomino-pelvic MRI, to reduce bowel motion artefacts and improve image quality. The hypothesis for our study is that use of **intravenous** HBB will reduce streak artefacts and improve image quality of CBCT in the process of target matching prior to delivery of SABR. Likert-type scales will be used to assess image quality. We also hypothesise that implementation of **intravenous** HBB will be feasible within a clinical abdomino-pelvic SABR workflow and that it will be tolerated by patients. If successful we anticipate that this strategy will be a useful component in the development of an adaptive SABR workflow.

Chapter 3 Study objectives

3.1 Primary objective

1. To determine the impact of **intravenous** HBB in reducing bowel motion artefacts on CBCT images used for image guidance of abdomino-pelvic SABR. The aim is to demonstrate an improvement in image quality as assessed by better scores on a Likert-type scale when HBB is administered.

3.2 Secondary objectives

1. To demonstrate that implementation of **intravenous** HBB into a clinical abdomino-pelvic SABR workflow is feasible and does not negatively impact on radiotherapy department scheduling.
2. To determine if an **intravenous** HBB injection is acceptable to both patients and radiotherapy department staff by use of an end of SABR treatment questionnaire.

3.3 Endpoints

1. Primary endpoints:

- ◆ Improvement in CBCT image quality with administration of **intravenous** HBB determined by proportion of images with better scores on a Likert-type scale.

2. Secondary endpoints:

- ◆ Feasibility of implementation of **intravenous** HBB into a clinical SABR workflow determined by absence of delays to radiotherapy department scheduling as a result of administering **intravenous** HBB.
 - Acceptability of **intravenous** HBB to both patients and radiotherapy department staff determined by end of SABR treatment questionnaire covering tolerance for receiving an injection, toxicity of HBB and convenience for departmental staff in administering the injection within clinical workflows.

Chapter 5 Trial design

- This is a prospective, non-randomised feasibility study of **intravenous** HBB administered on alternate SABR fractions in the management of oligometastatic disease in the lower abdomen and pelvis. The rationale for giving HBB is to try to improve image quality of CBCT by reducing bowel motion artefacts. Patients will act as their own controls to try to account for individual variation in bowel motion.
- The trial will be performed in Leeds Cancer Centre and other radiotherapy centres within the Cancer Research UK Advanced Radiotherapy Technologies Network (ART-NET) will be invited to participate. These centres are: Institute of Cancer Research/The Royal Marsden Hospital, Manchester Cancer Research Centre, (Leeds), Oxford and University College London.
- The primary endpoint is an improvement in CBCT image quality with administration of **intravenous** HBB determined by proportion of images with better scores on a Likert-type scale.
- The secondary endpoints are demonstrating feasibility of incorporating **intravenous** HBB into a clinical SABR workflow and demonstrating acceptability of **intravenous** HBB to both patients and radiotherapy department staff determined by means of an end of SABR treatment questionnaire.
- **Following interim review of CBCT images from the first 3 patients who completed the study, no clear improvement in CBCT image quality was observed when HBB was administered via intramuscular injection compared to when it was not. Therefore, a substantial amendment was made to the study protocol to change the route of administration of HBB to delivery via peripherally-sited intravenous cannula.**

Chapter 6 Clinical evaluation of HBB in SABR workflow

6.1 Prior to treatment

1. Of note, local trial activities will be coordinated by the local trial clinical research fellow. Within this protocol, where there are activities relating to the Clinical Research Fellow (and Chief Investigator) at the central trial site in Leeds the prefix 'Leeds' is used.
 - Patients will be assessed in outpatient clinic to determine suitability for SABR and HBB within this study. This will be done by documentation of patient history, clinical examination and review of relevant biochemical, histological and radiological investigations. Documentation of past medical history and drug history will be used to exclude patients not suitable for HBB.
 - Specific contraindications are severe cardiac disease, recent cardiac event, cardiac tachyarrhythmias, angle closure glaucoma, myasthenia gravis, pyloric stenosis, porphyria, severe ulcerative colitis, paralytic ileus, obstructive uropathy or allergy to HBB.
 - Patients will be approached by their clinical team at a clinic visit and if they appear potentially suitable the rationale, practicalities and risks of the trial will be discussed. If interested in participating the patient information sheet will be provided and contact details obtained. Participant name, date of birth, NHS number, and telephone number will be obtained to facilitate recruitment into the study by one of the trial investigators. Verbal consent will be obtained for this process to take place. This process will take place internally within each of the trial sites. Patients will be contacted by the local clinical research fellow within 1 week to arrange for assessment for recruitment into the study if the patient remains interested. They will be offered at least 24 hours to consider their decision to enter the trial. The process for consent and registration into the study will most likely take place in the radiotherapy department when the patient attends for their SABR planning CT scan, to try to avoid participants returning for a separate consent visit.

6.2 During treatment

- **Following substantial amendment to the study protocol, patients will receive intravenous HBB 20mg via a peripherally-sited intravenous cannula on fractions 1, 3 and 5 of a five-fraction**

Chapter 7 Statistical considerations

7.1 Study design

- This is a prospective, non-randomised feasibility study of **intravenous** HBB administered on alternate SABR fractions in the management of oligometastatic disease in the lower abdomen and pelvis. The rationale for giving HBB is to try to improve image quality of CBCT by reducing bowel motion artefacts. Patients will act as their own controls to try to account for individual variation in bowel motion.
- The null hypothesis of the primary endpoint is that administration of HBB does not result in increased proportion of images with an improved Likert-type scale score. The null hypotheses of the secondary endpoints are that incorporation of **intravenous** HBB into a clinical SABR workflow is neither feasible within the radiotherapy department schedule nor is it acceptable to patients because of toxicity or lack of tolerance for receiving an **intravenous** injection.

7.2 Significance level and sample size

- This is a feasibility study and therefore does not aim to demonstrate statistical significance.
- No published informative data exist upon to guide sample size calculation.
- Sample size required for feasibility study is minimum of 30, as recommended by Lancaster et al (Lancaster, 2004). Other authors have suggested a smaller sample size of 12 where there is no prior information to guide sample size calculation (Julious, 2005). Since patients are acting as their own controls 20 patients will permit analysis of 40 groups- 20 set of CBCT images acquired with and 20 without HBB.

7.3 Study accrual

- On average one patient referred to Leeds Cancer Centre per week for consideration of SABR for lower abdomen/pelvic oligometastatic disease therefore it is anticipated to recruit 20 patients over 12-24 months.
- All of the patients registered in the study will be accounted for. The number of patients who were not evaluable, who died or withdrew before treatment began will be specified. Final evaluation of patients will take place at the time of their last SABR fraction. Since patients will not be followed up within the context of this study no description of follow up time is required and there would be no impact from loss to follow up.

7.4 Safety monitoring

Toxicity will be assessed at the time of final SABR treatment by means of trial clinician assessment. Grading of toxicity will be performed using CTCAE version 5 (see Appendix B). Both events related and unrelated to treatment will be captured.

7.5 Statistical analysis

1. Data will be analysed using IBM SPSS (IBM, New York, USA)
 1. The number of patients accrued will be described.
 2. Safety analysis will be based on the number of patients accrued. All analyses of safety will be descriptive and will consist of frequency tables for binary and categorical variables and summary statistics (mean, median and range) for continuous variables.
 3. The adherence to the theoretical main protocol treatment (dose, schedule and modifications to administration of HBB) and the reasons for non-adherence by, as well as the reasons why administration of HBB was stopped will be described.
 4. Proportions of CBCT images with better or worse Likert-type scales scores for target matching will be described with confidence intervals to indicate the likely true proportion in the population. This is a feasibility study and therefore not expected to demonstrate statistical significance of differences between proportions to a p value of ≤ 0.05 , therefore no comparative statistical tests will be performed and no p value will be described.
 5. Analysis of Likert-type scale score data will be represented graphically to show the proportions of patents with each Likert-type scale score and proportions of images with better/worse scores with and without HBB.
 6. Assessors of image quality will be blinded to which SABR fraction the CBCT images are related to, to avoid confounding from knowledge of which fraction HBB was administered on. This will be performed by use of coded image file names.
 7. Measurements of inter and intra-observer variation may be performed to validate assessment of image quality using Cohen's kappa statistic. This ranges from -1 to +1. Agreement will be interpreted as: ≤ 0 (none); 0.01-0.2 (slight); 0.21-0.4 (fair); 0.41-0.6 (moderate); 0.61-0.8 (substantial); 0.81-1.0 (almost perfect). The process of intra-observer variation will likely be determined by including a copy of an image obtained with and without HBB within the set of images for the assessors to score.

8. Feasibility of clinical use of HBB in SABR workflow will be based on responses to end of treatment staff questionnaire. All analyses of feasibility will be descriptive and will consist of frequency tables for binary and categorical variables and summary statistics (mean, median and range) for continuous variables.

Chapter 8 Investigator authorisation procedure

1. This trial concept was discussed at the CTRad Proposals Guidance Meeting on 05.07.2018 and it was felt to be both feasible and achievable. This meeting included patient and public involvement and input into the trial design and methodology.
2. The trial will be approved by St James's Institute of Oncology Clinical Trials Review Approval Board (CTRAB), Leeds Teaching Hospitals Research and Development and the Local Research Ethics Committee.
3. This trial will be conducted in accordance with the professional and regulatory standards required for non-commercial research in the NHS under the Research Governance Framework for Health and Social Care and ICH GCP.
4. This trial will comply with the protocol and the protection of patients' rights as detailed in the Declaration of Helsinki adopted by the 18th World Medical assembly, Helsinki, Finland, 1964 and later revisions (last revised Edinburgh 2000).

Chapter 9 Patient registration

Patients will be registered to the trial after they have provided written informed consent.

The local ART-NET Clinical Research Fellow may be contacted by NHS telephone or NHS e-mail during office hours. The following information should be provided:

Patient name

Patient date of birth

Local hospital number

NHS number

Date and result of relevant radiological imaging (CT or PET-CT scan)

Performance status

Information about any potential contraindications to administration of HBB (severe cardiac disease, recent cardiac event, cardiac tachyarrhythmias, angle closure glaucoma, myasthenia gravis, pyloric stenosis, porphyria, severe ulcerative colitis, paralytic ileus, obstructive uropathy or allergy to HBB)

This process will take place within each of the participating trial sites (for example, Leeds clinical research fellow will contact participants treated in Leeds)

Chapter 10 Forms and procedures for collecting data

Data will be collected on dedicated case report forms and stored on a trial-specific secure database. Data will be collected by the ART-NET Clinical Research Fellow and other Investigators. Data will be analysed using IBM SPSS (IBM, New York, USA).

The following forms will be available:

1. Serious Adverse Events forms
2. Patient end of treatment questionnaire
3. Patient end of treatment toxicity assessment
4. Radiotherapy department staff end of treatment questionnaire
5. Cone beam CT image quality assessment form

10.1 Trial forms and procedure for completion

The following forms will be completed for all participants:

1. Consent form
1. All original Consent Forms are dated and signed by both the patient and investigator, and are kept in a central log at the participating trial site.
2. End of treatment patient and staff questionnaires and patient toxicity assessment
 1. End of treatment patient and staff questionnaires and patient toxicity assessment form should be completed at the time of the patient's final SABR fraction
 2. These should be completed for all patients and should not be made available to third parties. Each questionnaire should be photocopied. The original copy must be sent by the hospital to the clinical research fellow as soon as it is due. One other copy must be filed in the patients' notes. If information is not known it must be clearly stated.
 3. All non-serious adverse events, adverse reactions and unexpected adverse events should be should be graded by a member of the trial team using CTCAE version 5, and recorded in the end of treatment toxicity assessment form. These should be recorded and reported as per the adverse event section of the trial protocol.

4. Completed end of treatment patient, staff and toxicity assessment forms should be sent to the Leeds Clinical Research Fellow within 28 days of the form being due.
 5. The Chief Investigator reserves the right to amend or add to the end of treatment patient and staff questionnaires as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by centres with immediate effect.
 6. End of treatment patient and staff questionnaires should be returned as soon as possible by fax or by post to the following address: Dr Finbar Slevin, Radiotherapy Research Office, Level 4 Bexley Wing, St James's University Hospital, Beckett Street, Leeds LS9 7TF.
 7. The Leeds Clinical Research Fellow will monitor receipt of end of treatment patient and staff questionnaires. They will also check incoming end of treatment patient and staff questionnaires for compliance with the protocol, inconsistent and missing data.
3. Cone beam CT image quality assessment form.
 1. To be completed for every patient.
 2. Trial sites are using both X-ray volume imaging (XVI) (Elekta®, Stockholm, Sweden) and On-Board Imager® (OBI) (Varian, California, USA). Image quality assessment forms should be completed at the trial site treating the patient. This is to avoid problems with evaluation of imaging from one image guided radiotherapy platform on a different system. Form should be returned to the following address: Dr Finbar Slevin, Radiotherapy Research Office, Level 4 Bexley Wing, St James's University Hospital, Beckett Street, Leeds LS9 7TF.

The following forms may be required:

4. Serious adverse event (SAE) forms
 1. To be completed in the event of an SAE
 2. **The SAE form MUST be completed and the clinical research fellow must be notified of all non-exempt SAEs within one working day. The telephone number is 0113 206 8891**

3. The SAE form MUST be completed and the clinical research fellow must be notified of all SAEs that occur up to 30 days from the completion of radiotherapy, and all SARs and SUSARs indefinitely
4. An SAE form must be completed and signed by the investigator for all SAEs, SARs and SUSARs, including the information regarding grading, causality and expectedness. A member of the site trial team may complete and sign the SAE on behalf of the investigator if the specific responsible investigator is unavailable. When the responsible investigator becomes available they must check the SAE, make any necessary changes and sign and re-send the form to the clinical research fellow as soon as possible.
5. Completed SAE forms should be faxed to the clinical research fellow within one working day of the investigator becoming aware of the SAE, SAR or SUSAR. The telephone number is: 0113 206 8891.

10.2 Data flow

Data will be collected on dedicated case report forms and stored on a trial specific password secure NHS database. Serious Adverse Events forms must also be completed as necessary. Details from SAE forms will also be stored on the dedicated secure database.

Data will be collected by the clinical research fellow and other trial investigators. **The Leeds Chief Investigator/Clinical Research Fellow will monitor receipt of CRFs. They will also check incoming CRFs for compliance with the protocol, inconsistent and missing data. All SAE reports will be reviewed by the clinical research fellow. The causality as assessed by the investigator cannot be overruled by the clinical research fellow. In cases where there is disagreement, both opinions will be recorded on subsequent reports.**

The Clinical Research Fellow will maintain the confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, with the exception of the reporting of serious adverse events.

Sufficient data will be recorded for all participating patients to enable accurate linkage between hospital records and trial activities (for example, arranging consent appointment at the same time as participants attend for their

radiotherapy planning scan)- this process will be undertaken within each trial site by their clinical research fellow. No specific clinical information from medical records is required for the purposes of this trial.

Source data and all trial related documentation will be accurate, complete, maintained and accessible for monitoring and audit visits;

All original Consent Forms will be dated and signed by both the patient and investigator, and will be kept together in a central log together with a copy of the specific patient information sheet(s) they were given at the time of consent.

Copies of CRFs will be retained for 5 years to comply with international regulatory requirements.

Chapter 11 Reporting adverse events

11.1 Definitions

An **Adverse Event (AE)** is defined as any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs following the administration of the trial medication regardless of the dose or causal relationship. This can include any unfavourable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment. (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), 2016).

An **Adverse Drug Reaction (ADR)** is defined as any response to a medical product, that is noxious and/or unexpected, related to any dose. (ICH-GCP).

Response to a medicinal product (used in the above definition) means that a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

An **Unexpected Adverse Drug Reaction** is any adverse reaction for which the nature or severity is not consistent with the applicable product information (e.g., Investigators' Brochure). (ICH-GCP).

A **Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or**

Suspected Unexpected Serious Adverse Reaction (SUSAR): is defined as any undesirable experience occurring to a patient, whether or not considered related to the protocol treatment. A Serious Adverse Event (SAE) which is considered related to a protocol drug treatment is defined as a **Serious Adverse Drug Reaction (SADR)**.

Adverse events and adverse treatment related reactions which are considered as **serious** are those which result in:

- ◆ death
- ◆ a life threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- ◆ hospitalization or prolongation of hospitalization
- ◆ persistent or significant disability/incapacity

- ◆ a congenital anomaly/birth defect
- ◆ any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above) (ICH-GCP)

Medical judgment should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

The Leeds **Clinical Research Fellow** must be notified of all non-exempt SAEs within one working day, and the SAE from completed.

The Leeds **Clinical Research Fellow** must be notified of all SAEs that occur up to 30 days from the completion of radiotherapy, and all SARs and SUSARs indefinitely.

11.2 Exceptions specific to this trial in expedited SAE Notification and Reporting

Although meeting the definition of a 'serious' event, patients who are hospitalised:

1. Purely to simplify treatment delivery (e.g. due to large geographical distance to travel for treatment)
2. As a result of pre-existing conditions that, in the opinion of the investigator, have not been exacerbated by treatment are exempt from expedited notification as an SAE.

Institutional requirements

All non-serious AEs, ARs and UAEs should be recorded in the toxicity section of the CRF. Completed forms should be sent to the Leeds **Clinical Research Fellow** within 28 days of the form being due.

All AEs, ARs and UAEs, whether serious or not, should be graded using CTCAE version 5.

Investigator requirements

In the event of an AE or AR, expected or unexpected, the investigator responsible for the care of the patients must judge whether the event is considered serious or non-serious (see definitions and exceptions above). All non-exempt serious events must be immediately reported to the Leeds **Clinical Research Fellow** (within one working day) and recorded on an SAE form.

Causality

The investigator must also judge the causality of all serious events and reactions with regard to their relationship to the trial treatment. Causality can be defined as follows:

Unrelated: There is no evidence of any causal relationship- considered SAE

Unlikely: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment) - considered SAR

Possible: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication).

However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments) - considered SAR

Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely- considered SAR- considered SAR

Definite: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out- considered SAR

Expectedness

The investigator must assess whether the event is expected or unexpected (see definitions above). All unexpected SARs are considered SUSARs and are reported as such.

Reporting procedure

The Leeds Clinical Research Fellow must be notified within one working day of the investigator becoming aware of any non-exempt SAE, SAR or SUSAR. The Leeds Clinical Research Fellow must be notified of all SAEs that occur up to 30 days from the completion of radiotherapy, and all SARs and SUSARs indefinitely.

An SAE form must be completed and signed by the investigator for all SAEs, SARs and SUSARs, including the information regarding grading, causality and expectedness. A member of the site trial team may complete and sign the SAE on behalf of the investigator if the specific responsible investigator is unavailable. When the responsible investigator becomes available they must check the SAE, make any necessary changes and sign and re-send the form to the Leeds Clinical Research Fellow as soon as possible.

Completed SAE forms should be faxed to the Leeds Clinical Research Fellow within one working day of the investigator becoming aware of the SAE, SAR or SUSAR. The telephone number is 0113 206 8891.

The Leeds Clinical Research Fellow will inform the sponsor of all SAE, SAR or SUSARs within one working day of being made aware of the event.

Follow-up following Adverse events or reactions

Patients who have experienced a SAE, SAR or SUSAR must be followed up until complete clinical recovery and blood results have returned to baseline, or until the event has stabilised. Information regarding follow up should be recorded on a further SAE form and the box marked 'Follow-up' should be ticked. Completed forms should be faxed to the Leeds Clinical Research Fellow. Additional information may be provided separately. The patients should be identified by trial number, date of birth and initials only. The patient's name should not be used on any trial documentation.

Leeds Clinical research fellow Responsibilities

All SAE reports will be reviewed by the Leeds **Clinical Research Fellow**. The causality as assessed by the investigator cannot be overruled by the **Clinical Research Fellow**. In cases where there is disagreement, both opinions will be recorded on subsequent reports.

The Leeds **Clinical Research Fellow** is responsible for the reporting of all SARs and SUSARs to the research ethics committees and regulatory authorities as appropriate.

The Leeds **Clinical Research Fellow** will keep all investigators informed of any safety issues arising during the trial.

Chapter 12 Quality assurance

This trial will be conducted in accordance with the professional and regulatory standards required for non-commercial research in the NHS under the Research Governance Framework for Health and Social Care and ICH GCP.

The centre may be monitored by Health Authorities to carry out source data verification, and confirm compliance with the protocol and the protection of patients' rights as detailed in the Declaration of Helsinki adopted by the 18th World Medical assembly, Helsinki, Finland, 1964 and later revisions (last revised Edinburgh 2000). By participating in this trial the Chief Investigator is confirming agreement with his/her local NHS Trust to ensure that:

1. Sufficient data is recorded for all participating patients to enable accurate linkage between hospital records and CRFs;
2. Source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits;
3. All staff who are involved with the trial are trained appropriately;
4. All original Consent Forms are dated and signed by both the patient and investigator, and are kept together in a central log together with a copy of the specific patient information sheet(s) they were given at the time of consent.
5. Copies of CRFs are retained for 5 years to comply with international regulatory requirements;
6. Staff will comply with the Standard Operating Procedures for this trial.

The Leeds **Clinical Research Fellow** will monitor receipt of CRFs. They will also check incoming CRFs for compliance with the protocol, inconsistent and missing data.

Chapter 13 Ethical considerations

13.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), 2016).

The protocol will be approved by the NHS Ethics Committee.

13.2 Subject identification

The patient's full name, date of birth, hospital number and NHS number will be collected at registration to allow tracing through local medical records. This will be done to clarify suitability for the trial and permit identification of correct dates and times for trial team interactions with the participant during their radiotherapy treatment (for example, arranging appointment for consent when participant attends for their radiotherapy planning scan). The personal data recorded on all documents will be regarded as confidential. Only initials and date of birth will be recorded on Case Report Forms. The code linking identifiable data to the allocated study number is to be stored electronically within password protected database on a secure NHS server at each participating trial site.

The dedicated trial computer database where patient information is stored is password protected. The database is stored with the secure, password protected NHS computer system.

The local Principle Investigator must keep a separate log of patients' trial numbers, names, and hospital numbers. This log will be kept within a secure locked filing cabinet, within a locked office and access to the office area is with swipe card only. This is situated within Leeds Cancer Centre, within St James's University Hospital. Equivalent arrangements will be present in any of the other ART-NET centres who participate in the study. The investigators must maintain in strict confidence trial

documents, which are to be held in the local hospital (e.g. patients' written consent forms). The investigators must ensure the patient's confidentiality is maintained. The research team will maintain the confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, with the exception of the reporting of serious adverse events. Representatives of the trial team will be required to have access to patient notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times. In the case of special problems and/or competent authority queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

Radiotherapy department staff (who are asked to complete an end of treatment questionnaire) will be identified only by their name on the consent form and no other identifiable information will be collected. Only initials will be recorded on the end of treatment questionnaire.

13.3 Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It is the responsibility of the central trial site in Leeds to translate the enclosed informed consent document. The translated version should be dated and version controlled.

The bold sections of the enclosed informed consent document are the sections that **must** appear in the translation.

The translated informed consent form is part of the documents to be submitted to the ethics committee for approval. The competent ethics committee for each institution must validate local informed consent documents before the centre can join the study. It is the responsibility of the NHS ethics committee to guarantee that the translation is conforming to the ICH-GCP guidelines.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be

obtained for all patients included in the study before they are registered in the study. This must be done in accordance with the national and local regulatory requirements.

All healthcare staff approached to complete end of treatment staff questionnaire will be informed of the aims of the study. It is not anticipated that any possible adverse events will result from completion of the questionnaire. It will be emphasized that the participation is voluntary and that the staff member is allowed to refuse further participation in the protocol whenever he/she wants. Documented informed consent must be obtained for all patients included in the study before they are registered in the study. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that the written informed consent form should be signed and personally dated by the patient.

Chapter 14 Administrative responsibilities

Chief investigator: Dr Finbar Slevin

The person above accepts the responsibilities as outlined previously.

Chapter 15 Trial sponsoring and financing

The trial sponsor is the University of Leeds.

C/o Claire E Skinner

Faculty NHS Research Ethics Officer

Faculty Research Office

Room 9.29, Level 9, Worsley Building

Clarendon Way

Leeds

LS2 9NL

Telephone: 0113 343 7587

The trial is financed within a Cancer Research UK Accelerator award to the UK Advanced Radiotherapy Technologies Network (ART-NET).

Trial insurance

Insurance is provided under the NHS indemnity scheme.

Publications policy

All publications and presentations relating to the trial will be authorised by the Chief Investigator. Authorship will be determined by the Chief Investigator and will include the Chief Investigator and trial statisticians. Further authorship will be determined by centre accrual. All participating centres will be acknowledged in the manuscripts according to patient accrual.

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Chapter 17 Appendix B: CTCAE version 5 scoring for toxicity

Adverse Event	Grade				
	1	2	3	4	5
Abdominal distension	Asymptomatic ; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe discomfort; limiting self care ADL	-	-
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences ; urgent intervention indicated	Death
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related oedema/angioedema; hypotension	Life-threatening consequences ; urgent intervention indicated	Death
Bloating	No change in bowel function or oral intake	Symptomatic, decreased oral intake; change in bowel function	-	-	-

Blurred vision	Intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Bruising (intravenous injection site)	Localized or in a dependent area	Generalized	-	-	-
Cardiac arrest	-	-	-	Life-threatening consequences ; urgent intervention indicated	Death
Cardiac disorders - Other, specify: Dizziness	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences ; urgent intervention indicated	Death
Chest pain-cardiac	Mild pain	Moderate pain; pain on exertion; limiting instrumental ADL;	Pain at rest; limiting self care ADL; cardiac catheterization; new onset cardiac chest	-	-

		haemodynamically stable	pain; unstable angina		
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Constipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in stoma output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in stoma output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in stoma output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min	-	-

Glaucoma	Less than 8 mmHg of elevated intraocular pressure (EIOP); no visual field deficit	EIOP which can be reduced to 21 mmHg or under with topical medications and no visual field deficit	EIOP causing visual field deficits	Visual field deficit within the central 10 degrees of the visual field in the affected eye	-
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated	-	-	-
Intravenous injection procedure	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences ; urgent intervention indicated	Death
Urinary retention	Urinary, suprapubic or intermittent catheter placement not indicated; able to void	Placement of urinary, suprapubic or intermittent catheter placement indicated;	Elective invasive intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences ; organ failure; urgent operative intervention indicated	Death

	with some residual	medication indicated			
Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, TPN, or hospitalisation indicated	Life-threatening consequences	Death

Chapter 18 Appendix C: End of treatment participant questionnaire



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HBB-SABR: A feasibility study investigating the effect of hyoscine butylbromide injections on cone beam CT quality when delivering abdomino-pelvic stereotactic ablative radiotherapy (SABR)

(A study investigating whether hyoscine butylbromide can improve CT image quality during stereotactic ablative radiotherapy in the abdomen and pelvis)

End of treatment questionnaire (version 2.0 07/05/2019)

IRAS Project ID: 252816

Participant initials:

Participant study number:

Trial site:

Instructions: Below are some statements that describe how someone might feel about receiving the injection of hyoscine butylbromide. Please read each statement and circle the number 1 to 4 that best describes your feelings about the injection.

	Not at all	Somewhat	Moderately	Very much so
1. I understood why the injection was being given	1	2	3	4

2. Before it was given, I was anxious about having the injection	1	2	3	4
3. When it was given, I found having the injection frightening	1	2	3	4
4. I found the injection painful	1	2	3	4
5. I found the injection delayed my treatment	1	2	3	4
6. I found the injection gave me side effects	1	2	3	4
7. If the injection was shown to work and I needed to have this type of radiotherapy again, I would be prepared to have an injection before every treatment	1	2	3	4

Please turn over

If you had any other problems with the injection, please write them in the box below:

If you have any other comments about having the injection, please write them in the box below:

Chapter 19 Appendix D: End of treatment staff questionnaire



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HBB-SABR: A feasibility study investigating the effect of hyoscine butylbromide injections on cone beam CT quality when delivering abdomino-pelvic stereotactic ablative radiotherapy (SABR)

End of treatment staff questionnaire (version 2.0 07/05/2019)

IRAS Project ID: 252816

Participant initials:

Trial site:

Indicate staff role (e.g. therapy radiographer):

Instructions: Below are some statements that describe how you might feel about your patient receiving the injection of hyoscine butylbromide. Please read each statement and circle the number 1 to 4 that best describes your feelings about the injection.

	Not at all	Somewhat	Moderately	Very much so
1. I had enough information about why the patient was having the injection	1	2	3	4
2. I had to wait for someone to attend to administer the injection	1	2	3	4
3. I found the injection delayed the SABR treatment pathway for the patient	1	2	3	4

4. The injection appeared to be painful for the patient	1	2	3	4
5. The injection appeared to give the patient side effects	1	2	3	4
6. I thought that the CBCT image quality appeared better when the injection was given	1	2	3	4
7. I would be prepared for the injection to be given routinely for SABR treatments	1	2	3	4

Please turn over

If you had any other problems with the injection, please write them in the box below:

If you have any other comments about the injection, please write them in the box below:

Chapter 20 Appendix E: End of treatment toxicity assessment form

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HBB-SABR: A feasibility study investigating the effect of hyoscine butylbromide injections on cone beam CT quality when delivering abdominopelvic stereotactic ablative radiotherapy (SABR)

Participant toxicity assessment (version 1.0 06/11/2018)

(To be completed by study co-investigator)

IRAS Project ID: 252816

Participant initials:

Participant study number:

Trial site:

Score any toxicity judged to be related to hyoscine butylbromide injection using CTCAE version 5 criteria listed below. Insert score of 1 to 5 in box, or 0 if no toxicity elicited.

Gastrointestinal toxicity:

Abdominal distension

Abdominal pain

Bloating

Constipation

Diarrhoea

Nausea

Vomiting

Genitourinary toxicity:

Urinary retention

Cardiovascular toxicity:

Cardiac arrest

Chest pain- cardiac

Dizziness

Palpitations

Ocular toxicity:

Blurred vision

Acute glaucoma

General toxicity:

Allergic reaction Anaphylaxis Bruising (**intravenous** injection site) Dry mouth **Intravenous** injection procedure

Adverse Event	Grade				
	1	2	3	4	5
Abdominal distension	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe discomfort; limiting self care ADL	-	-
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral	Life-threatening consequences; urgent	Death

			intervention indicated; allergy-related oedema/angioedema; hypotension	intervention indicated	
Bloating	No change in bowel function or oral intake	Symptomatic, decreased oral intake; change in bowel function	-	-	-
Blurred vision	Intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Bruising (intravenous injection site)	Localized or in a dependent area	Generalized	-	-	-
Cardiac arrest	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Cardiac disorders - Other, specify: Dizziness	Asymptomatic or mild symptoms; clinical or diagnostic observations only;	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing	Life-threatening consequences; urgent intervention indicated	Death

	intervention not indicated		hospitalization indicated; limiting self care ADL		
Chest pain-cardiac	Mild pain	Moderate pain; pain on exertion; limiting instrumental ADL; haemodynamically stable	Pain at rest; limiting self care ADL; cardiac catheterization; new onset cardiac chest pain; unstable angina	-	-
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Constipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in stoma output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in stoma output compared to baseline	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in stoma output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet	Inability to adequately aliment orally; tube feeding or TPN indicated;	-	-

	alteration; unstimulated saliva flow >0.2 ml/min	limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	unstimulated saliva <0.1 ml/min		
Glaucoma	Less than 8 mmHg of elevated intraocular pressure (EIOP); no visual field deficit	EIOP which can be reduced to 21 mmHg or under with topical medications and no visual field deficit	EIOP causing visual field deficits	Visual field deficit within the central 10 degrees of the visual field in the affected eye	-
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated	-	-	-
Intravenous injection procedure	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life- threatening consequences; urgent intervention indicated	Death
Urinary retention	Urinary, suprapubic or intermittent	Placement of urinary, suprapubic or	Elective invasive intervention indicated; substantial	Life- threatening consequences;	Death

	catheter placement not indicated; able to void with some residual	intermittent catheter placement indicated; medication indicated	loss of affected kidney function or mass	organ failure; urgent operative intervention indicated	
Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, TPN, or hospitalisation indicated	Life-threatening consequences	Death

Chapter 21 Appendix F: Patient information sheet

The Leeds Teaching Hospitals **NHS**
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PATIENT INFORMATION SHEET: *A research study using hyoscine butylbromide to improve quality of images used to guide stereotactic radiotherapy in the lower abdomen and pelvis*

IRAS Project ID: 252816

LTHT R+D Number: CO18/113831

REC Number: 19/YH/0074

Version 3.0 21/01/2020

You are invited to take part in a research study. Before you decide whether or not you wish to take part it is important for you to understand why the study is being done and what it will involve if you agree to take part. Please read the following information carefully and discuss it with friends, relatives or your GP if you wish. Take time to decide whether or not you wish to take part. Please ask us if there is anything that is not clear, or if you would like more information.

Summary of the study

Accuracy of stereotactic radiotherapy is checked by using CT (computed tomography) scans. In the abdomen (tummy) and pelvis these scans are affected by motion of the bowel. In x-ray departments a drug called hyoscine butylbromide is used to reduce this motion and produce better images. It is not used in radiotherapy at present. We wish to perform a study to test if hyoscine butylbromide improves the image quality of the radiotherapy CT scans. Patients in the study will be given hyoscine butylbromide before some of their radiotherapy treatments and the images will be checked to see if they appear better when the drug is given.

What is the purpose of the study?

Radiotherapy has been advised for treatment of your cancer in the lower abdomen or pelvis. Radiotherapy is high-energy x-ray treatment. Stereotactic radiotherapy delivers a large amount of radiotherapy very accurately to the cancer and a small area around it. Each radiotherapy treatment is called a fraction and usually patients with your type of cancer have radiotherapy given in three or five fractions over one to two weeks. A type of scan called a CT (computed tomography) scan is performed before and after each fraction of radiotherapy. The images are used to check that the cancer is being accurately treated by the radiotherapy. However, movement of the bowel affects the quality of the images. Sometimes this makes it more difficult to see the cancer on the cone beam CT scan.

This trial will test a new way of improving the quality of the cone beam CT scans using a drug called hyoscine butylbromide. The main aim is to assess if this reduces the movement of the bowel and leads to better quality cone beam CT images. Hyoscine butylbromide is used routinely in the x-ray department for other types of scan such as MRI (magnetic resonance imaging). You may well have had it before if you have had an MRI scan. However, it is not used routinely in the radiotherapy department.

All patients in this trial would receive the hyoscine butylbromide. We did not see much improvement in image quality for the first five patients when the drug was given into the muscle of the buttock. This meant that we have made a change to the study. The drug would now be given into a plastic tube in your arm called a cannula just before your radiotherapy treatment. It would be given on alternate fractions of radiotherapy, which is before the first, third and fifth treatments if you are having five radiotherapy fractions (or the first and third treatments if you are having three radiotherapy fractions). This is so the trial can test whether the hyoscine butylbromide is having the predicted effect of reducing movement of the bowel or not.

This trial does not change any aspect of your radiotherapy treatment apart from having the hyoscine butylbromide injection. The drug could cause some patients side effects. This is discussed in the section 'Potential ways this study could harm those who take part' along with how we try to overcome this potential problem.

What will happen to me if I take part?

Before the treatment starts you will be assessed to check that you are suitable to take part in the study and you will be asked to read this patient information sheet. If you are happy to take part in the study you will be asked to sign a consent form.

About 3 weeks before the start of radiotherapy you will be asked to come to the radiotherapy department for a planning CT scan. This is used to design the radiotherapy. You may also be asked to drink some water or cordial an hour beforehand. You lie on a hard bed and pass through the scanner (which looks a bit like a large Polo mint) while a series of x-rays is taken. These let us see your insides around the cancer as a series of 'slices'. The planning scan shows us how to target the radiotherapy so that the cancer gets a high dose but the area around it does not get too much radiotherapy.

The radiotherapy treatment involves coming for three or five visits over one to two weeks. There will be a gap of at least 2 days between treatment visits. You may also be asked to drink some water or cordial an hour before each treatment. This helps keep most of the bowel out of the way from the radiotherapy.

On the day of the radiotherapy treatment the first thing that happens is that you will come to the radiotherapy department and be directed around to the radiotherapy machine. You will get changed into a gown, and drink some water if this is needed.

When it is time for the radiotherapy treatment you will have the cannula placed into your arm and the hyoscine butylbromide will be given into this tube. This is an additional part of this research study.

You will then lie on your back on a hard bed under the radiotherapy machine. The machine that delivers the radiotherapy is called a linear accelerator. This is always about 50cm away from you. Before the radiotherapy is given you have a cone beam CT scan taken to let us check that the cancer is lined up in the same as at the planning scan. This process is called image-guided radiotherapy (IGRT). We might have to move the bed to make sure it is lined up as closely as possible to the positions on the planning scan. Once everything is lined up the radiotherapy is started. The radiotherapy machine moves around you once or twice. Nothing

touches you during the radiotherapy and you do not see, feel or hear it- a bit like when you have an x-ray. It is important that you lie as still as you can during scans and radiotherapy. After the radiotherapy has been given another cone beam CT scan is taken. This is to check that nothing has moved during the treatment. The total length of time you will be lying in the treatment room is about 10 to 20 minutes.

After your final radiotherapy treatment you will be asked questions about any side effects that you might have experienced and you will be asked to complete a short questionnaire about the treatment.

What are the possible risks and side effects of taking part?

You might get side effects from the hyoscine butylbromide but we do not think that these are likely to be serious because the drug is routinely used in the x-ray department and most patients do not have significant problems with it.

Short term side effects

Hyoscine butylbromide can cause some temporary side effects but these usually settle within 30-60 minutes. Some patients may notice blurring of vision. We will ask you not to drive for around 45 minutes after the hyoscine butylbromide injection, or until any blurred vision has settled (usually within 60 minutes).

Rarely some patients can have a condition called acute glaucoma that they do not know about and it might be brought on by hyoscine butylbromide. If you notice painful blurred vision after having hyoscine butylbromide then you must go straight to the nearest A&E department.

It is relatively common to experience a temporary dry mouth after having hyoscine butylbromide. Other side effects that might happen include dizziness and palpitations (a feeling of your heart racing). Very uncommon side effects from hyoscine butylbromide might include an allergic reaction, difficulty in passing urine, abdominal pain or vomiting.

There have been cases where a small number of patients died after having tests in hospital where hyoscine butylbromide was also given. It is not certain whether or not

the hyoscine butylbromide contributed towards their death but these patients also had underlying heart problems. This risk from hyoscine butylbromide is thought to be very small but the recommendation is not to give hyoscine butylbromide to patients with heart problems. It is very important that you inform your oncologist if you have ever had any heart problems now or in the past.

Long term side effects

We do not think that there are long term side effects from hyoscine butylbromide because the effects of the drug wear off quickly.

What happens after treatment?

On the last day of your radiotherapy we will ask you to complete a questionnaire about any side effects that you might have experienced and how you found having the hyoscine butylbromide injections alongside your radiotherapy.

Once the radiotherapy has finished, your usual oncology doctor will follow you up.

What are the potential benefits of taking part?

Taking part is completely voluntary.

The study would not change the radiotherapy treatment for you but it could help improve the treatment for future patients.

The possible ways taking part in this study could help are:

We will gain a better understanding of whether hyoscine butylbromide helps give us better radiotherapy CT images. This could help us more accurately target radiotherapy for future patients.

What if something goes wrong?

We would not expect a significant risk of severe side effects in the short or long term following this treatment. If you are harmed while taking part in this research project there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms may be available to you.

Loss of capacity during the trial

In the very unlikely event that you became unwell during the research study and were no longer able to make decisions for yourself (this is called 'loss of capacity'), you would be withdrawn from the research study. No further information about you would be collected after this point, although we would use any information obtained prior to the event. Should you recover sufficiently you could continue within the study.

Will my taking part in this study be kept confidential?

The information collected about you during the course of the research will be kept strictly confidential. Your information will be entered into a password-protected database and no one outside the research group and the hospital team treating you will be allowed access to this information. Any information about you that leaves the hospital will be anonymous so that you cannot be recognised from it. Any forms completed about you during the trial will be anonymised using a unique identifying number and your initials rather than your name or other personal details.

What will happen to the results of the study?

The results of the study may be presented at scientific meetings nationally and internationally and published in the oncology literature. You will not be identified in any report or publication. This study forms part of a PhD research degree and will be described within a thesis for this degree.

Who is organising the study?

A research team, made up of consultant oncologists, clinical research fellow, physicists and a research radiographer is responsible for this study.

Who has reviewed the study?

The study has been reviewed and approved by Yorkshire and Humber- Leeds West Research Ethics Committee.

Contact for further information or to participate in the study:

If you require any further information please contact Dr Finbar Slevin at St James's Hospital on 0113 206 7630 saying you are calling about the hyoscine butylbromide SABR study, and we will call you back at a time convenient to you to discuss the study.

Contact for raising concerns or making a complaint about the care or service you receive within the study:

If you wish to raise a concern or make a complaint about the care or service you receive as a patient within the study, please contact the Leeds Teaching Hospitals NHS Trust PALS team.

Telephone: 0113 206 6261 (available during normal working hours only 9:00am-4.30pm Monday-Friday) or 0113 206 7168 (for queries out of normal working hours, please leave a voicemail).

Email: patientexperience.leedsth@nhs.net

General Data Protection Regulation statement

The University of Leeds is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will keep identifiable information about you for at least 5 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information by contacting the University data protection officer via e-mail on DPO@leeds.ac.uk.

Use of personal data in this research study

Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will collect information from you and/or your medical records for this research study in accordance with our instructions.

Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will keep your name, address, NHS number, date of birth and contact details confidential and will not pass this information to the University of Leeds. Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from the University of Leeds and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The University of Leeds will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, address, date of birth, NHS number or contact details.

Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will keep identifiable information about you from this study for at least 5 years after the study has finished.

Future research use of data

Your information could be used for research in any aspect of health or care, and could be combined with information about you from other sources held by researchers, the NHS or government.

Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will only be used for the purpose of health and care research, or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance.

Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

Thank you for taking the time to read this information sheet.

Chapter 22 Appendix G: Patient consent form



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IRAS Project ID: 252816

Participant Identification Number for this trial:

CONSENT FORM (version 3.0 21/01/2020)

Title of Project: HBB-SABR: A feasibility study investigating the effect of hyoscine butylbromide injections on cone beam CT quality when delivering abdomino-pelvic stereotactic ablative radiotherapy (SABR)

Name of Researcher:

Please
initial box

1. I confirm that I have read the information sheet dated 21st January 2020 (version 3.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. 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.
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University of Leeds, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
4. I understand that if I became unwell and could no longer make decisions for myself, I would be withdrawn from the study. I understand that no further information about me would be collected but any information already collected would be used.
5. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.
6. I understand that the information held and maintained by Leeds Teaching Hospitals NHS Trust (or other participating NHS Trusts)

may be used to help contact me or provide information about my health status.

7. I agree to take part in the above study.

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

Chapter 23 Appendix H: Image quality assessment form

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HBB-SABR: A feasibility study investigating the effect of hyoscine butylbromide injections on cone beam CT quality when delivering abdomino-pelvic stereotactic ablative radiotherapy (SABR)

Cone beam CT image quality assessment form (version 1.0 06/11/2018)

IRAS Project ID: 252816

Participant initials:

Participant study number:

Trial site:

Cone beam CT reference number:

Likert-type scale score:

- 1 impossible to match
- 2 poor quality imaging for matching
- 3 satisfactory quality imaging for matching
- 4 excellent quality imaging for matching

Factors influencing score:

- Streak artefact close to target
- Lack of soft tissue contrast
- Small target size
- Lack of surrogate for target matching

Please use this comments box to explain your decision:

Patient separation (cm):

Severity of streak artefact:

- None
- Mild
- Moderate
- Severe

Type of bowel causing artefact:

- Small bowel
- Colon
- Sigmoid
- Rectum

Location of node:

- Pre-sacral

- Right external iliac
- Left external iliac
- Right internal iliac
- Left internal iliac
- Right common iliac
- Left common iliac
- Para-aortic

Chapter 24 Appendix I: Healthcare staff participant information sheet



The Leeds Teaching Hospitals 
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HEALTHCARE STAFF INFORMATION SHEET: *A research study using hyoscine butylbromide to improve quality of images used to guide stereotactic radiotherapy in the lower abdomen and pelvis*

IRAS Project ID: 252816

LTHT R+D Number: CO18/113831

REC Number: 19/YH/0074

Version 2.0 21/01/2020

You are invited to take part in a research study. Before you decide whether or not you wish to take part it is important for you to understand why the study is being done and what it will involve if you agree to take part. Please ask us if there is anything that is not clear, or if you would like more information.

Summary of the study

Accuracy of stereotactic radiotherapy is checked by using CT (computed tomography) scans. In the abdomen and pelvis these scans are affected by motion of the bowel. In x-ray departments a drug called hyoscine butylbromide is used to

reduce this motion and produce better images. It is not used in radiotherapy at present. We wish to perform a study to test if hyoscine butylbromide improves the image quality of the radiotherapy CT scans. Patients in the study will be given hyoscine butylbromide before some of their radiotherapy treatments and the images will be checked to see if they appear better when the drug is given. We also wish to see if routinely giving hyoscine butylbromide within a busy radiotherapy department for stereotactic radiotherapy treatments would be possible.

What is the purpose of the study?

Radiotherapy has been advised for treatment of your patient's cancer in the lower abdomen or pelvis. Radiotherapy is high-energy x-ray treatment. Stereotactic radiotherapy delivers a large amount of radiotherapy very accurately to the cancer and a small area around it. Each radiotherapy treatment is called a fraction and usually patients with this type of cancer have radiotherapy given in three or five fractions over one to two weeks. A type of scan called a cone beam CT scan is performed before and after each fraction of radiotherapy. The images are used to check that the cancer is being accurately treated by the radiotherapy. However, movement of the bowel affects the quality of the images. Sometimes this makes it more difficult to see the cancer on the cone beam CT scan.

This trial will test a new way of improving the quality of the cone beam CT scans using a drug called hyoscine butylbromide. The main aim is to assess if this reduces the movement of the bowel and leads to better quality cone beam CT images. Hyoscine butylbromide is used routinely in the x-ray department for other types of scan such as MRI (magnetic resonance imaging). It is often used when patients have an MRI scan. However, it is not used routinely in the radiotherapy department.

All patients in this trial would receive the hyoscine butylbromide. We did not see much improvement in image quality for the first five patients when the drug was given into the muscle of the buttock. This meant that we have made a change to the study. The drug would now be given into a plastic tube in the patient's arm called a cannula. It would be given on alternate fractions of radiotherapy, which is before the first, third and fifth treatments if patients are having five radiotherapy fractions (or the first and third treatments if patients are having three radiotherapy fractions). This is so the trial can test whether the hyoscine butylbromide is having the predicted effect of reducing movement of the bowel or not.

This trial does not change any aspect of the radiotherapy treatment apart from having the hyoscine butylbromide injection.

We also wish to see whether hyoscine butylbromide injections could be routinely used for stereotactic radiotherapy treatments within a busy radiotherapy department (for example, whether it interfered with your work). We also wish to know whether it seemed to help improve the quality of the cone beam CT images used before and after each radiotherapy fraction.

What will happen to me if I take part?

You will be asked to read this participant information sheet. If you are happy to take part in the study you will be asked to sign a consent form.

When the patient attends for their final radiotherapy treatment you will be asked to complete a short questionnaire (end of treatment questionnaire). This will ask questions about how you found patients having the injection, any impact on your work and whether their cone beam CT images seemed to be of better quality when hyoscine butylbromide was given.

What are the possible risks and side effects of taking part?

We do not anticipate any risks or side effects occurring as a result of completing the questionnaire. No sensitive, embarrassing or upsetting topics will be discussed.

What are the potential benefits of taking part?

Taking part is completely voluntary.

The study could help improve the treatment for future patients.

The possible ways taking part in this study could help are:

We will gain a better understanding of whether hyoscine butylbromide helps give us better radiotherapy CT images. This could help us more accurately target radiotherapy for future patients.

What if something goes wrong?

We would not expect any risks or side effects as a result of completing the questionnaire. If you are harmed while taking part in this research project there are

no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms may be available to you.

Will my taking part in this study be kept confidential?

The information collected about you during the course of the research will be kept strictly confidential. Your name recorded on the consent form will be kept in a secure location and no one outside the research group will be allowed access to this information. We will not record any other personal information about you. The information that you provide in the end of treatment questionnaire that leaves the hospital will be anonymous so that you cannot be recognised from it. It will be anonymised using a unique identifying number and your initials rather than your name or other personal details.

What will happen to the results of the study?

The results of the study may be presented at scientific meetings nationally and internationally and published in the oncology literature. You will not be identified in any report or publication. This study forms part of a PhD research degree and will be described within a thesis for this degree.

Who is organising the study?

A research team, made up of consultant oncologists, clinical research fellow, physicists and a research radiographer is responsible for this study.

Who has reviewed the study?

The study has been reviewed and approved by Leeds (Central) Health Authority Research Ethics Committee.

Contact for further information or to participate in the study:

If you require any further information please contact Dr Finbar Slevin at St James's Hospital on 0113 206 7630 saying you are calling about the hyoscine butylbromide SABR study, and we will call you back at a time convenient to you to discuss the study.

General Data Protection Regulation statement

The University of Leeds is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will keep identifiable information about you for at least 5 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information by contacting the University data protection officer via e-mail on DPO@leeds.ac.uk.

Use of personal data in this research study

Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will collect information from you for this research study in accordance with our instructions.

Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will keep your name (recorded on the consent form) but will not pass this information to the University of Leeds or any other organisation. The University of Leeds will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out any of your other personal information or contact details.

Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will keep identifiable information about you (your name) from this study for at least 5 years after the study has finished.

Future research use of data

The information you provide in the end of treatment questionnaire could be used for research in any aspect of health or care. This is anonymised information so it could not be used to identify you.

Thank you for taking the time to read this information sheet.

Chapter 25 Appendix J: Healthcare staff consent form



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NHS Trust

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IRAS Project ID: 252816

Participant Identification Number for this trial:

CONSENT FORM (version 2.0 21/01/2020)

Title of Project: HBB-SABR: A feasibility study investigating the effect of hyoscine butylbromide injections on cone beam CT quality when delivering abdomino-pelvic stereotactic ablative radiotherapy (SABR)

Name of Researcher:

Please
initial
box

5. I confirm that I have read the information sheet dated 21st January 2020 (version 2.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
6. 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.
7. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.

8. I agree to take part in the above study.

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

**Appendix B CONSORT checklist: A feasibility study of
hyoscine butylbromide (buscopan) to improve image quality
of cone beam computed tomography during
abdominal/pelvic Stereotactic Ablative Radiotherapy**



**CONSORT 2010 checklist of information to include
when reporting a pilot or feasibility trial***

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	✓ Title page
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	✓ Pages 116-117
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	✓ Page 118 (non randomised feasibility study)
	2b	Specific objectives or research questions for pilot trial	✓ Page 118
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	✓ Pages 118-121
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	✓ Change to treatment, page 119
Participants	4a	Eligibility criteria for participants	✓ Page 119
	4b	Settings and locations where the data were collected	✓ Page 119
	4c	How participants were identified and consented	✓ Page 119

Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	✓ Page 119-120
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	✓ Pages 120-121
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	N/A
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	N/A feasibility potential for future trial. No progression criteria
Sample size	7a	Rationale for numbers in the pilot trial	✓ Page 121
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			N/A
Sequence generation	8a	Method used to generate the random allocation sequence	N/A
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	N/A
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	N/A
Blinding	11a	If done, who was blinded after	✓ Page 120

		assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	✓ Page 121
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned , received intended treatment, and were assessed for each objective	✓ Figure 4.1
	13b	For each group, losses and exclusions after randomisation, together with reasons	✓ Figure 4.1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	✓ Page 122
	14b	Why the pilot trial ended or was stopped	✓ Page 122
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	✓ Supplementary Table 4.1
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	✓ Tables 4.1-4.5
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	✓ Tables 4.1-4.5; IQR
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	✓ Tables 4.1-4.5
Harms	19	All important harms or unintended effects in each group (for specific	✓ Tables 4.3-4.5

		guidance see CONSORT for harms)	
	19a	If relevant, other important unintended consequences	N/A
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	✓ Pages 135-138
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	✓ Pages 135-138
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	✓ Pages 135-138
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	✓ Future applications to image guided radiotherapy; Pages 135-138
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	✓ ISRCTN24362767
Protocol	24	Where the pilot trial protocol can be accessed, if available	✓ Pages 143-225
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	✓ Title page
	26	Ethical approval or approval by research review committee, confirmed with reference number	✓ Page 118

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ*. 2016;355.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

**Appendix C Study protocol, invitation letter and participant
information sheet: An international Delphi consensus for pelvic
Stereotactic Ablative Radiotherapy**

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An international Delphi consensus concerning the practice of SABR/SBRT re-irradiation for malignancies in the pelvis

Protocol

Introduction

Radiotherapy is frequently used in the primary treatment of many pelvic malignancies but the management of an isolated pelvic recurrence often represents a challenge as to the optimal therapeutic approach[1, 2]. Such cases are often highly individualised and decision making is dependent on a combination of patient factors, the primary disease subtype, what previous treatments have been delivered and the volume and location of the recurrence. Salvage surgery may not be feasible or risks excessive morbidity and use of systemic anti-cancer therapies may not achieve adequate local control or symptomatic relief.

For a recurrence within or at the margin of a previous radiotherapy volume, re-irradiation may be an option but there is often concern with delivering a conventionally fractionated schedule given that organs at risk (OAR) including rectum, bowel, bladder and neural structures may have been previously treated close to tolerance[2, 3]. If an effective re-irradiation treatment is to be safely delivered, the decision making concerning re-irradiation should take into consideration several factors. These include careful patient selection (including time interval from first irradiation, the presence of any late toxicities, patient performance status and likely prognosis), meticulous treatment planning (including an assessment of previous and cumulative dose exposures to OAR as well as the arrangement of the functional subunits of those OAR in order to estimate the likelihood and consequences of late toxicities) and considerations regarding the optimum dose fractionation schedule and image guidance/treatment delivery techniques[1, 2, 4, 5].

Hyperfractionated schedules are commonly used in other sites to minimise risk of late effects but an alternative technique in patients with smaller pelvic recurrences is Stereotactic Ablative Radiotherapy (SABR)/Stereotactic Body Radiotherapy (SBRT), where a limited volume is exposed to high doses delivered in a small number of fractions with steep dose gradients to reduce doses to surrounding OAR[2, 5]. Initial results with SABR/SBRT re-irradiation in the management of limited sites of recurrent disease in the pelvis appear promising with good local control and acceptable rates of grade 3 or higher late toxicities[2, 6]. However, much of the published literature concerns single centre retrospective studies with small numbers of patients and there remains an absence of high level evidence to guide its use. Uncertainties also exist regarding optimum patient selection, cumulative OAR constraints and dose fractionation schedules[2].

A Delphi consensus is a highly structured approach to obtain consensus from a group of experts and may be useful when considering a clinical topic where

there exists limited prospective evidence to guide clinical decision making[7, 8]. Its key features include anonymity of participants, an iterative approach to survey questions, controlled feedback of group responses from previous rounds and statistical analysis of results[7-9]. The aim of this approach is to reduce participant loss to follow up, minimise the effects of individual bias/dominant individuals and encourage a focus on addressing the specific questions raised within the survey.

This document describes the protocol for an international Delphi consensus on SABR/SBRT re-irradiation in the pelvis, structured as per previous recommendations[8, 10].

Methods and Materials

Survey objectives

The aim of this survey is to develop consensus statements concerning the definition of SABR/SBRT re-irradiation in the pelvis, patient selection, pre-treatment investigations, radiotherapy planning technique and treatment delivery and OAR cumulative dose constraints.

Participant eligibility and selection

Clinical or radiation oncologists who have published articles about SABR/SBRT re-irradiation in the pelvis or who are considered to be experts within the field will be approached via e-mail to participate in the Delphi consensus. In the case of publications, the corresponding author will be contacted. Where the corresponding author is not a clinician or unable to participate in the survey, they will be asked to nominate a suitable alternative person. In addition within the United Kingdom (UK), a clinician practicing within centres delivering SABR/SBRT re-irradiation in the pelvis as part of the National Health Service (NHS) Commissioning through Evaluation (CtE) process will be approached to participate in the survey. The intention will be to recruit 10-20 participants, in keeping with previous recommendations[7]. All participants will be asked to consent to take part in the Delphi consensus. Participant responses will be anonymous to other participants, but not the survey organisers, and each participant will be allocated a unique identifying number so their responses through each round can be matched.

Questionnaires

An internal pilot will be performed to check for content validity. For the formal survey, three Delphi rounds are planned, structured in keeping with previous recommendations and other Delphi consensus surveys concerning clinical questions in radiotherapy[7-9]. A web-based platform will be used (Online Surveys, Jisc, UK). The survey organisers will not take part in any of the surveys. Each round will be open for four weeks. A reminder e-mail to non-responders will be sent after 2 weeks.

A modification to the original Delphi technique will be undertaken for round 1, where the survey questions will be based on a critical literature review[2, 11]. An open-ended approach to these questions will still be taken for round 1 to

allow information gathering from participants and remodelling of questions by the survey organisers for round 2. Round 1 will aim to discover participants' clinical practice and opinions regarding SABR/SBRT re-irradiation in the pelvis and will be divided into three sections: patient eligibility/pre-treatment investigations, re-irradiation planning and treatment delivery and OAR cumulative dose constraints. The survey organisers will review all responses and remodel questions within these sections into a series of statements for round 2.

In round 2, participants will be presented with a series of statements and a summary of the responses from round 1. They will be asked to rate each statement using a five point Likert scale (1=strongly agree, 2=agree, 3=neither agree nor disagree, 4=disagree, 5=strongly disagree). A free text box will allow participants to justify their response to each statement. Consensus for each statement will be considered to have been achieved if $\geq 75\%$ of responders agree or strongly agree[8]. The survey organisers will review all responses and remodel any statements not achieving group consensus for round 3.

In round 3, participants will be presented with remodelled statements that did not achieve consensus in round 2 and be asked to rate these using the Likert scale. They will also be presented with summary data of group responses to each statement from round 2. Statements that achieved consensus in round 2 will be visible with accompanying summary data but will not be scored.

Analysis of results and reporting


Statistical analysis will be undertaken using IBM SPSS (IBM, USA). Descriptive statistics summarising Likert scores for each statement, with a measure of central tendency (median) and a measure of dispersion (inter quartile range), will be presented[7]. The percent agreement and response rate for each statement will also be described. The percent agreement is the number of participants who indicate either agree or strongly agree divided by the total number of responders for that round. Non-responders will not be included in the denominator[8].

Any statement achieving $\geq 75\%$ agreement will be reported as a group recommendation. The median Likert score will be used to indicate the strength of a particular recommendation[8]. Any statement not achieving consensus after round 3 will be reported as no recommendation can be provided. The percent agreement will be presented alongside any such statements to indicate the level of agreement that was achieved.

References

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An international Delphi consensus concerning the practice of SABR/SBRT re-irradiation for malignancies in the pelvis

Invitation letter

[Insert date]

Dear [Insert name],

We would like to invite you to take part in a Delphi consensus regarding Stereotactic Ablative Radiotherapy (SABR)/Stereotactic Body Radiotherapy (SBRT) re-irradiation for malignancies in the pelvis. The project is being performed with the Cancer Research UK ARTNET and RADNET programmes.

The lead researcher (Finbar Slevin) is a Cancer Research UK ARTNET Clinical Research Fellow and is undertaking the survey as part of a doctoral research fellowship at the University of Leeds. The supervisory team are Ann Henry, Louise Murray, Peter Dickinson and Maria Hawkins.

Given the uncertainties that exist regarding the optimum patient selection criteria, radiotherapy planning and treatment delivery techniques and dose fractionation schedules/organ at risk constraints for SABR/SBRT re-irradiation in the pelvis, we believe that establishing a series of expert consensus statements would be a valuable aid to decision making in clinical practice.

We wish to include clinical/radiation oncologists who are experts in SABR/SBRT re-irradiation in the pelvis in the survey group. We have approached you since you have previously published in the field of SABR/SBRT re-irradiation in the pelvis and/or are known to work in this field. If you are not a clinical/radiation oncologist or are unable to take part in the survey, we would be grateful if you could suggest an alternate oncologist who we could approach.

Your responses to the survey will be anonymised and will not be identified to other participants.

The first round of the Delphi consensus is a structured information gathering round and should take approximately 60 minutes to complete via an online platform. The second/third rounds will involve voting on a series of consensus statements based on the information obtained in the first round and should be much quicker to complete.

If you take part in the survey, you would be included as a co-author on any publications that result from it.

If you are prepared to take part in the survey, we would be very grateful if you could inform us via e-mail (finbarslevin@nhs.net) and we will send you further information regarding completion of the survey.

Many thanks,

Yours sincerely,

Dr Finbar Slevin
Clinical Research Fellow
University of Leeds



The Leeds Teaching Hospitals
NHS Trust



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An international Delphi consensus concerning the practice of SABR/SBRT re-irradiation for malignancies in the pelvis

Information sheet

Title

An international Delphi consensus concerning the practice of SABR/SBRT re-irradiation for malignancies in the pelvis

Brief summary

This is a Delphi consensus of clinicians experienced in the practice of delivering Stereotactic Ablative Radiotherapy (SABR)/Stereotactic Body Radiotherapy (SBRT) to cancers in the pelvis where there has been prior treatment with radiotherapy. The survey will use electronic questionnaires over three rounds to establish a consensus regarding various aspects of the treatment pathway including patient selection and pre-treatment investigations, radiotherapy planning and treatment delivery and cumulative organs at risk dose constraints.

What is involved?

We wish to recruit clinical/radiation oncology experts who have either published and/or are experienced in the field of delivering SABR/SBRT re-irradiation for cancers in the pelvis for this Delphi consensus survey.

There is an absence of high quality evidence to support clinical decision-making regarding SABR/SBRT re-irradiation in the pelvis and we wish to use this survey to establish a series of recommendations for clinical practice and highlight potential areas for further research. The survey will focus on patient selection and pre-treatment investigations, radiotherapy planning and treatment delivery and cumulative organs at risk dose constraints.

The survey will take place over three rounds and use electronic questionnaires distributed via a web-based platform (Online Surveys). After you have read this information sheet, if you are happy to take part in the survey you will be asked to complete an online consent statement prior to responding to the first questionnaire.

The first round will ask open-ended style questions in order to establish the range of practice within the survey group. This information will be used to arrange a series of statements that will be contained within the questionnaire for the second round. You will be asked to respond to these statements using a simple scoring system to indicate the extent to which you agree/disagree with them. Those statements which have $\geq 75\%$ agreement of the group will be considered to have achieved consensus and will be

reported as a recommendation. Where the consensus is <75%, those statements will be remodelled by the survey team taking into account the responses in the second round and brought forward into a third round for voting. If after this third round statements have not achieved a consensus agreement, they will be reported as no recommendation could be made.

Who is organising the survey?

A team of clinical oncologists at the University of Leeds in the United Kingdom (UK) is organising the survey within the Cancer Research UK ARTNET and RADNET programmes. The lead researcher is an ARTNET clinical research fellow and doctoral research student.

How will my information be kept confidential?

Your responses to the questionnaires will remain anonymised to other participants. Your anonymised responses will be used to support other research in the future and may be shared with other researchers. Your personal data will be stored securely in keeping with University of Leeds data management policies and will be kept confidential.

What will happen to the results of the survey?

The results of the survey will help inform the development of trials of re-irradiation treatments with the Cancer Research UK RADNET programme. The results of the survey may be presented at scientific meetings nationally and internationally and published in the oncology literature. If you take part in the survey, you would be included as a co-author on any publications resulting from it. Your responses to the survey will not be identified in any report or publication. The survey forms part of a doctoral research degree and will be described within a thesis for this degree.

General Data Protection Regulation statement

We will be using information from you in order to undertake this survey and will act as the data controller for this survey. This means that we are responsible for looking after your information and using it properly.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the survey, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

Contact information for further information:

If you require any further information, please contact Dr Finbar Slevin at University of Leeds by e-mail: finbarslevin@nhs.net or by telephone: +44 113 206 7685.

Appendix D Round 1 questionnaire: An international Delphi consensus for pelvic Stereotactic Ablative Radiotherapy

Delphi consensus on re-irradiation in the pelvis- round 1 final version (copy)

Page 1: Consent statement

I have read and understood the information sheet regarding this Delphi consensus and I am happy to take part in it.

- Yes
 No

Page 2: Introduction

Thank you for agreeing to complete this Delphi consensus for Stereotactic Ablative Radiotherapy (SABR)/Stereotactic Body Radiotherapy (SBRT) re-irradiation in the pelvis.

We have decided to focus on SABR/SBRT re-irradiation in particular (rather than all re-irradiation in the pelvis) to try and achieve specific consensus statements that will aid decision making in clinical practice.

There are three sections in this first round:

Section 1. Patient selection and pre-treatment investigations

Section 2. SABR/SBRT planning and treatment delivery

Section 3. Cumulative organs at risk dose constraints

Please note, all questions except question 1 concern the delivery of SABR/SBRT as a re-irradiation treatment in the pelvis after initial definitive/curative/adjuvant external beam radiotherapy/brachytherapy.

SABR/SBRT refers to the precise irradiation of an image-defined extra-cranial lesion with the use of a high radiation dose/high dose per fraction (e.g. 5 Gy per fraction or greater) in a small number of fractions (e.g. 3 fractions or fewer).

You can save your progress and return to the survey later by clicking 'Finish later' at the bottom of the page.

Page 3: Section 1: Patient selection and pre-treatment investigations

Page 4: Section 1 Question 1

Are you a clinical/radiation oncologist who is a specialist in the re-irradiation of the following pelvic malignancies using SABR/SBRT?

- Genitourinary
 Gynaecological
 Lower Gastrointestinal
 Other

If you selected Other, please specify:

Page 5: Section 1 Question 2

Do you have a definition for which you consider a treatment to be SABR/SBRT re-irradiation in the pelvis (e.g. defined hot/cold overlap such as >50% hot/cold or overlap with a previously delivered dose such as >50 Gy EQD2)?

Page 6: Section 1 Question 3

Please select whether you agree, slightly agree or disagree with the following definition of SABR/SBRT re-irradiation in the pelvis: 'Delivery of SABR/SBRT, after initial radical/neo/adjunct/curative radiotherapy to the pelvis, provided there is overlap of previous dose with the new planning target volume (PTV) and/or organs at risk (OAR)'

- Agree
 Slightly agree
 Disagree

Please comment on the definition and/or suggest any modification to it

Page 7: Section 1 Question 4

Please describe whether the primary tumour type (e.g. lower GI, genitourinary, gynaecological cancer) and primary treatment previously delivered (e.g. previous surgery, (chemo)radiotherapy, brachytherapy etc) would influence your decision making in offering SABR/SBRT re-irradiation in the pelvis

Page 8: Section 1 Question 5

Would you recommend SABR/SBRT re-irradiation in the pelvis if surgical extirpation was also a treatment option? Please describe what factors would influence your decision

Page 9: Section 1 Question 6

Would you consider offering SABR/SBRT re-irradiation in the pelvis where there are sites of metastatic disease outside the pelvis? Please describe what factors influence your decision

Page 10: Section 1 Question 7

Please comment regarding whether the number of sites of relapse in the pelvis (and where the previously delivered dose would overlap with the new PTV and/or OARs) influences your decision to offer SABR/SBRT re-irradiation

Page 11: Section 1 Question 8

What do you consider should be the maximum size of any single site of recurrence for SABR/SBRT re-irradiation in the pelvis?

Page 12: Section 1 Question 9

Regarding multiple sites of recurrence in the pelvis, please comment regarding whether there is a maximum total volume of recurrences for which you would offer SABRSBRT

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Page 13: Section 1 Question 10

Are there particular locations within the pelvis where you would not consider offering SABRSBRT re-irradiation?

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Page 14: Section 1 Question 11

Please describe clinical scenarios in which you would not consider offering SABRSBRT re-irradiation in the pelvis (e.g. inflammatory bowel disease; previous gynaecological brachytherapy; fistulation; late toxicities from previous irradiation)

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Page 15: Section 1 Question 12

How does the time interval after initial radiotherapy affect your decision to offer SABRSBRT re-irradiation?

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Page 16: Section 1 Question 13

What do you consider should be the minimum acceptable WHO performance status for SABRSBRT re-irradiation in the pelvis?

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Page 17: Section 1 Question 14

How does previous acute radiation toxicity affect your decision to offer SABRSBRT re-irradiation in the pelvis?

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Page 18: Section 1 Question 15

How does previous/persistent late radiation toxicity affect your decision to offer SABRSBRT re-irradiation in the pelvis?

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Page 19: Section 1 Question 16

Please comment regarding whether you consider the following to be essential baseline investigations that should be performed prior to SABR/SBRT re-irradiation in the pelvis

Blood tests (e.g. full blood count and routine biochemistry; tumour markers)

Diagnostic imaging (e.g. CT, MRI, PET-CT)

Biopsy confirmation of recurrence

Other

Page 20: Section 1 Question 17

Please describe any other considerations that should be taken into account prior to offering SABR/SBRT re-irradiation in the pelvis

Page 21: Section 1 Question 18

Please describe what situations you would offer re-irradiation in the pelvis but not using SABR/SBRT. For example, where you might use conventionally fractionated (1.8-2 Gy per fraction), hyperfractionated (<math><1.8</math> Gy per fraction) or moderately hypofractionated (2-4 Gy per fraction) regimens. Possible reasons could include, for example, patient-related factors such as prognosis or size/location of recurrence within the pelvis

Page 22: Section 2: SABR/SBRT planning and treatment delivery

Page 23: Section 2 Question 1

Please describe the patient preparation and set up factors that you use for SABR/SBRT re-irradiation in the pelvis

Patient positioning

Patient immobilisation

Bladder and rectal protocols (i.e. bladder filling or emptying and rectal emptying)

Pelvic spacer devices

Other

Page 24: Section 2 Question 2

Please describe the planning imaging technique(s) you use for SABR/SBRT re-irradiation in the pelvis. Please tick all that apply

- Planning CT
- Planning CT/MRI image co-registration
- Planning CT/PET-CT image co-registration
- Planning MRI-only workflow (i.e. without planning CT)
- Intravenous contrast
- Small bowel contrast
- Other

If you selected Other, please specify:

Page 25: Section 2 Question 3

Please complete the following table to indicate the dose, fractionation, overall treatment time, prescription point and intended target volume coverage that you use for SABR/SBRT re-irradiation in the pelvis. If you use more than one SABR/SBRT schedule, please add the corresponding information for these in the additional columns.

	Schedule 1	Schedule 2 (if applicable)	Schedule 3 (if applicable)
Prescribed dose (e.g. 30 Gy)			
Number of fractions (e.g. 5 fractions)			
Overall treatment time (e.g. 10 days)			
Prescription point (e.g. prescribed to the 50% isodose)			
Intended minimum target volume coverage by the prescribed dose (e.g. 95% of the PTV to receive at least 100% of the prescribed dose)			
Maximum dose allowed within the target volume (e.g. 140% of the prescribed dose)			

Page 26: Section 2 Question 4

Please describe what factors influence the dose and fractionation schedule you deliver for SABR/SBRT re-irradiation in the pelvis.

Page 27: Section 2 Question 5

Does a radiologist help you with target volume/OAR contouring for SABR/SBRT re-irradiation in the pelvis?

- No
 Radiologist reviews target volume contours
 Radiologist performs target volume delineation
 Radiologist reviews OAR contours
 Radiologist performs OAR delineation

If a radiologist performs OAR contouring, which OARs do they delineate?

Page 28: Section 2 Question 6

Which of the following OARs do you delineate for SABR/SBRT re-irradiation in the pelvis? Please tick all that apply

- Bladder
- Bowel bag (outer contour of groups of bowel loops including mesentery and intervening spaces between loops but not full peritoneal cavity)
- Cauda Equina
- Colon
- Femoral Head
- Femoral Head and Neck
- Lumbosacral Plexus
- Major vessels (e.g. Aorta, IVC, Common, External and Internal Iliacs)
- Penile Bulb
- Peritoneal cavity (potential bowel space excluding abdominal/pelvic wall muscles and major vasculature)
- Rectum
- Sigmoid Colon
- Small Bowel (individual loops excluding intervening spaces between loops)
- Ureter
- Other

If you selected Other, please specify:

Page 29: Section 2 Question 7

Please describe whether there are circumstances in which you would use a Planning OAR Volume (POV) for SABR/SBRT re-irradiation in the pelvis and how you decide on what margins to use

Page 30: Section 2 Question 8

Do non-oncologists (i.e. physicists, radiographers/RTTs or dosimetrists) perform any OAR contouring for SABR re-irradiation in the pelvis?

- No
- Yes

If yes, please indicate which OARs are contoured by non-oncologists

Page 31: Section 2 Question 9

Please describe how the previous radiotherapy plan is taken into account during SABR/SBRT re-irradiation planning

- Visual comparison
- Rigid image registration
- Deformable image registration
- Other

If you selected Other, please specify:

Page 32: Section 2 Question 10

Please complete the following table (all sections that apply to you) to indicate which treatment delivery techniques you use for SABR/SBRT re-irradiation in the pelvis. Indicate in the relevant row(s) what GTV to CTV margins you use; what CTV to PTV margins you use; what treatment verification strategy you use and whether you use an adaptive radiotherapy strategy. Please make sure to scroll across to view the whole table.

	GTV to CTV margins	CTV to PTV margins	Treatment verification (e.g. online/offline cone beam CT; fiducial markers; intra-fraction monitoring; MRI guidance; treatment couch with six degrees of freedom)	Adaptive radiotherapy replanning; plan of the day or reactive replanning for a
Linac-based VMAT				
Linac-based step and shoot IMRT				
CyberKnife				
MR linac (e.g. Elekta Unity or ViewRay MRIdian)				
Proton beam therapy				
Heavy ion therapy				
Tomotherapy				
3D conformal radiotherapy				

Page 33: Section 2 Question 11

Please describe whether you would routinely offer concurrent or sequential systemic anticancer therapies with SABR/SBRT re-irradiation in the pelvis. Please indicate for Genitourinary, Gynaecological cancers and Lower Gastrointestinal cancers as relevant to your specific areas of expertise

Genitourinary

Gynaecological

Lower Gastrointestinal

Other

Page 34: Section 2 Question 12

What data, if any, do you collect concerning treatment outcomes and toxicity for patients receiving SABR/SBRT re-irradiation in the pelvis?

Page 35: Section Question 13

Approximately how many cases of SABR/SBRT re-irradiation in the pelvis do you treat per year?

What do you consider should be the minimum number of cases of SABR/SBRT re-irradiation in the pelvis each year for an individual professional to obtain sufficient clinical experience to maintain competencies?

Page 36: Section 2 Question 14

Do you have a specific multidisciplinary team meeting (MDT) for SABR/SBRT re-irradiation in the pelvis? If yes, please specify if this is for review of new referrals for SABR/SBRT and/or for peer review of contouring

- No
- MDT review of new referrals for SABR/SBRT
- Peer review of contouring for SABR/SBRT

If you do have a specific MDT for SABR/SBRT re-irradiation in the pelvis, who attends this meeting? e.g. oncologist, radiographer/RTT, physicist, radiologist

Page 37: Section 2 Question 15

What involvement, if any, do other non-oncologist members of the multidisciplinary team (e.g. physicist, radiographer/RTT) have regarding decision making about the feasibility of SABR/SBRT re-irradiation?

Page 38: Section 2 Question 16

What involvement, if any, do other members of the multidisciplinary team (e.g. physicist, radiographer/RTT) have regarding decision making about the SABR/SBRT re-irradiation dose to be delivered?

Page 39: Section 3: Cumulative organs at risk (OAR) dose constraints

Page 40: Section 3 Question 1

Please describe how the previous radiotherapy dose is taken into account (if at all) when considering OAR constraints for SABR/SBRT re-irradiation in the pelvis

Page 41: Section 3 Question 2

If a patient had received previous gynaecological or prostate brachytherapy, please describe how would you account for this dose when considering cumulative OAR constraints for SABR/SBRT re-irradiation in the pelvis

Page 42: Section 3 Question 3

Please describe what references you use for OAR dose constraints for SABR/SBRT re-irradiation in the pelvis (e.g. which published constraints, Quantic data, AAPM 101 report). Please also indicate if individual patient dose constraints are used instead of published constraints

Page 43: Section 3 Question 4

Please complete the following table as it applies to you. For each of the following OARs, please include the following information for SABR/SBRT re-irradiation in the pelvis: 1. Dose constraint and fractionation. Please indicate if this is a point dose e.g. D0.5cc 35 Gy in 5 fractions; a dose to a volume e.g. D10cc 25 Gy in 5 fractions; a percentage volume dose e.g. V20Gy <10% in 5 fractions or if this is a dose in either EQD2 or BED

	Dose constraint and fractionation. Please indicate if this is a point dose e.g. D0.5cc 35 Gy in 5 fractions; a dose to a volume e.g. D10cc 25 Gy in 5 fractions; a percentage volume dose e.g. V20Gy <10% in 5 fractions or if this is a dose in either EQD2 or BED	Is this a cumulative dose constraint (i.e. taking into account the previously delivered dose)?		If cumulative dose constraint calculations are performed, please indicate what alpha/beta ratio you use for each OAR (e.g. 3 Gy)	Time interval for repair/rec 25% repair after 6 months repair/recovery is
		Yes	No		
Bladder		<input type="checkbox"/>	<input type="checkbox"/>		
Bowel bag		<input type="checkbox"/>	<input type="checkbox"/>		
Cauda Equina		<input type="checkbox"/>	<input type="checkbox"/>		
Colon		<input type="checkbox"/>	<input type="checkbox"/>		
Femoral Head (with/without Neck)		<input type="checkbox"/>	<input type="checkbox"/>		
Lumbosacral plexus		<input type="checkbox"/>	<input type="checkbox"/>		
Major vessels (e.g. Aorta, IVC, Common, External and Internal Iliacs)		<input type="checkbox"/>	<input type="checkbox"/>		
Penile Bulb		<input type="checkbox"/>	<input type="checkbox"/>		
Peritoneal cavity		<input type="checkbox"/>	<input type="checkbox"/>		

Sacral roots		<input type="radio"/>	<input type="radio"/>		
Sigmoid Colon		<input type="radio"/>	<input type="radio"/>		
Small Bowel (individual loops)		<input type="radio"/>	<input type="radio"/>		
Rectum		<input type="radio"/>	<input type="radio"/>		
Ureter		<input type="radio"/>	<input type="radio"/>		
Other		<input type="radio"/>	<input type="radio"/>		

Page 44: Section 3 Question 5

If PTV coverage is compromised in order to meet an OAR constraint, please comment regarding whether there is a minimum percentage of PTV coverage below which you would not proceed with SABR/SBRT re-irradiation in the pelvis (e.g. minimum of 80% PTV coverage by prescription dose in order to proceed)

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Page 45: Section 3 Question 6

What rate (e.g. % risk) of grade 3+ late toxicity would you consider acceptable for re-irradiation in the pelvis? Please describe what factors influence your decision making (e.g. primary disease type, patient prognosis) and if this depends on the particular OAR concerned

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Page 46: Any other comments

Please enter any other comments you have regarding SABR/SBRT re-irradiation in the pelvis, especially if not covered during the survey

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Page 47: Final page

Thank you for completing this first round of the Delphi consensus. We will collate the responses and use this information to produce statements concerning the practice of re-irradiation in the pelvis. In the second round of the Delphi, you will be asked to review these statements and indicate your level of agreement to identify areas of consensus.

Appendix E Round 2 questionnaire: An international Delphi consensus for pelvic Stereotactic Ablative Radiotherapy

Round 2: Delphi consensus on SABR re-irradiation in the pelvis final version

Page 1: Page 1

1. I am happy to proceed with this second round of the international Delphi consensus on SABR/SBRT re-irradiation in the pelvis

- Yes
 No

Page 2: Introduction

Thank you very much for agreeing to take part in the international Delphi consensus on SABR/SBRT re-irradiation in the pelvis and for completing the first round.

We are delighted that 23 radiation/clinical oncologists completed the first round.

We have used the information you provided in the first round to assemble a series of statements for practice. The intention of these statements is to provide specific guidance for the major aspects of the patient pathway. This second round will aim to obtain consensus for these statements by asking you to indicate your level of agreement/disagreement with each statement. Of note, the statements will use SABR (Stereotactic Ablative Radiotherapy) to refer to both SABR and Stereotactic Body Radiotherapy (SBRT).

When considering the extent to which you agree/disagree with each statement, we would ask that you think about how these would apply *in general* to patients treated with SABR re-irradiation in the pelvis. There might be exceptions to these statements but we wish to produce guidance that would be of help to both centres currently using this treatment and those that are planning to establish a service.

Each statement is accompanied by the information provided by the group during the first round to illustrate how we framed the statement.

We ask you to indicate on the five-point scale whether you:

Strongly Disagree, Disagree, Neither Agree/Disagree, Agree or Strongly Agree

Very importantly, if you do not Agree/Strongly Agree with a statement we ask you to provide an explanation as to why not in the free-text box.

Consensus for a statement will be considered to have been achieved if at least 75% of participants Agree or Strongly Agree, as per ASCO Clinical Practice Guidelines methodology. Any statements not achieving consensus will be re-presented during the third round of the Delphi.

The statements cover guidance relating to patient selection, pre-treatment investigations, SABR re-irradiation planning and treatment delivery and cumulative OAR constraints. Some sections contain more than one statement to vote on. If you wish to save your progress and return later, please click 'Finish later' at the bottom of the page and you can either bookmark the page or send yourself an email link to the survey.

Page 3: Section 1: Definition of SABR re-irradiation in the pelvis, patient selection and pre-treatment investigations

Page 4: Definition of SABR re-irradiation in the pelvis

Statement:

Delivery of SABR, after initial radiotherapy to the pelvis, and where there is overlap of previously delivered dose with the new treatment that could result in excess dose to an Organ at Risk (OAR) and/or significant toxicity

2. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The information provided during the first round that was used to produce this statement:

3. How do you define re-irradiation?

- Overlap with defined dose in EQD2: 6 participants
 - 5 Gy, 30 Gy, 36 Gy, 45 Gy (2 participants), 50-70 Gy
- Overlap with defined isodose: 4 participants
 - 40% (2 participants), 50% (2 participants)
- Overlap with GI tract: 1 participant
- Overlap of previous/new PTVs: 2 participants
- Any degree of overlap: 1 participant
- Combined dose exceeds that of a single course of RT: 1 participant
- No specific definition/individual case assessment: 7 participants

4. Do you agree with this definition of SABR re-irradiation?

'Delivery of SABR/SBRT, after initial radical/neoadjuvant/adjvant radiotherapy to the pelvis, provided there is overlap of previous dose with the new planning target volume (PTV) and/or organs at risk (OAR)'

- Agree: 14 participants (61%)
- Slightly agree 7 participants (30%)
- Disagree: 2 participants (9%)

5. Comments on definition

- SABR re-irradiation is inappropriate
- Add overlap is 'relatively high'
- Add SABR re-irradiation is 'with radical intent'
- Previous palliative RT e.g. 20 Gy in 5 fractions for isolated rectal recurrence might still be suitable for SABR
- Overlap of new treatment isodose with a previously irradiated OAR rather than the PTV is potentially a problem
- Salvage RT for prostate cancer doesn't fit into radical/neoadjuvant/adjvant. An isodose cut off is needed e.g. <10% isodose not considered to be re-irradiation
- Add radical/neoadjuvant/adjvant 'with curative intent'
- How does one define how close OAR needs to be to PTV? Within 2 cm?
- Overlap could be at low isodoses therefore we use the definition of 'a dose exceeding that of a single course of RT'
- Overlap at lower isodoses e.g. 20% may result in varying extents of re-irradiation
- Definition should factor in actual previously delivered dose

3. If you do not Agree/Strongly Agree with this statement, please explain why not

Page 5: SABR as an alternative to surgical pelvic exenteration

Statement:

SABR re-irradiation in the pelvis can be considered as an alternative to surgical exenteration following an appropriate multidisciplinary team discussion which takes into account individual patient and disease factors and the respective feasibility/risks of SABR and surgery

4. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

7. Would you offer SABR if surgical exenteration was also an option?

- Yes: 17 participants (74%)
- No: 6 participants (26%)

• Factors that might influence this decision

- Patient preference: 3 participants
- Age: 4 participants
- Comorbidities/PS/fitness: 8 participants
- Prognosis: 1 participant
- Volume/location of recurrence (SABR if smaller/away from OAR; surgery if larger/luminal/short disease free interval): 3 participants
- SABR technical factors (prior dose/feasibility/toxicity): 5 participants
- Consider neoadjuvant SABR then exenteration: 3 participants

5. If you do not Agree/Strongly Agree with this statement, please explain why not

Page 6: Presence of extra-pelvic disease

Statement:

SABR re-irradiation in the pelvis may be considered in the presence of extra-pelvic oligometastatic disease where this extra-pelvic disease can be controlled with metastasis-directed therapy

6. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

8. Would you offer SABR if there was extra-pelvic disease?

- Yes: 22 participants (96%)
 - If part of oligometastatic/oligoprospective state where the extra-pelvic disease can be controlled by treatments including SABR: 13 participants
 - For local control/palliation of symptomatic pelvic disease: 6 participants
 - Depending on the biology of the disease (burden of metastases, disease free interval)
- No: 1 participant (4%)

7. If you do not Agree/Strongly Agree with this statement, please explain why not

Page 7: Number and maximum size of lesions within the pelvis

Statement:

When considering the feasibility of SABR re-irradiation in the pelvis it is necessary to take into account the number of lesions, the size of the target, and the target's location and proximity to OARs

8. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Statement:

The maximum number of pelvic lesions treated by SABR re-irradiation should not exceed 3

9. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Statement:

The maximum size of an individual pelvic lesion treated by SABR re-irradiation should not exceed 6 cm in maximum dimension

10. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce these statements:

9. Does the number of pelvic lesions influence decision to offer SABR?

- Yes: 16 (70%)
 - ≤5: 2 participants
 - ≤3: 7 participants
 - 1-2: 2 participants
 - ≤1: 2 participants
 - Number of lesions not offered: 1 participant
- No: 7 (30%)
 - Volume/location/mobility of organ (e.g. uterus)/OAR doses more important (e.g. volume of small bowel irradiated)

10. Is there a maximum size of a single lesion you would treat with SABR/SBRT?

- Yes: 18 participants (78%)
 - 3 cm: 4 participants
 - 3-4 cm: 2 participants
 - 3-5 cm: 1 participant
 - 4 cm: 1 participant
 - 5 cm: 4 participants
 - 5-8 cm: 1 participant
 - 6 cm: 3 participants
 - 8 cm: 1 participant
 - 10 cm: 1 participants
- No: 4 participants (17%)

11. If you do not Agree/Strongly Agree with the statement **When considering the feasibility of SABR re-irradiation in the pelvis it is necessary to take into account the number of lesions, the size of the target, and the target's location and proximity to OARs, please explain why not**



12. If you do not Agree/Strongly Agree with the statement **The maximum number of pelvic lesions treated by SABR re-irradiation should not exceed 3, please explain why not**



13. If you do not Agree/Strongly Agree with the statement **The maximum size of an individual pelvic lesion treated by SABR re-irradiation should not exceed 6 cm in maximum dimension, please explain why not**



Page 8: Lesion locations not suitable for SABR re-irradiation

Statement:

SABR re-irradiation in the pelvis is not usually appropriate where there is direct invasion of a luminal OAR

14. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Statement:

SABR re-irradiation in the pelvis may not be appropriate where the lesion is in contact with a luminal OAR

15. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce these statements:

12. Are there locations where you would not offer SABR?

- Yes: 22 participants
 - Infiltration/close proximity of luminal organ (small bowel, sigmoid, rectum, bladder, major arteries): 15 participants
 - Central female pelvis (uterus/cervix): 1 participant
 - Adjacent to urethra: 1 participant
 - Caution regarding neobladder/anastomoses/skin involvement: 1 participant
- No: 5 participants
 - OAR doses are more important

16. If you do not Agree/Strongly Agree with the statement SABR re-irradiation in the pelvis is not usually appropriate where there is direct invasion of a luminal/critical OAR, please explain why not

17. If you do not Agree/Strongly Agree with the statement SABR re-irradiation in the pelvis may not be appropriate where the lesion is in contact with a luminal/critical OAR, please explain why not



Page 9: Time interval between prior irradiation and SABR/SBRT re-irradiation

Statement:

A minimum time interval of 12 months should have elapsed between a previous course of radiotherapy in the pelvis and SABR re-irradiation in the pelvis

18. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

14. Should there be a minimum time interval between prior RT and SABR?

- ◆ Yes: 20 participants (87%)
 - ◆ 4-6 months: 1 participant
 - ◆ 6 months: 4 participants
 - ◆ 12 months: 6 participants
 - ◆ 1-2 years: 1 participant
 - ◆ 2 years: 2 participants
 - ◆ 5 years: 1 participant
 - ◆ Time interval important but no specific interval mentioned: 5 participants
 - ◆ In field relapse minimum 12 month time interval
 - ◆ Time informs on disease biology, radiobiology calculations (accepting flawed assumptions about recovery), chance of radioresistance and toxicity
- ◆ No: 3 participants (13%)
 - ◆ Location/OAR overlap more important
 - ◆ Time interval may be prognostic but wouldn't affect decision by itself
 - ◆ Marginal/out of field relapse decision not affected by time interval

19. If you do not Agree/Strongly Agree with this statement, please explain why not



Page 10: Minimum performance status

Statement:

Patients otherwise eligible for SABR re-irradiation in the pelvis should, in general, have a minimum WHO performance status score of 2 (or equivalent)

20. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

15. What should be the minimum WHO performance status score for SABR/SBRT?

- Zero-one: 5 participants (22%)
- Two: 13 participants (57%)
- Three: 2 participants (9%)

21. If you do not Agree/Strongly Agree with this statement, please explain why not

Page 11: Previous acute radiotherapy toxicity

Statement:

Previous acute radiotherapy toxicity that was expected/transient should not in itself preclude SABR re-irradiation in the pelvis, unless it was particularly severe or unexpected

22. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

16. How does previous acute RT toxicity affect decision about SABR?

- Little/no effect on decision making: 14 participants (61%)
 - No/little effect on decision making: 12 participants (including late toxicity more important: 2 participants)
 - Would still offer SABR if expected/transient low grade toxicities: 2 participants
- Some effect on decision making: 9 participants (39%)
 - If toxicity was persistent: 1 participant
 - If toxicity was unexpected: 1 participant
 - If toxicity was severe: 3 participants
 - Depends on nature of toxicity and dose to OAR with SABR: 1 participant
 - Reduce SABR prescription dose by 10-15%: 1 participant
 - Increase fractionation of SABR: 1 participant
 - Influences consent for SABR: 1 participant

23. If you do not Agree/Strongly Agree with this statement, please explain why not

Page 12: Previous/persistent late radiotherapy toxicity

Statement:

SABR re-irradiation in the pelvis should be used with caution in the presence of moderate (e.g. CTCAE grade 2) previous/persistent late radiotherapy toxicity

24. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Statement:

SABR re-irradiation in the pelvis should be avoided in the presence of severe (e.g. CTCAE grade 3 or greater) previous/persistent late radiotherapy toxicity

25. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce these statements:

17. How does previous/persistent late radiotherapy toxicity affected decision about SABR?

- Avoid SABR in the event of late toxicity: 16 (70%)

- Late toxicity, grade not specified: 8 participants
- 'Moderate to severe' late toxicity: 2 participants
- 'Severe' late toxicity: 2 participants
- Grade 2-4 late toxicity: 2 participants
- Grade 3+ late toxicity: 1 participant
- >Grade 1 toxicity for prostate SABR re-irradiation: 1 participant
- Significant caution with SABR in the event of late toxicity: 6 participants (26%)
 - Depending on the grade/OAR involved: 1 participant
 - Limit SABR dose based on the OAR involved: 1 participant
 - Minimise OAR doses: 1 participant
 - Consent patient appropriately: 1 participant
 - Counsel patient if grade 1-2 late toxicity: 1 participant
 - Late toxicity a potential contra-indication to re-irradiation: 1 participant

26. If you do not Agree/Strongly Agree with the statement SABR re-irradiation in the pelvis should be used with caution in the presence of moderate (e.g. CTCAE grade 2) previous/persistent late radiotherapy toxicity, please explain why not



27. If you do not Agree/Strongly Agree with the statement SABR re-irradiation in the pelvis should be avoided in the presence of severe (e.g. CTCAE grade 3 or greater) previous/persistent late radiotherapy toxicity, please explain why not



Page 13: Baseline diagnostic staging imaging

Statement:

Diagnostic staging imaging prior to SABR re-irradiation in the pelvis should include MRI pelvis and PET-CT

28. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

19. What baseline imaging should be performed prior to SABR?

- MRI pelvis, CT chest/abdomen/pelvis, PET-CT: 16 participants
- MRI pelvis, PET-CT: 5 participants
- MRI pelvis, CT thorax/abdomen/pelvis: 1 participant
- PET-CT: 1 participant

29. If you do not Agree/Strongly Agree with this statement, please explain why not

Page 14: Confirmation of diagnosis

Statement:

Histological confirmation of recurrence prior to SABR re-irradiation in the pelvis may not always be possible or necessary and treatment may be appropriate based on a clinical and radiological diagnosis of recurrence

30. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

20. Is it essential to obtain histological confirmation of recurrence prior to SABR?

- Yes: 9 participants (including 2 responses for primary prostate recurrence)
- If possible: 4 participants
- Sometimes, depending on clinical scenario: 2 participants
- No: 9 participants

31. If you do not Agree/Strongly Agree with this statement, please explain why not



Page 15: When non-SABR re-irradiation is preferred

Statement:

Non-SABR re-irradiation in the pelvis (e.g. using conventionally or hyperfractionated radiotherapy) is preferred for lesions >6 cm

32. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Statement:

Non-SABR re-irradiation in the pelvis (e.g. using conventionally or hyperfractionated radiotherapy) is preferred for lesions infiltrating or in contact with a luminal OAR

33. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce these statements:

23. When might you offer non-SABR re-irradiation in the pelvis?

- Size of lesion precludes SABR: 9 participants
- Location (e.g. close proximity to OAR): 8 participants

- Borderline resectable disease or new pelvic primary: 4 participants
- Poor prognosis (palliative hypofractionated RT): 4 participants
- Disease free interval <12 months: 3 participants
- Nodal relapse/nodal chain: 2 participants
- Toxicity from prior RT: 1 participant
- Anastomosis/neobladder: 1 participant
- Connective tissue disorders
- HDR brachytherapy also used for prostate re-irradiation

34. If you do not Agree/Strongly Agree with the statement **Non-SABR re-irradiation in the pelvis is preferred for lesions >6 cm**, please explain why not



35. If you do not Agree/Strongly Agree with the statement **Non-SABR re-irradiation in the pelvis is preferred for lesions infiltrating or in contact with a luminal/critical OAR**, please explain why not



Page 17: Patient position and immobilisation

Statement:

For SABR re-irradiation in the pelvis, patients should be positioned supine with the use of a device offering reproducible immobilisation (such as a vacuum bag or equivalent)

36. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

24. Positioning

- Supine: 18 participants
- As close to prior RT as possible: 2 participants
- Individualised decision of supine versus prone to maximise distance between target and OAR: 1 participant
- Comfortable position: 1 participant

25. Immobilisation

- Vacuum bag: 15 participants
- Standard pelvis immobilisation: 4 participants
- As per prior RT: 1 participant
- No specific immobilisation: 1 participant

37. If you do not Agree/Strongly Agree with this statement, please explain why not

Page 18: Bladder/rectal preparation

Statement:

During SABR re-irradiation in the pelvis, bladder preparation (filling/emptying) and rectal emptying should be determined on an individual patient basis, taking into account the position of the OAR during the prior treatment and the proximity of the OAR to the new target volume

38. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

26. Bladder/rectal preparation

- Full bladder/empty rectum: 11 participants
- Bladder filling/emptying depending on dose to bowel plus empty rectum: 7 participants (including 1 with use of rectal balloon)
- Full bladder: 1 participant
- Empty bladder/rectum: 1 participant
- MDT individual patient decision: 1 participant
- Bladder filling/emptying depending on prior RT: 1 participant
- Hydrogel spacer: 1 participant

39. If you do not Agree/Strongly Agree with this statement, please explain why not

Page 19: Planning image acquisition

Statement:

Image co-registration with MRI or PET-CT to the planning CT should be used where it will improve target or OAR delineation

40. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Statement:

Intravenous contrast should be used (unless contra-indicated) where it would improve target volume or OAR delineation

41. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

29. Planning image acquisition

- Planning CT: 15 participants
- Planning CT with MRI co-registration: 19 participants
- Planning CT with PET-CT co-registration: 17 participants

- Intravenous contrast: 13 participants
- Small bowel contrast: 6 participants
- MRI only workflow: 1 participant

42. If you do not Agree/Strongly Agree with the statement **Image co-registration with MRI or PET-CT to the planning CT should be used where it will improve target or OAR delineation**, please explain why not



43. If you do not Agree/Strongly Agree with the statement **Intravenous contrast should be used (unless contra-indicated) where it would improve target volume or OAR delineation**, please explain why not



Page 20: Dose fractionation schedules

Statement:

Acceptable dose fractionation schedules for SABR re-irradiation in the pelvis are 30-37.5 Gy in 5-6 fractions or 21-27 Gy in 3 fractions with treatment delivered on alternate days

44. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

30a. Dose fractionation schedules

- 15-21 Gy in 3 fractions over 3 days: 1 participant
- 21-27.5 Gy in 3 fractions over 10 days: 1 participant
- 24 Gy in 3 fractions over 5 days: 1 participant
- 25 Gy in 5 fractions over 10 days: 1 participant
- 25-35 Gy in 5 fractions over 10 days: 1 participant
- 27 Gy in 3 fractions over 5 days for small nodes: 1 participant
- 30-35 Gy in 5 fractions over 10 days: 1 participant
- 30 Gy in 3 fractions over 5 days: 1 participant
- 30 Gy in 3 fractions over 10 days: 1 participant
- 30 Gy in 5 fractions over 5 days: 1 participant
- 30 Gy in 5 fractions over 10 days: 10 participants
- 30 Gy in 5 fractions over 10 days plus GTV boost: 1 participant
- 30-39 Gy in 3-5 fractions over 5-10 days: 1 participant
- 35 Gy in 5 fractions over 5 days: 1 participant
- 35 Gy in 5 fractions over 10 days: 5 participants
- 35-45 Gy in 5 fractions over 5 days: 1 participant
- 36 Gy in 6 fractions over 12 days: 1 participant
- 36.25 Gy in 5 fractions over 10 days: 1 participant
- 37.5 Gy in 5 fractions over 10 days: 1 participant
- Unclear: 1 participant

Median dose (range): 30 Gy (21-45)

Median number of fractions (range): 5 fractions (3-5)

Median overall treatment time (range): 10 days (3-12)

Note- the larger value in a range was used to calculate the median value for the group

45. If you do not Agree/Strongly Agree with this statement, please explain why not

Page 21: Maximum allowable dose within the target volume

Statement:

For conventional linear accelerator-based SABR, the maximum allowable dose within the target volume for SABR re-irradiation in the pelvis should not exceed 140% of the prescribed dose

46. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

30d. Maximum allowable dose within the target volume

- 105-110%: 1 participant
- 110%: 6 participants
- 120%: 1 participant
- 120-130%: 3 participants
- 120-140%: 1 participant
- 125%: 2 participants
- 130%: 2 participants
- 140%: 5 participants
- 140-150%: 1 participant
- 145%: 2 participants
- 150%: 3 participants
- 153.85%: 1 participant
- No maximum: 1 participant

The three most common maximum allowable doses were: 120-130%, 140% and 150%

Median maximum dose: 130% of the prescribed dose

Note- the larger value in a range was used to calculate the median value for the group

47. If you do not Agree/Strongly Agree with this statement, please explain why not

Page 22: Target volumes and Organs at Risk (OAR)

Statement:

Target volume and OAR nomenclature should be based on the recommendations in American Association of Physicists in Medicine (AAPM) report TG-263

48. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Statement:

As a minimum, the following OARs should be delineated for SABR re-irradiation in the pelvis: Bladder, CaudaEquina, Femur_Head_L/R (with/without neck), Rectum, SacralPlex and a small and large bowel structure (e.g. Bowel_Small, Colon, Colon_Sigmoid)

49. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

33. Which OAR are delineated? (Names are indicated as per AAPM TG263 nomenclature#)

- Canal_Anal (anal canal): 1 participant (4%)

- Bladder: 22 participants (96%)
- Bag_Bowel* (bowel bag): 14 participants (61%)
- CaudaEquina (cauda equina): 17 participants (74%)
- Colon: 18 participants (78%)
- Femur_Head_L/R (femoral head): 16 participants (70%)
- Femur_Head_L/R (femoral head and neck): 17 participants (74%)
- SacralPlex (lumbosacral plexus): 14 participants (61%)
- Major vessels: 11 participants (48%)
- Genitals (male/female genitalia): 3 participants (13%)
- PenileBulb (penile bulb): 11 participants (48%)
- Spc_Bowel** (bowel space/peritoneal cavity): 4 participants (17%)
- Rectum: 23 participants (100%)
- Colon_Sigmoid (sigmoid colon): 17 participants (74%)
- Bowel_Small (individual small bowel loops): 18 participants (78%)
- Ureters: 12 participants (52%)
- Urethra: 2 participants (9%)

https://www.aapm.org/pubs/reports/RPT_263_Supplemental/

* Bag_Bowel is defined as the outer contour of groups of bowel loops including the intervening space and mesentery between the individual loops but not the entire peritoneal cavity

** Spc_Bowel is defined as the potential bowel space/peritoneal cavity excluding abdominal/pelvic wall muscles and major vasculature

50. If you do not Agree/Strongly Agree with the statement **Target volume and OAR nomenclature should be based on the recommendations in American Association of Physicists in Medicine (AAPM) report TG-263**, please explain why not

51. If you do not Agree/Strongly Agree with the statement **As a minimum, the following OARs should be delineated for SABR re-irradiation in the pelvis: Bladder, CaudaEquina, Femur_Head_L/R (with/without neck), Rectum, SacralPlex and a small and large bowel structure (e.g. Bowel_Small, Colon, Colon_Sigmoid)**, please explain why not

Page 23: Treatment delivery techniques

Statement:

SABR re-irradiation in the pelvis should use intensity modulated radiotherapy (IMRT) (or similar high conformity techniques)

52. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Statement:

Daily online treatment verification using volumetric imaging or fiducial markers should be used for SABR re-irradiation in the pelvis

53. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce these statements:

37.1 Linac-based VMAT (17 participants)

<i>GTV-CTV margins</i>	<i>CTV-PTV margins</i>	<i>Treatment verification</i>	<i>Adaptive RT</i>
0 mm: 9		Cone beam CT (timing not specified): 9	
0-1 mm: 1	0 mm: 1	Online cone beam CT: 8	
0-5 mm: 1	2-5 mm: 1	Six degrees of freedom couch: 6	
2 mm: 1	3 mm: 4		Not performed: 8
2-3 mm: 1	3-5 mm: 2	Fiducial markers: 3	Reactive replanning for significant changes: 4
3-5 mm: 1	5 mm: 7	Surface guided verification: 1	
5 mm: 2	Individual case assessment: 1	Intrafraction monitoring: 1	
Individual case assessment: 1		IGRT not further specified: 1	

37.2 Linac-based step-and-shoot IMRT (4 participants)

<i>GTV-CTV margins</i>	<i>CTV-PTV margins</i>	<i>Treatment verification</i>	<i>Adaptive RT</i>
	2-5 mm: 1	Cone beam CT (timing not specified)	
0 mm: 2			
	3 mm: 1	Online cone beam CT: 2	
0-1 mm: 1			Not performed: 3
	5 mm: 1	Six degrees of freedom couch: 1	
Individual case assessment: 1	Individual case assessment: 1	Fiducial markers: 1	

37.3 CyberKnife® (10 participants)

<i>GTV-CTV margins</i>	<i>CTV-PTV margins</i>	<i>Treatment verification</i>	<i>Adaptive RT</i>
	1-3 mm: 1		
0 mm: 7			
	2 mm: 3	Intrafraction monitoring: 9	Not performed: 3
0-3 mm: 1			
	2-3 mm: 1	Fiducial markers (for soft tissue lesions): 9	Reactive replanning for significant changes: 2
1 mm: 1			
	3 mm: 2		
5 mm (intraprostatic lesion): 1			
	3-5 mm: 2		

37.4 MR-linac (6 participants)

<i>GTV-CTV margins</i>	<i>CTV-PTV margins</i>	<i>Treatment verification</i>	<i>Adaptive RT</i>
	0 mm: 1		
0 mm: 3			
	3 mm: 2	MRI guidance: 3	
3-5 mm: 2			Daily online replanning
	3-5 mm: 1	Intrafraction monitoring: 3	
Individual case assessment: 1	Individual case assessment: 1		

37.5 Proton beam therapy (1 participant)

<i>GTV-CTV margins</i>	<i>CTV-PTV margins</i>	<i>Treatment verification</i>	<i>Adaptive RT</i>
0 mm: 1	3 mm: 1		

37.6 Heavy ion therapy (0 participants)

37.7 TomoTherapy® (3 participants)

<i>GTV-CTV margins</i>	<i>CTV-PTV margins</i>	<i>Treatment verification</i>	<i>Adaptive RT</i>
0 mm: 1			
	3 mm: 1		Not performed: 2
0-5 mm: 1		Daily online MVCT: 3	
	5 mm: 1		Reactive replanning for significant changes: 1
Not stated: 1			
	5-10 mm: 1		

37.8 3d conformal radiotherapy (3 participants)

<i>GTV-CTV margins</i>	<i>CTV-PTV margins</i>	<i>Treatment verification</i>	<i>Adaptive RT</i>
		Cone beam CT (timing not specified): 2	
0-1 mm: 1	5 mm: 1		
5 mm: 1		Daily online cone beam CT: 1	Not performed: 1
	5-12 mm: 1		
Individual case assessment: 1	Individual case assessment: 1	Fiducial markers: 1	Reactive replanning for significant changes: 1
		Six degrees of freedom couch: 1	

54. If you do not Agree/Strongly Agree with the statement SABR re-irradiation in the pelvis should use intensity modulated radiotherapy (IMRT) (or similar high conformity techniques), please explain why not

55. If you do not Agree/Strongly Agree with the statement Daily online treatment verification using volumetric imaging or fiducial markers should be used for SABR re-irradiation in the pelvis, please explain why not

Page 24: Concurrent administration of systemic anticancer therapies

Statement:

The concurrent administration of systemic anticancer therapies with SABR re-irradiation in the pelvis, aside from hormone therapy, is not recommended

56. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

38. What systemic anticancer therapies, if any, are given for Genitourinary cancers with SABR/SBRT?

- None: 5 participants
- Androgen deprivation therapy for prostate cancer: 12 participants
- Sequential delivery of SABR and SACT: 1 participant
- Individual case assessment: 1 participant

39. What systemic anticancer therapies, if any, are given for Gynaecological cancers with SABR/SBRT?

- None: 9 participants
- Sequential delivery of SABR and SACT: 1 participant
- Individual case assessment: 2 participants

40. What systemic anticancer therapies, if any, are given for Lower Gastrointestinal cancers with SABR/SBRT?

- None: 10 participants
- Chemotherapy: 2 participants
- Sequential delivery of SABR and SACT: 2 participants

- Individual case assessment: 2 participants

57. If you do not Agree/Strongly Agree with this statement, please explain why not

Page 25: Disease outcomes/toxicity data collection

Statement:

Long term disease outcomes and toxicity data should be prospectively recorded for patients treated with SABR re-irradiation in the pelvis

58. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

42. What data, if any, is collected concerning treatment outcomes/toxicity?

- Toxicity: 13 participants
- Disease outcomes: 14 participants
- Quality of life: 6 participants
- Dosimetric data: 5 participants
- None: 2 participants

59. If you do not Agree/Strongly Agree with this statement, please explain why not

Page 26: Multidisciplinary team working

Statement:

A multidisciplinary team including a radiation/clinical oncologist, medical physicist and radiographer/RTT, experienced in the practice of SABR re-irradiation in the pelvis, should be involved in determining the technical suitability of SABR re-irradiation cases and in the review of the treatment plan

60. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

43. How many cases of SABR/SBRT re-irradiation in the pelvis does each participant treat per year?

- ≤10: 15 participants
- 11-20: 2 participants
- 21-30: 2 participants
- 31-40: 1 participant
- 100: 2 participants

44. How many cases of SABR/SBRT re-irradiation in the pelvis should an individual oncologist treat per year in order to maintain competences?

- ≤5: 8 participants
- 6-10: 2 participants
- 11-20: 2 participants
- 21-30: 1 participant
- Not sure: 3 participants
- No opinion offered: 1 participant
- Not possible to say- disease site specific clinical trials required for this treatment: 2 participants

- More dependent on expertise in SABR in general than SABR re-irradiation specifically

45. Does a dedicated multidisciplinary team (MDT) exist for SABR/SBRT re-irradiation in the pelvis?

- No: 10 participants (43%)
- MDT for review of new referrals: 8 participants (35%)
- Peer review of target volume/OAR delineation: 10 participants (43%)

46. Who attends a SABR/SBRT re-irradiation specific MDT?

- Oncologist, radiologist, physicist and radiographer/RTT: 3 participants
- Oncologist, physicist and radiographer/RTT: 2 participants
- Oncologist and physicist: 1 participant

47. What involvement do other members of the MDT (e.g. medical physicist, radiographer/RTT, dosimetrist) have regarding the feasibility of SABR/SBRT re-irradiation in the pelvis?

- No/minimal involvement (i.e. oncologist decision): 7 participants
- MDT involved in decision making: 13 participants

48. What involvement do other members of the MDT (e.g. medical physicist, radiographer/RTT, dosimetrist) have regarding the dose to be delivered?

- No/minimal involvement (i.e. oncologist decision): 5 participants
- MDT involved in decision making: 13 participants

61. If you do not Agree/Strongly Agree with this statement, please explain why not

Page 27: Section 3: Cumulative Organ at Risk (OAR) dose constraints

Page 28: Previous radiotherapy dose

Statement:

Treatment planning for SABR re-irradiation in the pelvis should include a review of the previously delivered dose to each OAR and calculation of the maximum allowable dose to each OAR during the new treatment (in EQD2 or BED)

62. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

49. How is the previous radiotherapy dose accounted for, if at all?

- Calculation of maximum allowable remaining OAR doses based on conversion of the previously delivered dose into EQD2 or BED (with/without allowance for recovery): 7 participants
- Calculation of dose accumulation but specific method not described: 10 participants
- Previous RT dose reviewed: 2 participants
- Method not stated: 1 participant

63. If you do not Agree/Strongly Agree with this statement, please explain why not



Page 29: Previous brachytherapy

Statement:

Where there has been previous delivery of gynaecological brachytherapy, SABR re-irradiation is not recommended where there would be overlap of the planning target volumes

64. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

50. How is the dose previously delivered during gynaecological/prostate brachytherapy accounted for?

- SABR re-irradiation not used where there is overlap: 4 participants
- Dose accumulation based on EQD2/BED calculations: 5 participants
- Visual assessment of proximity of new lesion to previous brachytherapy volume: 2 participants
- Assessment of maximum point doses to OAR: 1 participant
- SABR dose/OAR constraints reduced: 1 participant
- Previous brachytherapy plan reviewed to evaluate whether cumulative dose remains within constraints: 1 participant
- Individual case assessment: 1 participant
- Brachytherapy volume not accounted for: 2 participants
- Not sure: 1 participant

65. If you do not Agree/Strongly Agree with this statement, please explain why not

Page 30: References for OAR constraints

Statement:

External peer-reviewed guidance/literature should be used to guide cumulative OAR constraints for SABR re-irradiation in the pelvis

66. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

51. What sources are used for OAR dose constraints?

- AAPM Report 101: 6 participants
- Quantec reports: 5 participants
- UK SABR Consortium guidelines: 4 participants
- In house protocol based on published literature: 6 participants
- GEC ESTRO EMBRACE trial: 1 participant
- GETUG AFU 31 trial (prostate SABR re-irradiation): 1 participant
- ASTRO guidelines: 1 participant
- UK Consensus on Normal Tissue Dose Constraints for Stereotactic Radiotherapy: 1 participant
- Abusaris et al publication: 2 participants
- Published constraints but not specified: 1 participant
- Unclear: 2 participants

67. If you do not Agree/Strongly Agree with this statement, please explain why not

Page 31: Cumulative OAR constraints

In the following section, statements concerning cumulative OAR constraints and whether it is reasonable to assume any degree of recovery after a time interval from previous irradiation are presented. The statements are followed by two sets of tables. Participant information regarding that OAR is included in the first table (or tables, where the statement applies to multiple OAR). In the second table, information based on the literature regarding cumulative constraints and allowance for recovery for that OAR is collated.

Page 32: Bladder

Statement:

Optimally, the Bladder should receive no more than a cumulative dose of 80 Gy₃ EQD2 to 0.5 cc (assuming no recovery)

68. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Statement:

The degree of recovery of Bladder after radiotherapy is uncertain but if 12 months or more have elapsed it is reasonable to assume some recovery and the Bladder may receive up to a maximum cumulative EQD2 of 110 Gy₃ to 0.5 cc

69. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce these statements:

Bladder (17 participants)

<i>Dose constraint in 5 fractions or EQD2</i>	<i>Cumulative constraint</i>	<i>Alpha-beta ratio used for calculations</i>	<i>Allowance for repair</i>	<i>Prioritise PTV coverage or OAR constraint</i>
D0.1cc <36.25 Gy: 1				
D0.5cc <38 Gy: 4				
D0.5cc <40 Gy: 1				
D0.5cc <45 Gy: 1		α/β 2: 1	No: 6	
D0.5cc <80-85 Gy EQD2: 3	Yes: 11	α/β 2.5: 1	50% after 6 months: 1	PTV: 2
D0.5cc <100 Gy EQD2: 1 No: 4		α/β 3: 9	15% after 12 months: 1	OAR: 11
V37.5Gy <5 cc: 1		α/β 4: 1	50% after 12 months: 3	
V27Gy <5 cc: 1 (bladder wall)		Unclear: 1	Unclear: 3	
D30% <10.6 Gy: 1				
Unclear: 2				

The following is a table of constraints for Bladder based on published results/common practice.

The relevant toxicity endpoint is grade 3+ cystitis/fistula

<i>Reference</i>	<i>Constraint</i>	<i>Alpha/beta ratio (Gy)</i>	<i>Maximum proportion of recovery incorporated after 12 months</i>	<i>Maximum cumulative dose to 0.5 cc in EQD2 (Gy) based on first treatment of 45 Gy in 25 fractions (EQD2 of 43.2 Gy#)</i>
Paradis ¹	85 Gy in 42.5 fractions	2.5	50%	106.6
Abusaris ² §	120 Gy in 60 fractions cumulative	3	None	120
Smith ³ ¶	120 Gy in 60 fractions cumulative	3	None	120
AAPM ⁴	38 Gy in 5 fractions	3	25%*	91.4
AAPM ⁴	38 Gy in 5 fractions	3	50%*	102.2
<i>Mean cumulative EQD2 (Gy) including recovery</i>				108

*Not specified by AAPM but assumed for illustration purposes as representative of practice

#Assuming an alpha/beta ratio of 3; 45 Gy in 25 fractions is an EQD2 of 43 Gy where an alpha/beta ratio of 2.5 is used

§In Abusaris et al, no grade 3+ toxicity was reported after a median follow up duration of 15 months (range 2-52 months)

¶In Smith et al, one patient experienced grade 3 pain but no other grade 3+ toxicity was reported after a median follow up duration of 24.5 months (inter-quartile range 17.8-28.8

months)

References:

¹Paradis et al. The Special Medical Physics Consult Process for Reirradiation Patients. *Adv Radiat Oncol.* 2019; 4(4): 559-565

²Abusaris et al. Re-Irradiation: Outcome, Cumulative Dose and Toxicity in Patients Retreated with Stereotactic Radiotherapy in the Abdominal or Pelvic Region. *Technol Cancer Res Treat.* 2012; 11(6): 591-597

³Smith et al. Stereotactic Body Radiation Therapy Reirradiation for Locally Recurrent Rectal Cancer: Outcomes and Toxicity. *Adv Radiat Oncol.* 2020; 5: 1311-1319

⁴AAPM. Report No. 101 - Stereotactic body radiation therapy: The report of AAPM Task Group 101 (2010). Available at: <https://www.aapm.org/pubs/reports/detail.asp?docid=102> [Accessed 15th December 2020]

70. If you do not Agree/Strongly Agree with the statement **Optimally, the Bladder should receive no more than a cumulative dose of 80 Gy₃ EQD2 to 0.5 cc (assuming no recovery)**, please explain why not



71. If you do not Agree/Strongly Agree with the statement **The degree of recovery of Bladder after radiotherapy is uncertain but if 12 months or more have elapsed it is reasonable to assume some recovery and the Bladder may receive up to a maximum cumulative EQD2 of 110 Gy₃ to 0.5 cc**, please explain why not



Page 33: Bowel_Small

Statement:

Optimally, Bowel_Small should receive no more than a cumulative dose of 70 Gy₃ EQD2 to 0.5 cc (assuming no recovery)

72. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Statement:

The degree of recovery of Bowel_Small after radiotherapy is uncertain but if 12 months or more has elapsed it is reasonable to assume some recovery and Bowel_Small may receive up to a maximum cumulative EQD2 of 90 Gy₃ to 0.5 cc

73. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce these statements:

Bowel_Small (11 participants)

<i>Dose constraint in 5 fractions or EQD2</i>	<i>Cumulative constraint</i>	<i>Alpha-beta ratio used for calculations</i>	<i>Allowance for repair</i>	<i>Prioritise PTV coverage or OAR constraint</i>
D0.5cc <27.5 Gy: 1				
D0.5cc <35 Gy: 4			No: 5	
D0.5cc <38 Gy: 1		α/β 2: 1	50% after 6 months: 1	
D1cc <30 Gy: 1	Yes: 8	α/β 3: 8	15% after 12 months: 1	PTV: 0
D2cc <60 Gy EQD2: 1	No: 2	α/β 4: 1	30-50% after 12 months: 1	OAR: 7
D0.5cc <70 Gy EQD2: 1				
D0.5cc <75 Gy EQD2: 1			Unclear: 3	
Unclear: 1				

The following is a table of constraints for Bowel_Small based on published results/common practice. The toxicity endpoint is grade 3+ enteritis/obstruction

Reference	Constraint	Alpha/beta ratio (Gy)	Maximum proportion of recovery incorporated after 12 months	Maximum cumulative dose to 0.5 cc in EQD2 (Gy) based on first treatment of 45 Gy in 25 fractions (EQD2 of 43.2 Gy#)
Paradis ¹	54 Gy in 27 fractions	2.5	25%	64.8
Abusaris ² §	110 Gy in 55 fractions cumulative	3	None	110
Smith ³ ¶	98 Gy in 49 fractions cumulative	3	None	98
AAPM ⁴	35 Gy in 5 fractions	3	25%*	80.8
AAPM ⁴	35 Gy in 5 fractions	3	50%*	91.6
<i>Mean cumulative EQD2 (Gy) including recovery</i>				89

*Not specified by AAPM but assumed for illustration purposes as representative of practice

#Assuming an alpha/beta ratio of 3; 45 Gy in 25 fractions is an EQD2 of 43 Gy where an alpha/beta ratio of 2.5 is used

§In Abusaris et al, no grade 3+ toxicity was reported after a median follow up duration of 15 months (range 2-52 months)

¶In Smith et al, one patient experienced grade 3 pain but no other grade 3+ toxicity was reported after a median follow up duration of 24.5 months (inter-quartile range 17.8-28.8 months)

References:

¹Paradis et al. The Special Medical Physics Consult Process for Reirradiation Patients. *Adv Radiat Oncol.* 2019; 4(4): 559-565

²Abusaris et al. Re-Irradiation: Outcome, Cumulative Dose and Toxicity in Patients Retreated with Stereotactic Radiotherapy in the Abdominal or Pelvic Region. *Technol Cancer Res Treat.* 2012; 11(6): 591-597

³Smith et al. Stereotactic Body Radiation Therapy Reirradiation for Locally Recurrent Rectal Cancer: Outcomes and Toxicity. *Adv Radiat Oncol.* 2020; 5: 1311-1319

⁴AAPM. Report No. 101 - Stereotactic body radiation therapy: The report of AAPM Task Group 101 (2010). Available at: <https://www.aapm.org/pubs/reports/detail.asp?docid=102> [Accessed 15th December 2020]

74. If you do not Agree/Strongly Agree with the statement **Optimally, Bowel_Small should receive no more than a cumulative dose of 70 Gy₃ EQD2 to 0.5 cc (assuming no recovery)**, please explain why not



75. If you do not Agree/Strongly Agree with the statement **The degree of recovery of Bowel_Small after radiotherapy is uncertain but if 12 months or more has elapsed it is reasonable to assume some recovery and Bowel_Small may receive up to a maximum cumulative EQD2 of 90 Gy₃ to 0.5 cc**, please explain why not



Page 34: CaudaEquina/SacralPlex

Statement:

Optimally, the CaudaEquina/SacralPlex should receive no more than a cumulative dose of 67 Gy₂ EQD2 to 0.1 cc (assuming no recovery)

76. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Statement:

The degree of recovery of CaudaEquina/SacralPlex after radiotherapy is uncertain but once 12 months or more have elapsed it is reasonable to assume some recovery and CaudaEquina/SacralPlex may receive up to a maximum cumulative EQD2 of 85 Gy₂ to 0.1 cc

77. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce these statements:

CaudaEquina (13 participants)

<i>Dose constraint in 5 fractions or EQD2</i>	<i>Cumulative constraint</i>	<i>Alpha-beta ratio used for calculations</i>	<i>Allowance for repair</i>	<i>Prioritise PTV coverage or OAR constraint</i>
D0.1cc <19 Gy: 1				
D0.1cc <28 Gy: 1				
D0.1cc <30 Gy: 1			No: 1	
D0.1cc <32 Gy: 3		α/β 1: 1	25% after 6 months: 1	
D0.1cc <34 Gy: 1	Yes: 9	α/β 1.5: 1	50% after 6 months: 1	PTV: 1
D0.1cc <54-46 Gy EQD2: 1	No: 1	α/β 2: 3	15% after 12 months: 2	OAR: 9
D0.1cc <60 Gy EQD2: 1		α/β 2.5: 2	30-50% after 12 months: 1	
D0.1cc <67 Gy EQD2: 1		α/β 3: 4	Unclear: 3	
D0.1cc <74 Gy EQD2: 1				
Unclear: 2				
SacralPlex (8 participants)				

<i>Dose constraint in 5 fractions or EQD2</i>	<i>Cumulative constraint</i>	<i>Alpha-beta ratio used for calculations</i>	<i>Allowance for repair</i>	<i>Prioritise PTV coverage or OAR constraint</i>
		α/β 1: 1	No: 1	
D0.1cc <19 Gy: 1				
		α/β 1.5: 1	25% after 6 months: 1	
D0.1cc <32 Gy: 3				
	Yes: 4	α/β 2: 2	35% after 6 months: 1	PTV: 4
D0.1cc <34 Gy: 1				
	No: 2	α/β 2.5: 1	15% after 12 months: 1	OAR: 4
D0.1cc <67 Gy EQD2: 1				
		α/β 3: 2	30-50% after 12 months: 1	
Unclear: 2				
			Unclear: 2	

The following is a table of constraints for CaudaEquina/SacralPlex based on published results/common practice. The toxicity endpoint is grade 3+ neuritis

<i>Reference</i>	<i>Constraint</i>	<i>Alpha/beta ratio (Gy)</i>	<i>Maximum proportion of recovery incorporated after 12 months Gy(t)</i>	<i>Maximum cumulative dose to 0.1 cc in EQD2 based on first treatment of 45 Gy in 25 fractions (EQD2 of 42.75)</i>
Paradis ¹	70 Gy in 35 fractions	2.5	50%	91.5

Smith ² ‡	60 Gy in 30 fractions	3	33.3%	74.4
AAPM ³	32 Gy in 5 fractions	2	25%*	77.9
AAPM ³	32 Gy in 5 fractions	2	50%*	88.6
<i>Mean cumulative EQD2 including recovery</i>				83.1

*Not specified by AAPM but assumed for illustration purposes as representative of practice

#Assuming an alpha/beta ratio of 2; 45 Gy in 25 fractions is an EQD2 of 43 Gy where an alpha/beta ratio of 2.5 is used and 43.2 Gy where an alpha/beta ratio of 3 is used

‡In Smith et al, one patient experienced grade 3 pain but no other grade 3+ toxicity was reported after a median follow up duration of 24.5 months (inter-quartile range 17.8-28.8 months)

References:

¹Paradis et al. The Special Medical Physics Consult Process for Reirradiation Patients. *Adv Radiat Oncol.* 2019; 4(4): 559-565

²Smith et al. Stereotactic Body Radiation Therapy Reirradiation for Locally Recurrent Rectal Cancer: Outcomes and Toxicity. *Adv Radiat Oncol.* 2020; 5: 1311-1319

³AAPM. Report No. 101 - Stereotactic body radiation therapy: The report of AAPM Task Group 101 (2010). Available at: <https://www.aapm.org/pubs/reports/detail.asp?docid=102> [Accessed 15th December 2020]

78. If you do not Agree/Strongly Agree with the statement **Optimally, the CaudaEquina/SacralPlex should receive no more than a cumulative dose of 67 Gy₂ EQD2 to 0.1 cc (assuming no recovery)**, please explain why not

79. If you do not Agree/Strongly Agree with the statement **The degree of recovery of CaudaEquina/SacralPlex after radiotherapy is uncertain but once 12 months or more have elapsed it is reasonable to assume some recovery and CaudaEquina/SacralPlex may receive up to a maximum cumulative EQD2 of 85 Gy₂ to 0.1 cc**, please explain why not

Page 35: Colon, Colon_Sigmoid and Rectum

Statement:

Optimally, the Colon/Colon_Sigmoid/Rectum should receive no more than a cumulative dose of 80 Gy₃ EQD2 to 0.5 cc (assuming no recovery)

80. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Statement:

The degree of recovery of Colon/Colon_Sigmoid/Rectum after radiotherapy is uncertain but once 12 months or more have elapsed it is reasonable to assume some recovery and Colon/Colon_Sigmoid/Rectum may receive up to a maximum cumulative EQD2 of 100 Gy₃ to 0.5 cc

81. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce these statements:

Colon (13 participants)

<i>Dose constraint in 5 fractions or EQD2</i>	<i>Cumulative constraint</i>	<i>Alpha-beta ratio used for calculations</i>	<i>Allowance for repair</i>	<i>Prioritise PTV coverage or OAR constraint</i>
D0.5cc <32 Gy: 4				
D0.5cc <35 Gy: 1			No: 6	
		α/β 2.5: 1		
D0.5cc <40 Gy: 1			35% after 6 months: 1	
		α/β 3: 9		
D1cc <30 Gy: 1	Yes: 11		50% after 6 months: 1	PTV: 1
		α/β 4: 1		
D0.5cc <80 Gy EQD2: 2	No: 1		15% after 12 months: 2	OAR: 9
		α/β 5: 1		
D2cc <60 Gy EQD2: 1			30-50% after 12 months: 1	
D2cc <75 Gy EQD2: 1			Unclear: 2	
Unclear: 2				

Colon_Sigmoid (10 participants)

<i>Dose constraint in 5 fractions or EQD2</i>	<i>Cumulative constraint</i>	<i>Alpha-beta ratio used for calculations</i>	<i>Allowance for repair</i>	<i>Prioritise PTV coverage or OAR constraint</i>
D0.5cc <32 Gy: 3				
D0.5cc <35 Gy: 1				
D0.5cc <40 Gy: 1		α/β 2.5: 1	No: 2	
	Yes: 5			PTV: 1
D1cc <30 Gy: 1		α/β 3: 6	35% after 6 months: 1	
	No: 2			OAR: 7
D2cc <65 Gy EQD2: 1		α/β 4: 1	Unclear: 2	
D0.5cc <80 Gy EQD2: 1				
Unclear: 2				

Rectum (16 participants)

<i>Dose constraint in 5 fractions or EQD2</i>	<i>Cumulative constraint</i>	<i>Alpha-beta ratio used for calculations</i>	<i>Allowance for repair</i>	<i>Prioritise PTV coverage or OAR constraint</i>
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D0.5cc <32 Gy: 3			
D0.5cc <35 Gy: 2			
D0.5cc <36.25 Gy: 1			
D0.5cc <38 Gy: 1			No: 6
D0.5cc <40 Gy: 1		α/β 2.5: 1	35% after 6 months: 1
D2cc <65 Gy EQD2: 1	Yes: 9	α/β 3: 9	50% after 6 months: 1 PTV: 2
D2cc <75 Gy EQD2: 1	No: 2	α/β 4: 1	15% after 12 months: 1 OAR: 10
D0.5cc <80 Gy EQD2: 1			30-50% after 12 months: 1
V27Gy <2cc (rectal wall): 1			Unclear: 2
V100% <5cc: 1			
Unclear: 2			

The following is a table of constraints for Colon/Colon_Sigmoid/Rectum based on published

results/common practice. The toxicity endpoint is grade 3+ colitis/fistula

<i>Reference</i>	<i>Constraint</i>	<i>Alpha/beta ratio (Gy)</i>	<i>Maximum proportion of recovery incorporated after 12 months</i>	<i>Maximum cumulative dose to 0.5 cc in EQD2 based on first treatment of 45 Gy in 25 fractions (EQD2 of 43.2 Gy#)</i>
Paradis ¹	70 Gy in 35 fractions	2.5	50%	91.5
Abusaris ^{2§}	110 Gy in 55 fractions cumulative	3	None	110
Smith ^{3¶}	110 Gy in 55 fractions cumulative	3	None	110
AAPM ⁴	38 Gy in 5 fractions	3	25%*	91.4
AAPM ⁴	38 Gy in 5 fractions	3	50%*	102.2
<i>Mean cumulative EQD2 including recovery</i>				101

*Not specified by AAPM but assumed for illustration purposes as representative of practice

#Assuming an alpha/beta ratio of 3; 45 Gy in 25 fractions is an EQD2 of 43 Gy where an alpha/beta ratio of 2.5 is used

§In Abusaris et al, no grade 3+ toxicity was reported after a median follow up duration of 15 months (range 2-52 months)

¶In Smith et al, one patient experienced grade 3 pain but no other grade 3+ toxicity was reported after a median follow up duration of 24.5 months (inter-quartile range 17.8-28.8 months)

References

- ¹Paradis et al. The Special Medical Physics Consult Process for Reirradiation Patients. *Adv Radiat Oncol.* 2019; 4(4): 559-565
- ²Abusaris et al. Re-Irradiation: Outcome, Cumulative Dose and Toxicity in Patients Retreated with Stereotactic Radiotherapy in the Abdominal or Pelvic Region. *Technol Cancer Res Treat.* 2012; 11(6): 591-597
- ³Smith et al. Stereotactic Body Radiation Therapy Reirradiation for Locally Recurrent Rectal Cancer: Outcomes and Toxicity. *Adv Radiat Oncol.* 2020; 5: 1311-1319
- ⁴AAPM. Report No. 101 - Stereotactic body radiation therapy: The report of AAPM Task Group 101 (2010). Available at: <https://www.aapm.org/pubs/reports/detail.asp?docid=102> [Accessed 15th December 2020]

82. If you do not Agree/Strongly Agree with the statement **Optimally, the Colon/Colon_Sigmoid/Rectum should receive no more than a cumulative dose of 80 Gys EQD2 to 0.5 cc (assuming no recovery), please explain why not**



83. If you do not Agree/Strongly Agree with the statement **The degree of recovery of Colon/Colon_Sigmoid/Rectum after radiotherapy is uncertain but once 12 months or more have elapsed it is reasonable to assume some recovery and Colon/Colon_Sigmoid/Rectum may receive up to a maximum cumulative EQD2 of 100 Gys to 0.5 cc, please explain why not**



Page 36: Prioritising target volume coverage/OAR constraints

Statement:

OAR constraints should usually take priority over target volume coverage for SABR re-irradiation in the pelvis

84. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Statement:

If PTV coverage is compromised in order to meet an OAR constraint, a minimum of 70% of the PTV should receive the prescribed dose in order to proceed with SABR re-irradiation in the pelvis

85. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce these statements:

52.1-52.14. See tables above for participant information regarding prioritisation of PTV coverage/OAR constraint for each OAR

53. Where PTV coverage is compromised to meet an OAR constraint, what is the minimum acceptable PTV coverage to proceed with SABR re-irradiation in the pelvis?

- 90%: 1 participant
- 87%: 1 participant
- 85%: 2 participants
- 80%: 6 participants
- 70%: 2 participants
- 60-70%: 1 participant
- 50%: 2 participants
- If greater than 20 Gy in 5 fractions can be delivered: 1 participant
- Individual case assessment: 2 participants
- No fixed minimum: 4 participants

86. If you do not Agree/Strongly Agree with the statement **OAR constraints should usually take priority over PTV coverage for SABR re-irradiation in the pelvis**, please explain why not



87. If you do not Agree/Strongly Agree with the statement **If PTV coverage is compromised in order to meet an OAR constraint, a minimum of 70% of the PTV should receive the prescribed dose in order to proceed with SABR re-irradiation in the pelvis**, please explain why not



Page 37: Acceptable risk of late toxicity

Statement:

The accepted risk of toxicity associated with SABR re-irradiation in the pelvis will depend on the prognosis and availability of effective alternative treatments and should be a shared decision with the patient

88. Please indicate the extent to which you agree/disagree with this statement

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

The following information provided during the first round was used to produce this statement:

54. What rate/percentage risk of grade 3 or greater late toxicity is acceptable for SABR re-irradiation in the pelvis and what factors influence this?

- <5%: 7 participants
 - <3% for prostate cancer: 1 participant
 - <1% for neural OAR: 1 participant
- 10%: 7 participants
- 15%: 2 participants
- 15-20%: 2 participants
 - 15-20% for gynaecological/lower GI cancers
- Depends on individual clinical scenario: 4 participants
- Factors that influence this decision
 - Prognosis: 10 participants
 - Disease type: 6 participants
 - Availability of alternative treatment options: 6 participants
 - Performance status/comorbidity: 5 participants
 - Patient opinion/acceptance of risk: 4 participants
 - Extent of symptoms: 3 participants
 - Likelihood of response: 2 participants
 - Which OAR is concerned: 2 participants
 - Time interval between prior RT: 2 participants
 - Possibility of treating subsequent late toxicity: 1 participant

89. If you do not Agree/Strongly Agree with this statement, please explain why not

Page 38: Final page

Many thanks for completing the second round of the Delphi. We will contact you shortly after this round has closed regarding the third (final round) for any statements that did not achieve consensus agreement during this second round.

If you have any questions, please contact Dr Finbar Slevin at: finbarslevin@nhs.net

Appendix F Round 3 questionnaire: An international Delphi consensus for pelvic Stereotactic Ablative Radiotherapy

Round 3: Delphi consensus on SABR re-irradiation in the pelvis final version

Page 1: Page 1

I am happy to proceed with this second round of the international Delphi consensus on SABR/SBRT re-irradiation in the pelvis

- Yes
 No

Page 2

Many thanks for completing Round 2 of the Delphi. Twenty one participants who completed Round 1 also completed Round 2.

The 29 of 44 statements which achieved consensus during Round 2 (where $\geq 75\%$ of respondents indicated that they agree/strongly agree with a statement) have been summarised in a document attached to the email invitation for Round 3.

The 15 of 44 statements included in the following survey did not achieve consensus during Round 2.

In Round 3, we ask you to review each of these statements alongside the percentage agreement from Round 2 and the summary of free text comments provided by participants who did not agree with the statement. We ask you to reflect on whether you might re-consider your response in Round 2 based on seeing the group response.

Please then indicate the extent to which you now agree/disagree with each of these re-presented statements.

Of note, we have not modified the statements after Round 2 (in keeping with typical Delphi practice).

As emphasised in Round 2, our intention is to obtain consensus statements that would apply *in general* to SABR re-irradiation in the pelvis, rather than exceptional/individual cases.

Page 3: Section 1: Definition of SABR re-irradiation in the pelvis, patient selection and pre-treatment investigations

Page 4

Statement:

The maximum number of pelvic lesions treated by SABR re-irradiation should not exceed 3

Results from Round 2:

Strongly disagree: 0 participants

Disagree: 9 participants (42.9%)

Neither Agree/Disagree: 3 participants (14.3%)

Agree: 8 participants (38.1%)

Strongly Agree: 1 participant (4.8%)

21 participants in total, 42.9% agreement

Comments from Round 2

- The size/location of lesions and proximity to OARs is more relevant than the number of lesions: 9 participants
- Limit should be 1 (or possibly 2) lesions: 1 participant

Please indicate the extent to which you now agree/disagree with the statement '**The maximum number of pelvic lesions treated by SABR re-irradiation should not exceed 3**'

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Page 5

Statement:

The maximum size of an individual pelvic lesion treated by SABR re-irradiation should not exceed 6 cm in maximum dimension

Results from Round 2:

Strongly disagree: 0 participants

Disagree: 6 participants (30%)

Neither Agree/Disagree: 2 participants (10%)

Agree: 9 participants (45%)

Strongly Agree: 3 participants (15%)

20 participants in total, 60% agreement

Comments from Round 2

- The location of a lesion and proximity to OARs is more relevant than the size of the lesion: 6 participants
- Limit should be 3-4 cm: 1 participant

Please indicate the extent to which you now agree/disagree with the statement '**The maximum size of an individual pelvic lesion treated by SABR re-irradiation should not exceed 6 cm in maximum dimension**'

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Page 6

Statement:

SABR re-irradiation in the pelvis may not be appropriate where the lesion is in contact with a luminal/critical OAR

Results from Round 2:

Strongly disagree: 0 participants

Disagree: 7 participants (33.3%)

Neither Agree/Disagree: 4 participants (19%)

Agree: 8 participants (38.1%)

Strongly Agree: 2 participants (9.5%)

21 participants in total, 47.6% agreement

Comments from Round 2

- More dependent on target coverage- inhomogenous PTV coverage in area of overlap/lower SABR doses e.g. 30 Gy in 5 fractions can be considered: 3 participants
- A small area of contact, especially for a mobile OAR, should not be a contraindication with careful monitoring during treatment: 2 participants
- This should not be an absolute contraindication for selected/well informed patients: 2 participants
- Salvage prostate SABR for local recurrence is feasible where there is contact with bladder/rectum: 1 participant
- In prostate cancer, the low α/β ratio would provide a favourable therapeutic ratio for lower dose SABR compared with OARs such as bladder/rectum: 1 participant

Please indicate the extent to which you now agree/disagree with the statement '**SABR re-irradiation in the pelvis may not be appropriate where the lesion is in contact with a luminal/critical OAR**'

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Page 7

Statement:

A minimum time interval of 12 months should have elapsed between a previous course of radiotherapy in the pelvis and SABR re-irradiation in the pelvis

Results from Round 2:

Strongly disagree: 1 participant (4.8%)

Disagree: 7 participants (33.3%)

Neither Agree/Disagree: 5 participants (23.8%)

Agree: 8 participants (38.1%)

Strongly Agree: 0 participants

21 participants in total, 38.1% agreement

Comments from Round 2

- More dependent on target location and OAR dosimetry from first course and SABR: 3 participants
- A time interval of 6 months may be sufficient where overlap is at lower isodoses: 2 participants
- The minimum time interval should be >12 months: 1 participant
- There is no reliable data regarding the safe minimum time interval between two courses of radiation: 1 participant
- The time interval may depend on the histological subtype of disease; for example, treatment of a pelvic node in cervical cancer <12 months might be reasonable compared with prostate cancer: 1 participant
- 2 years may be needed to avoid false positive biopsy results in prostate cancer: 1 participant

Please indicate the extent to which you now agree/disagree with the statement '**A minimum time interval of 12 months should have elapsed between a previous course of radiotherapy in the pelvis and SABR re-irradiation in the pelvis**'

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Page 8

Statement:

Diagnostic staging imaging prior to SABR re-irradiation in the pelvis should include MRI pelvis and PET-CT

Results from Round 2:

Strongly disagree: 2 participants (9.5%)

Disagree: 3 participants (14.3%)

Neither Agree/Disagree: 1 participant (4.8%)

Agree: 10 participants (47.6%)

Strongly Agree: 5 participants (23.8%)

21 participants in total, 71.4% agreement

Comments from Round 2

- MRI may not be necessary for pelvic nodal disease: 3 participants
- MRI and PET-CT should be encouraged but not mandated: 1 participant
- Choice of imaging is dependent on the primary tumour type: 1 participant
- PET-CT should be recommended but not MRI: 1 participant
- MRI/PET-CT are not necessary: 2 participants

Please indicate the extent to which you now agree/disagree with the statement
'Diagnostic staging imaging prior to SABR re-irradiation in the pelvis should include MRI pelvis and PET-CT'

Strongly Disagree

Disagree

Neither Agree/Disagree

Agree

Strongly Agree

Page 9

Statement:

Non-SABR re-irradiation in the pelvis (e.g. using conventionally or hyperfractionated radiotherapy) is preferred for lesions >6 cm

Results from Round 2:

Strongly disagree: 0 participants

Disagree: 5 participants (23.8%)

Neither Agree/Disagree: 6 participants (26.8%)

Agree: 7 participants (33.3%)

Strongly Agree: 3 participants (14.3%)

21 participants in total, 47.6% agreement

Comments from Round 2

- More dependent on OAR constraints than the size of the target: 5 participants
- A recurrent pelvic lesion >6 cm is unlikely to be cured by radiation and therefore treatment would be with palliative intent: 3 participants

Please indicate the extent to which you now agree/disagree with the statement '**Non-SABR re-irradiation in the pelvis (e.g. using conventionally or hyperfractionated radiotherapy) is preferred for lesions >6 cm**'

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Page 10

Statement:

Non-SABR re-irradiation in the pelvis is preferred for lesions infiltrating or in contact with a luminal/critical OAR

Results from Round 2:

Strongly disagree: 0 participants

Disagree: 4 participants (19%)

Neither Agree/Disagree: 6 participants (26.8%)

Agree: 9 participants (42.9%)

Strongly Agree: 2 participants (9.5%)

21 participants in total, 52.4% agreement

Comments from Round 2

- More dependent on dose to OARs than the fractionation/treatment technique: 2 participants
- A patient in this situation would be treated with palliative intent: 2 participants
- SABR (including salvage prostate SABR for local recurrence) may still be possible with OAR contact: 2 participants
- Statement would be supported for infiltration of luminal OAR but not infiltration or contact: 1 participant
- Total radiation dose delivered more important than the fractionation: 1 participant
- Conventional fractionation preferred for vascular, bowel or bladder invasion: 1 participant

Please indicate the extent to which you now agree/disagree with the statement '**Non-SABR re-irradiation in the pelvis is preferred for lesions infiltrating or in contact with a luminal/critical OAR**'

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Page 11: Section 2: Patient set up, target volume/OAR delineation, treatment planning and delivery

Page 12

Statement:

For conventional linear accelerator-based SABR, the maximum allowable dose within the target volume for SABR re-irradiation in the pelvis should not exceed 140% of the prescribed dose

Results from Round 2:

Strongly disagree: 1 participant (4.8%)

Disagree: 4 participants (19%)

Neither Agree/Disagree: 1 participant (4.8%)

Agree: 15 participants (71.4%)

Strongly Agree: 0 participants

21 participants in total, 71.4% agreement

Comments from Round 2

- The maximum allowable dose will depend on proximity to OARs: 2 participants
- 140% is a significant hot spot if prescription dose is 35-37.5 Gy- would limit to 115-125% as an alternative: 1 participant
- Would suggest aligning limit to traditional prescription isodoses (for example, 80% isodose (125% max dose), 65% isodose (150% max dose): 1 participant
- Heterogeneity within the PTV may aid OAR sparing: 1 participant

Please indicate the extent to which you now agree/disagree with the statement '**For conventional linear accelerator-based SABR, the maximum allowable dose within the target volume for SABR re-irradiation in the pelvis should not exceed 140% of the prescribed dose**'

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Page 13

Statement:

Where there has been previous delivery of gynaecological brachytherapy, SABR re-irradiation is not recommended where there would be overlap of the planning target volumes

Results from Round 2:

Strongly disagree: 0 participants

Disagree: 7 participants (33.3%)

Neither Agree/Disagree: 1 participant (4.8%)

Agree: 11 participants (52.4%)

Strongly Agree: 2 participants (9.5%)

21 participants in total, 61.9% agreement

Comments from Round 2

- SABR may be feasible if cumulative OAR constraints can be met: 2 participants
- Depends on the location of the new target to the high dose of the brachytherapy volume: 1 participant
- Would agree if the target was previously treated with brachytherapy but not if only the PTV of the new target overlaps with the previous brachytherapy PTV: 1 participant
- Feasibility of SABR decided on an individual case basis: 2 participants

Please indicate the extent to which you now agree/disagree with the statement '**Where there has been previous delivery of gynaecological brachytherapy, SABR re-irradiation is not recommended where there would be overlap of the planning target volumes**'

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Page 14: Section 3: Cumulative Organ at Risk (OAR) dose constraints

Page 15

Statement:

Optimally, the Bladder should receive no more than a cumulative dose of 80 Gy₃ EQD2 to 0.5 cc (assuming no recovery)

Results from Round 2:

Strongly disagree: 0 participants

Disagree: 4 participants (19%)

Neither Agree/Disagree: 2 participants (9.5%)

Agree: 13 participants (61.9%)

Strongly Agree: 2 participants (9.5%)

21 participants in total, 71.4% agreement

Comments from Round 2

- Up front SABR to prostate may deliver 8 Gy x5 and the bladder may receive an EQD2 of 88 Gy, so perhaps the constraint should be 90 Gy: 1 participant
- 2cc of bladder commonly receives >80 Gy during cervical cancer primary treatment without a gap between external beam radiotherapy and brachytherapy: 1 participant
- Prostate cancer literature suggests this threshold could be exceeded: 1 participant
- Accuracy of cumulative dose calculation is debatable, especially when a wide range of commercial solutions are available. The accepted risk of toxicity associated with SABR re-irradiation in the pelvis will depend on the prognosis and availability of effective alternative treatments and should be a shared decision with the patient: 1 participant
- A typical re-treatment scenario is the following: previous elective nodal irradiation to a dose of 46 Gy in 23 fractions, so bladder wall gets 46 Gy in 23 fractions. Now there is a pelvic node recurrence close to bladder wall which we want to deliver SBRT to. If we limit the EQD2 of 80 Gy, then the maximum re-irradiation dose to prescribed to the bladder would be approximately 22 Gy in 5 fractions, which is essentially palliative RT. After 46 Gy in 23 fractions, I think most people would think the bladder can tolerate more than a palliative dose of RT in 5 fractions: 1 participant

Please indicate the extent to which you now agree/disagree with the statement
'Optimally, the Bladder should receive no more than a cumulative dose of 80 Gy₃ EQD2 to 0.5 cc (assuming no recovery)'

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Page 16

Statement:

Optimally, Bowel_Small should receive no more than a cumulative dose of 70 Gy₃ EQD2 to 0.5 cc (assuming no recovery)

Results from Round 2:

Strongly disagree: 2 participants (10.5%)

Disagree: 5 participants (26.3%)

Neither Agree/Disagree: 2 participants (10.5%)

Agree: 9 participants (47.4%)

Strongly Agree: 1 participant (5.3%)

19 participants in total, 52.7% agreement

Comments from Round 2

- Limit should be ~50-54 Gy EQD2: 1 participant
- Limit should be <60 Gy: 2 participants
- Limit should be 100 Gy EQD2: 1 participant
- In common scenario, a microscopic elective pelvic nodal irradiation dose may have been delivered (like 46 Gy in 23 fractions) previously. Giving a subsequent palliative dose of radiotherapy (like 20 Gy in 5 fractions) is fairly safe, but this would already exceed the cumulative 70 Gy EQD2 already: 1 participant
- Depends on time between treatments: 1 participant
- No literature about this threshold: 1 participant
- Some recovery expected and no toxicity seen in patients treated to date: 1 participant
- The accuracy of the cumulative dose calculation is debatable especially when there's a wide range of commercial solutions available. The accepted risk of toxicity associated with SABR re-irradiation in the pelvis will depend on the prognosis and availability of effective alternative treatments and should be a shared decision with the patient: 1 participant

Please indicate the extent to which you now agree/disagree with the statement
'Optimally, Bowel_Small should receive no more than a cumulative dose of 70 Gy₃ EQD2 to 0.5 cc (assuming no recovery)'

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Page 17

Statement

The degree of recovery of Bowel_Small after radiotherapy is uncertain but if 12 months or more has elapsed it is reasonable to assume some recovery and Bowel_Small may receive up to a maximum cumulative EQD2 of 90 Gy₃ to 0.5 cc

Results from Round 2:

Strongly disagree: 2 participants (9.5%)

Disagree: 2 participants (9.5%)

Neither Agree/Disagree: 6 participants (28.6%)

Agree: 10 participants (47.4%)

Strongly Agree: 1 participant (4.8%)

21 participants in total, 52.4% agreement

Comments from Round 2

- Depending on the indication and what is to be gained by good local control and what is to be lost by not having local control I would push to Abusaris or higher in trial: 1 participant
- Small bowel should not get more than ~50-54 Gy EQD2. You should simply calculate prior dose multiplied by recovery factor, and then add the new dose = 50-54 Gy: 1 participant
- Limit should be <70 Gy: 1 participant
- **Abusaris and Smith data suggests that the dose can go higher: 1 participant**
- In common scenario, a microscopic elective pelvic nodal irradiation dose may have been delivered (like 46 Gy in 23 fractions) previously. Allowing cumulative 90 Gy EQD2 means a maximum of 26-27 Gy in 5 fractions treatment. I think this is very conservative. Unsure how much of this is actually based on actual re-treatment data, or rather expert opinion: 1 participant
- Depends on the time interval between treatments: 1 participant
- Insufficient data to support this statement: 1 participant
- The accuracy of the cumulative dose calculation is debatable especially when there's a wide range of commercial solutions available. The accepted risk of toxicity associated with SABR re-irradiation in the pelvis will depend on the prognosis and availability of effective alternative treatments and should be a shared decision with the patient: 1 participant

Please indicate the extent to which you now agree/disagree with the statement '**The degree of recovery of Bowel_Small after radiotherapy is uncertain but if 12 months or more has elapsed it is reasonable to assume some recovery and Bowel_Small may receive up to a maximum cumulative EQD2 of 90 Gy₃ to 0.5 cc**'

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Page 18

Statement:

The degree of recovery of CaudaEquina/SacralPlex after radiotherapy is uncertain but once 12 months or more have elapsed it is reasonable to assume some recovery and CaudaEquina/SacralPlex may receive up to a maximum cumulative EQD2 of 85 Gy₂ to 0.1 cc

Results from Round 2:

Strongly disagree: 1 participant (5.3%)

Disagree: 2 participants (10.5%)

Neither Agree/Disagree: 3 participants (15.8%)

Agree: 11 participants (57.9%)

Strongly Agree: 2 participants (10.5%)

19 participants in total, 68.4% agreement

Comments from Round 2

- Individual case assessment; for a tumour invading SacralPlex, if it is not controlled there is a 100% risk of sacral plexopathy versus a lower risk if constraint exceeded in attempt to get local control: 1 participant
- You should simply calculate prior dose multiplied by recovery factor of 50% if beyond 1 year, and then add the new dose. Total dose should be the same as the CaudaEquina constraint: 1 participant
- Cumulative dose of 85 Gy seems too high in my opinion: 1 participant
- If you are setting an absolute maximum, should it not reflect the maximum/near maximum with published data to support rather than the mean? I would prefer 90 Gy: 1 participant
- The accuracy of the cumulative dose calculation is debatable especially when there's a wide range of commercial solutions available. The accepted risk of toxicity associated with SABR re-irradiation in the pelvis will depend on the prognosis and availability of effective alternative treatments and should be a shared decision with the patient: 1 participant
- One comment unclear

Please indicate the extent to which you now agree/disagree with the statement '**The degree of recovery of CaudaEquina/SacralPlex after radiotherapy is uncertain but once 12 months or more have elapsed it is reasonable to assume some recovery and CaudaEquina/SacralPlex may receive up to a maximum cumulative EQD2 of 85 Gy₂ to 0.1 cc**'

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Page 19

Statement:

Optimally, the Colon/Colon_Sigmoid/Rectum should receive no more than a cumulative dose of 80 Gy₃ EQD2 to 0.5 cc (assuming no recovery)

Results from Round 2:

Strongly disagree: 2 participants (9.5%)

Disagree: 4 participants (19%)

Neither Agree/Disagree: 2 participants (9.5%)

Agree: 13 participants (61.9%)

Strongly Agree: 0 participants

21 participants in total, 61.9% agreement

Comments from Round 2

- Limit should be 70 Gy: 1 participant
- Limit should be <65 Gy: 1 participant
- A common scenario in prostate RT is to deliver 78 Gy in 39 fractions, which means the anterior rectal wall (large bowel) gets that full dose. It is not that uncommon that a subsequent palliative dose of 20 Gy in 5 fractions can be safely delivered in the same area if patient's tumour recurs locally, which will exceed 80 Gy EQD2 cumulatively: 1 participant
- Some recovery expected- no toxicity seen in patients I have treated to date: 1 participant
- Prostate cancer literature suggests this threshold could be exceeded: 1 participant
- The accuracy of the cumulative dose calculation is debatable especially when there's a wide range of commercial solutions available. The accepted risk of toxicity associated with SABR re-irradiation in the pelvis will depend on the prognosis and availability of effective alternative treatments and should be a shared decision with the patient: 1 participant

Please indicate the extent to which you now agree/disagree with the statement
'Optimally, the Colon/Colon_Sigmoid/Rectum should receive no more than a cumulative dose of 80 Gy₃ EQD2 to 0.5 cc (assuming no recovery)'

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Page 20

Statement:

The degree of recovery of Colon/Colon_Sigmoid/Rectum after radiotherapy is uncertain but once 12 months or more have elapsed it is reasonable to assume some recovery and Colon/Colon_Sigmoid/Rectum may receive up to a maximum cumulative EQD2 of 100 Gy₃ to 0.5 cc

Results from Round 2:

Strongly disagree: 1 participant (4.8%)

Disagree: 6 participants (28.6%)

Neither Agree/Disagree: 3 participants (14.3%)

Agree: 10 participants (47.6%)

Strongly Agree: 1 participant (4.8%)

21 participants in total, 52.4% agreement

Comments from Round 2

- Depends on the risk/benefits of not gaining local control; if a lot to gain/little to lose, I would give a dose in keeping with the Abusaris constraint: 1 participant
- You should simply calculate prior dose multiplied by recovery factor of 50% if beyond 1 year, and then add the new dose. Total dose should be the same as the Colon constraint: 1 participant
- I think that Colon_Sigmoid should receive less dose than Rectum or Colon: 1 participant
- Limit should be <80 Gy: 1 participant
- Insufficient data to support this statement: 1 participant
- Prostate cancer literature suggests this threshold could be exceeded: 1 participant
- I would prefer the higher end of the range to be presented which has data to support i.e. use 110 Gy if single figure or present as a range: 1 participant
- A common scenario in prostate RT is to deliver 78 Gy in 39 fractions, which means the anterior rectal wall (large bowel) gets that full dose. It is not that uncommon that a subsequent palliative dose of 20 Gy in 5 fractions can be safely delivered in the same area if patient's tumour recurs locally, which will exceed 100 Gy EQD2 cumulatively: 1 participant
- The accuracy of the cumulative dose calculation is debatable especially when there's a wide range of commercial solutions available. The accepted risk of toxicity associated with SABR re-irradiation in the pelvis will depend on the prognosis and availability of effective alternative treatments and should be a shared decision with the patient: 1 participant

Please indicate the extent to which you now agree/disagree with the statement '**The degree of recovery of Colon/Colon_Sigmoid/Rectum after radiotherapy is uncertain but once 12 months or more have elapsed it is reasonable to assume some recovery and Colon/Colon_Sigmoid/Rectum may receive up to a maximum cumulative EQD2 of 100 Gy₃ to 0.5 cc'**

- Strongly Disagree
- Disagree
- Neither Agree/Disagree
- Agree
- Strongly Agree

Page 21: Final page

This is the final round of the Delphi- we will contact you after it has closed to provide the final results and draft manuscript.

Many thanks again for taking part,

Dr Finbar Slevin

Clinical Research Fellow, University of Leeds, UK
