Optimising treatment outcomes using Stereotactic Body Radiotherapy (SBRT) for prostate cancer

Louise Janet Murray

Submitted in accordance with the requirements for the degree of

Doctor of Philosophy

The University of Leeds School of Medicine and Health

October 2014

The candidate confirms that the work submitted is her own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and 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.

Publication	**Chapter which will include elements of this work**	**Work attributable to the candidate**	**Work attributable to co-authors**
Murray L, Henry A, Hoskin P, Siebert FA, Venselaar J on behalf of the BRAPHYQS/ PROBATE group of GEC ESTRO. Second primary cancers after radiation for prostate cancer: a review of planning studies. *Radiation Oncology* 2013;8:172	6	Search strategy, paper review and appraisal, write-up	Supervision, review of draft manuscript
Murray LJ, Cosgrove V, Lilley J, Thompson CM, Sykes J, Franks KN, Sebag-Montefiore D, Henry AM. Developing a class solution for prostate stereotactic ablative radiotherapy (SABR) using volumetric modulated arc therapy (VMAT). *Radiotherapy and Oncology* 2014;110(2):213-228	2	Study design, plan creation and analysis, statistical analysis, write-up	Supervision, review of draft manuscript (all), assistance with plan verification (CT)
Murray L, Henry A, Hoskin P, Siebert FA, Venselaar J on behalf of the BRAPHYQS/ PROBATE group of GEC ESTRO. Second primary cancers after radiation for prostate cancer: A systematic review of the clinical data and impact of treatment technique*. Radiotherapy and Oncology* 2014; 110(2):298-302	5	Search strategy, paper review and appraisal, write-up	Supervision, review of draft manuscript
Murray LJ, Lilley J, Thompson CM, Mason J, Sykes J, Franks KN, Sebag-Montefiore D, Cosgrove V, Henry AM. Prostate stereotactic ablative radiotherapy (SABR) using volumetric modulated arc therapy (VMAT) to dominant intra-prostatic lesions (DILs). *International Journal of Radiation Oncology, Biology and Physics* 2014; 89(2):406-415	3	Study design, plan creation and analysis, statistical analysis, write-up	Supervision, review of draft manuscript (all except JM), provision of technical MRI details, image transfer and fusion (JM)
Murray LJ, Thompson CM, Lilley J, Cosgrove V, Franks KN, Sebag-Montefiore D, Henry AM. Radiation-induced second primary cancer risks from modern external beam radiotherapy for early prostate cancer: impact of stereotactic ablative radiotherapy (SABR), volumetric modulated arc therapy (VMAT) and flattening filter free (FFF) radiotherapy. *Physics in Medicine and Biology* 2015;60:1237-1257	6	Study design, plan creation, analysis and delivery, statistical analysis, write-up	Supervision, review of draft manuscript (all), assistance with plan delivery (CT)

Acknowledgements

I would firstly like to thank all my Supervisors, Dr Ann Henry, Dr Vivian Cosgrove, Dr Kevin Franks, Professor Alan Melcher and Professor David Sebag-Montefiore for all their guidance and encouragement over the past three years. I would particularly like to thank Dr Ann Henry as my day to day Supervisor for her ongoing patience, guidance and unflappable nature.

I also received significant support from others who I also wish to thank:

Mr John Lilley for all his ongoing guidance in terms of study design and execution, his advice regarding plan creation, for reviewing plans, for his enthusiasm for my work and for his unrelenting support for “proper science” in the linear accelerator.

Dr Jonathan Sykes for suggestions regarding the image-guidance and motion aspects of this work.

Dr Brendan Carey for contouring the dominant intra-prostatic lesions, prostates and urethras used in Chapter 3 of this work.

Mr Joshua Mason for his assistance in transferring and co-registering the dominant intra-prostatic lesion contours used in Chapter 3 and for providing the technical MRI information contained in this chapter.

Mr Christopher Thompson for his extensive practical assistance, from planning tips to moulding the anthropomorphic phantom into a vacuum bag and putting it on a trolley so that I could manoeuvre it independently. His patience and good humour throughout several lengthy “experiments” were very much appreciated.

Lastly, I would like to thank my husband for ‘allowing’ me to move to Leeds during the week to carry out this project, for patience that knows no bounds and for always believing in me. This work was funded by Cancer Research UK (C37059/A11941).

Abstract

Aims: to optimise linear accelerator-based prostate stereotactic ablative radiotherapy (SABR) through planning studies, tumour control probability (TCP) and normal tissue complication probability (NTCP) calculations and radiation-induced second primary cancer (RISPC) risk assessment.

Methods: A planning study was performed to develop a class solution for prostate SABR. A second planning study delivered boosts to dominant intra-prostatic lesions (DILs) and TCP and NTCP were calculated. A third planning study compared prostate SABR planning using flattened and flattening filter free (FFF) beams. A systematic review examined RISPC risk following prostate radiotherapy. A final study estimated RISPC risks following prostate SABR in comparison to other contemporary radiation techniques.

Results: Prostate SABR was optimal using a single anterior arc which resulted in highly conformal plans, lower rectal doses and improved delivery times and monitor unit requirements for most patients. Boosting DILs resulted in small TCP increases, but the benefit was offset by increases in NTCP. SABR to the whole prostate without DIL boosting resulted in high TCP and low NTCP. Plans using flattened and FFF beams were dosimetrically similar but FFF resulted in reduced delivery times. Clinical evidence, largely based on older radiation techniques, suggests that prostate radiotherapy increases RISPC risk. Clinical evidence concerning risk following modern techniques is too immature to draw firm conclusions. The final study demonstrated that SABR techniques resulted in lower estimated RISPC risks in all organs compared to conventionally fractionated techniques, while FFF techniques reduced RISPC risks in out-of-field organs.

Conclusions: Linear accelerator-based prostate SABR delivered with a single partial arc is optimal and high levels of TCP and low levels of NTCP are predicted from whole prostate SABR. FFF allows faster treatment delivery. Second malignancy risk is lower using SABR, particularly with FFF, compared to conventionally fractionated techniques. Phase III trials are required to investigate prostate SABR in practice.

Table of Contents

Acknowledgements ..... **iv**
Abstract ..... **v**
Table of Contents ..... **vi**
List of Abbreviations ..... **xvii**
Chapter 1 : Introduction **1**
1.1 Prostate cancer 1
1.2 Conventional EBRT 1
1.3 3D-Conformal EBRT and dose escalation 2
1.4 IMRT 2
1.5 Volumetric modulated arc therapy 3
1.6 The rationale for hypofractionation 4
1.7 Moderate hypofractionation 5
1.8 SABR and ultra-hypofractionation 6
1.9 Clinical evidence regarding SABR in prostate cancer 10
1.9.1 Patient selection 10
1.9.2 Use of androgen deprivation 11
1.9.3 Dose and fractionation 12
1.9.4 Treatment platform 12
1.9.5 Data acquisition 13
1.9.6 Patient preparation 13
1.9.7 CTV contents 13
1.9.8 CTV-PTV margins and image-guidance 13
1.9.9 Target coverage, prescription and dose distribution 14
1.9.10 Organ at risk constraints 16
1.9.11 Efficacy 17
1.9.12 PSA bounce 22
1.9.13 Acute toxicity 23
1.9.14 Late toxicity 27
1.9.15 Quality of life outcomes 31
1.9.16 Cost effectiveness 33
1.9.17 Conclusions about SABR in prostate cancer 34

1.10 The influence of overall treatment time 35
1.11 Image guided radiotherapy (IGRT) and associated interventions for SABR 35
1.11.1 Portal imaging matching to bony anatomy 36
1.11.2 Fiducial markers 36
1.11.3 Cone Beam CT 38
1.11.4 Endorectal Balloons 39
1.11.5 Prostate-rectal spacers 39
1.12 SABR delivered using VMAT 40
1.13 Aims…… 40
Chapter 2 : Developing a class solution for prostate stereotactic ablative radiotherapy 41
2.1 Introduction 41
2.2 Materials and Methods 42
2.2.1 Patients and volumes 42
2.2.2 Selection of SABR dose 43
2.2.3 PTV coverage 46
2.2.4 Defining organ at risk constraints 46
2.2.5 Planning 50
2.2.6 Plan evaluation 56
2.2.7 Verification 56
2.2.8 Statistics 57
2.3 Results 57
2.3.1 Part I: arc arrangements 57
2.3.2 Part II: CTV-PTV margins 65
2.3.3 Part III: inclusion of proxSV 72
2.3.4 Verification 75
2.4 Discussion 77
2.5 Conclusions 83
2.6 Acknowledgements 84
Chapter 3 : Prostate stereotactic ablative radiotherapy (SABR) using volumetric modulated arc therapy (VMAT) to dominant intra-prostatic lesions (DILs) 85
3.1 Introduction 85
3.2 Methods 86

3.2.1 Imaging and contouring 86
3.2.2 Prescription and coverage 89
3.2.3 Organs at risk 92
3.2.4 Plans 92
3.2.5 Planning 93
3.2.6 Modelling 95
3.2.7 TCP sensitivity analysis 102
3.2.8 Statistics 102
3.3 Results 103
3.4 Discussion 114
3.5 Conclusions 122
3.6 Acknowledgements 123
Chapter 4 : Impact of flattening filter free mode on prostate stereotactic ablative radiotherapy (SABR) planning 124
4.1 Introduction 124
4.2 Methods 125
4.2.1 Planning 125
4.2.2 Plan evaluation 127
4.2.3 Statistics 129
4.2.4 Verification 129
4.3 Results 129
4.3.1 Plans 129
4.3.2 Verification 135
4.4 Discussion 135
4.5 Conclusions 138
4.6 Acknowledgements 138
Chapter 5 : Radiation-induced second primary cancers in patients irradiated for prostate cancer: a systematic review of clinical evidence 139
5.1 Introduction 139
5.2 Objectives 140
5.3 Methods 141
5.4 Results 143
5.4.1 Overall second cancer risk associated with EBRT for prostate cancer 143

5.4.2 Second rectal cancer risk associated with EBRT for prostate cancer 150
5.4.3 Second bladder cancer risk associated with EBRT for prostate cancer 162
5.4.4 Impact of treatment technique: older treatments 164
5.4.5 Impact of treatment technique: 3D-conformal radiotherapy and IMRT 164
5.4.6 Impact of treatment technique: Brachytherapy 167
5.4.7 Impact of treatment technique: Proton therapy 180
5.4.8 Post-operative radiotherapy 181
5.5 Discussion 185
5.6 Conclusions 188
5.7 Update at time of thesis write-up 189
Chapter 6 : Radiation-induced second primary cancer risks from modern external beam radiotherapy for early prostate cancer: impact of stereotactic ablative radiotherapy (SABR), volumetric modulated arc therapy (VMAT) and flattening filter free (FFF) radiotherapy 193
6.1 Introduction 193
6.2 Methods 194
6.2.1 Contouring 194
6.2.2 Advanced radiotherapy planning 195
6.2.3 3D-conformal planning 197
6.2.4 In-field and close-to-field RISPC risk assessment 197
6.2.5 Out-of-field RISPC risk assessment 198
6.2.6 Assessment of head leakage and scatter 202
6.2.7 Second malignancy risk assessment 202
6.2.8 Integral dose assessment 206
6.3 Results 208
6.3.1 Plans 208
6.3.2 In-field or close-to-field RISPC risks 210
6.3.3 Out-of-field RISPC risks 217
6.3.4 Dose from machine head and machine scatter 221
6.3.5 Components of dose and distance 223
6.3.6 Relationship between RISPC risk and integral dose 227
6.3.7 Femoral head doses 232

6.4 Discussion 233
6.5 Conclusions 255
6.6 Acknowledgements 255
Chapter 7 : Summary and Future Work 256
7.1 Summary 256
7.2 Future work 258
Chapter 8 : References 261
Appendix A: Definitions of biochemical failure used in prostate cancer 287
Appendix B: Risk groups in prostate cancer 288
Appendix C: Clinical evidence for prostate SABR 290
Appendix D: Systematic review search strategy 317

List of Tables

Table 1.1 Comparison of conventionally fractionated and SABR regimens used for the treatment of prostate cancer 8

Table 1.2 Efficacy outcomes for different prostate cancer treatment modalities 19

Table 1.3 Summarised toxicity rates reported in prostate SABR studies (median (and range)) 24

Table 1.4 Acute toxicities following alternative radiotherapy techniques for prostate cancer 26

Table 1.5 Late toxicities following alternative radiotherapy techniques for prostate cancer 29

Table 2.1 Biologically equivalent doses with conventional and SABR dose and fractionation schedules 44

Table 2.2 Comparison of rectal dose-volume constraints from i) the CHHiP trial for 74Gy in 37 fractions, ii) calculated biologically equivalent constraints for a 7 fraction treatment and iii) dose-volume constraints from the Scandinavian trial using 42.7Gy in 7 fractions 49

Table 2.3 Dose-volume constraints adopted for planning study 50

Table 2.4 Explanation for prescription components shown in Figure 2-2 53

Table 2.5 Coverage using four different arc arrangements 59

Table 2.6 Conformity and plan delivery using four different arc arrangements 60

Table 2.7 Plan statistics for organs at risk using four different arc arrangements 62

Table 2.8 Coverage comparing PTVs: Prostate + 6mm (P+6mm), Prostate + 8mm (P+8mm) and Prostate + proximal seminal vesicles + 6mm ((P+SV)+6mm) 68

Table 2.9 Plan statistics for organs at risk for PTVs: Prostate + 6mm (P+6mm), Prostate + 8mm (P+8mm) and Prostate + proximal seminal vesicles + 6mm ((P+SV)+6mm) 69

Table 2.10 Conformity and delivery data for PTVs: Prostate + 6mm (P+6mm), Prostate + 8mm (P+8mm) and Prostate + proximal seminal vesicles + 6mm ((P+SV)+6mm) 71

Table 2.11 Verification outcomes 75

Table 3.1 Clinical and imaging characteristics 87

Table 3.2 Coverage requirements and organ at risk constraints.....90

Table 3.3 TCP parameters 97

Table 3.4 NTCP parameters.....101

Table 3.5 Plan parameters.....105

Table 3.6 Tumour control probability (TCP) and normal tissue complication probability (NTCP) 107

Table 3.7 Relative variation rates (%) following a change in TCP parameter by up or down 10% (median (and range)) 108

Table 3.8 Median sensitivity indices (and ranges) based on changing each TCP parameter up or down by 10%.....109

Table 3.9 Impact of re-planning five 'worst' rectal NTCP plans 112

Table 3.10 Anorectal NTCP (%) calculated using alternative parameters (median and (range)) 113

Table 3.11 Urethral doses ($PRV_{urethra}$) in non-boost plans (Plan set A)121

Table 4.1 Coverage requirements and organ at risk constraints.....126

Table 4.2 Plan statistics for FFF plans compared to flattened plans: coverage 130

Table 4.3 Plan statistics for FFF plans compared to flattened plans: dose spread, monitor unit requirements and estimated delivery times 131

Table 4.4 Plan statistics for FFF plans compared to flattened plans: organs at risk 132

Table 5.1 Studies examining second primary cancers at any site in prostate cancer patients irradiated using external beam radiotherapy compared to general population.....145

Table 5.2 Studies examining second primary cancers at any site in prostate cancer patients irradiated using external beam radiotherapy compared to non-irradiated prostate cancer patients 146

Table 5.3 Studies reporting second cancer rates in irradiated prostate cancer patients without comparison to other populations 148

Table 5.4 Deaths due to second cancers following irradiation in prostate cancer patients 149

Table 5.5 Studies examining second rectal and second bladder cancers in prostate cancer patients irradiated using external beam radiotherapy compared to general population 152

Table 5.6 Studies examining second rectal and bladder cancers in prostate cancer patients irradiated using external beam radiotherapy compared to non-irradiated prostate cancer patients 156

Table 5.7 Studies examining second primary cancers at any site, rectal cancers and bladder cancers in prostate cancer patients irradiated using modern external beam techniques compared to general population and compared to surgical prostate cancer patients 166

Table 5.8 Studies examining second primary cancers at any site, second rectal cancers and second bladder cancers in prostate cancer patients irradiated using brachytherapy compared to general population 169

Table 5.9 Studies examining second primary cancers at any site in prostate cancer patients irradiated using brachytherapy compared to non-irradiated prostate cancer patients 171

Table 5.10 Studies examining second rectal and bladder cancers in prostate cancer patients irradiated using brachytherapy compared to non-irradiated prostate cancer patients 173

Table 5.11 Studies examining second primary cancers at any site in prostate cancer patients irradiated using brachytherapy compared to patients irradiated using external beam radiotherapy 177

Table 5.12 Studies reporting second cancer rates in patients treated with brachytherapy or combination external beam radiotherapy and brachytherapy without comparison 179

Table 5.13 Risk of second rectal and bladder cancers following post-operative radiotherapy for prostate cancer compared to the general population and compared to non-irradiated patients 182

Table 6.1 Organ at risk constraints 196

Table 6.2 Source of dosimetric data and parameters for RED and EAR calculations 200

Table 6.3 Monitor units and beam on time for delivered plan 208

Table 6.4 Organ equivalent doses averaged over three datasets in in-field or close-to-field organs for whole treatment 212

Table 6.5 Organ equivalent doses in out-of-field organs for whole treatment course (Gy) 219

Table 6.6 Integral doses in 2Gy fraction equivalent (Gy-litres) 228

Table 6.7 Correlations between integral dose in 2Gy fraction equivalent (IDEQD2) and organ equivalent dose 229

Table 6.8 Left and right femoral head doses using 240° arc (median values (and range)) 232

Table 6.9 Competition model calculation and parameters 235

Table 6.10 Predicted percentage risks (%) of second rectal and bladder cancers based on competition model averaged for three datasets 236

List of Figures

Figure 1-1 Impact of different prescribing strategies on the does received by the target and by the surrounding normal tissues.....16

Figure 2-1 Impact of hypofractionation in exploiting the low α/β ratio of prostate cancer.....45

Figure 2-2 Class solution for prostate SABR with explanation of prescription components in table below 52

Figure 2-3 Example of prostate plans from one dataset using a) one 360° arc, b) one 210° partial arc, c) two full arcs and d) two partial arcs (210° and 180°), all using 6mm CTV-PTV margins 58

Figure 2-4 DVH comparisons for four beam arrangements (median values plotted) 64

Figure 2-5 DVH comparisons for 6mm and 8mm CTV to PTV margins (median values plotted).....66

Figure 2-6 Example of prostate plans from one dataset using a) one 210° partial arc with 6mm CTV-PTV margins, b) one 210° partial arc with 8mm CTV-PTV margins and c) one 210° partial arc including the proximal seminal vesicles within the CTV with 6mm CTV-PTV margins 67

Figure 2-7 Dose received by 95% of the PTV (D95%) using 6mm and 8mm CTV-PTV margins 72

Figure 2-8. Dose received by 95% of the PTV (D95%) when treating prostate alone and treating the prostate plus proximal seminal vesicles.....73

Figure 2-9 DVH comparisons for CTV containing prostate alone and CTV containing prostate + proximal seminal vesicles (median values plotted) 74

Figure 2-10 Delta4 verification for one of the three plans 75

Figure 2-11 High dose film verification 76

Figure 3-1 DIL defined on a) T2-weighted, b) Diffusion-weighted and c) Dynamic contrast-enhanced MRI, d) Combined DIL volume (CTV_{DIL}), e) dose distribution without DIL boost, f) dose distribution with PTV_{DIL} boost to 125%.....88

Figure 3-2 Prescription used for boosting DILs.....94

Figure 3-3 Correlation between the maximum dose received by 0.5cm^3 of rectum and rectal NTCP 110

Figure 3-4 Impact of prostate cancer α/β ratio and dose on TCP based on a seven fraction schedule 119

Figure 4-1 Prescription 128

Figure 4-2 Box and whisker comparison of treatment times for flattening filter free (FFF) and standard (flattened) plans 133

Figure 4-3 Dose-volume histograms for standard (flattened) and flattening filter free (FFF) plans (median values plotted) 134

Figure 5-1 Schema of article selection process 142

Figure 6-1 Experimental set-up for assessment of out-of-field dose ..199

Figure 6-2 Comparison of physical dose distributions for different techniques.....209

Figure 6-3 Relative risks of second malignancy in in-field or close-to-field tissues relative to 3D-conformal radiotherapy for whole treatment course.....211

Figure 6-4 Excess absolute risks of second malignancy in in-field or close-to-field tissues for whole treatment course 216

Figure 6-5 Relative risks of second malignancy in out-of-field tissues relative to 3D-conformal radiotherapy (linear model) for whole treatment course.....218

Figure 6-6 Excess absolute risks of second malignancy in out-of-field organs (linear model) for whole treatment course 220

Figure 6-7 Out-of-field dose resulting from head leakage and head scatter.....222

Figure 6-8 Total dose for whole treatment course with increasing distance from isocentre 224

Figure 6-9 Out-of-field dose for whole treatment course resulting from head leakage and head scatter with increasing distance from isocentre.....225

Figure 6-10 Out-of-field dose for whole treatment course resulting from within patient scatter (total dose minus dose from head leakage/ scatter) with increasing distance from isocentre 226

Figure 6-11 Correlations between integral dose in 2Gy fraction equivalent (IDEQD2) and Organ Equivalent Dose (OED) for a) the rectum (rectal organ equivalent dose calculated according to mechanistic model, p=0.018, not significant at selected significance level) and b) the stomach (representative of all out-of-field organs, p<0.001) 230

Figure 6-12 Correlations between integral dose in 2Gy fraction equivalent (IDEQD2) and Organ Equivalent Dose (OED) for a) pelvic bone sarcoma (p<0.001) and b) pelvic soft tissue sarcoma (p<0.001).....231

Figure 6-13 Differential dose-volume histograms comparing 78Gy techniques: rectum.....240

Figure 6-14 Differential dose-volume histograms comparing 78Gy techniques: bladder.....241

Figure 6-15 Differential dose-volume histograms comparing 78Gy techniques: pelvic bones.....242

Figure 6-16 Differential dose-volume histograms comparing 78Gy techniques: pelvic soft tissues.....243

Figure 6-17 Differential dose-volume histograms comparing SABR techniques: rectum.....246

Figure 6-18 Differential dose-volume histograms comparing SABR techniques: bladder.....247

Figure 6-19 Differential dose-volume histograms comparing SABR techniques: pelvic bones.....248

Figure 6-20 Differential dose-volume histograms comparing SABR techniques: pelvic soft tissue.....249

List of Abbreviations

α/β	Alpha beta ratio
1FA	One full arc
1PA	One partial arc
2FA	Two full arcs
2PA	Two partial arcs
3D-CRT	3-dimensional conformal radiotherapy
95% CI	95% Confidence interval
ADC	Apparent diffusion coefficient
ASTRO	American Society for Radiation Oncology
AUA	American Urology Association
BED_x	Biologically equivalent dose based on α/β ratio of xGy
BIOPROP	BIologically Optimised Prostate cancer Radiotherapy Or dose Painting
BT	Brachytherapy
C$	Canadian dollars
CaPSURE	University of California, San Francisco Cancer of the Prostate Surveillance Urology Research Endeavor
CBCT	Cone beam computed tomography
CHHiP	Conventional versus Hypofractionated High-dose intensity-modulated radiotherapy for Prostate Cancer
CI	Conformity index
CN	Conformation number
cT	Clinical T stage
CT	Computer Tomography
CTCAEvX	Common Terminology Criteria of Adverse Events version X

CTV	Clinical Target Volume
d	Dose per fraction
D	Total dose
D50%	Median dose received by a structure
DCE	Dynamic contrast enhanced
DIL	Dominant intra-prostatic lesion
Dmax	The maximum dose received by a structure
Dmax0.5cc	Maximum dose received by $0.5cm^3$ of structure
Dmax2cm	Maximum dose at 2cm from the Planning Target Volume
Dmean	Mean dose received by a structure
Dmin	Minimum dose received by a structure
DVH	Dose-volume histogram
DW	Diffusion weighted
Dx%/xcc	The dose received by x%/ xcc of the volume
EAR	Excess absolute risk
EBRT	External beam radiotherapy
EBRT-BT	Combination external beam radiotherapy and brachytherapy
EDT	Estimated delivery time
EMBASE	Excerpta Medica dataBASE
EPIC	Expanded Prostate Index Composite
$EQD2_x$	The equivalent dose in 2Gy fractions based on α/β ratio of xGy
EUD	Equivalent uniform dose
FFF	Flattening filter free
FH	Femoral head
FLAME	Focal Lesion Ablative Microboost in Prostate Cancer
GI	Gastrointestinal
GS	Gleason score

GTV	Gross Tumour Volume
GU	Genitourinary
Gy	Gray
HEIGHT	Hypofractionated External Beam Image-Guided Highly Targeted Radiotherapy
HDR	High dose rate
HI	Homogeneity index
HR	Hazard ratio
ICRU	International Commission on Radiation Units and Measurements
IDEQD2	Integral dose in 2Gy fraction equivalent
IGRT	Image-guided radiotherapy
IMAT	Intensity-modulated arc therapy
IMRT	Intensity-modulated radiotherapy
IPSS	International Prostatic Symptom Score
kV	Kilovoltage
LDR	Low dose rate
LQ	Linear-quadratic
MC	Monte Carlo
MLC	Multileaf collimator
MRI	Magnetic resonance imaging
MU	Monitor unit
MV	Megavoltage
NCCN	National Comprehensive Cancer Network
ng/ml	Nanogram per millilitre
NTCP	Normal tissue complication probability
OED	Organ Equivalent Dose
OR	Odds ratio

PACE	Prostate Advances in Comparative Evidence
PB	Penile bulb
PCa	Prostate cancer
PD	Prescription dose
PET	Positron emission tomography
PLCO	Prostate, Lung, Colorectal and Ovarian screening trial
PORT	Post-operative radiotherapy
proxSV	Proximal seminal vesicles
PRV	Planning organ at Risk Volume
PSA	Prostate Specific Antigen
PTV	Planning Target Volume
PY	Person-Years
QA	Quality Assurance
QUANTEC	Quantitative Analysis of Normal Tissue Effects in the Clinic
R50	The volume of the 50% isodose divided by the volume of the PTV
RED	Risk equivalent dose
RISPC	Radiation-induced second primary cancer
RR	Relative risk
RTOG	Radiation Therapy Oncology Group
SABR	Stereotactic Ablative Radiotherapy
SBRT	Stereotactic Body Radiotherapy
SEER	Surveillance, Epidemiology and End Results
SI	Sensitivity Index
SIB	Simultaneous integrated boost
SIR	Standardised incidence ratio
SPSS	Statistical Package for the Social Sciences
SV	Seminal Vesicles

T stage	Tumour stage
TCP	Tumour control probability
TLD	Thermoluminescent dosimeter
TURP	Trans-urethral resection of the prostate
UK	United Kingdom
USA	United States of America
VMAT	Volumetric modulated arc therapy
Vx%/xGy	The volume of structure receiving at least x% of the prescription dose/ xGy
WPRT	Whole pelvic radiotherapy

Chapter 1 : Introduction

1.1 Prostate cancer

Prostate cancer (PCa) is the most common cancer in males in the United Kingdom (UK), accounting for one-quarter of male cancer diagnoses [1]. In 2011, 41,736 new diagnoses of prostate cancer were made, equivalent to a one in eight lifetime risk in males with the peak incidence in the 75 to 79 year age group [1]. There has been a marked increase in the incidence of prostate cancer over the past thirty years which is at least in part attributable to increased detection, initially as a result of increased rates of transurethral resection of the prostate (TURP), and laterly to increased Prostate Specific Antigen (PSA) testing [2-4]. The majority of patients present with localised disease (i.e. disease that has not breached the prostate capsule) [5,6]. These patients have a variety of treatment options influenced by disease characteristics (i.e. tumour (T) stage, Gleason Score (GS) and PSA at presentation as well as prostate volume and severity of urinary symptoms) and patient choice. Current standard treatment options for patients with localised prostate cancer include prostatectomy, external beam radiotherapy (EBRT), brachytherapy (BT) and combination EBRT with a BT boost (EBRT-BT).

1.2 Conventional EBRT

Conventional EBRT delivered doses of up to 70 Gray (Gy), often in 2Gy fractions, but long term follow-up showed biochemical control to be sub-optimal, with 5-year and 10-year biochemical failure rates in the region of 60% (defined at that time as: i) PSA increasing or nadir above 1.5ng/ml, or ii) failure to achieve or maintain PSA below a specified level (4ng/ml or 1ng/ml) two or more years after radiotherapy, or iii) two sequential increases in PSA or iv) development of radiological or symptomatic metastases or palpable local recurrence) [7,8]. Delivering a higher radiation dose in an effort to improve outcomes, however, was technically difficult without causing an unacceptable increase in normal tissue damage.

1.3 3D-Conformal EBRT and dose escalation

The introduction of 3-dimensional conformal radiotherapy (3D-CRT), employing 3D contouring and planning techniques together with accurate beam shaping around target volumes, resulted in significant reductions in acute and late gastrointestinal (GI) toxicities at conventional doses, with no significant change in urological side-effects [9-11]. This provided the opportunity to evaluate dose escalation and several randomised trials demonstrated that escalation to 74-79.2Gy in 1.8-2Gy fractions delivered using 3D-CRT, compared to 64-70Gy, resulted in a 10-20% improvement in biochemical control at five years, with 5-year freedom from biochemical failure rates of 64-80% [12-15]. The data suggest a dose-response relationship with increasing biochemical control with increasing dose. Increased doses were, however, accompanied by increased acute GI and genitourinary (GU) toxicity together with increased late rectal toxicity [12,13,15-19]. For example, long term follow-up (median 8.7 years) from the MD Anderson dose escalation trial (comparing 78Gy with 70Gy) revealed that RTOG (Radiation Therapy Oncology Group) grade 2 and 3 late rectal toxicity following dose escalation was more than double that with non-escalated treatment (78Gy:26% vs. 70Gy:12%, p=0.014) [18,19].

1.4 IMRT

Intensity-modulated radiotherapy (IMRT) delivers radiotherapy which conforms closely to the shape of a target. Typically multiple (i.e. 5-9) beams are angled around a patient and multileaf collimators (MLCs) move across each beam, thus altering the intensity of treatment over multiple small regions (or beamlets) within the beam. This allows complex shapes to be treated precisely and improves organ at risk shielding. IMRT is often inversely planned where acceptable plan parameters are specified prior to plan creation and the treatment planning system performs a series of iterations to try to meet these.

The advent of IMRT has therefore facilitated further improvements in conformity. Trials comparing IMRT with 3D-CRT in prostate cancer demonstrated significant reductions

in acute and late GI toxicity using IMRT [20,21]. This has facilitated further dose escalation. One series of 478 men demonstrated that dose escalation up to 86.4Gy in 48 fractions using IMRT was feasible with excellent biochemical control: 5-year PSA relapse free survival using the Phoenix definition (see Appendix A) was 98%, 85% and 70% in low, intermediate and high risk patients respectively (see Appendix B for definitions of risk group). Acute and late toxicities were lower than what would be expected with conformal radiotherapy (Common Terminology Criteria version 3 (CTCAEv3) late grade 2 and 3 GU toxicity in 13% and <3% of patients and CTCAEv3 late grade 2 and 3 GI toxicity reported in 3% and <1% of patients respectively) [22]. Ten-year biochemical relapse free survival rates (Phoenix definition) of 81%, 78% and 62% for low, intermediate and high risk patients were recently reported for a series of 170 patients treated with IMRT to a dose of 81Gy in 45 fractions [23]. Toxicity was acceptable: the 10-year likelihoods of CTCAEv3 grade 2 and 3 late GU toxicity were 9% and 5%. The 10-year likelihoods of CTCAEv3 grade 2 and 3 late GI toxicity were 2% and 1% respectively [23].

1.5 Volumetric modulated arc therapy

Volumetric modulated arc therapy (VMAT) is a form of IMRT that uses a standard linear accelerator to deliver radiotherapy in one or more arcs. Gantry rotation speed, dose rate and MLC positions are altered to create highly conformal plans [24]. VMAT encompasses the terms IMAT (intensity-modulated arc therapy), RapidArc® (a VMAT delivery system made by Varian (United States of America (USA))) and the Elekta (Sweden) VMAT system named VMAT. VMAT produces highly conformal plans compared to 3D-CRT as a result of the multiple angles of dose delivery, the dose rate variability and the modulation which are achievable using this technique [25]. Compared to IMRT, VMAT prostate planning studies have demonstrated at least equivalent conformity, improved monitor unit (MU) efficiency and faster delivery times [25-33] (e.g. average delivery time for one 2Gy fraction using VMAT vs. IMRT: 90s vs. 292s [31]).

1.6 The rationale for hypofractionation

As discussed above, dose escalation can be achieved by increasing the number of 1.8 to 2Gy fractions and results in improved biochemical control. An alternative means of delivering a higher total dose (i.e. a higher biological effective dose; BED) is through hypofractionation (i.e. delivering higher doses per fraction). There is a good rationale for hypofractionation in PCa. Prostate cancer exhibits slow growth kinetics and so responds to changes in fractionation in a manner similar to late responding tissues [34,35]. Tissue sensitivities to changes in fractionation are mathematically modelled by the linear-quadratic (LQ) equation and quantified by the α/β ratio. In general, late responding tissues have low α/β ratios (~3Gy) and are highly sensitive to changes in fraction size while early responding tissues and tumours typically have high α/β ratios (~8-10Gy). Conventional radiotherapy, delivered with 1.8 to 2Gy fractions, aims to cause a degree of tumour kill but at the same time spare late responding tissues. Delivering higher doses per fraction, as in hypofractionation, will theoretically have a larger impact on tissues with low α/β ratios. Although debated, evidence suggests PCa has a low α/β ratio making it theoretically more sensitive to large dose per fraction treatments [34-37]. A recent retrospective study including 5969 irradiated PCa patients concluded that the α/β ratio of PCa was 1.4Gy (95% confidence interval (CI):0.9-2.2Gy) [37], in-keeping with that previously reported by Fowler (1.5Gy (95%CI:1.3-1.8Gy) and Brenner (1.2Gy (95%CI:0.03-4.1Gy) [34,35].

Importantly, there is also evidence that the neighbouring late responding rectal and bladder tissues have higher α/β ratios than PCa (~3-6Gy) [35,36,38-41]. This allows exploitation of the potential biological advantage of the low prostate α/β in one of two ways: i) delivering larger hypofractionated doses to the prostate for equivalent late normal tissue toxicity, or ii) delivering iso-effective hypofractionated doses to the prostate aiming for reduced normal tissue toxicity. This is illustrated further below and in Chapter 2.

Calculating the BED and equivalent dose in 2Gy (EQD2) fractions can be helpful when comparing alternative dose-fractionation schedules. These can be calculated according to:

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

and

$$\text{EQD2} = D\left(\frac{d + (\alpha/\beta)}{2 + (\alpha/\beta)}\right)$$

where *D* is the total dose, *d* is the dose per fraction and α/β for the prostate is considered to be 1.5Gy. When considering toxicities, the BED and EQD2 received by acute and late responding tissues can be calculated using α/β ratios of 10Gy and 3Gy respectively. These calculations assume no ongoing tumour cell repopulation or repopulation delay time, which is acceptable in this setting [42,43].

For example, standard UK radiotherapy delivers 74Gy in 37 fractions. This is equivalent to a BED of 173Gy to the prostate (i.e. $BED_{1.5}$) and 88Gy and 123Gy to the acute (BED_{10}) and late (BED_3) responding tissues respectively. Because the dose is delivered in 2Gy fractions, the EQD2 to the prostate, early and late responding tissues is 74Gy.

1.7 Moderate hypofractionation

Several studies have examined moderate hypofractionation using fraction sizes of 2.5 to 4Gy [44-50]. One randomised trial comparing hypofractionation (55Gy in 20 fractions; $BED_{1.5}$:156Gy, $EQD2_{1.5}$:67Gy) with conventional fractionation (64Gy in 32 fractions; $BED_{1.5}$:149Gy, $EQD2_{1.5}$:64Gy) in 217 patients showed equivalent biochemical control [46]. Another trial, comparing 52.5Gy in 20 fractions ($BED_{1.5}$:144Gy, $EQD2_{1.5}$:62Gy) with 66Gy in 33 fractions ($BED_{1.5}$:154Gy, $EQD2_{1.5}$:66Gy) in 936 patients showed hypofractionation to be inferior [45], perhaps the result of the lower BED in the hypofractionated regimen. As the control arms in both trials used non-escalated doses, it is not possible to draw conclusions about hypofractionation in comparison to current dose-escalated treatments.

The CHHiP (Conventional versus Hypofractionated High-dose intensity-modulated radiotherapy for Prostate cancer) trial was a recent phase III randomised trial comparing 74Gy in 34 fractions ($BED_{1.5}$:173Gy, BED_3:123Gy), 60Gy in 20 fractions ($BED_{1.5}$:180Gy, $EQD2_{1.5}$:77Gy, BED_3:120Gy, $EQD2_3$:72Gy) and 57Gy in 19 fractions ($BED_{1.5}$:171Gy, $EQD2_{1.5}$:73Gy, BED_3:114Gy, $EQD2_3$:68Gy), delivered using IMRT [51]. A planned phase II analysis revealed similar low levels of 2-year grade 2+ bladder and bowel toxicity amongst conventionally and hypofractionated regimens [52]. Mature outcome data are awaited.

1.8 SABR and ultra-hypofractionation

There has been recent interest in trying to exploit the low α/β of PCa further with stereotactic ablative body radiotherapy (SABR), also referred to as stereotactic body radiotherapy (SBRT) [53]. The Stereotactic Working Group define SABR as: "the precise irradiation of an image-defined extra-cranial lesion associated with the use of high radiation dose in a small number of fractions" [54]. To avoid excessive normal tissue toxicity as a result of the high BED delivered, Clinical Target Volume (CTV) to Planning Target Volume (PTV) margins are generally tighter (i.e. only few millimetres) than with conventionally fractionated radiotherapy. High quality image guidance is therefore essential so that the target is not missed and surrounding normal tissues are not inappropriately irradiated. Strategies such as daily online imaging of fiducial markers or intra-fraction motion tracking facilitate the accurate delivery of SABR with tighter CTV-PTV margins. Dose distributions are often more heterogeneous than the traditional -5% to +7% considered acceptable by ICRU (International Commission on Radiation Units and Measurements) Report 50 [55] and hotspots greater than 110% of the prescription dose are also common [56]. This is often achieved by prescribing to a peripheral isodose, thus facilitating marked dose escalation within the target and rapid dose fall-off beyond [56]. It is not known, however, if, in the context of prostate SABR, such heterogeneity is more or less desirable than more homogenous dose distributions [57].

A range of dose-fractionation schedules have been used in localised PCa, including 35-36.25Gy in 5 fractions, 40Gy in 5 fractions and 38Gy in 4 fractions [58-61].

Treatment is delivered over consecutive or alternate days. As well as theoretically offering increased tumour control, SABR is convenient for patients and economically attractive. Using the BED and EQD2 equations above, Table 1.1 compares the doses received by the prostate tumour, early responding and late responding tissues between SABR schedules and conventionally fractionated regimens. It can be seen that compared to conventionally fractionated dose-escalated regimens, SABR doses of 35-36.25Gy in 5 fractions deliver a higher dose to the prostate for lower doses to the early responding tissues and similar or slightly lower doses to the late responding tissues.

Table 1.1 Comparison of conventionally fractionated and SABR regimens used for the treatment of prostate cancer

Treatment	EBRT dose	No. fractions	Dose per fraction	BED to prostate tumour (α/β=1.5Gy)	EQD2 to prostate tumour (α/β=1.5Gy)	BED to early responding tissues (α/β=10Gy)	EQD2 to early responding tissues (α/β=10Gy)	BED to late responding tissues (α/β=3Gy)	EQD2 to late responding tissues (α/β=3Gy)
European standard fractionation	78Gy	39	2Gy	182.0Gy	78.0Gy	93.6Gy	78.0Gy	130.0Gy	78.0Gy
CHHiP trial standard arm fractionation	74Gy	37	2Gy	172.7Gy	74.0Gy	88.8Gy	74.0Gy	123.3Gy	74.0Gy
SABR fractionation 1	35Gy	5	7Gy	198.3Gy	85.0Gy	59.5Gy	49.6Gy	116.7Gy	70.0Gy
SABR fractionation 2	36.25	5	7.25	211.5Gy	90.6Gy	62.5Gy	52.1Gy	123.9Gy	74.3Gy
SABR fractionation 3	40Gy	5	8Gy	253.3Gy	108.6Gy	72.0Gy	60Gy	146.7Gy	88.0Gy
SABR fractionation 4	38Gy	4	9.5Gy	278.7Gy	119.4Gy	74.1Gy	61.8Gy	158.3Gy	95.0Gy

BED: Biologically equivalent dose, CHHiP: Conventional versus Hypofractionated High-dose intensity-modulated radiotherapy for Prostate cancer, EQD2: equivalent dose in 2Gy fractions, EBRT: external beam radiotherapy, SABR: stereotactic ablative radiotherapy

Thus, the lower α/β of PCa can be exploited by SABR in order to deliver a higher BED to the prostate but a dose to the late responding tissues that is biologically similar to that received from conventional fractionation. Doses of 40Gy in 5 fractions or 38Gy in 4 fractions, compared to conventionally fractionated regimens, deliver a much higher BED to the prostate as well as a higher dose to the late responding tissues.

SABR can be delivered using standard linear accelerators and the Cyberknife™ (Accuray®, USA). The Cyberknife™ is a miniature 6MV linear accelerator mounted on a robotic arm which allows multiple small radiation beams to be focused at a target from multiple directions thus producing highly conformal plans. Gold fiducials are implanted in the prostate and are detected by two in-room stereoscopically mounted kilovoltage (kV) imagers. This allows accurate localisation prior to each fraction and intra-fraction tracking [62]: real-time images are compared with reconstructed images from the planning CT and any intra-fraction prostate motion is automatically corrected. The high precision of the system allows small CTV-PTV margins. Delivery time is around 40 minutes per fraction [63] thus intra-fraction motion is potentially of concern, although real-time tracking is used to correct for this. The Cyberknife™ is not widely available in the UK: there are four Cyberknife™ centres within the National Health Service and two in the private sector.

Of note, evidence to support ultra-hypofractionation using EBRT in the treatment of prostate cancer exists from several years ago. In 1991, Collins et al reported encouraging outcomes from a series of 232 patients treated between 1964 and 1984 with 36Gy in 6 fractions ($BED_{1.5}$:180Gy, $EQD2_{1.5}$:77Gy) using either a linear accelerator or cobalt-60 [64]. Urinary and rectal catheters were used for localisation. Rates of long term morbidity were low (two patients (1%) developed rectal strictures) and survival was similar to other dose and fractionation schedules in use at that time [64]. The promise of ultra-hypofractionation has also been successfully applied in phase II trials using high dose rate (HDR) brachytherapy monotherapy [65-67]. Typical schedules include 36Gy in 4 fractions over three days ($BED_{1.5}$:252Gy, $EQD2_{1.5}$:108Gy) and 54Gy in 9 fractions over five days ($BED_{1.5}$:270Gy, $EQD2_{1.5}$:116Gy). HDR brachytherapy, however, is invasive, involving anaesthetics, in-patient care and strong analgesics. If SABR were shown to be an effective and well tolerated means of delivering ultra-hypofractionation, then it may become an attractive alternative.

1.9 Clinical evidence regarding SABR in prostate cancer

The current evidence regarding SABR in localised PCa is in the form of non-randomised trials or series, generally involving small numbers of patients. Considering SABR according to the Stereotactic Working Group definition above, and schedules that deliver more than 5Gy per fraction, a literature search, last updated September 2014, identified 23 individual clinical studies from 21 groups which used SABR as the sole radiation therapy in localised PCa in the first line setting, 15 using Cyberknife™ [57,59-61,68-78] and 8 using linear accelerators [58,79-85]. Based on these studies, SABR, as the sole radiation therapy, has been delivered to over 1800 patients using the Cyberknife™ and over 300 patients using a linear accelerator. SABR has also been used as a boost in addition to conventional fractionation in three additional studies, two using the Cyberknife™ and one using a linear accelerator [86-88], and two Cyberknife™ studies have delivered SABR as either the sole radiation treatment or as a boost following conventional fractionation [71,72]. The use of prostate SABR as a boost is reported in over 170 patients. Most of these studies present prospective data. Details of treatment, efficacy and toxicity for individual studies are provided in tables in Appendix C. Some groups have published multiple papers concerning different patient populations within the same study, as illustrated in Appendix C. The following discussion focuses on the 23 prostate SABR studies which deliver SABR as the sole radiation modality (and not as a boost following conventionally fractionated radiotherapy). Where SABR boost studies are mentioned, these are highlighted as such.

1.9.1 Patient selection

Most studies have examined SABR in organ-confined PCa, particularly low and intermediate risk disease. A small number of Cyberknife™ studies have included patients with T3 disease, or other higher risk features (GS≥8, PSA>20) and although outcomes in this group appear encouraging [59,68,70,71,74-76,78], data are too immature and too few in number to draw firm conclusions.

Part of the concern about the treatment of non-low risk PCa using SABR is that intermediate and high risk patients are at higher risk of extra-capsular extension and microscopic seminal vesicle (SV) invasion, and so very localised treatments such as SABR could be inadequate. To investigate this further, Ju et al examined outcomes and dose distributions in 41 patients with intermediate risk prostate cancer treated using SABR [89]. The group specifically examined areas around the prostate considered at highest risk of extra-capsular spread. Based on the CTV used in this study (which included the proximal SV until the point where the left and right SV split), it was found that areas of expected extra-capsular extension received adequate doses for microscopic tumour cell kill. Given this observation, and positive early clinical outcomes, the group concluded that prostate SABR appeared a suitable treatment option for intermediate risk patients, but acknowledged that further clinical outcomes were required [89].

Further clinical data has since been provided by Katz and Kang who compared clinical outcomes between patients treated for prostate SABR using 35-36.25Gy in 5 fractions with low-intermediate risk (GS 6 with PSA>10 or GS 3+4 with PSA<10) and high-intermediate risk (GS 3+4 with PSA 10-20 or GS 4+3) disease [90]. The CTV contained the prostate alone for all patients. Biochemical disease free survival at seven years was inferior in the high-intermediate risk group (79.3% vs 93.5%), perhaps suggesting that some caution is required when treating higher risk patients, particularly when not including any SV within the CTV [90].

Some studies have excluded patients with large prostate volumes, marked urinary symptoms or a previous history of TURP [60,73,79,82,83,85,91], factors which are at least relative contra-indications to brachytherapy [92,93].

1.9.2 Use of androgen deprivation

The use of androgen suppression has an uncertain role in the setting of intermediate risk PCa patients treated with dose-escalated conventionally fractionated radiotherapy [94]. Its use in the setting of SABR is therefore variable between and within studies making it difficult to draw conclusions about its role with SABR. Where used, it tends to be in the short term (i.e. a few months to one year) and in the setting

of intermediate or high risk disease [91]. In a pooled analysis of 1100 SABR patients reported by King et al, the use of androgen suppression had no impact on 5-year biochemical relapse free survival [91]. It should be noted, however, that this was a non-randomised, non-matched comparison and so case selection may introduce bias into this comparison.

1.9.3 Dose and fractionation

SABR has been delivered using various dose-fractionation schedules. As the sole radiation treatment, fraction sizes have ranged from 6.7-10Gy, equivalent to total prostate BED of 183-383Gy or $EQD2_{1.5}$ of 78-164Gy. Doses of 35-36.25Gy in 5 fractions are most commonly used in Cyberknife™ and linear accelerator-based platforms ($BED_{1.5}$:198-211Gy, $EQD2_{1.5}$ of 85-90Gy), although doses up to 50Gy have been delivered in a 5 fraction schedule ($BED_{1.5}$:383Gy, $EQD2_{1.5}$:164Gy) [83]. In addition, four Cyberknife™ studies have delivered 32-38Gy in 4 fractions ($BED_{1.5}$:203-279Gy, $EQD2_{1.5}$:87-119Gy) [57,60,70,72], schedules which are similar to those used in HDR brachytherapy monotherapy. As a boost, fractions have varied from 5-8Gy (total $BED_{1.5}$ including conventional fractionated treatment: 189-268Gy, $EQD2_{1.5}$:81-115Gy). Most studies have delivered treatment over consecutive days although King et al found alternate day schedules to cause less low grade (i.e. grade 1 or 2) late urinary and rectal toxicity [61].

1.9.4 Treatment platform

The majority of evidence comes from studies using the Cyberknife™ although eight studies from six centres delivered SABR using linear accelerators (Appendix C), which are widely available in the UK.

1.9.5 Data acquisition

Magnetic resonance imaging (MRI) fusion with planning computer tomography (CT) scans has often been performed to assist with target delineation [57,59,60,68,69,71-73,75,76,78,84].

1.9.6 Patient preparation

Low fibre diets, bowel preparation and enemas have often been used to ensure an empty rectum. Vacuum bags, endorectal balloons, rectal-prostate spacers, drinking protocols and urinary catheters have been employed in some studies (see Appendix C).

1.9.7 CTV contents

All studies encompass the whole prostate within the CTV. The inclusion of some or all of the SV within the CTV has differed between and within studies. Of the studies which provide sufficient information, nine consider the prostate alone as the CTV, without inclusion of the SV, even in the setting of intermediate or high risk disease [60,61,71,73,74,79,81-83]. In addition, four studies include a proximal portion of the SV in all patients [57,59,68,76] and seven studies include some or all of the SV in higher risk or selected cases [69,70,72,75,78,84,85]. Of the five studies which deliver SABR as a boost, two boost the prostate alone [71,86], one includes the proximal SV in the boost CTV in all patients [88] and two include some or all of the SV within the boost CTV in selected cases [72,87].

1.9.8 CTV-PTV margins and image-guidance

CTV-PTV margins have been variable but generally no more than 5mm margins have been employed. Often the posterior CTV-PTV margin is smaller than that in other directions. The most commonly adopted margin ‘recipe’ is 5mm in all directions, except 3mm posteriorly. The small size of CTV-PTV margin is generally considered

acceptable in the setting of Cyberknife™ based treatments where intra-fraction motion tracking of implanted fiducials is possible. Two linear accelerator-based studies used implanted electro-magnetic beacons in some or all patients in order to allow intra-fraction motion tracking and accompanying small CTV-PTV margins [58,83]. In four of the remaining linear accelerator-based studies, fiducial markers (or intra-prostatic calcifications) have been employed to allow pre-treatment localisation using cone beam computer tomography (CBCT) or portal images (without intra-fraction motion tracking [81,82,84,95]). Only two small studies have used CBCT soft tissue matching alone (i.e. without fiducials) for daily online IGRT, also without intra-fraction motion tracking [79,85]. Image guidance is discussed in greater detail below.

1.9.9 Target coverage, prescription and dose distribution

In most studies the volume of PTV receiving the prescribed dose was at least 95%. As stated before, prescription doses of 35-36.25Gy in 5 fractions are most commonly used for both Cyberknife™ and linear accelerator-based prescriptions, while 32-38Gy in 4 fractions is also used in four Cyberknife™ studies [57,60,70,72]. In the setting of Cyberknife™ delivery, the prescription dose is frequently prescribed to a peripheral isodose (e.g.75-90% isodose), thereby facilitating rapid dose fall-off beyond the PTV and marked dose escalation towards the centre of the PTV. Prescription strategies in the setting of linear accelerator-based treatments are more variable. Mantz et al adopted a similar strategy to the Cyberknife™ by prescribing to 36.25Gy in 5 fractions to a peripheral isodose [79], while Pham et al prescribed 33.5Gy in 5 fractions to the isocentre [80]. Importantly, the doses received by the prostate will vary depending on whether an isocentric or peripheral isodose prescription strategy is adopted.

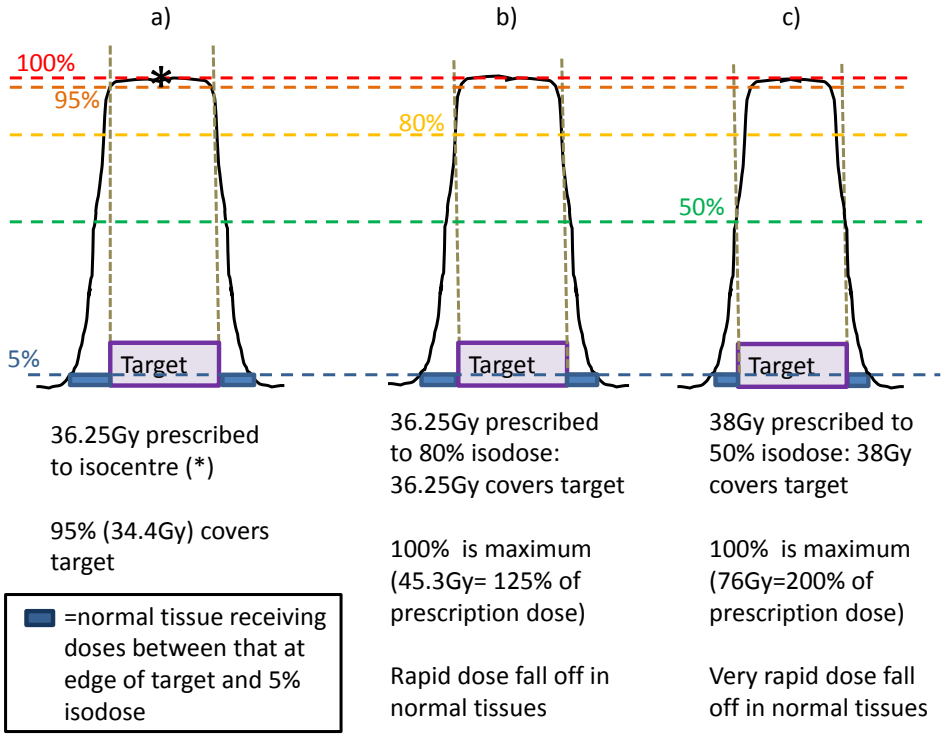
SABR dose distributions, particularly in the setting of Cyberknife™ prescribing, are often considered ‘homogeneous’, when doses of 35-36.25Gy in 5 fractions are used, as in the majority of Cyberknife™ studies, or ‘heterogeneous’, when doses of 32-38Gy in 4 fractions are prescribed, and in this situation the dose distribution is designed to reflect that achieved by HDR brachytherapy, with large proportions of the PTV receiving 125% and 150% of the prescription dose, and with a dose maximum of 200% of the prescription dose [57]. Despite being considered a ‘homogenous’ dose distribution, because the prescription dose is prescribed to a peripheral isodose, the

homogeneity within a ‘homogenous’ plan, is far more heterogeneous than the traditional 95 to 107% coverage that is considered homogenous in the setting of conventionally fractionated, linear accelerator-based treatments [55]. For example, if a dose of 35Gy in 5 fractions is prescribed to the 80% isodose (the strategy adopted by Bolzicco et al [59]), then the dose in the centre of the PTV can escalate to 43.75Gy, which is 125% of the prescription dose. The relative merits of applying a ‘homogenous’ dose distribution, or mimicking the very heterogeneous distribution of HDR brachytherapy is uncertain [57,72]. Figure 1-1 illustrates the impact of different prescribing strategies on the dose received by the target and normal tissues.

In the setting of linear accelerator-based prostate SABR dose distributions, differing approaches are reported. Loblaw et al specified that the maximum PTV dose should be no more than 105% of the prescription dose and that the volume of PTV receiving 95% of the prescription dose should be at least 99% [82]. Such a strategy would achieve a much more homogeneous, and traditional, dose distribution as compared to those achieved with the Cyberknife™. Similarly, Alongi et al adopted a homogenous prescribing strategy, aiming for a mean dose equal to the prescription dose and aiming to limit the maximum dose to 105% of the prescription dose [84]. Boike et al, however, also using a linear accelerator-based platform, specified that rapid dose fall-off beyond the PTV was prioritised over target homogeneity, resulting in considerable dose heterogeneity, more similar to that achieved using the Cyberknife™ [83]. As above, Mantz et al prescribed to a peripheral isodose to limit doses to organs at risk, and by doing so would also achieve heterogeneous dose distributions [79].

Figure 1-1 Impact of different prescribing strategies on the does received by the target and by the surrounding normal tissues

a) dose is prescribed to the isocentre as in some of the prostate SABR linear accelerator based studies, b) dose is prescribed to the 80% isodose, a similar strategy as used in some linear accelerator SABR studies and also when delivering a 'homogenous' dose using the Cyberknife™ and c) dose is prescribed to the 50% isodose resulting in a very heterogeneous dose distribution, a strategy similar to that used when using the Cyberknife™ to deliver a heterogeneous dose



1.9.10 Organ at risk constraints

The most appropriate organ at risk constraints remain to be defined [96] and a variety have been employed. King et al recently reported outcomes for a pooled analysis of 1100 patients from 8 institutions treated with 35-40Gy in 5 fractions [91]. For the majority of patients, the following constraints were adopted:

Rectum:

volume receiving ≥50% of prescription dose (PD): <50%,

volume receiving ≥80% of PD: <20%,

volume receiving ≥90% of PD: <10%

volume receiving ≥100% of PD: <5%.

Bladder:

volume receiving ≥50% of PD: <40%,

volume receiving ≥100% of PD: <10%

Femoral head:

volume receiving ≥40% of PD: <5%

1.9.11 Efficacy

Drawing conclusions about the efficacy of prostate SABR is partly challenging because of the different definitions of PSA failure and different outcome measures used in different studies. Where figures for efficacy are quoted below, these are accompanied by the definition of PSA failure used in that particular study (i.e. ASTRO (American Society for Radiation Oncology) definition or Phoenix definition). In terms of biochemical outcome measures (e.g. freedom from biochemical failure, biochemical relapse free survival, biochemical control, biochemical progression free survival etc.), these are considered equivalent when the same definition of PSA failure has been used. Where clinically detected failure (in the absence of biochemical failure) is included in the measure of efficacy, this has been stated.

Most studies are limited in that they have too few patients and too short follow-up to draw firm conclusions regarding treatment efficacy. Some early conclusions can be drawn from those studies with the longest durations of follow-up. King et al recently pooled and updated data from eight institutions which used the Cyberknife™ to deliver doses of 35 to 40Gy in 5 fractions to the prostate with a 5mm margin (and 3mm

posteriorly) [91]. In total 1100 patients were included in the analysis, of whom 14% received four months of neoadjuvant and concurrent androgen deprivation. Median follow-up was 36 months. The 5-year biochemical relapse free survival rate was excellent at 93% for all patients, 95% for low risk patients, 84% for intermediate risk patients and 81% for high risk patients (Phoenix definition). For 135 patients who had a minimum of five years follow-up in this study, the 5-year biochemical relapse free survival rate was 99% and 93% for low and intermediate risk patients respectively [91]. Similarly, Katz et al reported outcomes for a series of 477 patients treated using the Cyberknife™ using doses of 35 to 36.35Gy in 5 fractions [90]. After a median follow-up of 72.1 months, 7-year freedom from biochemical relapse (Phoenix definition) was 95.6% and 89.3% for patients with low and intermediate risk disease [90].

In terms of linear accelerator-based treatments with longer follow-up, Pham et al reported outcomes after 60 months median follow-up for 45 low risk patients prescribed 33.5Gy in 5 fractions [80]. Biochemical relapse free survival was excellent at 93% (Phoenix definition) [80]. Loblaw et al also reported encouraging 5-year biochemical relapse free survival rates of 98% (Phoenix definition) for 83 low risk patients prescribed 35Gy in 5 fractions after median follow-up of 55 months [82].

Of the trials delivering SABR as a boost, after 63 months median follow-up, one study reported 5-year biochemical relapse free survival (Phoenix definition) at 98% [87].

In the pooled analysis, King et al considered any treatment that achieved 5-year biochemical relapse free survival of greater than 90% equivalent [91]. As such, the outcomes achieved for prostate SABR were similar to those predicted using nomograms for radical prostatectomy and EBRT delivering 78Gy [91]. Examples of efficacy outcomes reported for other prostate cancer treatment modalities are shown in Table 1.2. Based on limited follow-up, it appears that the outcomes from SABR compare favourably with existing radiation modalities and surgical treatment.

Table 1.2 Efficacy outcomes for different prostate cancer treatment modalities

Continued overleaf.

Study	Median follow-up	Efficacy measure*	Efficacy
Dose-escalated (≥74Gy) external beam radiotherapy			
RT01 trial (Dearnaley et al; *n*=422; 74Gy, 3- and 6-field conformal [15])	5.3 years	5-year biochemical progression free survival (increase in PSA of ≥50% and to >2ng/ml)	Low risk: 85% Intermediate risk: 79% High risk: 57%
MD Anderson trial (Kuban et al; *n*=151; 78Gy, 4-field box and 6-field conformal [19])	8.7 years	8-year biochemical (Phoenix)/ clinical freedom from failure	Low risk: 88% Intermediate risk: 86% High risk: 63%
Dutch trial (Al-Mamgani et al; *n*=333; 78Gy, conformal [97])	5.8 years	7-year biochemical (ASTRO and Phoenix)/ clinical freedom from failure	ASTRO: 54% Phoenix: 56% (>50% high risk patients)
Zietman et al (*n*=195;79.2Gy, conformal [13])	5.5 years	5-year biochemical freedom from failure (ASTRO)	Low risk: 81% Intermediate and high risk: 80%
Zelefsky et al (*n*=772; 81Gy, IMRT [20])	7 years	8-year biochemical relapse free survival (ASTRO)	Low risk: 85% Intermediate risk: 76% High risk: 72%
Cahlon et al (*n*=478; 86.4Gy, IMRT [22])	4.4 years	5-year biochemical relapse free survival (Phoenix)	Low risk: 98% Intermediate risk: 85% High risk: 70%
Radical prostatectomy			
Kupelian et al (*n*=1034 [98])	5.5 years	5-year biochemical relapse free survival (PSA ≤0.2ng/ml)	T1/T2 disease: 81%
Potters et al (*n*=746 [99])	4.7 years	5-year freedom from biochemical recurrence (detectable PSA)	T1/T2 disease: 83%
Martinez et al (*n*=157 [100])	5.5 years	5-year biochemical control (PSA ≤0.2ng/ml)	Low risk: 84%
Aizer et al (*n*=204 [101])	3.8 years	5-year biochemical disease free survival (PSA ≤0.2ng/ml)	Low risk: 93% Intermediate risk: 87% High risk: 38%
Low dose rate brachytherapy			
Kupelian et al (*n*=950 [98])	3.9 years	5-year biochemical relapse free survival (ASTRO)	T1/T2 disease: 83%
Potters et al (*n*=733 [99])	4.3 years	5-year freedom from biochemical recurrence (ASTRO)	T1/T2 disease: 84%

Table 1.2 cont. Efficacy outcomes for different prostate cancer treatment modalities

Study	Median follow-up	Efficacy measure*	Efficacy
Low dose rate brachytherapy cont.			
Grimm et al (*n*=125 [102])	6.8 years	10-year PSA progression free survival	Low risk: 87%
Zelefsky et al (*n*=248 [103])	4.0 years	5-year PSA relapse free survival (ASTRO)	Low risk: 88% Intermediate risk: 77% High risk: 38%
External beam radiotherapy plus high dose rate (HDR) brachytherapy boost			
Hoskin et al (*n*=110 [104])	7.1 years	5-year biochemical (phoenix)/ clinical relapse free survival	75% (Mainly intermediate and high risk patients)
Galalae et al (*n*=611 [105])	5 years	5-year biochemical control (ASTRO)	Low risk: 96% Intermediate risk: 88% High risk: 69%
High dose rate (HDR) brachytherapy monotherapy			
Tselis et al (*n*=351 [106])	4.9 years	5-year biochemical control (Phoenix)	Low risk: 94% Intermediate risk: 92% High risk: 92%
Demanes et al (*n*=298 [67])	5.2 years	8-year biochemical control (Phoenix)	97% (Mainly low and intermediate risk patients)
Yoshioka et al (*n*=112 [66])	5.4 years	5-year biochemical freedom from failure (Phoenix)	Low risk: 85% (95% CI: 66-100%), Intermediate risk: 93% (95% CI: 83-100) High risk: 79% (95% CI: 69-89%)
Prostate SABR (trials with longest follow-up)			
King et al (pooled results, *n*=135 [91])	Minimum of 5 years follow-up	5-year biochemical relapse free survival (Phoenix)	Low risk: 99% Intermediate risk: 93% High risk: 81%**
Katz et al (*n*=477 [90])	6 years	7-year freedom from biochemical failure (Phoenix)	Low risk: 96% Intermediate risk: 90%
Pham et al (*n*=40 [80])	5 years	5-year biochemical relapse free survival (Phoenix)	Low risk: 93%
Loblaw et al (*n*=84 [82])	4.6 years	5-year biochemical relapse free survival (Phoenix)	Low risk: 98%

CI: confidence interval, MSK: Memorial Sloan Kettering, *See Appendix A and B for PSA failure and risk group definitions, **For high risk patients, 5-year biochemical relapse free survival based on all patients, and not just patients with >5 years follow-up, median follow-up 36 months here.

Following SABR, delivered using the Cyberknife™ or a linear accelerator, PSA is reported to fall from baseline levels in all patients, frequently reaching nadirs of less than 1ng/ml at 12 to 24 months post treatment [58-60,68-70,72-74,76,80,82,107].

Initial efficacy results, for both Cyberknife™ and linear accelerator-based platforms, are encouraging. Given the long natural history of PCa, particularly low risk PCa, longer term follow-up and larger patient numbers are required before the efficacy of SABR in localised PCa can be fully determined. In addition, follow-up is too immature to determine if the much more homogenous dose distributions adopted in some of the linear accelerator-based studies, are equally as efficacious as the more heterogeneous dose distributions used in Cyberknife™ based treatments, or whether HDR brachytherapy-like dose distributions are preferable to the 'homogenous' dose distributions which can be achieved when using the Cyberknife™.

Three groups have investigated if there is evidence of a dose-response for prostate SABR doses [78,90,91,108]. Katz et al demonstrated no difference in biochemical relapse free survival in 430 low and low-intermediate risk patients treated with 35Gy in 5 fractions and 36.25Gy in 5 fractions [90]. The same group performed a matched-pair analysis of 41 patients treated with 35Gy and 41 patients treated with 36.25Gy [108]. Low and intermediate risk patients were included. After a median follow-up of 51 months, 4-year freedom from biochemical relapse was 97.5% in both groups (Phoenix definition) [108]. There was, however, a non-significant suggestion of increased urinary toxicity with the higher dose [108]. Similarly, in the pooled analysis of data from 1100 patients from eight institutions, King et al found no dose-response in terms of biochemical relapse free survival when comparing doses of 35-40Gy delivered in 5 fractions [91]. This group suggested that prostate SABR doses which achieve biochemical control in excess of 90% lie on the upper plateau portion of the dose-response curve. The group therefore concluded that since the doses examined were effective and well tolerated, then further dose escalation was not justified [91]. When examining a small series of intermediate and high risk patients (n=34) with shorter follow-up (median 31 months), Oliai et al demonstrated a significant dose-response in patients receiving low (35-36.25Gy) and high (37.5Gy) doses [78]. The 3-year actuarial freedom from biochemical failure (Phoenix definition) was 72% in intermediate and high risk patients receiving low dose SABR and 100% in intermediate and high risk patients

receiving high dose SABR (p=0.0363). When low risk patients were also included in the analysis (total n=70), however, statistical significance was lost (p=0.0775) [78]. Definitive evidence regarding a dose-response for this range of SABR doses has, therefore, not yet been demonstrated, although the relatively small number of patients involved in the existing studies may mean these studies were underpowered to detect a true dose-response relationship.

1.9.12 PSA bounce

This phenomena, mainly defined as a transient rise in PSA of greater than 0.2ng/ml or 0.4ng/ml, is reported in between 9% and 42% of patients, with the median time to bounce occurring between 9 and 36 months post SABR [59,60,73-76,78,80,82,90]. Similarly, the pooled analysis of 1100 patients from eight institutions recorded bounces in 16% of patients after a median of 18 months [91]. The magnitude of bounce is generally small, with median values of 0.5 to 0.7ng/ml reported [74-76,91]. PSA bounce was specifically examined in a recent paper produced by Vu et al, as part of the Flushing Group [109]. In keeping with the bounce observed in other studies, in a series of 120 patients (none of whom received androgen deprivation during the follow-up period) with a median follow-up of 24 months, 28% of patients experienced a bounce (defined as a rise of at least 0.2ng/ml) after a median of nine months with a median bounce magnitude of 0.5ng/ml [109]. On univariate analysis, only age was a significant predictor of bounce, with younger men being more likely to experience a bounce. Patient race, family history, prior hormone therapy, prostate size, T stage, GS, pre-radiotherapy PSA and risk group had no impact on the development of a bounce. Similarly, on multivariate analysis, only younger age was predictive of developing a PSA bounce [109]. Mcbride et al also noted that patients who experienced a bounce were younger than those who did not, although the impact of other factors on PSA bounce was not examined [73]. Younger age has previously been found to be predictive of PSA bounce in patients treated with seed brachytherapy [110].

1.9.13 Acute toxicity

SABR is reported to be well tolerated. Toxicity outcomes for individual trials are included in Appendix C (Tables C4 to C6) and summarised in Table 1.3. Acute toxicities are usually reported as those which occur within three or six months of treatment. Based on available evidence, acute grade 4 toxicities are not reported and acute grade 3 toxicities are uncommon. Of the 12 Cyberknife™, 7 linear accelerator and 5 SABR boost studies which provide sufficient detail, 16 studies (8 Cyberknife™, [59,69,70,72-76] 5 linear accelerator [79,81,83-85] and 3 boost studies [72,86,88]) report no acute grade 3 urinary toxicities. The remaining eight studies report acute grade 3 urinary toxicity in 1 to 8% of patients receiving Cyberknife™ treatment (8%=4 patients) [60,68,71,78], 1 to 3% of patients receiving linear accelerator treatment [82,95] and 4 to 9% of patients receiving a SABR boost (9%=1 patient) [71,87]. In some cases grade 3 acute urinary toxicity occurred in patients with a history of urethral instrumentation, or large volume prostates and marked pre-treatment urinary symptoms, both of which are known to predict increased acute urinary toxicity [59,60,76,95,111,112]. Of the studies which provide sufficient detail, grade 2 acute GU toxicity is reported in 4 to 45% of patients treated using the Cyberknife™, 0 to 40% of patients treated using a linear accelerator and 4 to 46% of patients receiving SABR as a boost (Table 1.3). The most frequent acute GU toxicities appear to be urinary frequency, urgency, dysuria and obstructive symptoms.

Table 1.3 Summarised toxicity rates reported in prostate SABR studies (median (and range))

See Appendix C for results from individual studies

Treatment modality	BED (and EQD2) received by normal tissue based on SABR prescription dose (Gy) (acute tissue α/β=10Gy, late tissue α/β=3Gy)	Genitourinary/ urinary toxicity (%) Grade:				Gastrointestinal/ rectal toxicity (%) Grade:			
		1	2	3	4	1	2	3	4
Acute toxicity									
Cyberknife™ studies	58-74 (48-62)	56 (10-75)	15 (4-45)	0 (0-8)	0	27 (14-76)	6 (0-24)	0 (0-2)	0
Linear accelerator studies	56-100 (47-83)	33 (20-71)	19 (0-40)	0 (0-3)	0	40 (0-67)	7 (0-27)	0	0
Studies delivering SABR boost	82-106 (68-88)	59 (34-75)	27 (4-46)	0 (0-9)	0	39 (0-75)	5 (0-17)	0	0
Late toxicity									
Cyberknife™ studies	117-158 (70-95)	9 (3-48)	8 (3-32)	2 (0-7*)	0	5 (2-14)	3 (0-11)	0 (0-5)	0
Linear accelerator studies	108-217 (65-130)	16 (0-23)	5 (0-13)	0 (0-7**)	0	25 (0-35)	7 (0-8)	0 (0-7)	0 (0-3)[†]
SABR boost studies	126-179 (76-108)	15 (3-46)	8 (5-12)	0 (0-5)	0	19 (3-38)	3 (0-10)	0 (0-10)	0

Note: where more than one publication exists concerning overlapping subsets of patients within the same study (e.g. toxicities in all patients and toxicities in intermediate risk patients only), then the study containing all patients, as opposed to one particular subset of patients, was used to create this summary data in order to avoid double-counting of toxicity and provide a better overall view.

BED: biologically equivalent dose, EQD2: equivalent dose in 2Gy fractions

*7% represents two patients in series of 29, **7% represents one patient in series of 15, [†]3% represents two patients in series of 61 and one of these episodes may not have been attributable to the radiotherapy.

Of studies reporting acute GI toxicities in detail, 13 of 14 Cyberknife™ studies [57,59,68-78], 7 of 7 linear accelerator studies [79,81-85,95] and 5 of 5 SABR boost studies [71,72,86-88] report no grade 3 or greater acute GI toxicities. The one remaining study reported grade 3 toxicity in 2% of patients and no grade 4 events [60]. Grade 1 and 2 acute rectal toxicity are more common and grade 2 acute rectal toxicity is reported in 0 to 24% of patients treated using the Cyberknife™, 0 to 27% of patients treated using a linear accelerator and 0 to 17% of patients receiving SABR as a boost (Table 1.3 and Appendix C). The most commonly reported acute GI symptoms were diarrhoea, rectal frequency and rectal discomfort.

The evidence suggests acute symptoms are worst during and within the first few weeks of treatment but largely settle over the following few months. In comparison to other radiation modalities used for the treatment of PCa, acute toxicities compare favourably (Table 1.4).

Table 1.4 Acute toxicities following alternative radiotherapy techniques for prostate cancer

	Acute GU toxicity (%)				Acute GI toxicity (%)			
Grade:	1	2	3	4	1	2	3	4
External beam radiotherapy								
RT01 trial (Dearnaley et al; *n*=422; 74Gy, conformal [15])*	52	24	7	1	52	20	2	0
Dutch trial (Peeters et al; *n*=333;78Gy, conformal [113])	NR	42	13	0	NR	47	4	0
Zietman et al (*n*=195; 79.2Gy, conformal [13])	39	45	1	1	54	33	12	0
Zelefsky et al (*n*=772; 81Gy, IMRT [20])	46	36	0.5	0	25	57	0	0
Cahlon et al (*n*=478; 86.4Gy, IMRT [22])	59	22	0.6	0	34	8	0	0
Low dose rate (LDR) brachytherapy								
Zelefsky et al (*n*=248 [103])	40	55	3	0	61	33	6	0
Tanaka et al (*n*=155 [114])	72	4	2	0	7	0.5	0	0
External beam radiotherapy with high dose rate (HDR) brachytherapy boost								
Viani et al (*n*=131 [115])	40†		2	0	13†		0	0
High dose rate (HDR) brachytherapy								
Tselis et al (*n*=351 [106])	48	17	5	0	16	2	0	0
Yoshioka et al (*n*=112 [66])	52	17	5	0	52	17	5	0
Prostate SABR (selected studies with larger patient numbers and sufficient detail)								
Bolzicco et al (*n*=100 [59])	34	12	0	0	27	18	0	0
Katz et al (35Gy patients; *n*=50 [75])	72	4	0	0	76	4	0	0
Katz et al (36.25Gy patients; *n*=254 [75])	75	5	0	0	74	4	0	0
Boike et al (all dose groups combined; *n*=45 [83])	29	22	0	0	33	11	0	0
Loblaw et al (*n*=84 [82])	71	19	1	0	67	10	0	0

*acute toxicities read from graph, † rate of most frequent acute toxicity

1.9.14 Late toxicity

With regard to late toxicity (which is usually reported as developing or persisting beyond three or six months of SABR completion), grade 3 toxicities are uncommon and grade 4 toxicities are rare. Late grade 3 urinary toxicity is not reported in 2 of the 12 Cyberknife™ studies [68,70], 3 of the 5 linear accelerator studies [58,82,84] and 2 of the 4 SABR boost studies [87,88] where sufficient detail is available (Appendix C Tables C4, C5 and C6). The remaining studies which provide sufficient detail mostly report grade 3 late urinary toxicity in one or two cases in each, usually (where reported) the result of obstructive symptoms [59-61,69,72-76,78,83,86,95]. This is often equivalent less than 5% of cases, although in some smaller series, where only one patient is affected, the percentage of patients affected can appear higher [78,83]. Specifically, grade 3 late GU toxicity is reported in 0 to 7% of patients treated using the Cyberknife™ (7%=2 patients), 0 to 7% of patients treating using a linear accelerator (7%=1 patient) and 0 to 5% of patients receiving a SABR boost (Table 1.3 and Appendix C). Grade 4 late urinary toxicity has not been reported. Grade 2 late GU toxicity is reported in 3 to 32% of patients treated using the Cyberknife™, 0 to 13% of patients treated using a linear accelerator and 5 to 12% of patients receiving SABR as a boost (Table 1.3 and Appendix C). Low grade symptoms often included urinary frequency, urgency, dysuria and nocturia.

As opposed to urinary toxicity as a whole, Arscott et al specifically examined urinary retention in a series of 269 patients with low, intermediate and high risk prostate cancer treated with 35-36.25Gy in 5 fractions using the Cyberknife™ [116]. After median follow-up of three years, the 2-year actuarial incidence of CTCAEv3 grade 2 or greater late (defined as occurring beyond six months of SABR) urinary retention was 41.4% [116]. In total 4 of the 269 patients (1.5%) required catheterisation and/ or TURP [116].

Of the studies which provide sufficient detail, late grade 3 or worse rectal toxicity is not reported in 11 of 13 Cyberknife™ studies [59-61,69,70,72,74-78], 3 of 5 linear accelerator-based studies [58,84,95] and 3 of 4 SABR boost studies [72,86,88]. Of the two remaining Cyberknife™ studies, late grade 3 GI toxicity is reported in one or two patients, equivalent to 1% or 5% of the study population respectively, largely the result

of rectal bleeding/proctitis [68,73]. Of the two remaining linear accelerator studies, one reported late grade 3 rectal toxicity necessitating colostomy formation in four patients (7%), all of whom received the highest prescription dose of all studies at 50Gy in 5 fractions ($BED_{1.5}$:383Gy, $EQD2_{1.5}$:164Gy BED_3:217Gy, $EQD2_3$:130Gy) [117]. Although these toxicities were considered grade 3 events according to CTCAEv3 scoring, surgery that results in a colostomy is such a dramatic and life-changing event, that it could be argued that these events should be considered grade 4. In addition, two patients (3%) in this study (who also received 50Gy in 5 fractions) experienced late grade 4 rectal toxicity according to CTCAEv3 scoring [117]. One episode occurred in a patient who developed a grade 4 bleeding rectal ulcer but who had significant co-morbidities which may have contributed to this episode [83]. The patient required surgery with colostomy formation and treatment with hyperbaric oxygen. The second episode of late grade 4 rectal toxicity occurred in a patient who developed rectal bleeding from a Dieulafoy lesion situated on the posterior rectal wall which was not contained within the high dose region and may, therefore, not be attributable to the radiotherapy [117]. The bleeding was treated with argon plasma laser cauterisation and symptoms resolved fully within 24 hours. The other linear accelerator-based study which reported high grade (i.e. grade 3 or greater) late rectal toxicity reported no grade 3 events and one grade 4 event in a patient with a history of diverticulitis who developed an anal fistula which required surgery [82]. Although this event was not life threatening, it was considered grade 4 given its severity and consequences [82]. The one SABR boost study to report high grade late GI toxicity reported grade 3 late rectal toxicity in five patients, equivalent to 10% of the study population, and no grade 4 events [87]. Grade 2 late GI toxicity was reported in 0 to 11% of patients treated using the Cyberknife™, 0 to 8% of patients treated using a linear accelerator and 0 to 10% of patients receiving SABR as a boost (Table 1.3 and Appendix C). Low grade late rectal symptoms mainly included proctitis, diarrhoea and occasional bleeding. As mentioned above, one group found grade 1 and 2 late urinary and rectal toxicity to be less frequent with alternate day as opposed to consecutive daily treatments [61].

Although a more comprehensive understanding of the frequency and severity of toxicities will only be gained once larger trials with longer follow-up are available, crude numerical comparisons between late toxicity rates reported for prostate SABR and other radiation treatments for prostate cancer are favourable when considering schedules other than 50Gy in 5 fractions (Table 1.5).

Table 1.5 Late toxicities following alternative radiotherapy techniques for prostate cancer

	Late GU toxicity (%)				Late GI toxicity (%)			
Grade:	1	2	3	4	1	2	3	4
External beam radiotherapy								
RT01 trial (Dearnaley et al; *n*=422; 74Gy, conformal [15])	15	7	4		27	23	10	
MD Anderson trial (Kuban et al; *n*=151; 78Gy;4-and 6-field [19])	21	11	5	0	42	28	10	0
Dutch trial (Al-Mamgani et al; *n*=333; 78Gy, conformal [97])	NR	27	12	1	NR	29	5	1
Zietman et al (*n*=195, 79.2Gy, conformal [13])	43	20	1	0	43	17	1	0
Zelefsky et al (*n*=772, 81Gy, IMRT [20])	23	9	5	0	19	2	1	0
Cahlon et al (*n*=478; 86.4Gy, IMRT [22])	16	13	2.5	0	13	3	0.4	0
Low dose rate (LDR) brachytherapy								
Zelefsky et al (*n*=248 [103])	NR	41	9	0.4	NR	9	0	0.4
Tanaka et al (*n*=155 [114])	54	8	1	0	12	1	0	0
External beam radiotherapy with high dose rate (HDR) brachytherapy boost								
Hoskin et al (*n*=110 [104])	NR	NR	26	0	NR	NR	7	0
High dose rate (HDR) brachytherapy								
Tselis et al (*n*=351 [106])	30*	5*	3	0	2	1	1	0
Yoshioka et al (*n*=112 [66])	NR	6	1	0	NR	5	2	0
Prostate SABR (trials with longest follow-up)								
Freeman and King (pooled data; *n*=41, 5-year follow-up [118])	25	7	3	0	13	3	0	0
Katz et al (35Gy patients; *n*=50 [75])	6	4	0	0	4	2	0	0
Katz et al (36.25Gy patients; *n*=254 [75])	8	9	2	0	5	5	0	0
Pham et al (*n*=40 [80])	23	13	3	0	23	8	0	0
Loblaw et al (*n*=84 [82])	2	5	0	0	35	7	0	1

MSK: Memorial Sloan Kettering, NR: not reported, *represents rate of most common GU toxicity

Some concern, however, was raised following a recent publication by Yu et al who compared toxicity at 6, 12 and 24 months post-radiation in a 1:2 matched analysis comparing patients treated with SABR and patients treated with conventionally fractionated IMRT [119]. The group used claims within the Medicare database to indicate toxicity and to determine costs. At 6, 12 and 24 months post-treatment, SABR patients experienced more GU toxicity compared to patients treated with IMRT (SABR vs. IMRT, toxicity at 6 months: 15.6% vs. 12.6%, odds ratio (OR):1.29 (95%CI:1.05-1.53, *p*=0.009), at 12 months: 27.1% vs. 23.2%, OR:1.23, (95%CI:1.03-1.43, *p*=0.01) and at 24 months: 43.9% vs. 36.3%, OR: 1.38 (95%CI:1.12-1.63). The increase in claims in the SABR group was due to urinary incontinence, obstruction and urethritis. There was also an increase in GI toxicity in SABR patients compared to IMRT patients at six months (toxicity at six months SABR vs IMRT: 5.8% vs 4.1% OR:1.42 (95%CI:1.00-1.85, *p*=0.02). No specific symptom subgroup within GI toxicity was more frequent in SABR patients compared to patients treated with IMRT [119]. The group acknowledged, however, that there were limitations in their findings, particularly since none of the toxicities could be graded and, additional, potentially confounding factors, such as baseline GU and GI function, prostate gland volume, stage and histology, radiation dose and radiation fields, could not be adjusted for [119]. Concern was also raised that the absolute rates of GU toxicity reported for SABR in this analysis were higher than what has been observed clinically [120]. Despite these limitations, this study has led others to conclude that SABR should not be considered a routine treatment for PCa until the results of ongoing randomised trials which compare SABR with conventionally fractionated IMRT are available [120].

A very recent paper by Kim et al is the first to try to determine predictors of severe rectal toxicity (grade 3 or greater) in prostate SABR patients [117]. The evaluated patients were the 45 patients treated in the phase I dose escalation trial reported by Boike et al [83], as well as an additional 46 patients who were treated within the phase II component of the trial and received the highest dose level, 50Gy in 5 fractions. The timing of acute and late toxicity were categorised differently for this analysis [117] compared to the phase I trial [83] such that acute toxicity was considered as that which occurred within 270 days of the start of SABR and late toxicity was considered as that which occurred or persisted beyond 270 days from the start of SABR. After median follow-up of 24.5 months, of the 61 patients in the highest dose arm, one patient (1.6%) experienced grade 3 acute rectal toxicity and one patient (1.6%) developed grade 4

acute rectal toxicity. In addition, three patients (4.9%) experienced grade 3 late rectal toxicity and two patients (3.3%) experienced grade 4 late rectal toxicity. No patients in the 45Gy or 47.5Gy arms experienced grade 3 or 4 rectal toxicity [117]. On multivariate analysis, the volume of rectum receiving more that 50Gy and the percent of rectal circumference receiving 39Gy were predictive of grade 3 or greater delayed rectal toxicity while the percent of rectal circumference receiving 24Gy was predictive of grade 2 or greater acute rectal toxicity. The group went on to define thresholds for each of these parameters and concluded that for a five fraction schedule, less than $3cm^3$ of rectum should receive 50Gy, less than 35% of the rectal circumference should receive 39Gy and less than 50% of the rectal circumference should receive 24Gy [117]. This is a relatively small study and the prescription dose used was much higher than that used in other SABR studies, making the 50Gy and 39Gy constraints less relevant for the more commonly used five fraction schedules. In addition, the timing of acute and late toxicity is categorised differently to what would be considered routine. Further data is therefore required before definitive conclusions can be drawn about the dose-volume parameters required for safe SABR delivery.

1.9.15 Quality of life outcomes

Several studies have evaluated quality of life outcomes. The Expanded Prostate Cancer Index Composite (EPIC) questionnaire has frequently been used to assess urological, rectal and sexual domains and the American Urological Association (AUA)/ International Prostatic Symptom Score (IPSS) has often been used to assess urinary symptoms. It appears that urinary and bowel quality of life tends to decline in the first few months following treatment but frequently returns to baseline by one year, if not earlier [58,68,69,75,76,83,121].

The Georgetown group have examined patient reported outcomes and quality of life in several papers [76,116,122-124]. A biphasic decline in urinary and bowel scores was noted: a transient decline in urinary and bowel summary scores, as well as urinary and bowel bother scores, was observed at one month post treatment, which recovered at three months [123]. This was followed by a second longer-lasting decline in scores between 9 and 18 months, although scores returned to baseline at 24 months [123]. The group went on to further characterise the second deterioration in urinary symptoms

as a ‘urinary symptom flare’ which was observed in 13% of patients at 6 to 18 months following SABR [124]. Symptoms consisted of a transient increase dysuria, frequency, urgency and retention. Symptoms returned to close to baseline by 24 months [124]. In a paper examining patient reported urinary incontinence specifically, urinary bother and incontinence scores worsened at one month (but the statistically significant change was not considered clinically relevant), then improved rapidly. A second worsening in bother and incontinence scores occurred over the next three years but these were of borderline clinical relevance only [122]. The same group specifically reported outcomes in terms of obstructive urinary symptoms [116]. As was observed in terms of urinary symptoms overall, and in terms of incontinence specifically, a worsening of obstructive symptoms was observed at one month, which resolved by three months [116]. Further late declines in obstructive symptoms were also noted which were transient [116]. Poor correlations were noted between doctor and patient reported outcomes [116]. The Georgetown group also examined fatigue scores in prostate SABR patients [125]. There was a statistically significant decline in fatigue scores at one month (which was only considered clinically relevant in African Americans) [125]. Beyond one month, fatigue scores returned to baseline.

Studies examining sexual function and quality of life frequently report a gradual worsening in scores over time, which does not recover [73,75,121,123,126,127]. Outcomes are usually only assessed in hormone naïve patients. Of patients who were potent at the start of SABR, it is reported that between 62% and 82% maintain potency at one year [68,69,107,126,127] and further declines in potency occur beyond this time point [126,127]. The observed declines in erectile function are not considered to be solely attributable to normal ageing [123,127]. Declines in potency following prostate SABR are considered comparable to those reported following treatment with other radiation modalities [126,127]. No correlation between erectile dysfunction and penile bulb dose has been identified in prostate SABR studies [126,127].

Quon et al examined the impact of dose on quality of life by comparing outcomes from two prospective trials, one delivering 35Gy in 5 fractions and one delivering 40Gy in 5 fractions [128]. The CTV-PTV margin size was slightly larger in the higher dose trial (5mm) than in the lower dose trial (4mm) and in both trials the CTV was the prostate alone. Most quality of life scores remained high (i.e. reflecting a good quality of life) in both dose groups, although, at 12 months, a higher proportion of patients treated with

40Gy experienced clinically relevant reductions in bowel bother scores [128]. There was, however, no significant difference in the proportions of patients reporting moderate to severe bowel problems [128].

Katz et al compared quality of life outcomes in patients treated with prostate SABR and patients undergoing radical prostatectomy [129]. As observed above, in SABR patients, bowel and urinary quality of life declined in the first few months, but scores returned to baseline at one year [129]. Surgical patients displayed larger declines in urinary and sexual quality of life in the first six months after treatment while SABR patients experienced worse bowel quality of life over the first six months [129]. Longer term, declines in urinary and sexual quality of life scores remained significantly lower than baseline in surgical patients, but recovered to baseline levels in SABR patients [129]. Compared with other prostate cancer treatment modalities, in addition to radical prostatectomy, the quality of life outcomes that have so far been reported for prostate SABR patients appear comparable [130].

1.9.16 Cost effectiveness

Loblaw et al estimated that a patient receiving five fraction SABR would save on average 1928 Canadian dollars (C$, £1050 approximately, range: C$170 to C$13,937 (~£92 to ~£7720)) in terms of travel, accommodation and time away from work compared to attending for a 39 fraction schedule [82].

Two groups have performed Markov modelling to compare prostate SABR cost-effectiveness with conventionally fractionated IMRT [131,132]. SABR was found to be the more cost-effective modality, although it was acknowledged that the size of the benefit would be influenced by efficacy, toxicity and quality of life outcomes, which, for prostate SABR, are not currently mature enough to draw definitive conclusions [131,132]. Yu et al, who assessed toxicity following SABR and IMRT (above) based on Medicare claims, also calculated the cost of both treatments based on the Medicare database. Despite the finding of increased GU toxicity in SABR patients, overall SABR costs (which included cancer-related, radiation-related, non-cancer-related and complication costs), were less than overall costs for IMRT [119].

1.9.17 Conclusions about SABR in prostate cancer

Overall SABR in PCa is well tolerated with most acute and late toxicities being grade 1 or 2. Acute rectal and urinary symptoms peak during and within the first few weeks of treatment but largely settle after a few months. Overall, toxicity rates appear broadly comparable with those reported for other routinely used forms of prostate radiation. The highest dose delivered (50Gy in 5 fractions) has, however, been associated with a greater number of high grade toxicities than any of the other lower dose schedules, urging some caution in the use of such marked ultra-hypofractionation. In terms of PSA control, outcomes are promising and comparable with other modalities of prostate cancer treatment for low and intermediate risk patients. Clarification regarding optimal dose-fractionation, target volume definition, margin definition, dose-volume constraints, dose distribution and the addition of androgen deprivation are still required. Longer term follow-up from large randomised trials are required to clarify these matters. One such trial is the ongoing HYPO-RT-PC phase III randomised Scandinavian trial comparing conventional IMRT, 78Gy in 39 fractions ($BED_{1.5}$:182Gy, BED_3:130Gy) with linear accelerator delivered SABR, 42.7Gy in 7 fractions ($BED_{1.5}$:216Gy, $EDQ2_{1.5}$:93Gy, BED_3:130Gy, $EDQ2_3$:78Gy) in patients with intermediate risk prostate cancer [133]. Initially this trial aimed to demonstrate a 10% improvement in 5-year freedom from failure in the SABR group, but has recently changed to a non-inferiority trial. Another phase III trial is the recently opened non-inferiority PACE (Prostate Advances in Comparative Evidence) trial. Originally this trial aimed to compare outcomes in low and intermediate risk prostate cancer patients treated with robotic prostatectomy, conventionally fractionated IMRT (78Gy in 39 fractions) and SABR delivered using the Cyberknife™ (delivering either 36.25Gy in 5 fractions ('homogeneous' dose distribution) or 38Gy in 4 fractions (HDR-brachytherapy like dose distribution) [134]. More recently the protocol has been amended to also allow SABR delivery using a linear accelerator, delivering a dose of 36.25Gy in 5 fractions. In addition, the 38Gy in 4 fraction Cyberknife™ schedule has been removed, and so all SABR patients receive 36.25Gy in 5 fractions [135].

1.10 The influence of overall treatment time

It was previously thought that overall treatment time did not have an impact on outcomes following prostate radiotherapy [136]. Recently, however, a large analysis has demonstrated that prolonged overall treatment time has a significant negative effect on biochemical control in low and intermediate risk PCa patients receiving at least 70Gy [137]. This analysis also confirmed dose as another significant predictor of biochemical outcome. The group therefore suggested that that optimisation of biochemical outcomes could potentially be achieved by increases in total dose and reductions in overall treatment time [137]. Hypofractionation, and in particular the ultra-hypofractionation used to deliver SABR, meets both these requirements. In terms of acute toxicity, however, it has been suggested that shortening treatment times too dramatically could result in increased acute side effects, and as such reductions in overall treatment times to less than five weeks should be avoided [38]. In practice, however, reductions in treatment times to 4 or 5 fractions delivered over consecutive days have not been shown to have detrimental effects on acute tissue reactions (see above).

1.11 Image guided radiotherapy (IGRT) and associated interventions for SABR

One of the challenges in treating PCa is the fact that the prostate and SV do not remain in the same position and can change shape (deformation) [138-144]. The prostate and SV may move or deform between treatments (inter-fraction motion/ deformation) and during treatment (intra-fraction motion/ deformation). Movement may be translational (i.e. superior-inferior, anterior-posterior, left-right) or rotational, and both position and deformation are influenced by rectal and, to a lesser extent, bladder filling [145,146]. The degree of intra-fraction and inter-fraction motion is variable from one individual to another. Furthermore, changes in rectal and bladder position can result in variable and, at times, excessive doses being delivered to these structures [147-149]. It is preferable, therefore, to plan and deliver treatment with an empty rectum, in order to minimise the dose delivered here, and with a constant level of bladder filling [145,148,149]. Not only has rectal volume been shown to influence the dose received by the rectum, clinical

practice has shown that a distended rectum, resulting in a change in prostate position or shape, and thus increasing geographical miss, is associated with increased biochemical failure [150-152].

As interest grows in the use of higher dose per fraction treatments, as adopted in SABR, it becomes increasingly important to be certain that the desired treatment is being delivered to the target volume and not to the surrounding normal tissues. Improved image guidance techniques allow reduced PTV margins, thus increased normal tissue sparing and, in turn, the potential for further dose escalation. There is no gold standard technique to ensure optimal IGRT for the prostate. A variety of techniques exists, all of which have strengths and weaknesses. Methods of the more commonly used image-guidance strategies are discussed briefly below, with particular reference to their use in SABR.

1.11.1 Portal imaging matching to bony anatomy

Traditionally electronic portal images have been used to match treatment fields to pelvic bony anatomy. It has been demonstrated, however, that there is significant inter-fraction prostate motion and that this is independent of the bony anatomy and, as such, bony anatomy should not be considered a reliable surrogate for prostate position [153]. In the situation where electronic portal imaging is the only technique available, then large PTV margins are required to take account of uncertainties in target position. Portal imaging with matching to bony anatomy has not been used for image guidance in any of the prostate SABR studies discussed above. Portal imaging can be used, however, to visualise fiducial markers [82,95] (see below).

1.11.2 Fiducial markers

The implantation of gold fiducial markers (usually three) into the prostate using a rectal or transperineal approach provides radio-opaque markers which should move with the prostate and so provide an accurate surrogate for prostate position. These can be identified on kV or megavoltage (MV) portal images or cone beam images and so changes in prostate position can be corrected. Fiducials have been shown to allow

highly accurate verification of the prostate and have facilitated reductions in conventional CTV-PTV margins and lower rectal wall doses [154-157]. The technique, despite being invasive, has been shown to be feasible, safe and acceptable and without a negative impact on patient quality of life [158,159]. Potential clinical complications include pain, infection and bleeding. There is also a risk of seed migration although migration distances tend to be small [154,158-160]. Other concerns related to fiducial marker use include the production of artefact on treatment planning scans and the inability to fully visualise changes in the surrounding soft tissues and SV movement or deformation which may be independent of prostate movement (unless fiducial marks are aligned using CBCT to provide additional soft tissue information) [139,161]. Furthermore, the use of fiducial markers for online daily set up does not correct for prostate intra-fraction deformation or rotation [141,162].

As well as being one potential method for the correction of inter-fraction motion, fiducial markers are also used with the Cyberknife™ for intra-fraction motion monitoring and tracking [62]. As mentioned above, the Cyberknife™ system has two in room stereoscopically mounted kV x-ray cameras which are capable of real-time fiducial marker tracking, and so intra-fraction changes in prostate position can be automatically and precisely corrected [62]. Similarly the Calypso® system (Varian, USA) uses an electromagnetic tracking system whereby transponders are implanted into the prostate and detected externally. Prostate motion can therefore be tracked and movements accurately corrected in real time [163]. In either case, 'live' intra-fraction motion correction means that CTV-PTV margins can be further reduced. The frequency of fiducial marker imaging during intra-fraction monitoring must, however, be appropriate for the CTV-PTV margin size used [164].

All of the Cyberknife™ SABR studies have utilised fiducial markers and kV imaging for daily online set up as well as for intra-fraction motion tracking. Of the linear accelerator-based studies, three have utilised fiducial markers for daily online set up [81,82,95], one has used the Calypso® electromagnetic beacon system to facilitate online set up and intra-fraction motion tracking [58]) and one has used either fiducials or Calypso® beacons [83]. One of the remaining studies [84] used intra-prostatic calcifications as markers for online daily set up as these have been shown to be adequate surrogates for prostate localisation [165]. The remaining two studies did not use any fiducial markers, but used CBCT alone [79,85] (see below). Of the five linear accelerator SABR

studies which used fiducials for online set up (be those simple fiducials, beacons or calcifications) and which provide sufficient details, two have localised fiducials using portal images [82,95] and three have localised fiducial markers (or intra-prostatic calcifications) using CBCT [58,83,84].

1.11.3 Cone Beam CT

Cone beam CT (kV or MV) is one means of assessing prostate position and correcting for movement. CBCT allows alignment of soft tissue to soft tissue on planning and treatment scans, and/ or it can be used to match to fiducial markers. CBCT allows visualisation of the prostate as well as the bladder and rectum, and has been shown to allow a reduction in CTV-PTV margins and has demonstrated a reduction in acute GU toxicity compared to the use of electronic portal imaging with matching to bony anatomy [166,167]. CBCT has the advantage of being non-invasive but image quality can be poor making accurate soft tissue matching difficult, and considerable inter-observer variability has been demonstrated in defining the prostate and surrounding soft tissue boundaries [168-170]. In addition, performing CBCT prolongs the time that the patient is in the treatment room and exposes the patient to further radiation. Comparisons of the shifts made as a result of CBCT soft tissue matching to with those made in response to imaging of fiducial markers have shown variable correlation [168,171,172]. The evidence demonstrates that when using CBCT for soft tissue matching (i.e. without fiducials in situ), discrepancies of greater than 5mm between CBCT soft tissue matching and marker guided matching are relatively uncommon, while alignment within 3mm is more prone to discrepancies between techniques. It has been suggested, therefore, that margins of 5 to 7 mm are adequate to account for misalignments as a result of interobserver variation in the interpretation of where the edges of the prostate lie in relation to the surrounding normal structures on CBCT images [141,168]. In most of the linear accelerator SABR studies discussed above, CBCT is used in conjunction with fiducial markers, and so smaller CTV-PTV margins are considered acceptable [58,83,84]. Only two small studies have used CBCT without fiducials, although the CTV-PTV margins adopted were not necessarily larger than those used for fiducial based IGRT [79,85].

Despite appropriate PTV margins, and regardless of the image guidance technique, marked prostate or organ at risk deformation cannot be adequately corrected unless the treatment is re-planned. Adaptive radiotherapy is a relatively new addition to the field of radiotherapy whereby image guidance is used not only for localisation but also to facilitate re-planning. This approach has not yet been reported in the context of prostate SABR. There is also recent interest in performing simultaneous CBCT while rotational radiotherapy is being delivered (termed kilovoltage intra-fraction motion monitoring) in order to assess prostate intra-fraction motion [173]. Again, this is a very recent area and has not yet been used in the context of prostate SABR.

1.11.4 Endorectal Balloons

Endorectal balloons have been used in an effort to immobilise the rectum in one of the prostate SABR studies discussed above [83]. Their use in the setting of more conventional fractionation has been shown to reduce prostate motion and improve rectal sparing when delivering IMRT and conformal RT, and reduce late rectal toxicity following conformal RT [174-177]. In the context of prostate SABR, it has been demonstrated that endorectal balloons can cause prostate deformation which can result in reduced target coverage [178,179]. Careful positioning and diligent correction of positioning errors are required to ensure optimal target coverage [178,179].

1.11.5 Prostate-rectal spacers

A temporary biodegradable gel or biodegradable balloon filled with biodegradable gel can be injected transperineally under transrectal ultrasound guidance to act as a spacer between the prostate and rectum. Insertion of the gel or balloon has been shown to be feasible and well tolerated [180,181]. These interventions have been shown to increase rectal-prostate distance by about 1 to 2.5cm and result in reduced rectal doses on plans [180,181]. Longer follow-up and larger patient numbers are required to establish the clinical impact of these products on long term rectal toxicity. One of the SABR studies used spacers in 20% of patients [84].

1.12 SABR delivered using VMAT

One potentially attractive option in PCa is to deliver SABR with VMAT thus drawing on the potential radiobiological benefits of ultra-hypofractionation, the efficiency and convenience of a few fraction treatment, and the high conformity, MU efficiency and rapid delivery speed achievable with VMAT. At the time of project set up, the delivery of prostate SABR using VMAT had not been widely documented, and details were only available as abstracts with corresponding conference posters [182,183] (discussed in Chapter 2).

1.13 Aims

The aims of this thesis are:

- To develop a class solution for prostate SABR delivered using VMAT

- To investigate if it is feasible to dose-escalate image-defined dominant intra-prostatic lesions in the context of whole prostate SABR, and assess the impact of this strategy on tumour control probability and normal tissue complication probability

- To investigate the impact of flattening filter free beams for prostate SABR planning compared to planning using conventional flattened beams

- To perform a systematic review of the literature regarding radiation-induced second malignancies following prostate radiotherapy

- To compare radiation-induced second malignancy estimates for prostate SABR delivered using VMAT with other external beam techniques used for prostate cancer treatment.

Chapter 2 : Developing a class solution for prostate stereotactic ablative radiotherapy

2.1 Introduction

Radiation dose escalation in localised PCa has been shown to result in improved biochemical control [184]. Ultra-hypofractionation within the context of SABR is an attractive approach to dose escalation, allowing higher biologically equivalent doses to be delivered in a small number of high dose fractions. There is also radiobiological rationale for such an approach: evidence suggests that PCa has a low α/β ratio (~1.5Gy), making it theoretically more sensitive to large dose per fraction treatments [34,35,37,38]. There is also evidence that the neighbouring late responding rectal and bladder tissues have higher α/β ratios than PCa (~3-6Gy) [35,36,38-41]. This situation can be exploited by delivering larger hypofractionated doses to the prostate for equivalent levels of late toxicity (Chapter 1).

Volumetric modulated arc therapy (VMAT) uses a linear accelerator to deliver radiotherapy in one or more arcs. While the beam is continuously switched on, the dose rate, gantry rotation speed and MLC positions are continuously altered to create highly conformal plans [24-26]. In comparison to IMRT, VMAT plans display at least comparable conformity with more efficient MU use and faster delivery times [24-33].

Delivering prostate SABR with VMAT is an attractive option: it offers dose escalation, the theoretical benefits of hypofractionation, the convenience of a few fraction treatment, together with the high conformity, MU efficiency and rapid delivery achievable with VMAT. While much has been published regarding VMAT in PCa [25-33] and regarding prostate SABR (Chapter 1), little exists in the literature regarding the PCa SABR planning with VMAT.

This planning study assesses prostate SABR using VMAT as a key preparatory step in facilitating future clinical studies. The impact of different arc arrangements is assessed

and CTV-PTV margins consistent with daily online fiducial based image guidance and CBCT are compared. The impact of the inclusion of the proximal seminal vesicles (proxSV) within the CTV is also evaluated.

2.2 Materials and Methods

2.2.1 Patients and volumes

Datasets from 15 early PCa patients were chosen. Patients were asked to have comfortably full bladders and received enemas prior to scanning to ensure empty rectums. The bladder, rectum (anus to recto-sigmoid junction), femoral heads (FH), penile bulb (PB) and bowel were contoured as organs at risk. The CTV was the whole prostate gland. Patients were CT-scanned in the supine position using 2mm slices.

Part I: Seven datasets were used. The CTV was expanded isotropically by 6mm to create the PTV. Each dataset was planned using four different arrangements of one and two arcs:

- one full 360° arc (1FA)
- one partial 210° arc (255°→105°; 1PA)
- two full 360° arcs (2FA)
- two partial arcs (210° (255°→105°) and 180° (270°→90°); 2PA)

Seven datasets were chosen as this was the minimum number of cases required to achieve statistical significance at the level selected (see below) [185]. Within the local department three to five datasets are usually considered adequate for the initial phases of class solution development.

Part II: Fifteen datasets were planned using 1PA and 6mm CTV-PTV margins, reflecting margins used with fiducial marker based daily online IGRT [186-188]. All 15 datasets were re-planned using 8mm CTV-PTV margins, reflecting margins compatible with daily CBCT (without fiducials) [141].

Part III: the fifteen datasets were re-planned including the prostate and proximal 1cm of SV within the CTV, expanded by 6mm to PTV.

2.2.2 Selection of SABR dose

The PTV prescription dose was 42.7Gy in 7 fractions, intended for delivery on alternate weekdays over three weeks. The BED and EQD2 received by the prostate and late and early responding tissues can be calculated as described in Chapter 1. The α/β for the prostate was considered as 1.5Gy. For late and early responding tissues, α/β was considered as 3Gy and 10Gy respectively [35]. This assumes no ongoing tumour cell repopulation or repopulation delay time which is acceptable in this setting [42,43]. Thus, as shown in Table 2.1, compared to conventionally fractionated radiotherapy delivering a dose of 78Gy in 39 fractions (standard European prostate fractionation), a higher BED is delivered to the prostate but a similar BED is delivered to the late responding tissues which will theoretically result in equivalent late effects. In addition, the SABR regimen also delivers a lower dose to the early responding tissues. As with the SABR doses of 35-36.25Gy in 5 fractions discussed in Chapter 1, using a dose of 42.7Gy in 7 fractions results in the exploitation of the lower α/β of PCa in order to deliver a higher BED to the prostate but a dose to the late responding tissues that is biologically equivalent to that received from conventional fractionation. Figure 2-1 also illustrates how the lower α/β of PCa can be exploited by using high doses per fraction.

Assuming that the late responding tissues have a traditional α/β ratio of 3Gy adopts a more conservative approach than assuming a higher α/β ratio for the late responding tissues, as has been suggested [35,36,38-41]. For example, assuming a higher α/β ratio for the late responding rectal tissues at 5.4Gy [41], and delivering a dose of 42.7Gy in 7 fractions, would result in these tissues receiving a dose that is lower than that delivered using conventional fractionation ($BED_{5.4}$ and $EQD2_{5.4}$: 90.9Gy and 66.4Gy respectively), i.e. the radiobiological advantage of the low α/β ratio of PCa increases with higher α/β values for the late responding rectal tissues.

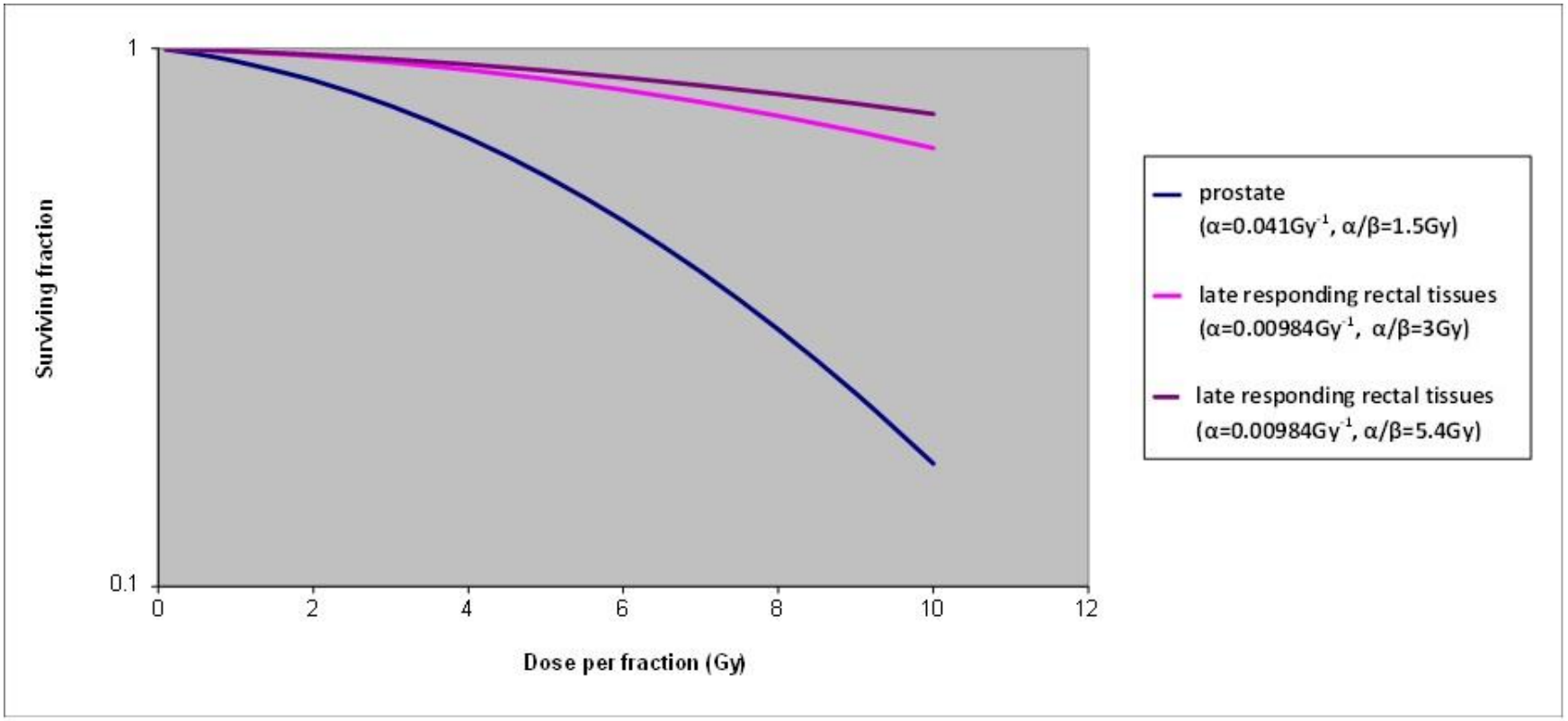
Table 2.1 Biologically equivalent doses with conventional and SABR dose and fractionation schedules

Treatment	EBRT dose	Dose per fraction	BED to prostate tumour (α/β=1.5Gy)	EQD2 to prostate tumour (α/β=1.5Gy)	BED to early responding tissues (α/β=10Gy)	EQD2 to early responding tissues (α/β=10Gy)	BED to late responding tissues (α/β=3Gy)	EQD2 to late responding tissues (α/β=3Gy)
78Gy in 39 fractions	78Gy	2Gy	182.0Gy	78Gy	93.6Gy	78Gy	130.0Gy	78Gy
SABR	42.7Gy	6.1Gy	216.3Gy	92.7Gy	68.7Gy	57.3Gy	129.5Gy	77.7Gy

BED: Biologically equivalent dose, EQD2: equivalent dose in 2Gy fractions, EBRT: external beam radiotherapy, SABR: stereotactic ablative radiotherapy

Figure 2-1 Impact of hypofractionation in exploiting the low α/β ratio of prostate cancer

At higher doses per fraction, the ratio of prostate cells killed to late responding rectal tissues killed is greater than at lower doses per fraction. The higher the α/β ratio of the late responding tissues (or the lower the α/β of the prostate), the greater the gap between cell kill and late rectal damage. Prostate α from [37] and rectal α from [189]. Surviving fraction=$exp\ -(\alpha d+\beta d^2)$. ($d$=dose per fraction)



The SABR prescription dose used in this study is currently used in the Hypo-RT-PC trial, a phase III Scandinavian trial comparing 42.7Gy in 7 fractions with 78Gy in 39 fractions (for the same biological rationale as above) delivered using IMRT or 3D-CRT [133].

2.2.3 PTV coverage

The following coverage requirements were specified and were in line with the coverage requirements specified in the Hypo-RT-PC trial [133]:

- Dose received by 95% of the PTV was at least 95% of the PD (D95%≥40.6Gy)
- minimum prostate dose: ≥40.6Gy, (Dmin≥40.6Gy (95%))
- dose received by 99% of the PTV: ≥38.4Gy (D99%≥38.4Gy (90%))

In addition, it was specified that:

- maximum dose: ≤120% (Dmax ≤51.2Gy)
- conformity index (to limit high dose spill and as recommended by the ASTRO Emerging Technology Committee recommendations [190]; CI; defined below) should be less than 1.2
- where feasible, dose received by 98% of the PTV: ≥95% of the PD (D98%≥95%) and dose received by 2% of the PTV: ≤107% (D2%≤107%).

As SABR generally encourages dose escalation, it was acceptable if the median dose exceeded the prescription dose of 42.7Gy, as long as the maximum dose did not exceed 51.2Gy (120%).

2.2.4 Defining organ at risk constraints

There is no consensus regarding the appropriate dose-volume constraints which should be adopted when delivering prostate SABR. As shown above, the BED to the late responding tissues is similar with doses of 42.7Gy in 7 fractions and 78Gy in 39 fractions, assuming a late responding tissue α/β ratio of 3Gy. Late responding tissues, however, are not only exposed to a dose of 42.7Gy but receive a range of doses, the

magnitude and proportions of which will influence the risk of late toxicity. The Hypo-RT-PC trial protocol specifies three dose-volume constraints for the rectum for the SABR schedule (V38.4Gy≤15%, V32Gy≤35% and V28Gy≤45%, where VxGy is the volume of structure receiving at least xGy [133]). There is, therefore, no constraint controlling the very high dose regions (e.g. above 40Gy). As the long term consequences of the doses used for prostate SABR are uncertain it seemed prudent to assess if treatment planning was feasible with the addition of further dose-volume constraints. The recently completed UK CHHiP trial delivered 74Gy in 37 fractions as standard and specified a range of dose-volume constraints for the rectum [191,192]. Preliminary safety results reported low rates of RTOG grade 2 or greater late rectal and bladder toxicity at two years (4.3% and 2.2% respectively) [52]. In the first instance, therefore, using the CHHiP trial dose-volume constraints for 74Gy in 37 fractions, biologically equivalent constraints were calculated for a seven fraction schedule (as used for SABR).

For example, the CHHiP trial specified that the rectal V70Gy should be less than 15% [191,192]. In a 37 fraction treatment (such that *d*=1.892Gy) the BED to late rectal tissues is 114.144Gy. For the same BED using an alternative fraction regimen therefore:

$$114.144 = D\left(1+\frac{d}{(\alpha/\beta)}\right)$$

For a seven fraction regimen therefore,

$$114.144 = 7d\left(1+\frac{d}{(3)}\right) \qquad \text{or:}$$

$$114.144 = 7d+\frac{7}{3}d^2 \qquad \text{or:}$$

$$0 = \frac{7}{3}d^2+7d-114.144$$

This must be solved as a linear-quadratic equation according to the formula:

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

where: $a = \frac{7}{3}$, $b = 7$ and $c = -114.114$

Thus, $d = 5.653$Gy

For 7 fractions, $D = 7d = 7 \times 5.653 = 39.57$Gy

Thus the biologically equivalent constraint to the CHHiP trial V70Gy<15% for a 74Gy in 37 fraction regimen is V39.57Gy<15% for a 7 fraction treatment. In order to be conservative, all numbers were rounded *down* to one decimal place, i.e. V39.5Gy<15%.

The same process was employed to derive biologically equivalent constraints for a 7 fraction schedule using all the CHHiP trial 74Gy in 37 fraction rectal constraints (Table 2.2).

It is clear from Table 2.2 that the three dose-volume constraints from the Hypo-RT-PC trial are more stringent for intermediate doses, but no very high and low dose constraints are specified. The rectal constraints adopted in this study therefore consisted of a combination of calculated biologically equivalent constraints for the very high and low dose regions and the Hypo-RT-PC trial constraints for the intermediate and high dose regions (Table 2.3).

Biologically equivalent constraints to 74Gy in 37 fractions for a 7 fraction schedule were also derived for the bladder, femoral heads, bowel and penile bulb using the same process described above and are also shown in Table 2.3.

Table 2.2 Comparison of rectal dose-volume constraints from i) the CHHiP trial for 74Gy in 37 fractions, ii) calculated biologically equivalent constraints for a 7 fraction treatment and iii) dose-volume constraints from the Scandinavian trial using 42.7Gy in 7 fractions

i	ii	iii
CHHiP trial [191]	Calculated biologically equivalent constraint for 7 fraction treatment	Dose-volume constraints used in Hypo-RT-PC Scandinavian trial protocol using 7 fraction treatment [133]
V74Gy<3%	V41.4Gy<3%	
V70Gy<15%	V39.5Gy<15%	
		V38.4Gy≤15%
V65Gy<30%	V37.1Gy<30%	
V60Gy<50%	V34.7Gy<50%	
		V32Gy≤35%
V50Gy<60%	V29.9Gy<60%	
		V28Gy≤45%
V40Gy<70%	V24.8Gy<70%	
V30Gy<80%	V19.6Gy<80%	

CHHiP: Conventional versus Hypofractionated High-dose intensity-modulated radiotherapy for Prostate cancer

Table 2.3 Dose-volume constraints adopted for planning study

Volume	Constraints
Rectum	V41.4Gy(97%)<3%
	V38.4Gy(90%)≤15%*
	V32.0Gy(75%)≤35%*
	V28.0Gy(65%)≤45%*
	V24.8Gy(58%)<70%
	V19.6Gy(46%)<80%
Bladder	V41.4Gy(97%)<5%
	V34.7Gy(81%)<25%
	V29.9Gy(70%)<50%
Femoral heads	Dmax≤29.9Gy (70%)*
	V29.9Gy(70%)<50%
Bowel	V29.9Gy(70%)< 17cc
Penile bulb (objective only)**	V29.9Gy(70%)<50%
	V34.7Gy(81%)<10%

* Dose-volume constraints adopted from Hypo-RT-PC phase III trial. Those constraints without an asterisk are biologically equivalent to those used in the CHHiP (Conventional versus Hypofractionated High-dose intensity-modulated radiotherapy for Prostate cancer) trial for 74Gy in 37 fraction treatments.

**Constraints for the penile bulb were for guidance only and did not have to be achieved.

2.2.5 Planning

Monaco® version 3.2 (Elekta AB, Sweden) with a Monte Carlo (MC) calculation, the Agility™ 5mm MLC system (Elekta AB, Sweden), a maximum of 150 control points per arc, 1% MC variance per plan, 6MV photons, 30° sectors and a 3mm calculation grid were employed. Monaco® is a treatment planning system that allows the user to specify both physical (i.e. dose-volume) objectives and biological objectives, where organs at risk may be handled as serial or parallel structures and the specified doses are stated as equivalent uniform doses (EUD), rather than physical doses. The concept of EUD is such that two different dose distributions are considered equivalent if the biological effects of these dose distributions are the same [193]. Thus a non-uniform

dose distribution can be represented by a single dose value (the EUD) which states the biological effect of the non-uniform dose distribution if it were delivered homogeneously. It can be calculated according to [194]:

$$\text{EUD}= \left(\sum_i D_i^{\frac{1}{n}} \frac{V_i}{V_{total}} \right)^n$$

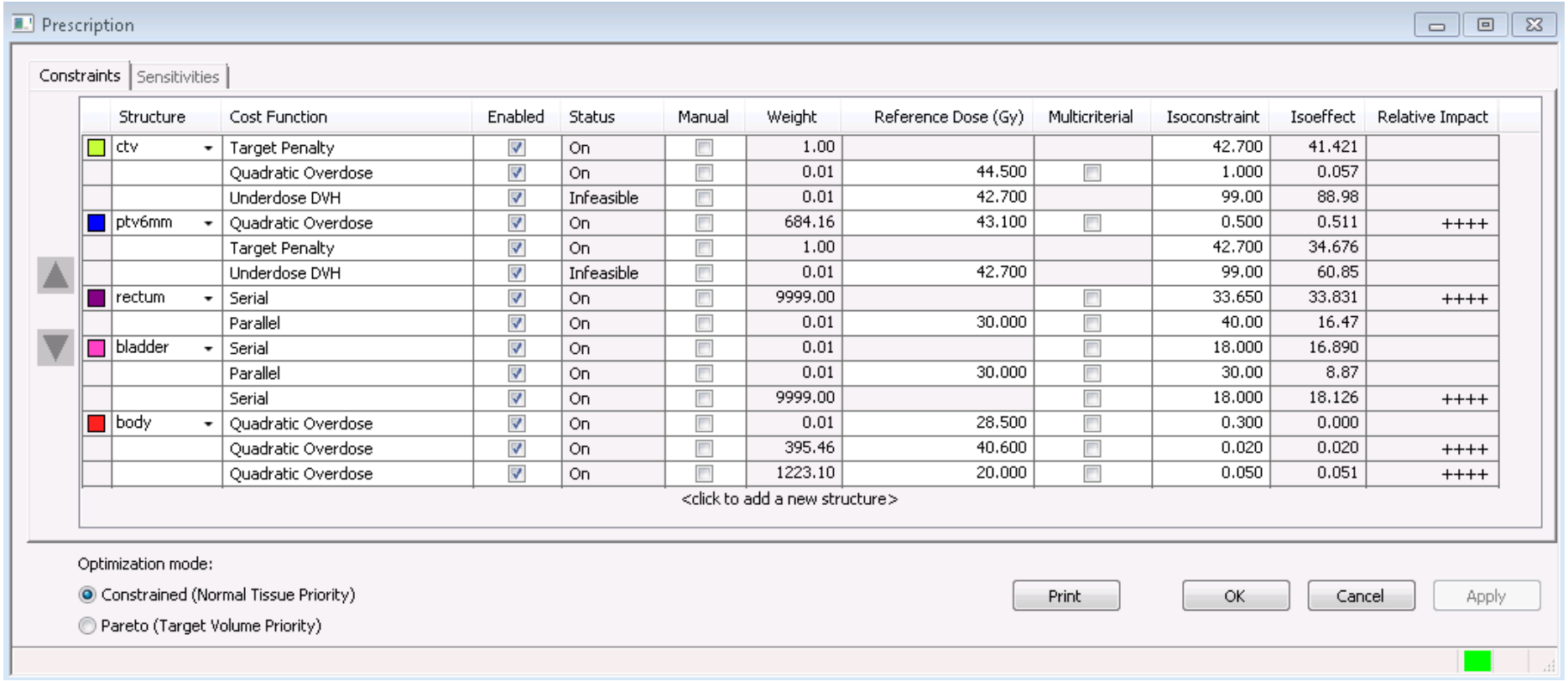
where D_i is the dose to dose bin i, V_i is the volume of dose bin i, V_{total} is the total volume of the tissue and n is a volume effect parameter. Large values of n (i.e. close to 1) represent a large volume effect as in parallel structures, and so EUD is approximately equal to the mean dose) and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

As such the doses entered when creating EUD based prescriptions in Monaco® can be very different to the desired physical dose-volume outcomes. Although biological cost functions were employed in this planning study, these were purely used as levers to meet the desired physical constraints, as per Departmental policy. This explains why cost functions for parallel organs were often used alongside cost functions for serial organs within the same structure (see below).

The class solution that was developed is shown in Figure 2-2 with explanation of the various prescription components in Table 2.4 below.

Figure 2-2 Class solution for prostate SABR with explanation of prescription components in table below

This solution could be applied to any of the four arc arrangements investigated.



Structure	Cost Function	Enabled	Status	Manual	Weight	Reference Dose (Gy)	Multicriterial	Isoconstraint	Isoeffect	Relative Impact
ctv	Target Penalty	☑	On	☐	1.00			42.700	41.421	
	Quadratic Overdose	☑	On	☐	0.01	44.500	☐	1.000	0.057	
	Underdose DVH	☑	Infeasible	☐	0.01	42.700		99.00	88.98	
ptv6mm	Quadratic Overdose	☑	On	☐	684.16	43.100	☐	0.500	0.511	++++
	Target Penalty	☑	On	☐	1.00			42.700	34.676	
	Underdose DVH	☑	Infeasible	☐	0.01	42.700		99.00	60.85	
rectum	Serial	☑	On	☐	9999.00		☐	33.650	33.831	++++
	Parallel	☑	On	☐	0.01	30.000	☐	40.00	16.47	
bladder	Serial	☑	On	☐	0.01		☐	18.000	16.890	
	Parallel	☑	On	☐	0.01	30.000	☐	30.00	8.87	
	Serial	☑	On	☐	9999.00		☐	18.000	18.126	++++
body	Quadratic Overdose	☑	On	☐	0.01	28.500	☐	0.300	0.000	
	Quadratic Overdose	☑	On	☐	395.46	40.600	☐	0.020	0.020	++++
	Quadratic Overdose	☑	On	☐	1223.10	20.000	☐	0.050	0.051	++++

<click to add a new structure>

Table 2.4 Explanation for prescription components shown in Figure 2-2

Continued overleaf.

Structure	Cost function	Explanation
Target	Target Penalty	Specifies dose to be received by the target. The required dose shown in 'Isoconstraint' column. Dose is prescribed to the volume of target which should receive at least this dose (not visible here).
	Quadratic overdose	To stop dose 'over-shooting'. The preferred dose limit is shown in the 'Reference dose' column, and the size of the penalty for overdosing is shown in the 'Isoconstraint' column. Larger numbers indicate a lesser penalty for overdosing.
	Underdose DVH	Aims to ensure optimal dose coverage of the structure, thus reinforcing the coverage requirements from the 'Target Penalty' function. Desired dose specified ('Reference dose' column) with volume ('Isoconstraint' column) that should ideally receive this. This objective is frequently found to be 'infeasible' ('Status' column), but in this situation the optimiser still works to come as close to achieving the objective as possible.
Organ at risk (rectum/ bladder)	Serial (continued overleaf)	Works to limit dose at one point of the DVH and in cases used here, the objective is acting on the high dose end of the DVH. Specifies maximum equivalent uniform dose that it desired that the structure receives. Dose (as equivalent uniform dose) specified in 'Isoconstraint' column. Penalty for overdosing must also be specified (not visible here). Reducing the isoconstraint to bring structure into tolerance effectively 'tucks-in' the tip of the DVH curve, while tightening the penalty attempts to pull the whole of the DVH curve to the left. In cases where there is overlap of an organ at risk with the PTV, and there is concern that the organ at risk may easily receive too high a dose, this objective can be 'optimised over all voxels' so that it is applied to the whole of the structure, including areas of overlap with the PTV. 'Optimising over all voxels' can create an area of conflict between trying reduce the dose received by an organ at risk and achieving optimal target coverage, but normal tissues are given priority over target coverage. The 'optimise over all voxels' option was employed for the rectum in the above prescription.

Table 2.4 cont. Explanation for prescription components shown in Figure 2-2. Continued overleaf.

Structure or prescription element	Cost function	Explanation
Organ at risk cont. (rectum/ bladder)	Serial cont.	It is also possible to specify that the cost function is only applied at a specified distance from the PTV, allowing a dose gradient to form between the target and organ at risk. In the case of the bladder, a 5mm shrink margin was applied to the serial objective so that it was only applied to areas of bladder more than 5mm from the PTV: because the bladder volumes were generally large, the objective could often be achieved while still allowing small portions of bladder that were within 5mm of the PTV, or were overlapping with the PTV, to receive doses around the prescription dose.
	Parallel	Works to try to reduce doses across a range of the DVH. A dose is specified (as equivalent uniform dose) and the corresponding volume of tissue is specified which may receive this dose or higher (and so may be safely sacrificed; 'Isoconstraint' column). A penalty for overdose is also specified (not visible here).
Body (i.e. non-specified normal tissue)	Quadratic overdoses	Limits dose to normal tissues surrounding the target. Maximum dose specified ('Reference dose') and penalty specified ('Isoconstraint' column) for overdosing (small numbers indicate stricter penalties). Each objective is also specified with shrink margin to determine how far from the PTV the objective is applied. In general the 40.6Gy objective was prescribed with 0mm shrink margin and so was applied immediately beyond the PTV while the 20Gy was prescribed with a shrink margin of 2cm, and so was only applied at distances greater than 2cm from the PTV.
Structure layering	-	Any structure above another in the prescription 'owns' any overlapping voxels. A cost function is only applied to the voxels within a structure that are 'owned' by that structure. For example, PTV is below CTV in the prescription so that PTV cost functions are only applied to PTV voxels outside CTV. The situation can be altered by selecting to 'optimise over all voxels' so that areas of overlap between structures are acted on by the objectives specified for both overlapping structures. Note: regardless of layering or which voxels are 'owned' by which structures, the DVH statistics reported by the planning system relate to the whole structure.

Table 2.4 cont. Explanation for prescription components shown in Figure 2-2

Structure or prescription element	Cost function	Explanation
Isoeffect column	-	Number displayed shows how close the plan is to the desired 'Isoconstraint' in the neighbouring column.
Relative impact, Weight and Status columns	-	Displays how hard the optimiser is working to achieve the desired objective. '++++' indicates the hardest work. Also indicated in the 'Weight' column, where higher numbers up to 9999 indicate difficulty in meeting the objective. When an objective harder than this, it is then considered 'infeasible' in the 'Status' column. In this situation the optimiser continues to try to get the best possible outcome, despite not being able to achieve the desired objective. If the objective is considered impossible, then it is considered 'offensive' and the optimiser will not try to meet the objective at all.
Multicriterial (not used here)	-	If 'Multicriterial' is selected, then not only does the optimiser try to meet the specified objective, but it tries to achieve the best possible outcome for that structure (e.g. the lowest possible rectal dose). Although this is an attractive option, it increases planning time considerably and was therefore found to be infeasible.
Manual (not used here)	-	This would be selected if manual optimisation, rather than computer based optimisation, was desired. This was not used here.
Optimisation mode: constrained	-	Using the constrained mode, normal tissues are given priority over target coverage when the optimiser is trying to create the best plan.

DVH: dose-volume histogram

2.2.6 Plan evaluation

The following were recorded:

- CTV: median dose (D50%), D2%, D98% (Dx% represents the dose received by volume x) and volume receiving 100% of the PD (V100%)
- PTV: D50%, D2%, D98% and D95%
- Organ at risk mean doses and D2%
- Volume of rectum and bladder receiving at least 95% (V95%), 80% (V80%), 50% (V50%) and 20% (V20%) of the PD to reflect very high, high, intermediate and low doses respectively
- CI: volume of 95% isodose/PTV volume [195]- reflects high dose spill
- conformation number (CN): (Volume of PTV receiving 95% isodose/PTV volume) x (Volume of PTV receiving 95% isodose/volume of 95% isodose) [195]- reflects coverage and high dose spill
- homogeneity index (HI): (D2%-D98%)/D50% [196]
- R50 (to assess intermediate dose spill): volume of 50% isodose/PTV volume
- maximum dose 2cm from PTV (Dmax2cm; also to assess intermediate dose spill)
- MU per fraction
- estimated delivery time (EDT)

2.2.7 Verification

Three 210° partial arc plans were delivered using a Synergy® linear accelerator (Elekta AB, Sweden) and verified using the Delta4 phantom (ScandiDos AB, Sweden). Plans were evaluated at the 3%/3mm level (i.e. all doses analysed with respect to lying within 3% of the expected dose and within 3mm of the expected position) and at the 2%/2mm level. A gamma index of <1 has to be achieved in >95% of points for a plan to pass verification (Departmental standard is to verify plans at 3mm and 3%). One of these plans was also verified using high dose film at the 3%/3mm level. Delivery was also timed during verification.

2.2.8 Statistics

The Wilcoxon signed-rank test was used to compare parameters as data was not presumed to be normally distributed. Median values and ranges are therefore presented throughout. Statistical Package for the Social Sciences (SPSS) version 19.0 (IBM Corporation, Armonk, New York, USA) was used for calculations. Tests were two-tailed.

Multiple statistical comparisons are made but a full Bonferroni correction would be over-conservative as several tests are not independent. In part I of the study, the small sample size limits the degree of statistical significance achievable. As a pragmatic approach, $p \leq 0.02$ was considered statistically significant for part I of the study (this corresponded to all seven alternate arc plans displaying a change in the same direction from the corresponding 360° plans in order for statistical significance to be reached) and $p \leq 0.005$ was considered significant in parts II and III.

2.3 Results

2.3.1 Part I: arc arrangements

Adequate CTV (prostate only) and PTV coverage was achieved and organ at risk constraints were met using all arc arrangements (Figure 2-3; Table 2.5). Plans were highly conformal with CI<1.2 and CN≥0.81, and doses were homogeneous (HI: 0.08-0.12; Table 2.6; D98%≥95% and D2%≤107% in all cases). Compared to 1FA, there were no significant differences in CTV and PTV coverage with different arc arrangements, with the exception of 2FA, where there was a significant reduction in CTV V100% (1FA vs. 2FA: 97.9% vs. 95.2%, $p=0.016$; median values presented) and a statistically significant, but clinically insignificant, reduction in PTV D50% (43.5Gy vs. 43.4Gy, $p=0.016$, Table 2.5).

Figure 2-3 Example of prostate plans from one dataset using a) one 360° arc, b) one 210° partial arc, c) two full arcs and d) two partial arcs (210° and 180°), all using 6mm CTV-PTV margins

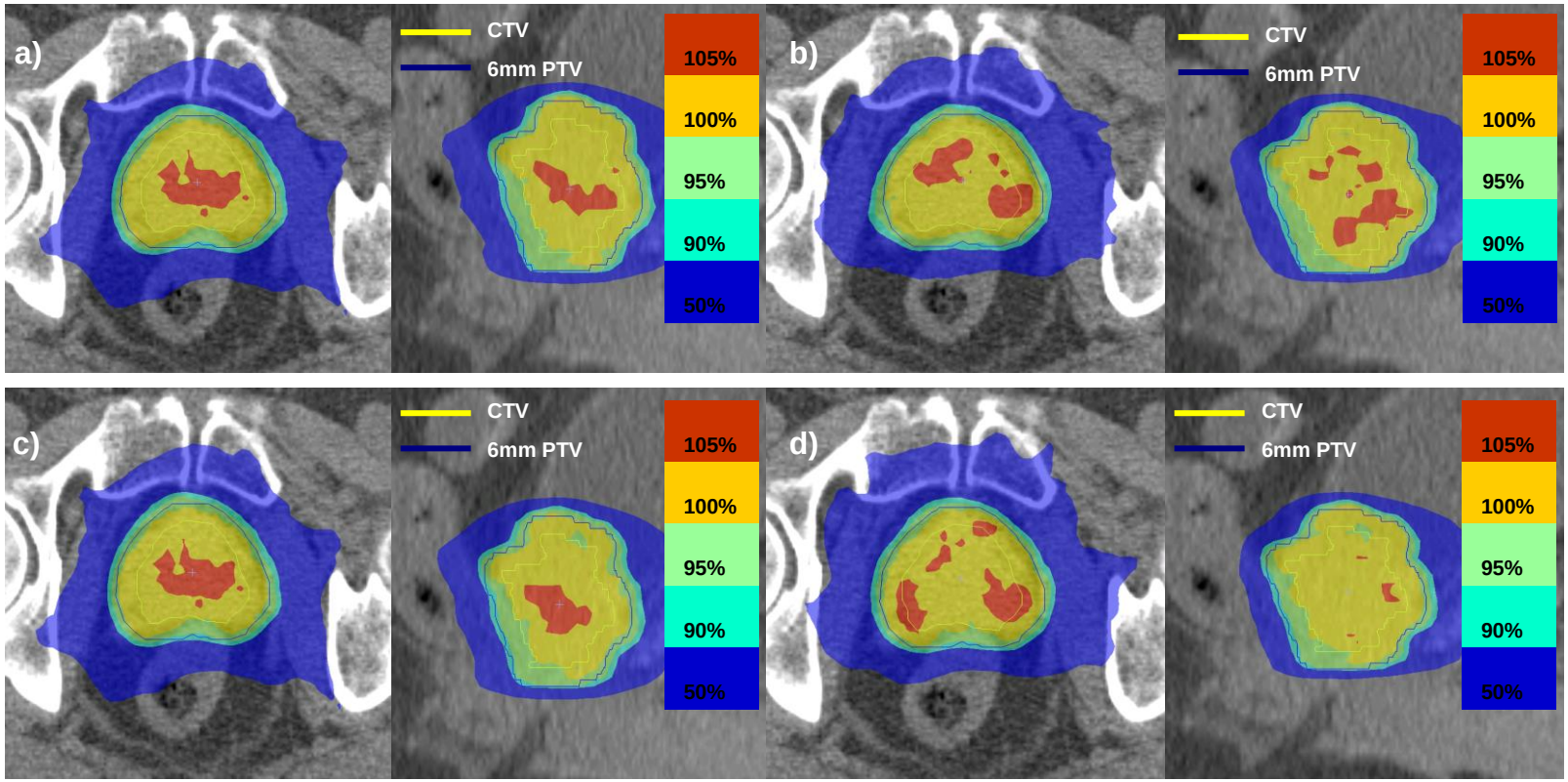


Table 2.5 Coverage using four different arc arrangements

Median (and range) shown. All alternative arc arrangements are compared to one full arc. Non-significant *p* values not shown. $p \leq 0.02$ considered statistically significant. *: $p=0.016$

	Beam arrangement			
	One full arc	One partial arc	Two full arcs	Two partial arcs
CTV coverage				
D50% (Gy)	44.0 (43.8-44.6)	44.3 (43.8-44.5)	43.9 (43.8-44.5)	44.1 (43.8-44.6)
D2% (Gy)	45.9 (45.5-46.1)	45.8 (45.2-46.1)	45.7 (45.0-46.3)	45.8 (45.5-46.2)
D98% (Gy)	42.7 (42.3-43.5)	42.7 (42.4-43.3)	42.3 (42.1-43.0)	42.6 (42.3-43.5)
V100% (%)	97.9 (94.3-100)	98.7 (94.1-99.9)	**95.2 (91.3-99.4)***	97.4 (93.4-99.9)
PTV coverage				
D50% (Gy)	43.5 (43.4-44.0)	43.7 (43.6-43.9)	**43.4 (43.3-43.9)***	43.7 (43.3-44.1)
D2% (Gy)	45.6 (45.2-45.9)	45.5 (45.1-45.7)	45.3 (44.7-45.8)	45.6 (45.3-45.7)
D98% (Gy)	40.8 (40.6-41.8)	40.8 (40.6-41.6)	40.8 (40.8-41.6)	40.9 (40.6-41.5)
D95% (%)	41.6 (41.4-42.3)	41.5 (41.2-42.1)	41.5 (41.4-42.2)	41.6 (41.4-42.2)

Table 2.6 Conformity and plan delivery using four different arc arrangements

Median (and range) shown. All alternative arc arrangements are compared to one full arc. Non-significant *p* values not shown. $p \leq 0.02$ considered statistically significant. *: $p=0.016$

	Beam arrangement			
	One full arc	One partial arc	Two full arcs	Two partial arcs
Conformity				
Conformity index**	1.16 (1.12-1.18)	1.14 (1.10-1.18)	1.16 (1.14-1.19)	1.15 (1.09-1.19)
Conformation number†	0.85 (0.83-0.87)	0.85 (0.84-0.88)	0.84 (0.81-0.85)	0.85 (0.82-0.88)
Homogeneity index‡	0.11 (0.09-0.11)	0.11 (0.09-0.12)	0.10 (0.08-0.11)	0.11 (0.09-0.12)
Intermediate dose spill				
Maximum dose at 2cm (Gy)	25.3 (23.2-25.9)	25.7 (23.9-26.7)	25.1 (23.2-27.5)	24.9 (24.2-25.2)
R50§	3.7 (3.5-3.9)	3.8 (3.6-4.0)	**3.9 (3.8-4.0)***	3.8 (3.7-4.1)
Plan delivery				
Monitor units per fraction	2049 (1559-2498)	1785 (1423-1922)	2209 (1742-2445)	2010 (1747-2234)
Estimated delivery time (seconds)	173 (143-216)	152 (126-165)	**206 (159-231)***	188 (158-212)

** Conformity index: volume of the 95% isodose/volume of PTV, † Conformation number: (Volume of PTV receiving 95% isodose/ volume of PTV) x (Volume of PTV receiving 95% isodose/volume of 95% isodose), ‡ homogeneity index: (D2%-D98%)/D50%, §R50: volume of 50% isodose/volume of PTV

Compared to 1FA, partial arc arrangements resulted in significant reductions in rectal mean dose (1FA vs. 1PA: 15.1Gy vs. 13.2Gy, p=0.016, 1FA vs. 2PA: 15.1Gy vs. 13.0Gy, p=0.016), V50% and V20%, Table 2.7, Figure 2-4). Compared to 1FA, there were no statistically significant differences in bladder doses when using alternative arc arrangements. Partial arc arrangements resulted in significant increases in FH mean doses and D2% (Table 2.7), although doses remained well within tolerance. A statistically significant, but clinically insignificant, increase in R50 occurred using 2FA (1FA vs. 2FA: 3.7 vs. 3.9, p=0.016). Compared to 1FA, 1PA resulted in reduced EDTs in 6 of 7 cases but this result did not reach the selected level for statistical significance (1FA vs. 1PA: 173s vs. 152s, p=0.047; Table 2.6). Similarly, compared to 1FA, 1PA resulted in reduced MU requirements in 6 of 7 cases but this also did not reach the selected level for statistical significance (1FA vs. 1PA: 2049MU vs. 1785MU, p=0.031; Table 2.6). There was a significant increase in EDT using 2FA (1FA vs. 2FA: 173s vs. 206s, p=0.016).

Given target coverage and conformity equivalence, significant reductions in rectal mean dose, V50% and V20%, together with the MU and EDT advantages for most patients, the 210° partial arc was selected for further investigation.

Table 2.7 Plan statistics for organs at risk using four different arc arrangements

Median (and range) shown. All alternative arc arrangements are compared to one full arc. Non-significant *p* values not shown. $p \leq 0.02$ considered statistically significant. *: $p=0.016$. Continued overleaf.

	Beam arrangement			
	One full arc	One partial arc	Two full arcs	Two partial arcs
Organs at risk				
Rectal Dmean (Gy)	15.1 (13.0-18.1)	**13.2 (11.3-15.4)***	16.5 (12.5-18.9)	**13.0 (11.4-15.1)***
Rectal D2% (Gy)	41.8 (41.6-42.2)	41.9 (41.7-42.2)	41.7 (41.6-42.0)	41.8 (41.7-41.9)
Rectal V95% (%)	4.0 (3.3-4.8)	4.2 (3.8-5.1)	3.9 (3.6-5.0)	3.8 (3.4-5.2)
Rectal V80% (%)	10.5 (8.0-11.6)	10.2 (8.0-11.7)	10.9 (8.5-11.9)	**10.0 (7.6-11.4)***
Rectal V50% (%)	26.5 (21.7-41.7)	**20.0 (16.1-24.9)***	39.2 (19.7-48.2)	**19.0 (15.1-23.6)***
Rectal V20% (%)	64.1 (53.3-76.1)	**56.8 (45.3-70.6)***	66.7 (54.3-76.5)	**60.3 (50.0-69.6)***
Bladder Dmean (Gy)	7.5 (4.4-8.4)	7.5 (0.3-8.1)	7.6 (4.5-8.7)	7.3 (4.6-8.5)
Bladder D2% (Gy)	42.6 (40.9-43.4)	41.9 (1.2-43.6)	42.6 (40.3-43.4)	42.7 (40.9-43.6)
Bladder V95% (%)	2.9 (2.1-5.2)	2.8 (1.8-5.0)	2.9 (1.9-5.1)	2.9 (2.1-4.9)
Bladder V80% (%)	4.7 (3.4-8.0)	4.4 (3.3-7.8)	4.6 (3.3-7.9)	4.4 (3.6-7.7)
Bladder V50% (%)	11.4 (7.1-14.3)	12.1 (7.6-13.9)	11.7 (7.2-15.1)	12.2 (7.8-15.3)
Bladder V20% (%)	22.7 (14.0-34.5)	22.7 (14.4-33.4)	23.1(14.8-34.0)	22.1 (14.4-33.1)

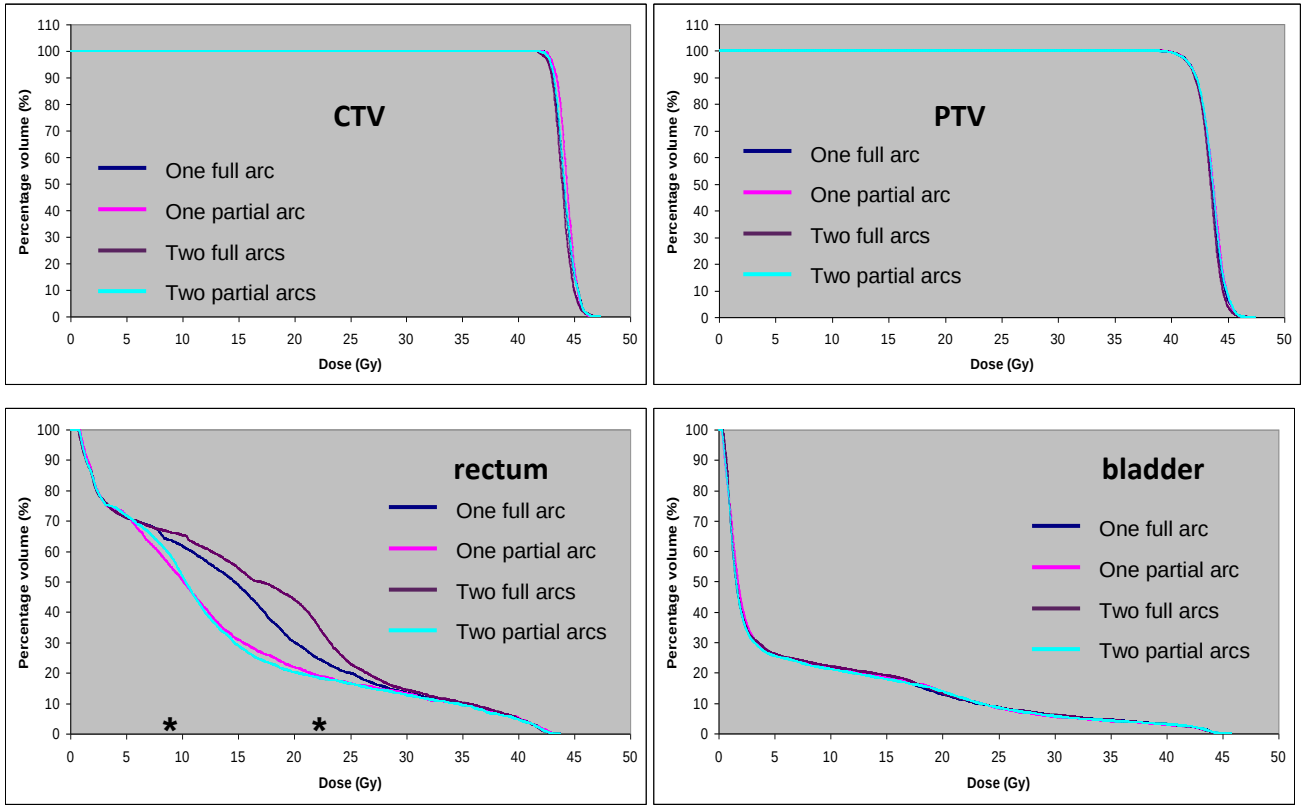
Table 2.7 continued. Plan statistics for organs at risk using four different arc arrangements

Median (and range) shown. All alternative arc arrangements are compared to one full arc. Non-significant *p* values not shown. $p \leq 0.02$ considered statistically significant. *: $p=0.016$

	Beam arrangement			
	One full arc	One partial arc	Two full arcs	Two partial arcs
Organs at risk				
Left femoral head Dmean (Gy)	7.8 (0.7-12.3)	8.9 (0.8-13.1)	6.9 (0.8-11.1)	**10.0 (0.8-14.4)***
Left femoral head D2% (Gy)	14.7 (2.6-19.9)	15.9 (2.8-18.2)	12.7 (3.0-16.9)	19.3 (2.4-20.5)
Right femoral head Dmean (Gy)	8.7 (1.4-11.3)	**12.2 (2.0-15.9)***	8.1 (1.5-11.5)	**12.2 (1.9-15.5)***
Right femoral head D2% (Gy)	15.7 (7.1-18.3)	**19.5 (9.9-20.6)***	13.5 (7.4-15.9)	**19.4 (12.3-20.3)***
Bowel Dmean (Gy)	0.5 (0.3-1.2)	0.5 (0.3-1.1)	0.5 (0.3-1.2)	0.5 (0.3-1.1)
Bowel D2% (Gy)	1.1 (0.6-3.8)	1.2 (0.7-3.7)	1.2 (0.7-3.9)	1.2 (0.7-3.7)
Penile bulb Dmean (Gy)	9.1 (1.3-37.3)	8.8 (1.4-38.7)	9.9 (1.3-38.8)	9.0 (1.2-37.5)
Penile bulb D2% (Gy)	19.7 (1.7-43.5)	19.6 (1.9-43.4)	22.1 (1.7-43.6)	20.0 (1.6-42.9)

Figure 2-4 DVH comparisons for four beam arrangements (median values plotted)

* Rectal V20% and V50% for one partial arc and two partial arcs significantly less than one full arc (p<0.02)



2.3.2 Part II: CTV-PTV margins

Fifteen datasets were planned using 1PA and 6mm CTV-PTV margins. Adequate CTV and PTV coverage was achieved and organ at risk constraints were met, and were generally well within desired limits (Figure 2-5). In order to achieve adequate coverage and/or respect organ at risk constraints it was necessary to accept D2%>107% and/or D98%<95% in five cases (33%).

Datasets were re-planned using 1PA and 8mm CTV-PTV margins (Figure 2-5 and Figure 2-6). In 12 cases (80%) it was possible to achieve CTV and PTV coverage and meet organ at risk constraints. In three cases it was necessary to relax the uppermost bladder constraint (V41.4Gy<5%) to up to 8.7% to achieve adequate coverage. Other bladder constraints were achieved. It was necessary to accept D2%>107% and/or D98%<95% in 12 cases (80%), resulting in a small reduction in homogeneity using 8mm margins (6mm vs. 8mm HI: 0.11 vs. 0.13, p<0.001). Of the three patients where the uppermost bladder constraint had to be relaxed, two had median lobe hypertrophy protruding into the bladder and relatively small bladder volumes (208cm^3 and 249cm^3). The third patient had a very large median lobe and the largest volume prostate in the series (60.0cm^3).

Compared to plans using 6mm CTV-PTV margins, there were no significant differences in CTV and PTV median doses although 8mm margins resulted in a small but significant reductions in PTV D95% (6mm vs. 8mm: 41.4Gy vs. 40.8Gy, p<0.001, Figure 2-7, Table 2.8) and PTV D98% (6mm vs. 8mm: 40.6Gy vs. 40.0Gy, p=0.001, Table 2.8), and significant increases in rectal and bladder mean doses and V95%, V80%, V50% and V20% (Figure 2-5, Table 2.9). There were statistically significant, but clinically insignificant, increases in mean bowel dose using 8mm margins (Table 2.9; i.e. despite a statistically significant difference, the magnitude of difference between mean bowel doses was very small, and the absolute mean bowel doses for both 6mm and 8mm margins were also very low). There was also a significant increase in right mean FH dose, but this remained well within tolerance, as well as an increase in PB mean dose and D2% (Table 2.9). There was no significant difference in CI, which considers high dose spill (but not PTV coverage), nor CN, which reflects PTV coverage as well as high dose spill (Table 2.10).

Figure 2-5 DVH comparisons for 6mm and 8mm CTV to PTV margins (median values plotted)

† PTV D95% significantly less using 8mm margins compared to 6mm margins (p<0.005)

*rectal/ bladder V20%, V50%, V80% and V95% significantly less using 6mm vs. 8mm margins (p<0.005)

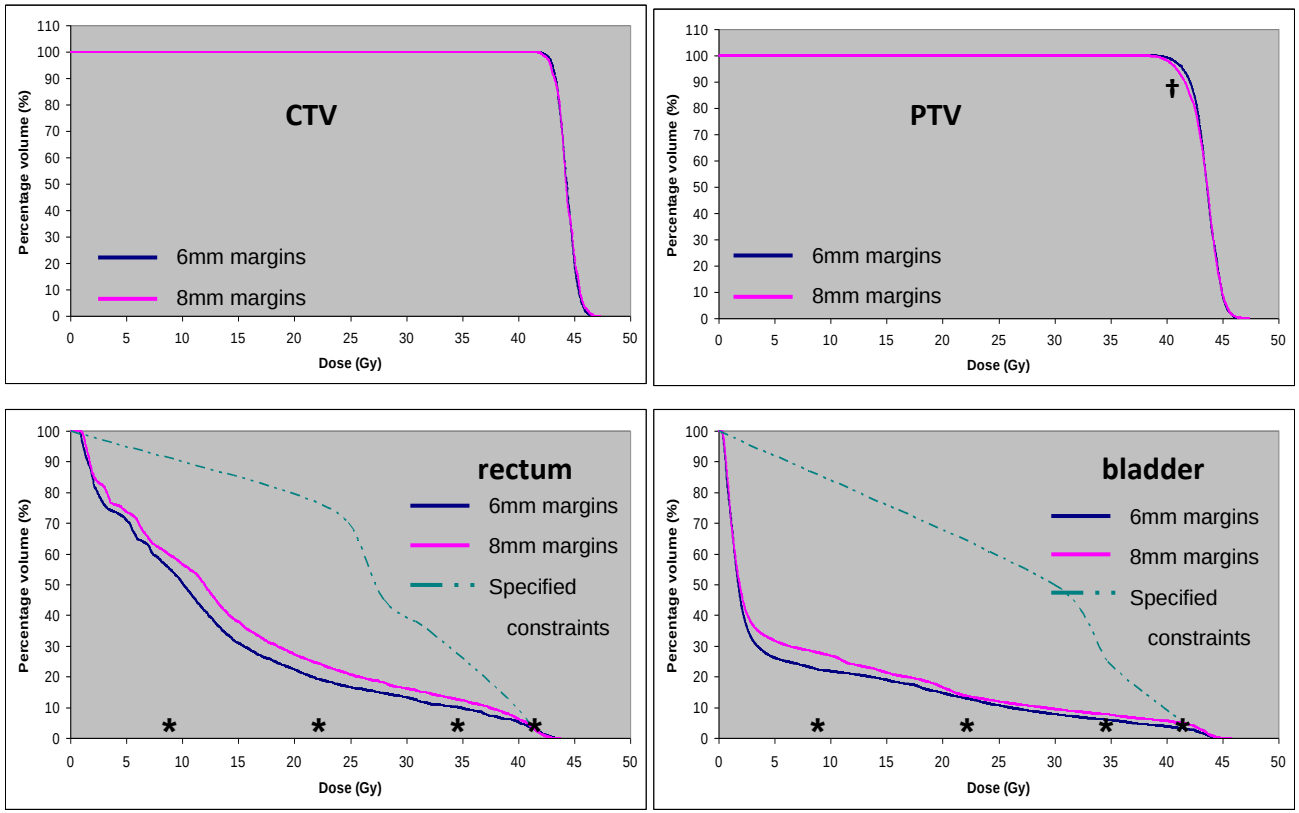


Figure 2-6 Example of prostate plans from one dataset using a) one 210° partial arc with 6mm CTV-PTV margins, b) one 210° partial arc with 8mm CTV-PTV margins and c) one 210° partial arc including the proximal seminal vesicles within the CTV with 6mm CTV-PTV margins

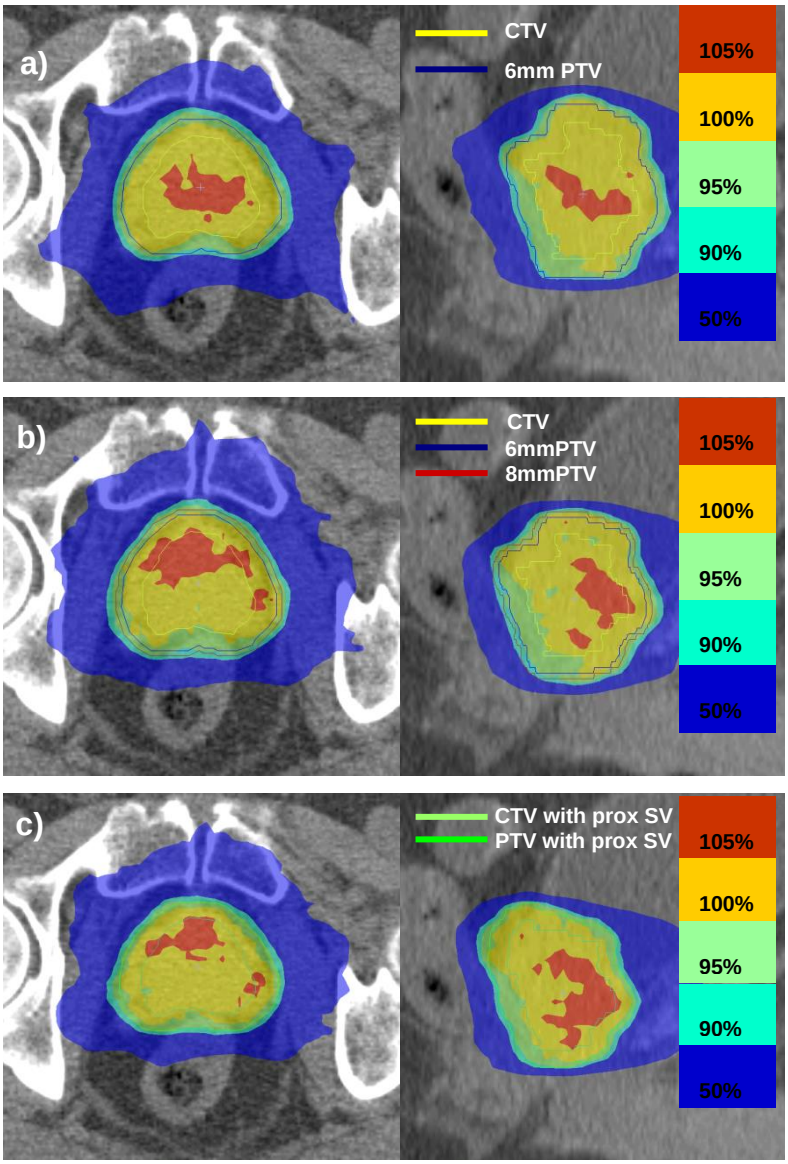


Table 2.8 Coverage comparing PTVs: Prostate + 6mm (P+6mm), Prostate + 8mm (P+8mm) and Prostate + proximal seminal vesicles + 6mm ((P+SV)+6mm)

Median (and range) shown. Non-significant *p* values not shown. P+8mm and (P+SV)+6mm compared to P+6mm. $p \leq 0.005$ considered statistically significant. *: $p<0.001$, ¥: $p=0.001$

	PTV		
	P+6mm	P+8mm	(P+SV)+6mm
CTV coverage			
D50% (Gy)	44.3 (43.8-45.0)	44.2 (43.8-45.5)	44.4 (43.6-45.9)
D2% (Gy)	45.9 (45.2-46.7)	46.2 (45.4-48.0)	**46.4 (46.0-48.2)¥**
D98% (Gy)	42.7 (41.9-43.6)	42.4 (41.7-43.5)	42.6 (42.0-43.3)
V100% (%)	97.8 (88.5-100)	96.7 (88.8-99.9)	97.4 (85.8-99.9)
PTV coverage			
D50% (Gy)	43.6 (43.2-44.1)	43.6 (43.3-44.8)	43.5 (43.0-44.7)
D2% (Gy)	45.6 (45.1-46.4)	45.7 (45.1-47.7)	45.7 (44.7-48.1)
D98% (Gy)	40.6 (39.5-41.6)	**40.0 (39.4-41.3)¥**	**40.2 (39.6-41.1)***
D95% (Gy)	41.4 (40.6-42.1)	**40.8 (40.6-41.9)***	**40.9 (40.6-41.7)¥**

Table 2.9 Plan statistics for organs at risk for PTVs: Prostate + 6mm (P+6mm), Prostate + 8mm (P+8mm) and Prostate + proximal seminal vesicles + 6mm ((P+SV)+6mm)

Median (and range) shown. Non-significant *p* values not shown. P+8mm and (P+SV)+6mm compared to P+6mm. p≤0.005 considered statistically significant. *: *p*<0.001, ¥: *p*=0.001, #: *p*=0.004, §: *p*=0.005. Continued overleaf.

	PTV		
	P+6mm	P+8mm	(P+SV)+6mm
Organs at risk			
Rectal Dmean (Gy)	13.2 (10.2-15.5)	**15.0 (11.3-17.6)***	**14.5 (11.7-18.1)***
Rectal D2% (Gy)	41.8 (41.6-42.5)	41.7 (41.6-42.0)	41.9 (41.6-42.2)
Rectal V95% (%)	4.3 (3.4-5.1)	**5.2 (3.7-7.1)***	4.9 (3.5-6.5)
Rectal V80% (%)	10.2 (6.7-14.0)	**12.8 (7.0-19.0)***	**12.7 (7.2-17.4)***
Rectal V50% (%)	20.1 (14.5-30.5)	**25.2 (16.2-32.9)***	**25.8 (16.3-36.8)***
Rectal V20% (%)	56.2 (44.4-70.6)	**60.5 (48.0-71.0)***	**66.1 (49.3-73.8)***
Bladder Dmean (Gy)	7.5 (0.3-11.0)	**7.9 (5.2-13.5)***	**8.0 (5.0-14.2)¥**
Bladder D2% (Gy)	42.8 (1.2-49.9)	43.4 (42.5-45.4)	43.2 (40.5-46.0)
Bladder V95% (%)	3.5 (1.8-5.7)	**5.2 (3.1-9.4)***	4.4 (2.0-7.1)
Bladder V80% (%)	6.1 (3.3-9.3)	**7.8 (4.60-13.6)***	**7.3 (4.0-10.9)§**
Bladder V50% (%)	13.4 (7.6-19.5)	**14.4 (9.6-27.0)***	**14.4 (9.3-22.8)¥**
Bladder V20% (%)	22.7 (14.4-42.9)	**28.1 (15.9-49.1)***	**26.2 (15.0-59.6)#**

Table 2.9 cont. Plan statistics for organs at risk for PTVs: Prostate + 6mm (P+6mm), Prostate + 8mm (P+8mm) and Prostate + proximal seminal vesicles + 6mm ((P+SV)+6mm)

Median (and range) shown. Non-significant *p* values not shown. P+8mm and (P+SV)+6mm compared to P+6mm. $p \leq 0.005$ considered statistically significant. *: $p<0.001$, ¥: $p=0.001$, #: $p=0.004$, §: $p=0.005$

	PTV		
	P+6mm	P+8mm	(P+SV)+6mm
Organs at risk			
Left femoral head Dmean (Gy)	9.3 (0.8-13.1)	11.3 (0.8-14.7)	11.4 (0.7-13.6)
Left femoral head D2% (Gy)	17.0 (2.8-19.8)	17.8 (2.6-23.0)	**18.6 (2.4-21.3)***
Right femoral head Dmean (Gy)	11.0 (2.0-15.9)	**12.8 (2.3-16.7)***	13.4 (1.6-16.6)
Right femoral head D2% (Gy)	19.9 (9.9-20.8)	20.2 (11.4-21.1)	19.9 (9.6-21.0)
Bowel Dmean (Gy)	0.6 (0.1-2.0)	**0.8 (0.3-2.2)***	**0.8 (0.3-4.2)***
Bowel D2% (Gy)	1.9 (0.7-12.5)	1.9 (0.8-10.7)	**2.6 (0.7-17.2)***
Penile bulb Dmean (Gy)	4.5 (1.4-38.6)	**5.5 (1.6-41.5)***	4.3 (1.3-37.3)
Penile bulb D2% (Gy)	8.0 (1.8-43.4)	**14.5 (2.0-44.8)***	11.0 (1.6-42.5)

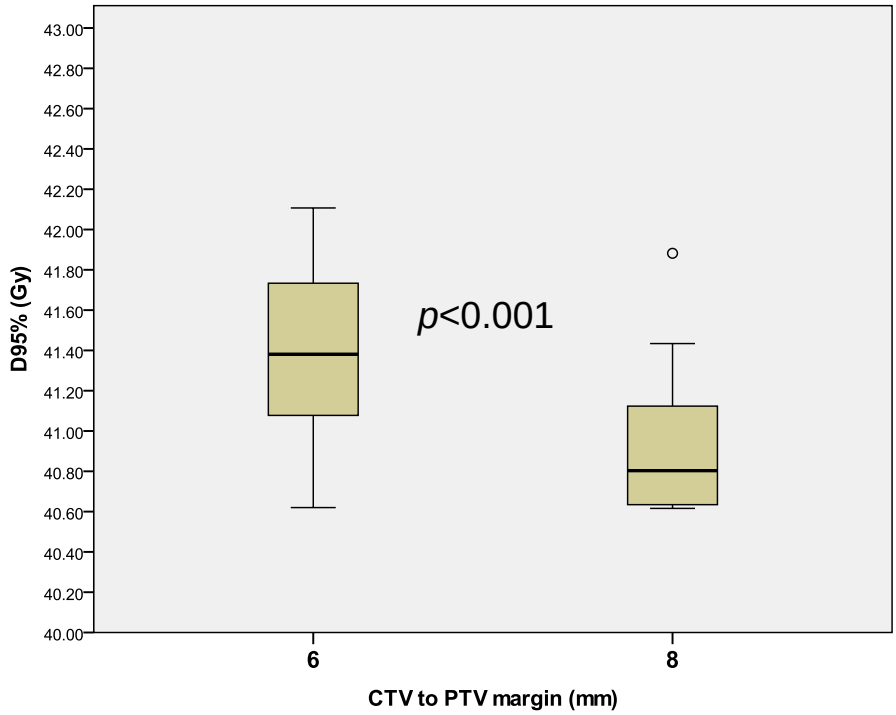
Table 2.10 Conformity and delivery data for PTVs: Prostate + 6mm (P+6mm), Prostate + 8mm (P+8mm) and Prostate + proximal seminal vesicles + 6mm ((P+SV)+6mm)

Median (and range) shown. Non-significant *p* values not shown. P+8mm and (P+SV)+6mm compared to P+6mm. $p \leq 0.005$ considered statistically significant. *: $p<0.001$, $: $p=0.002$

	PTV		
	P+6mm	P+8mm	(P+SV)+6mm
Conformity			
Conformity index**	1.13 (1.00-1.18)	1.05 (1.02-1.19)	1.07 (1.00-1.17)
Conformation number†	0.86 (0.84-0.91)	0.88 (0.82-0.90)	0.87 (0.84-0.91)
Homogeneity index‡	0.11 (0.09-0.15)	**0.13 (0.10-0.18)***	**0.13 (0.10-0.19)***
Intermediate dose spill			
Maximum dose at 2cm (Gy)	25.7 (23.9-27.6)	25.8 (24.8-29.3)	26.0 (24.4-31.2)
R50^	3.7 (3.3-4.0)	3.5 (3.3-4.1)	3.6 (3.5-4.1)
Plan delivery			
Monitor units per fraction	1814 (1423-1989)	1795 (1168-2201)	**1910 (1653-2496)$**
Estimated delivery time (seconds)	160 (126-174)	157 (131-190)	161 (117-216)

** Conformity index: volume of the 95% isodose/volume of PTV, † Conformation number: (Volume of PTV receiving 95% isodose/ volume of PTV) x (Volume of PTV receiving 95% isodose/volume of 95% isodose), ‡ homogeneity index: (D2%-D98%)/D50%, ^R50: volume of 50% isodose/volume of PTV

Figure 2-7 Dose received by 95% of the PTV (D95%) using 6mm and 8mm CTV-PTV margins

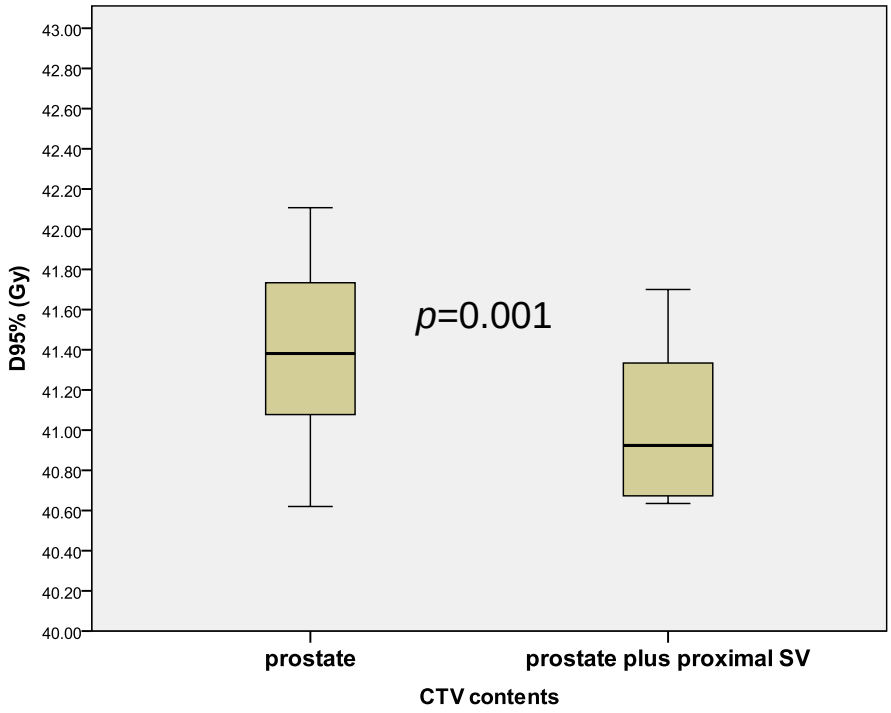


2.3.3 Part III: inclusion of proxSV

Datasets were re-planned using 1PA and 6mm CTV-PTV margins but including the proxSV within the CTV (Figure 2-6). In 13 cases CTV and PTV coverage was achieved and all organ at risk constraints were met. In two cases (13%; the same two cases with small bladder volumes and median lobe hypertrophy requiring relaxation of the uppermost bladder constraints using 8mm CTV-PTV margins) it was necessary to relax the uppermost bladder and rectal constraints up to 6.6% and 3.9% respectively to achieve coverage. Other constraints were met. It was possible to re-plan both to achieve coverage and meet all constraints by defining two PTVs: prostate plus 6mm, prescribed 42.7Gy, and prostate and proximal 1cm of SV plus 6mm, prescribed 32.4Gy (76%; $EQD2_{1.5}$=56.7Gy, a dose similar to that received by the base of the SV (proximal 2cm) in the CHHiP trial: $EQD2_{1.5}$=52Gy [192]).

Adequate CTV and PTV coverage was achieved although, compared to treating the prostate alone, there were small but significant reductions in PTV D95% (prostate alone vs. prostate+SV: 41.4Gy vs. 40.9Gy, p=0.001, Figure 2-8) and PTV D98% (prostate alone vs. prostate+SV: 40.6Gy vs. 40.2Gy, p<0.001) and a small increase in CTV D2% (prostate alone vs. prostate+SV: 45.9Gy vs. 46.4Gy, p=0.001; Table 2.8). The bladder and rectum received significantly higher mean doses and V80%, V50% and V20% (Figure 2-9, Table 2.9). There were significant increases in left FH D2% and bowel mean dose and D2%, although these remained well within tolerance (Table 2.9). Compared to treating the prostate alone, plans were less homogeneous (prostate alone vs. prostate+SV HI: 0.11 vs. 0.13, p<0.001; in 11 cases (73%) it was necessary to accept D98%<95% and/or D2%>107%) and required increased MU (prostate alone vs. prostate+SV: 1814MU vs. 1910MU, p=0.002; Table 2.10).

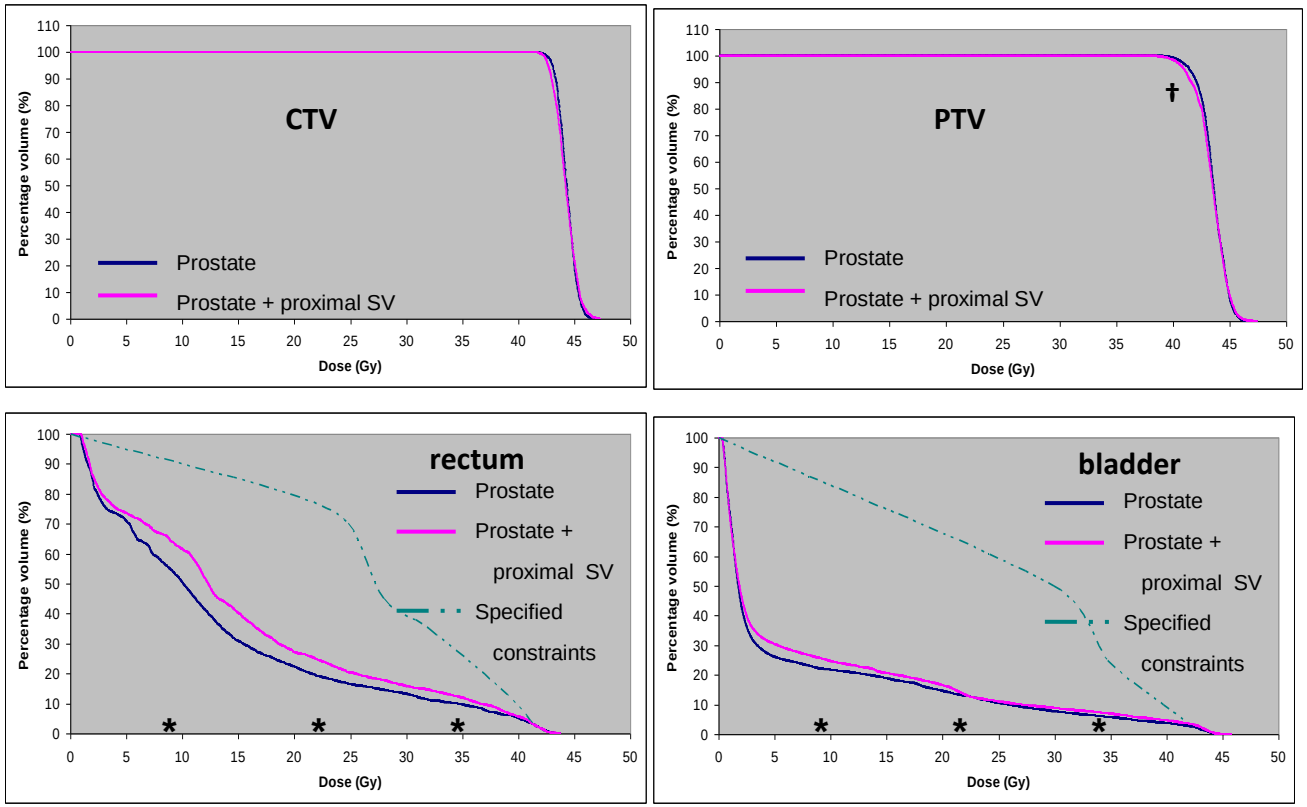
Figure 2-8. Dose received by 95% of the PTV (D95%) when treating prostate alone and treating the prostate plus proximal seminal vesicles



SV: Seminal vesicles

Figure 2-9 DVH comparisons for CTV containing prostate alone and CTV containing prostate + proximal seminal vesicles (median values plotted)

† PTV D95% significantly less with prostate + proximal seminal vesicles in CTV compared to prostate alone ($p \leq 0.005$)
*rectal/ bladder V20%, V50% and V80% significantly less with prostate alone in CTV compared to prostate plus proximal seminal vesicles ($p \leq 0.005$), SV: seminal vesicles



2.3.4 Verification

The pass rates for the three plans verified using the Delta4 phantom and delivery times are shown in Table 2.11. Thus all plans verified well. An example of the Delta4 output is shown in Figure 2-10. The one plan which was also verified using high dose film (Figure 2-11), also passed with 95.75% of points having a gamma index of <1 at 3% and 3mm.

Table 2.11 Verification outcomes

Plan	Pass rate (Gamma index <1) at 3%/3mm	Pass rate (Gamma index <1) at 2%/2mm	Delivery time (seconds)
1	99.8%	97.3%	203
2	100.0%	99.6%	213
3	99.8%	98.1%	192

Figure 2-10 Delta4 verification for one of the three plans

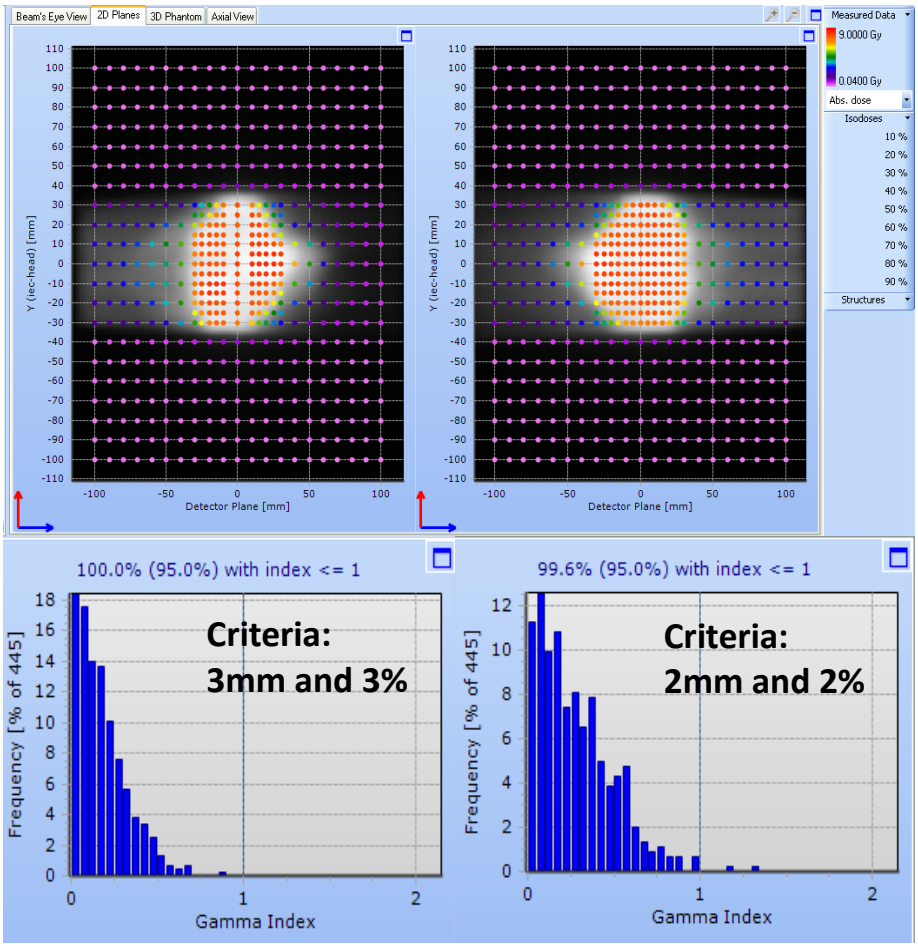
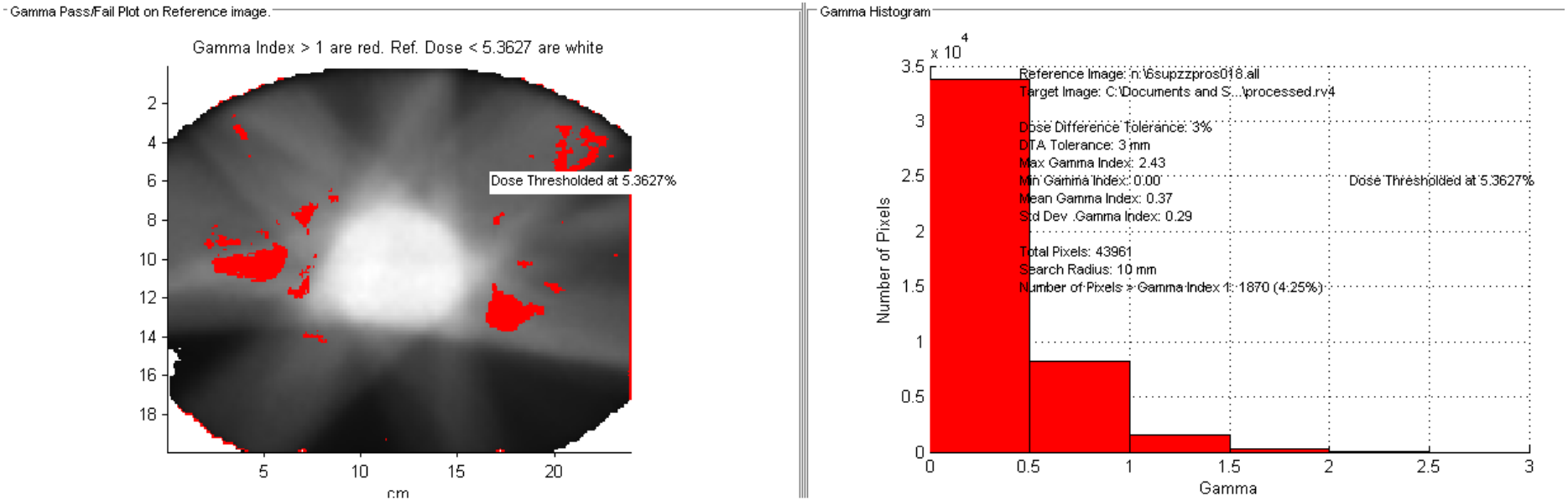


Figure 2-11 High dose film verification



2.4 Discussion

Much has been published regarding SABR in PCa (Chapter 1) and the use of VMAT in PCa [25-30,33]. There is, however, very little in the literature regarding the optimal planning of prostate SABR using VMAT. It is important and relevant to develop linear accelerator-based solutions for prostate SABR as this delivery method is more widely available than alternatives such as Cyberknife™ (Accuray®, USA). In this current study, prostate SABR planned with VMAT was found to be optimal using 1PA. Using 6mm CTV-PTV margins, compatible with daily fiducial based IGRT, was consistently feasible in terms of target objectives and organ at risk constraints. All arc arrangements investigated resulted in highly conformal plans but a single 210° partial arc was preferred: conformity was maintained while rectal mean dose, V50% and V20% were reduced, and most patients also benefitted in terms of EDT and MU requirements. FH doses increased but remained well within tolerance.

It was possible to plan treatment using 8mm CTV-PTV margins but it was necessary to relax the uppermost bladder constraint in three cases (20%) with smaller bladder volumes and/or median lobe hyperplasia. Similarly, it was possible to treat the prostate and proximal SV but it was necessary to relax the uppermost bladder and rectal constrains in two cases (13%). When using 8mm CTV-PTV margins, or including the proximal SV within the target, although PTV coverage was adequate, there was a significant reduction in V95% and a significant increase in rectal and bladder mean doses and in volumes receiving very high, high, intermediate and low doses. This is unsurprising as the PTV overlaps with the rectum and bladder, thus CTV volume and CTV-PTV margin width influence the extent of overlap, limiting the extent of PTV coverage possible while respecting organs at risk.

The optimal organ at risk constraints for prostate SABR remain unknown [96]. In this study constraints from the HYPO-RT-PC trial were adopted and additional constraints were added which were biologically equivalent to those used in the CHHiP trial which reported low 2-year toxicity [52,133,191,192].

In the Hypo-RT-PC trial, which employs the same SABR dose, no constraint is specified for very high rectal doses and there are no bladder constraints [133]. Several

of the Cyberknife™ prostate SABR trials stipulate that rectal and bladder V100% should not exceed 5% and 10% respectively [61,76,90,91]. This study specified a 3% restriction on rectal V97% and a 5% restriction on bladder V97%. This approach, therefore, may be considered conservative. With a new technique, however, caution is appropriate. Furthermore, when uppermost constraints were met, or minimally exceeded, in this current study, all lower constraints were more than adequately achieved. This may translate into low late toxicity rates when these constraints are employed clinically. Caution must be exercised, however, when comparing constraints from different studies as the length of contoured rectum may differ, and this should be specified to aid meaningful comparisons. Once a consensus is reached regarding constraints for prostate SABR, these must be accompanied by specification of the length of rectum over which they apply. Absolute volume-based constraints (i.e. dose to $1cm^3$) would be an alternative strategy which would remove some of the variation resulting from differences in rectal contouring, although at present there is insufficient data on which to define such parameters.

As discussed in Chapter 1, the current evidence for SABR as primary treatment for localised PCa is mainly in the form of small prospective studies, 15 using Cyberknife™ and 8 using linear accelerators [57-61,68-85]. There is variation in dose-fractionation schedules, organ at risk constraints, use of androgen deprivation, CTV-PTV margins, IGRT techniques and inclusion of SV within the CTV (often the SV are not treated, even in non-low risk patients). Overall, toxicity rates, quality of life outcomes and PSA control appear encouraging.

At the time this study was performed, delivering prostate SABR using VMAT had not been widely reported. Two groups had reported production and delivery of SABR VMAT plans [182,183]. Agazaryan et al, using RapidArc® VMAT (Varian, USA) in 10 patients, delivered 40Gy in 5 fractions and found that two full arcs resulted in improved homogeneity and conformity compared to one. It is currently uncertain whether homogenous or heterogeneous dose distributions are preferable [57]. In contrast to the RapidArc® study, this current study found no significant improvement in homogeneity or conformity using two arcs which may relate to differences in the planning algorithms and linear accelerator delivery associated with each technique.

Miften et al delivered 50Gy in 5 fractions to six patients mainly using 1FA [182]. CI ranged from 1.09 to 1.21, CN from 0.75 to 0.82 and treatment times from 8 to 13

minutes. This current study demonstrated similar CI, slightly improved CN, and measured delivery times were shorter than those measured by Miften et al.

Robust IGRT is required for SABR. Several SABR trials employ intra-fraction motion tracking and correction, allowing small CTV-PTV margins (3-5mm) [58,83,197]. For this study, 6mm margins were evaluated which are sufficient to account for residual set-up inaccuracy and uncorrected intra-fraction motion when using fiducial markers for daily online IGRT [186-188], particularly in the setting of relatively fast treatment delivery [164,198,199]. Larger CTV-PTV margins carry the risk of increased toxicity but with 6mm margins, planning was successful in terms of target coverage and organ at risk constraints.

CBCT soft tissue matching (without fiducials) is an alternative IGRT technique. Given uncertainties and inter-observer variability, CTV-PTV margins of about 8mm are required [141]. When planning with 8mm margins, although PTV coverage was adequate, there was a small but significant reduction in D95%, and significant increases in rectal and bladder mean doses and in volumes receiving very high, high, intermediate and low doses. Furthermore, in three patients (20%) it was necessary to relax the uppermost bladder constraint to achieve coverage: two had small bladder volumes and median lobe hyperplasia and one had the largest volume prostate in the series and a very large median lobe (all resulting in a larger proportion of bladder within or close to the PTV). The clinical consequences of such bladder overdoses are unknown [40]. Neo-adjuvant androgen deprivation could reduce prostate and median lobe volume, potentially facilitating planning in these cases. Since 6mm margins were consistently feasible in terms of organ at risk constraints, then implanted fiducial markers, and the accompanying smaller CTV-PTV margins, should be used in preference to CBCT without fiducials.

When including the proxSV in the CTV, and using 6mm CTV-PTV margins (a potential solution for patients with early intermediate risk disease who are at increased risk of SV invasion) although PTV coverage was adequate, there was a small but significant reduction in D95%. In addition, significant increases in rectal and bladder mean doses and in volumes of rectum and bladder receiving high, intermediate and low doses were observed when the proxSV were included in the CTV. Furthermore, in 13% of cases it was necessary to relax the uppermost bladder and rectal constraints. Ensuring full bladders and using biodegradable spacers to increase prostate to rectal distance could

potentially allow proxSV inclusion, without exceeding constraints [180]. The use of neo-adjuvant hormone deprivation could also facilitate planning. Another strategy is to create two PTVs (prostate and prostate plus proxSV) and prescribe a reduced dose to the PTV containing the prostate plus proxSV. Given that constraints could not be met consistently when including the proximal 1cm of SV, it is unlikely that prescribing the same dose to greater lengths of SV would be feasible, thus excluding higher risk patients from this linear accelerator-based treatment option. Treating the prostate alone, as in many of the existing SABR trials, appears likely to be the safest option.

The HYPO-RT-PC trial which uses the same SABR dose as here, and from where some of the coverage requirements and constraints for this study were adopted, prescribes 42.7Gy as the *mean* dose to the PTV [133]. The trial also specifies that the global maximum dose should be no more than 107%. Prescribing to the mean dose is not common practice in radiotherapy, and so this approach was not adopted here. When delivering IMRT, prescribing to the median PTV dose is recommended by ICRU83 [196], but this report was not written in the SABR era, and the concept of SABR generally promotes dose escalation within the centre of the volume [56,200], in part facilitating the ablative nature of the treatment. Prescribing to the median PTV dose in the context of SABR is therefore somewhat counter-productive and this approach is generally not adopted. For this current study it was therefore decided not to prescribe to the mean or median PTV dose (which is also practically difficult in Monaco®) but to allow cautious dose escalation (to a maximum point dose of 120% of the prescription dose). The median dose received by the PTV was therefore higher than the prescribed dose, and so the overall strategy was more in-keeping with SABR. At the same time, however, this strategy was sufficiently cautious so that the urethra (although not identified here) would be unlikely to receive damaging doses (urethral constraints for 7 fraction regimen: Dmax 58.1Gy, D10%<53.3Gy, D50%<50.7Gy; with maximum permissible point dose of 120%, (51.2Gy), exceeding these constraints is unlikely- see Chapter 3 for further explanation and discussion). When designing this study it was also specified that where possible the D2% should be limited to ≤107%. During planning it was noted that where this was not quickly and easily achieved, marked losses in target coverage could result from trying to lower the D2% by only a small amount. As the target dose was already being controlled through the specification of a maximum dose, the additional benefit from also specifying a desirable limit for the D2%, which could potentially restrict the opportunity for gentle dose escalation and compromise coverage, was ultimately considered questionable. For future planning, therefore, the desirable D2% limit of 107% was not used, and the

target dose was limited by the maximum point dose of 120% and organ at risk constraints.

This approach remains conservative compared to SABR in other tumour sites where not only are higher doses per fraction employed, but very heterogeneous distributions are utilised allowing much greater dose escalation towards the centre of the PTV (e.g. lung cancer SABR in the UK prescribes 54Gy in 3 fractions, 55Gy in 5 fractions and, most conservatively, 60Gy in 8 fractions, and doses can escalate to a maximum of 140%, or 145% as a minor deviation [201]). Indeed, the need to respect the urethra, and so restrict the degree of permissible heterogeneity and accompanying dose escalation within the prostate, has led to the suggestion that the term SABR in the context of prostate ultra-hypofractionation is inappropriate [63]. While this suggestion is perhaps justified when a linear accelerator is used for prescribing SABR and where the urethra has not been defined, the comment is perhaps less justified with the Cyberknife™ is used: where a dose of 38Gy in 4 fractions is prescribed, the dose distribution is designed to reflect that achieved by HDR-brachytherapy, and doses up to 150% and 200% of the prescribed dose have been permitted [57,202]. Here the urethra is defined to avoid marked escalation in this region.

This planning study has limitations: patient numbers were limited, the appropriate dose-volume constraints are unknown and only one treatment planning system and delivery device were evaluated. Despite these limitations, it remains important to develop linear accelerator-based solutions for prostate SABR: as mentioned above, this delivery method is more widely available than alternatives such as Cyberknife™ and is also considerably faster than Cyberknife™, (where delivery times per fraction are in the order of 40 minutes [63]), potentially making linear accelerator-based VMAT solutions a more applicable and practical option for the majority.

Since performing this work, two groups have compared prostate SABR plans using RapidArc® with Cyberknife™. Both groups used full arc RapidArc® plans.

MacDougall et al compared six prostate datasets, each planned using RapidArc® and Cyberknife™ [63]. To ensure a level platform for comparison, the target coverage and organ at risk constraints were the same for both planning modalities, although, appropriately, smaller CTV-PTV margins were used for Cyberknife™ plans since intra-

fraction motion tracking is possible using this system. A relatively homogenous prescription was used so that 99% of the PTV received 35Gy (in 5 fractions) which contained the prostate but no SV, and the maximum dose was limited to 39.4Gy. This resulted in a mean PTV dose of around 37Gy (95% of 37Gy=35.2Gy, 107% of 37Gy=39.6Gy). The group found no dosimetric disadvantage to using RapidArc®, and homogeneity was more consistently achieved and conformity was consistently better using RapidArc®. There was also a clear time delivery benefit using RapidArc® (mean estimated delivery time for Cyberknife™ 39 minutes vs. 3 minutes for RapidArc®) [63].

Lin et al also recently compared RapidArc® and Cyberknife™ plans for prostate SABR, delivering a dose of 37.5Gy in 5 fractions to the prostate and proxSV [203]. Ten datasets were compared using a maximum rectal dose constraint only (Group 1) and 10 datasets were compared using dose-volume rectal constraints (without a maximum rectal dose constraint; Group 2). CTV-PTV margins were 5mm in all directions except for 3mm posteriorly. In both groups, 95% of the PTV received at least 95% of the prescription dose. PTV coverage was superior in the RapidArc® plans in both group 1 and group 2, and maximum CTV and PTV doses were higher in the Cyberknife™ plans. In the RapidArc® plans, conformity was improved, heterogeneity was less and the volume of tissue receiving low dose irradiation (considered as the volume of the 5% isodose) was also lower. Maximum rectal doses were lower using RapidArc®, as was the volume of rectum receiving low doses (V10%, V20%, V30% and V40% in Group 1, and V10% and V20% in Group 2). Although not compared statistically, using dose-volume constraints (Group 2) as opposed to a maximum rectal dose constraint (Group1) resulted in improved target coverage, increased maximum rectal doses and V100% and V90%, but lower volumes of rectal V10% to V80%. The group acknowledged that although these statistically significant differences were observed, in clinical terms, the RapidArc® and Cyberknife™ plans were likely to be indistinguishable. There were, however, significant advantages to RapidArc® in terms of MU efficiency (RapidArc® plans required about one-third of the MU compared to Cyberknife™) and delivery times (median delivery time for Cyberknife™ was 54 minutes per fraction and for RapidArc® was 2.5 to 3.5 minutes of beam on time per arc, with clinical treatment slots of 20 to 25 minutes (including time for IGRT)) [203].

While the conclusions from both studies are justified, it should be acknowledged that the relatively homogenous prescription strategy adopted in the first of the two studies [63], is not how prostate SABR Cyberknife™ treatments would necessarily be

prescribed as these are usually prescribed to a peripheral isodose (between the 60% and 92% isodose [61,71,72,204]), in order to facilitate rapid dose fall-off beyond the PTV and dose escalation in the centre of the PTV [56,200]. In the second of these two RapidArc® vs. Cyberknife™ planning studies [203], the prescription dose was normalised to the 80 to 90% isodose which would allow escalation to up to around 125% of the prescription dose in the centre of the PTV. This strategy, by allowing more dose heterogeneity, is more similar to existing prostate SABR Cyberknife™ prescribing strategies and, although not in-keeping with traditional linear accelerator prescribing (i.e. restricting target doses to between 95% and 107%), is more in-keeping with the concept of SABR, whether delivered by Cyberknife™ or linear accelerator platforms [56,200]. The approach adopted in this current study, by allowing escalation up to a maximum of 120%, is similar to prescribing to the 83% isodose, again in-keeping with the concept of SABR.

2.5 Conclusions

In conclusion, delivering prostate SABR using VMAT offers dose escalation, the theoretical benefits of hypofractionation, the convenience of a few fraction treatment, and the highly conformal plans, MU efficiency and rapid delivery achievable with VMAT. It has been demonstrated that prostate SABR planning using VMAT is consistently feasible when treating the prostate alone using 6mm CTV-PTV margins, compatible with fiducial marker daily online IGRT which is, therefore, the preferred method for SABR IGRT. A 210° arc treating the prostate alone was optimal, allowing highly conformal plans to be delivered quickly and efficiently. Clinical trials are required to evaluate this technique in practice.

2.6 Acknowledgements

Mr John Lilley and Mr Christopher Thompson for advice about planning and for reviewing plans.

Mr Christopher Thompson for assistance with verification.

Dr Mitchell Naisbit for producing the median data used to generate the DVH curves.

Dr Helene Thygesen, Statistician, University of Leeds, for statistical advice.

Chapter 3 : Prostate stereotactic ablative radiotherapy (SABR) using volumetric modulated arc therapy (VMAT) to dominant intra-prostatic lesions (DILs)

3.1 Introduction

External beam radiotherapy in PCa traditionally considers the whole prostate as the CTV, without Gross Tumour Volume (GTV) definition. Modern imaging allows identification of dominant intra-prostatic lesions (DILs) [205]. These are frequently the source of local failure and so can be considered as GTVs [206-208]. Increased radiation doses in PCa result in increased biochemical control [184], but dose escalation to the whole prostate is limited by the tolerance of surrounding normal tissues. An alternative strategy could irradiate the whole prostate but simultaneously dose-escalate DILs [207].

Delivering boosts to DILs has been the subject of a small number of planning studies and early phase trials where boost doses have been delivered using BT or EBRT, either sequentially or as simultaneous integrated boosts (SIB) [207,209-218]. In addition, phase III trials are in progress which compare conventionally fractionated dose-escalated EBRT to the whole prostate, with and without SIB to the DILs (the FLAME (Focal Lesion Ablative Microboost in Prostate Cancer) trial [219] and the HEIGHT (Hypofractionated External Beam Image-Guided Highly Targeted Radiotherapy) trial [220]. The existing literature concerning simultaneous EBRT DIL boosts uses conventional fractionation or at most moderate hypofractionation to treat the prostate and DILs [207,209-219].

As discussed before, SABR uses ultra-hypofractionation to deliver escalated doses in a small number of treatments. Theoretically this is radiobiologically advantageous. Prostate cancer may have a low α/β ratio (~1.5Gy) and so should be sensitive to high doses per fraction [34,35,37,38], while the neighbouring late responding tissues are thought to have higher α/β ratios (~3-6Gy) [35,36,38-41], allowing escalated doses to

be delivered to the prostate, for levels of late toxicity which are theoretically equivalent to those observed following conventional fractionation.

This study investigates boosting DILs using volumetric modulated arc therapy (VMAT) within the context of SABR: a SABR dose was prescribed to the prostate with a simultaneous DIL SABR boost. The impact on tumour control probability (TCP) and normal tissue complication probability (NTCP) was examined.

3.2 Methods

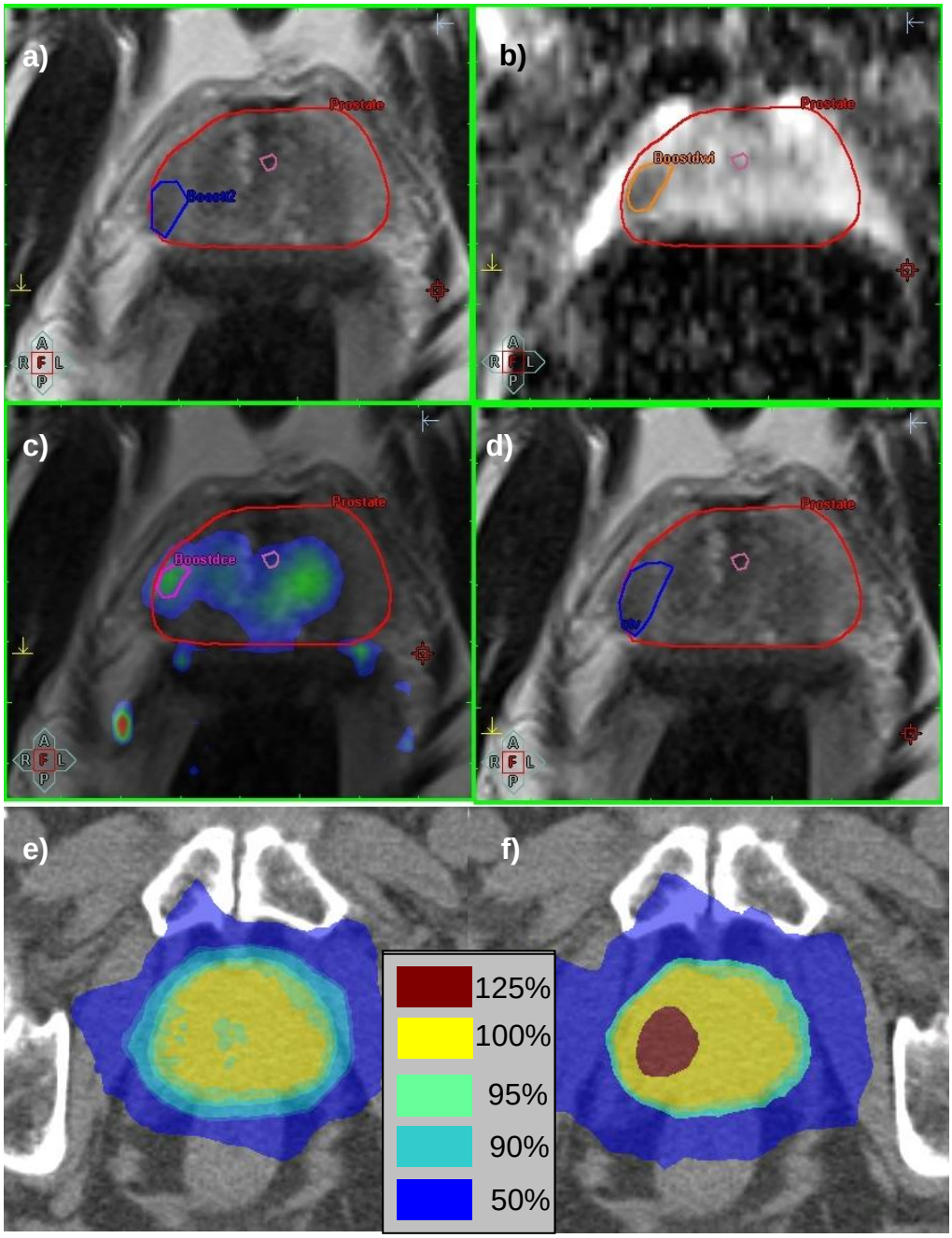
3.2.1 Imaging and contouring

Ten prostate datasets were selected (the first patients in an in-house pilot study investigating DIL boosting in the context of HDR-brachytherapy). Clinical characteristics are shown in Table 3.1. Patients received multi-parametric MRI and planning CT scans within a period of a few hours. MRI datasets were acquired on an Avanto (Siemens AG, Munich, Germany) 1.5-Tesla scanner, using phased-array pelvic coils and consisted of T2-weighted MRI, diffusion-weighted (DWI) and dynamic contrast-enhanced (DCE) MRI. For DWI MRI, apparent diffusion coefficient (ADC) maps were generated from a single-shot spin echo-echo planar imaging sequence with b-values 0, 150, 500smm^{-2}. For DCE MRI, Ktrans maps were generated by fitting a Tofts [221] 1-compartment model to concentration-time data for 200 acquisitions with temporal resolution 2s, acquired using a 3D spoiled gradient echo sequence, with a bolus injection of 0.1mmolkg^{-1} Dotarem (Guerbet Group, Villepinte, France) administered at 3mls^{-1} after 10s and a patient-specific arterial input function measured in the iliac artery. An experienced radiologist delineated DILs on the MRI sequences based on low-intensity on T2W MRI, low ADC map values and high Ktrans map values, together with the prostate and prostatic urethra. The CTV_{DIL} was the combined DIL volume from each MRI sequence (Figure 3-1), expanded by 4mm in all directions to create the PTV_{DIL}.

Table 3.1 Clinical and imaging characteristics

Patient	Age	Clinical T stage	Gleason score	Presenting PSA	Use of neo-adjuvant androgen deprivation	Prostate volume (cm^3)	Number of DILs	Volume of DILs (cm^3)	Distance of closest PTV_{DIL} edge from rectum (negative if overlapping; cm)	Distance of closest PTV_{DIL} edge from bladder (negative if overlapping; cm)
1	66	T2a	7	27	Yes	52.6	1	25.6	-0.2	-0.3
2	56	T1c	7	4	Yes	24.1	2	3.6	0	0
								0.2	0.3	1.5
3	69	T2	7	7	No	44.2	2	4.6	-0.6	0.2
								1.1	-0.5	1.6
4	58	T2	7	3	Yes	21.7	3	1.0	-0.1	1.0
								0.2	0.2	0.2
								0.2	0	1.1
5	76	T2c	9	21	Yes	12.3	1	0.5	0.6	0.2
6	64	T2a	7	6	Yes	28.9	3	0.3	0.3	0.6
								0.2	0	1.4
								0.6	-0.3	2.0
7	69	T2	7	31	Yes	14.9	2	0.3	0.7	0.9
								0.1	0.3	0.8
8	65	T2	8	39	Yes	23.9	1	1.0	0.6	1.0
9	68	T1c	7	11	Yes	59.7	1	0.1	0.6	2.6
10	61	T1c	7	5	No	21.8	1	4.4	-0.4	-0.4

Figure 3-1 DIL defined on a) T2-weighted, b) Diffusion-weighted and c) Dynamic contrast-enhanced MRI, d) Combined DIL volume (CTV_{DIL}), e) dose distribution without DIL boost, f) dose distribution with PTV_{DIL} boost to 125%



Images were co-registered with the planning CT using automatic soft tissue matching (non-deformable) with manual alteration if necessary, paying particular attention to the prostate-rectal interface and regions containing DILs. Patients received enemas and were encouraged to have comfortably full bladders. The rectum, bladder and femoral heads were contoured as organs at risk. Due to the small size of the urethra, this structure was expanded ~1.5mm circumferentially to create Planning organ at Risk $Volume_{urethra}$ ($PRV_{urethra}$), with diameter 5-6mm. For the purposes of anal NTCP evaluation, the anus was defined as the most caudal 3cm of the rectal structure [222].

The $CTV_{prostate}$ was the prostate alone which was expanded by 6mm in all directions to create the $PTV_{prostate}$.

The proximal 1cm of SV were included in a separate CTV: $CTV_{prostate+SV}$, which was expanded 6mm to form $PTV_{prostate+SV}$.

3.2.2 Prescription and coverage

The $PTV_{prostate}$ prescription was 42.7Gy in 7 fractions (intended for delivery on alternate weekdays over 15 days). Coverage requirements are shown in Table 3.2. Plans were initially produced prescribing 42.7Gy to the prostate, without DIL boosts. Plans were then created with simultaneous DIL boosts: the PTV_{DIL} prescription was increased in 5% increments, starting at 115% of the $PTV_{prostate}$ prescription, until organ at risk or conformity constraints were reached. If a boost of 115% was not achievable, the PTV_{DIL} prescription was reduced in 5% increments until the plan became acceptable.

Plans were then created which delivered the highest achievable PTV_{DIL} prescription to DILs, 42.7Gy to the prostate, and with inclusion of the proxSV within $PTV_{prostate+SV}$, initially prescribed 32.4Gy in 7 fractions ($EQD2_{1.5}$:56.7Gy), a microscopic tumoricidal dose, and then 36.5Gy in 7 fractions ($EQD2_{1.5}$:70.0Gy), a higher dose which has been suggested as more realistic for achieving tumour control [89].

Table 3.2 Coverage requirements and organ at risk constraints

Continued overleaf.

Volume	Requirement/ Constraint	Source/ Explanation
$CTV_{prostate}$	Minimum dose=40.6Gy (95%)	HYPO-RT-PC Phase III trial, 42.7Gy in 7 fraction arm [133]
$PTV_{prostate}$	Volume receiving 40.6Gy (V95%)≥95%/ Dose to 95%(D95%)≥40.6Gy (95%)	HYPO-RT-PC Phase III trial, 42.7Gy in 7 fraction arm [133]
$PTV_{prostate}$	Dose to 99% (D99%) ≥38.4Gy (90%)	HYPO-RT-PC Phase III trial, 42.7Gy in 7 fraction arm [133]
PTV_{DIL}	Volume receiving 95% of prescribed dose ≥95%/ Dose to 95%(D95%)≥95% of prescribed dose	
$PTV_{prostate+SV}$ minus $PTV_{prostate}$	Volume receiving 95% of prescribed dose (V95%)≥95%	Applicable when including proximal SV within prescription
Conformity index	≤1.2	Volume of 95% isodose/PTV volume To limit high dose spill [190]
R50	≤5.5	Volume of 50% isodose/PTV volume To limit intermediate dose spill [190]
Maximum dose at 2cm from PTV	≤29.9Gy (70%)	To limit intermediate dose spill Minor deviation to ≤34.2Gy (80%) permitted if all other constraints met

Table 3.2 cont. Coverage requirements and organ at risk constraints

Volume	Requirement/ Constraint	Source/ Explanation
Rectum (recto-sigmoid junction to anus)	V41.4Gy(97%)<3%	Biologically equivalent for 7 fraction regimen to 74Gy in 37 fraction arm of Phase III CHHiP trial [191]
	V38.4Gy(90%)≤15%	HYPO-RT-PC Phase III trial, 42.7Gy in 7 fraction arm [133]
	V32.0Gy(75%)≤35%	HYPO-RT-PC Phase III trial, 42.7Gy in 7 fraction arm [133]
	V28.0Gy(65%)≤45%	HYPO-RT-PC Phase III trial, 42.7Gy in 7 fraction arm [133]
	V24.8Gy(58%)<70%	Biologically equivalent for 7 fraction regimen to 74Gy in 37 fraction arm of Phase III CHHiP trial [191]
	V19.6Gy(46%)<80%	Biologically equivalent for 7 fraction regimen to 74Gy in 37 fraction arm of Phase III CHHiP trial [191]
Bladder	V41.4Gy(97%)<5%* V34.7Gy(81%)<25% V29.9Gy(70%)<50%	All biologically equivalent for 7 fraction regimen to 74Gy in 37 fraction arm of Phase III CHHiP trial [191]
Femoral heads	Dmax≤29.9Gy (70%)	HYPO-RT-PC Phase III trial, 42.7Gy in 7 fraction arm [133]
	V29.9Gy(70%)<50%	Biologically equivalent for 7 fraction regimen to 74Gy in 37 fraction arm of Phase III CHHiP trial [191]
Urethra	Dmax <58.1Gy D10% <53.3Gy D50% <50.7Gy	Biologically equivalent for 7 fraction regimen to 38Gy in 4 fraction arm of phase III PACE trial (based on high dose rate brachytherapy monotherapy constraints) [134]

CHHiP: Conventional versus Hypofractionated High-dose intensity-modulated radiotherapy for Prostate cancer, PACE: Prostate Advances in Comparative Evidence, * V41.4Gy relaxed to <9% in two cases with median lobe hypertrophy and small bladder volumes which meant prescription of prostate dose without DIL boost not possible if maintaining V41.4Gy<5%.

The prescription doses for both the prostate and DIL PTVs were such that 95% of the structure received at least 95% of the prescription dose (i.e. D95%≥95%) and in the case of PTVs including the proxSV, ≥95% of the volume formed from $PTV_{prostate+SV}$ minus $PTV_{prostate}$ received ≥95% of the prescribed dose. In addition, the minimum dose received by the prostate was 40.6Gy (95% of the prostate PD) and the minimum dose received by 99% of the $PTV_{prostate}$ was 38.4Gy (90% of the prostate PD). To allow gradients for DIL boosting and to maximise PTV_{DIL} doses, there were no limits on dose heterogeneity.

3.2.3 Organs at risk

Constraints are shown in Table 3.2 and are the same as those developed in Chapter 2. Urethral constraints (applied to the $PRV_{urethra}$) were added, and were biologically equivalent for a seven fraction schedule as those used in the PACE trial for patients receiving Cyberknife™ (Accuray®, USA) prostate SABR in a heterogeneous dose distribution (38Gy in 4 fractions [134]). These constraints were originally based on those used for HDR brachytherapy.

3.2.4 Plans

Four plans were produced for each dataset:

Plan set A: No DIL boost delivery, no SV in prescription

Plan set B: Boost to DILs, no SV in prescription

Plan set C: Boost to DILs, proxSV prescribed intermediate dose

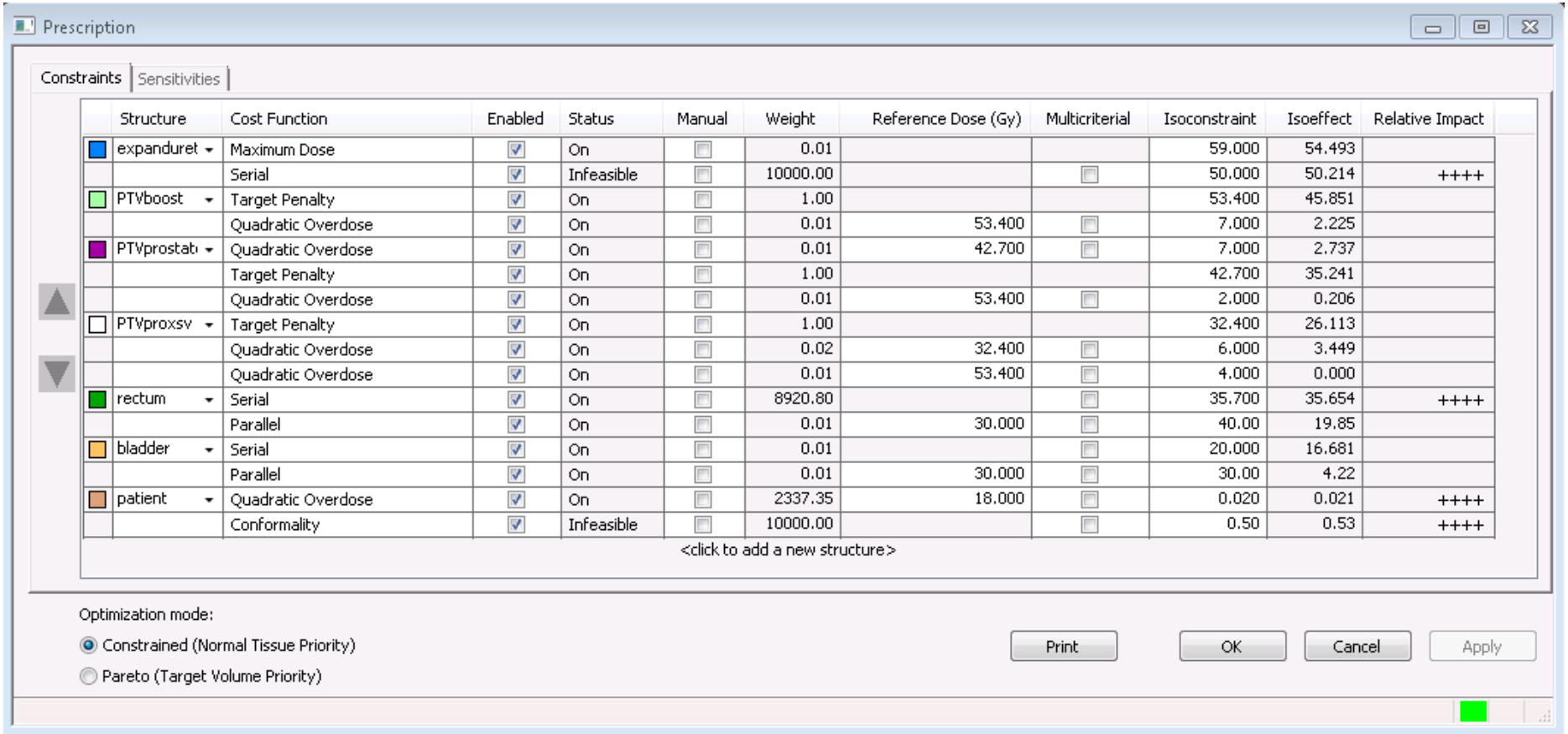
Plan set D: Boost to DILs, proxSV prescribed higher dose

3.2.5 Planning

Monaco® version 3.3 (Elekta AB, Sweden) was used for planning with a MC algorithm and the Agility™ Multi-leaf collimator with 5mm leaves (Elekta AB, Sweden) and 6MV photons. VMAT was planned with one anterior 270° arc (225°→135°) for nine patients and for one patient, with bilateral hip prostheses, three partial arcs (290°→70°,180°→240°,120°→180°). A 270° arc was selected for patients without artificial hips in preference to the 210° arc from Chapter 2 since it was presumed that providing additional posterior radiation would assist with dose delivery to the SV but, by continuing to exclude the rectum from entry beams, the rectal dose disadvantages observed when using full arc beam arrangements in Chapter 2 would not occur. The final plan in each set was calculated using a 2mm grid. There were a maximum of 150 control points per arc and 30° sectors were used for planning. An uncertainty of 1% per plan was accepted. Normal tissues were prioritised over target coverage.

An example of the prescription used for boosting DILs is shown in Figure 3-2. Explanations for the prescription components are those in Chapter 2, Table 2.4. In addition, as the $PRV_{urethra}$ was contained within the prostate, the $PRV_{urethra}$ was placed at the top of the prescription so that it 'owned' its voxels. This meant that the cost functions applied to the $PRV_{urethra}$ did not have to compete with those applied to the prostate (or PTV_{DIL}s, if these overlapped). A maximum dose cost function was applied to the $PRV_{urethra}$ structure to prevent marked urethral overdose and this was not altered during planning. A serial objective was also applied and this cost function was 'tweaked' during planning to either bring the $PRV_{urethra}$ into tolerance (by applying a stricter penalty for overdose) or to allow further dose escalation in DILs (by relaxing the penalty for overdose). In addition, target structures below the PTV_{DIL} (=PTVboost in Figure 3-2) in the prescription (i.e. PTVprostate and PTVproxsv in Figure 3-2) employed two quadratic overdoses rather than just one. The one specifying a lower dose was applied with a 3mm shrink margin and so was only applied to voxels more than 3mm away from the higher target structure in the prescription (often with a very loose penalty to facilitate dose escalation), while the second quadratic overdose permitted a higher dose (up to that prescribed to the PTV_{DIL}) and was applied with a 0mm shrink margin so that it was applied to all voxels beyond the higher target structure in the prescription, including those next to and within 3mm of that target. This allowed a dose gradient to form between one dose level and the next.

Figure 3-2 Prescription used for boosting DILs



DIL: dominant intra-prostatic lesion

The ‘Conformality’ constraint was also used in the prescription (Figure 3-2; ‘patient’ structure). This was a new function in Monaco® version3.3 for use in the non-specified normal tissues. It aims to limit dose spread in the 5cm of normal structures surrounding the lowest PTV structure in the prescription and tries to replace the requirement for multiple quadratic overdoses with multiple shrink margins in the region around the PTV. A quadratic overdose cost function was still required to act on regions more than 5cm beyond the lowest PTV structure in the prescription.

3.2.6 Modelling

TCP was calculated using the LQ-Poisson Marsden model, originally described by Nahum and Sanchez-Nieto [223]. As described in the original paper, TCP in response to dose *D*, delivered in *n* fractions of dose *d*, and initial clonogen number N_0, is determined according to the equation:

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

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

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

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 dose-volume histogram (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:

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

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

The potential for accelerated repopulation can also be included in the above calculation such that:

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

where $\gamma = ln2/T_d$ where T_d is average doubling time, *T* is overall treatment time and T_k is the time at which proliferation commences after the first radiotherapy fraction.

Therefore six parameters are required for TCP calculation:

i) $\bar{\alpha}$ (mean population radiosensitivity)

ii) σ_α (standard deviation of population radiosensitivity)

iii) α/β (alpha/beta ratio of tumour)

iv) ρ_{clon} (initial clonogen cell density)

v) T_d (average doubling time)

vi) T_k (time at which repopulation begins after first fraction of radiotherapy)

Three sets of parameters are used for TCP calculation, each representing a different α/β for PCa: 10Gy, 3Gy and 1.5Gy (Table 3.3). The parameters used were those that

Uzan and Nahum fitted to the RT01 trial data [224]. These parameters include a realistic clonogen number for all the α/β ratios assessed, and also take into account individual variation in radiation sensitivity (σ_α). This is in contrast to other studies which have demonstrated very low α/β ratios for PCa, but only in the setting of an unrealistically low number of clonogens or without taking into account population variation in radiation sensitivity [37,225,226]. Given the short overall time required for SABR delivery (i.e. 15 days) and the greater presumed time for repopulation to begin (i.e. T_k=45 days (Table 3.3)), the effect of repopulation is excluded from TCP calculations in this study.

Table 3.3 TCP parameters

Parameters from [224]

	$\bar{\alpha}$ (Gy^{-1})	σ_α (Gy^{-1})	α/β (Gy)	ρ_{clon} (cm^{-3})	T_d (days)	T_k (days)
High α/β						
Non-DIL prostate*	0.301	0.114	10	$6.2 \cdot 10^4$	0	45
DIL	0.301	0.114	10	$1.0 \cdot 10^7$	0	45
Low α/β						
Non-DIL prostate*	0.217	0.082	3	$6.2 \cdot 10^4$	0	45
DIL	0.217	0.082	3	$1.0 \cdot 10^7$	0	45
Very low α/β						
Non-DIL prostate*	0.155	0.058	1.5	$6.2 \cdot 10^4$	0	45
DIL	0.155	0.058	1.5	$1.0 \cdot 10^7$	0	45

TCP: tumour control probability, DIL: dominant intra-prostatic lesion

*Non-DIL prostate is the whole prostate structure minus DIL(s)

Clonogen density in the DIL region was assumed as $1x10^{7}cm^{-3}$. Using a similar approach to Nutting et al [213], it was assumed the ratio of clonogens in DIL(s) to clonogens in the non-DIL prostate was 90:10. Clonogen density (ρ_{clon}) in the non-DIL prostate was therefore:

$$\rho_{clon} = \frac{1 \bullet 10^{7} \bullet median\_total\_DIL\_volume\_per\_prostate\_(1.21cm^{3}) \bullet \frac{10}{90}}{median\_(prostate - DIL)\_volume\_(21.65cm^{3})}$$

TCP was calculated using differential DVHs for the CTV_{DIL} and the non-DIL prostate (i.e. $CTV_{prostate}$ minus CTV_{DIL}(s)).

NTCP for the rectum, bladder and femoral heads were calculated according to the Lynam-Kutcher-Burman model [227,228] using Niemierko's concept of equivalent uniform dose (EUD) [194]:

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

$$EDQ2 = D \bullet \frac{(\alpha/\beta + d)}{(\alpha/\beta + 2)}$$

As a conservative approach [38], an α/β ratio of 3Gy was used for equivalent dose conversion.

EUD was then calculated: as before, 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:

$$\text{EUD}= \left(\sum_i D_i^{\frac{1}{n}} \frac{V_i}{V_{total}} \right)^n$$

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:

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

and

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

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 vs. dose response curve (thus larger values of m represent more shallow dose-complication slopes).

Thus three parameters are required for NTCP calculation:

i) TD_{50} (the dose that will result in a 50% probability of complication in a uniformly irradiated tissue)

ii) *m* (inversely related to slope at the steepest point of the NTCP curve)

iii) *n* (volume effect parameter)

NTCP parameters are shown in Table 3.4. The QUANTEC (Quantitative Effects of Normal Tissue Effects in the Clinic) rectal NTCP parameters used for the principal analysis of rectal NTCP were selected as these were derived from meta-analysis and thus included a large number of patients [229]. These consider the risk of grade 2+ rectal bleeding or toxicity. Additional parameters, albeit derived from smaller patient numbers, were also selected to explore additional endpoints (severe rectal bleeding and frequency, and anal incontinence) and to personalise NTCP calculations based on a previous history of abdominal surgery or not (Table 3.4). The correct NTCP parameters for the bladder have proven difficult to define [40] and, in the setting of ultra-hypofractionation and modern radiotherapy dose distributions, little guidance is available. The traditional Burman parameters were therefore adopted for NTCP, accepting that these may not provide completely reliable NTCP estimates in the setting in which they have been used here [230]. The traditional Burman NTCP parameters were also selected for calculation of femoral head NTCP [230]. VMAT results in low femoral head doses and so low complication rates would be expected. This is not the only recent study to use relatively old parameters for bladder and femoral head NTCP calculations [210,212]. Long term clinical SABR data is required before the appropriateness of these NTCP parameters in the setting of SABR and VMAT can be further addressed.

TCP and NTCP calculations were performed using BioSuite [224] using differential DVHs with 0.1Gy bin width.

Table 3.4 NTCP parameters

Organ	End-point	TD_{50} (Gy)	*m*	*n*	Source
Principal rectal NTCP evaluation					
Rectum	Grade 2+ late toxicity or rectal bleeding	76.9	0.13	0.09	Michalski et al [229]
Supplementary anorectal NTCP evaluation					
Rectum	Severe** rectal bleeding- all patients	81	0.14	0.13	Peeters et al [222]
Rectum	Severe** rectal bleeding- patients without history of abdominal surgery	85	0.14	0.11	Peeters et al [222]
Rectum	Severe** rectal bleeding- patients with history of abdominal surgery	78	0.14	0.11	Peeters et al [222]
Rectum	Severe** frequency- all patients	84	0.24	0.39	Peeters et al [222]
Anus*	Severe** anal incontinence- all patients	105	0.43	1	Peeters et al [222]
Anus*	Severe** anal incontinence- patients without history of abdominal surgery	157	0.45	1	Peeters et al [222]
Anus*	Severe** anal incontinence- patients with history of abdominal surgery	74	0.45	1	Peeters et al [222]
Bladder	Contracture/ volume loss	80	0.11	0.5	Burman et al [230]
Femoral heads	Necrosis	65	0.12	0.25	Burman et al [230]

NTCP: normal tissue complication probability
*Anus defined as most caudal 3cm of the rectal structure [222].
**Severe symptoms considered as: i) rectal bleeding requiring transfusion or laser treatment, ii) faecal incontinence with the loss of mucus, blood or stools requiring the use of pads more than two times each week and iii) stool frequency of 6 or more episodes per day [222].

3.2.7 TCP sensitivity analysis

To assess the sensitivity of the TCP calculations to small alterations in TCP input parameters, a one-factor-at-a-time sensitivity analysis was performed [231]. For each plan, TCP for the prostate and DILs were recalculated after changing each of the following input parameters up and down by 10%: $\bar{\alpha}$, clonogen density, α/β and σ_α.

The relative variation rate was calculated according to:

$$\text{Relative variation rate (\%)} = \left(\frac{O_2 - O_1}{O_1}\right) \bullet 100$$

where O_1 is the original TCP and O_2 is the modified TCP.

A sensitivity index (SI) was calculated for each plan according to:

$$\text{SI} = \frac{(O_2 - O_1)}{\left((O_2 + O_1)/2\right)} \Bigg/ \frac{(I_2 - I_1)}{\left((I_2 + I_1)/2\right)}$$

where I_1 is the original input factor and I_2 is the modified input factor (i.e. ±10%), and O_1 and O_2 are as above. SI values of 1 would indicate the same magnitude of change in output as the change in input (i.e. a 10% change in output in response to a 10% change in input). SI values closer to 0 indicate a smaller change in TCP in response to a 10% alteration in input parameter. Negative values represent a change in TCP in the opposite direction to the change in the input parameter.

3.2.8 Statistics

The Wilcoxon signed-rank exact test was used to compare plan parameters, TCP and NTCP as a normal distribution was not presumed. Median values and ranges are therefore presented. The following were compared:

- Plan set B to Plan set A (i.e. boost to DIL(s), no SV in prescription vs. no boost to DILs, no SV in prescription)
- Plan set C to Plan set B (i.e. boost to DILs, proxSV prescribed intermediate dose vs. boost to DILs, no SV in prescription)
- Plan set D to Plan set C (i.e. boost to DILs, proxSV prescribed higher dose vs. boost to DILs, proxSV prescribed intermediate dose).

Linear correlations were examined using Pearson's correlation coefficient (*r*). SPSSv19 (IBM corporation, Armonk, New York, USA) was used. Tests were two-tailed. A *p* value of <0.05 was considered statistically significant.

3.3 Results

17 PTV_{DIL}s were defined (one, two and three DILs in five, three and two cases respectively). Median PTV_{DIL} volume was 3.4cm^3 (range:1.5-51.6cm^3). Median $PTV_{prostate}$ volume was 61.8cm^3 (range:38.9-128.5cm^3).

In two cases, when creating the non-boost plans (Plan Set A), it was not possible to achieve adequate coverage and also meet the uppermost bladder constraint of V41.4Gy<5%. In both cases this was the result of median lobe hypertrophy accompanied by relatively small bladder volumes (163cm^3 and 173 cm^3) at the time of planning. When the uppermost bladder constraint was relaxed to 9%, then coverage was achieved. In these two cases, therefore, when creating the boost plans, boost doses were escalated until reaching rectal, urethral or conformity constraints, and ensuring that the uppermost bladder constraint was limited to less than 9%.

When treating the prostate alone, and prescribing the highest feasible boost to DILs (Plan set B), the median PTV_{DIL} prescription was 125% of the $PTV_{prostate}$ prescription (53.4Gy in 7 fractions, $EQD2_{1.5}$:139.3Gy), and ranged from 110% ($EQD2_{1.5}$:110.3Gy) to 140% ($EQD2_{1.5}$:171.6Gy). The median D50% received by a PTV_{DIL} was 55.1Gy ($EQD2_{1.5}$:147.5Gy, range: 49.6Gy ($EQD2_{1.5}$:121.7Gy) to 62.6Gy ($EQD2_{1.5}$:186.8Gy)).

Unsurprisingly, delivering boosts to PTV_{DIL}s compared to not, resulted in significant increases in PTV_{DIL} D50%. This was accompanied by increases in monitor units and estimated delivery times (Table 3.5).

When including the proxSV, prescribed 32.4Gy (Plan set C) or 36.5Gy (Plan set D), it was possible to deliver the same PTV_{DIL} prescription as when boosting DILs without proxSV inclusion. Furthermore, there was no significant difference in PTV_{DIL} D50% (Table 3.5). Plans prescribing 32.4Gy to the proxSV (Plan set C), compared to plans delivering DIL boosts but without proxSV prescription (Plan set B), resulted in significant increases in CI, R50 and Dmax2cm. Similarly, prescribing 36.5Gy (Plan set D) to the proxSV, compared to 32.4Gy (Plan set C), resulted in increases in CI, R50 and Dmax2cm (Table 3.5).

During planning, the rectum was the most frequent dose-limiting structure. For all boost plans (Plan sets B, C and D) linear correlations were observed between the PTV_{DIL} prescription achieved and the minimum distance of a PTV_{DIL} from the rectum (r=0.56, p=0.019) and the volume of PTV_{DIL} overlapping with the rectum (r=-0.66, p=0.004). In addition, PTV_{DIL} D50% correlated with the volume of PTV_{DIL} overlapping with the rectum (Plan sets B, C and D: r=-0.69, -0.58, -0.62, p=0.002, 0.016, 0.008) and, in Plan sets B and D, with the minimum distance of PTV_{DIL} from the rectum (Plan set B: r=0.62, p=0.008, Plan set D: r=0.50, p=0.045). No significant correlations were observed between PTV_{DIL} minimum distance from, or volume of overlap with, the urethra or bladder, and the PTV_{DIL} prescription or D50%. There was no correlation between DIL volume and PTV_{DIL} prescription or PTV_{DIL} D50%.

In the case of smaller volume prostate PTVs (e.g. $PTV_{prostate}$ volume <60cm^3), respecting conformity index (CI) constraints was an additional dose-limiting factor and for large volume prostate PTVs (e.g. $PTV_{prostate}$ volume >100cm^3), respecting the maximum dose 2cm from the $PTV_{prostate}$ (Dmax2cm) was also dose-limiting.

Table 3.5 Plan parameters

	Volume treated								*p* value where significant (Plan set B compared with Plan set A, Plan set C compared with Plan set B and Plan set D compared with Plan set C)
	Plan set A: No boost to dominant intra-prostatic lesions (DILs), Prostate alone (n=10)		Plan set B: Boost to DILs, Prostate alone (n=10)		Plan set C: Boost to DILs, Proximal seminal vesicles treated to intermediate dose (n=10)		Plan set D: Boost to DILs, Proximal seminal vesicles treated to high dose (n=10)		
	Median	Range	Median	Range	Median	Range	Median	Range	
Highest achievable PTV_{DIL} prescription (% of $PTV_{prostate}$ prescription)	-	-	125	110-140	125	110-140	125	110-140	Identical
Median dose to PTV_{DIL} (D50%; Gy)	43.8	43.4-45.3	55.1*	49.6-62.6	54.9	50.1-62.5	55.3	49.5-61.8	*Plan set B > A: $p<0.001$
Conformity index (see Table 3.2 for definition)	1.05	1.00-1.12	1.06	1.02-1.11	1.13†	1.09-1.17	1.16‡	1.12-1.20	† Plan set C > Plan set B: $p=0.004$ ‡ Plan set D > Plan set C $p=0.004$
R50 (see Table 3.2 for definition)	3.55	3.31-4.05	3.57	3.34-4.14	4.16†	3.97-4.73	4.32‡	4.06-4.94	† Plan set C > Plan set B: $p=0.002$ ‡ Plan set D > Plan set C: $p=0.004$
Maximum dose at 2cm from PTV (Gy)	26.1	23.2-31.0	27.4	25.5-32.7	29.0†	26.8-33.4	29.8‡	27.2-33.2	† Plan set C > Plan set B: $p=0.002$ ‡ Plan set D > Plan set C: $p=0.049$
Monitor units per fraction	1980	1655-2654	2313*	2117-2562	2314	1948-2618	2372	2099-2773	* Plan set B > A: $p=0.027$
Estimated delivery time (seconds)	209	173-314	253*	230-353	248	211-343	260	229-312	* Plan set B > A: $p=0.01$

TCP for DILs and the non-DIL prostate varied depending on the α/β and accompanying parameters employed (Table 3.6). TCP levels were lowest for α/β=10Gy (TCP non-DIL prostate <90%, TCP DIL ≤96%) and highest with α/β=1.5Gy (TCP non-DIL prostate ≥94%, TCP DIL ≥89%). For all α/β ratios, boosting DILs resulted in significant increases in TCP in DILs and the non-DIL prostate. The higher the α/β, the greater the benefit of boosting DILs, with gains in median TCP of 14% (from 76.5% to 90.5%) when boosting for α/β=10Gy, compared to 6.7% (90.3% to 97.0%) for α/β=3Gy and 4.4% (94.4% to 98.8%) for α/β=1.5Gy. There was no difference in TCP when including the proxSV within the prescription. With α/β=1.5Gy, in non-boost plans (Plan set A), TCP for DILs and for the remaining prostate exceeded 90% and 95% respectively in 9 of 10 cases. The one remaining patient had an exceptionally large DIL (CTV_{DIL}: 25.6cm^3). TCP in this case (based on α/β=1.5Gy) was 89.3% and 94.4% for the DIL and non-DIL prostate respectively. TCP relative variation rates and sensitivity analysis results are shown in Table 3.7 and Table 3.8 respectively. Small changes in TCP input parameters had greatest impact with α/β~10Gy and least with α/β~1.5Gy.

NTCP for Grade 2+ late rectal complications (QUANTEC parameters) was consistently low (<3.5%) when prescribing SABR to the whole prostate, without DIL boosting (Plan set A; Table 3.6). There was a significant increase in rectal NTCP when delivering DIL boosts. Prescribing to the proxSV did not increase rectal NTCP further. Rectal NTCP was <15% in 35 of 40 plans. A strong linear correlation was noted between the maximum dose received by 0.5cm^3 (Dmax0.5cc) of rectum and rectal NTCP in all boost plans (i.e. Plan sets B, C and D; *r*: 0.88, 0.97, 0.95 respectively, all $p \leq 0.001$, Figure 3-3). Rectal NTCP did not exceed 5% and 15% in cases where rectal Dmax0.5cc did not exceed 44.1Gy and 47.1Gy respectively. There was no correlation between rectal NTCP and PTV_{DIL} prescription or D50%, except in Plan set C, where a moderate correlation was observed between rectal NTCP and D50% (r=0.488, p=0.047).

Table 3.6 Tumour control probability (TCP) and normal tissue complication probability (NTCP)

		Plan set A: No boost to dominant intra-prostatic lesions (DILs), Prostate alone		Plan set B: Boost to DILs, Prostate alone		Plan set C: Boost to DILs, Proximal seminal vesicles treated to intermediate dose		Plan set D: Boost to DILs, Prostate plus proximal seminal vesicles treated to high dose		*p* value where significant (Plan set B vs. A, C vs. B and D vs, C)
	α/β (Gy)	Median (%)	Range (%)	Median (%)	Range (%)	Median (%)	Range (%)	Median (%)	Range (%)	
TCP Non-DIL Prostate (Prostate minus DIL(s))	10	80.5	76.9-83.0	87.9*	82.2-89.9	87.7	83.9-89.0	87.2	82.6-88.5	*Plan set B > A: *p*=0.002
	3	92.0	90.4-93.1	95.5*	93.1-96.5	95.3	93.6-96.1	95.2	93.3-95.8	*Plan set B > A: *p*=0.002
	1.5	95.5	94.4-96.2	97.7*	96.3-98.4	97.5	96.5-98.1	97.4	96.4-97.9	*Plan set B > A: *p*=0.002
TCP DIL(s)	10	76.5	58.6-84.0	90.5*	79.5-96.3	90.7	80.0-96.2	90.6	79.4-96.0	*Plan set B > A: *p*<0.001
	3	90.3	81.6-93.7	97.0*	92.7-99.2	97.0	93.0-99.2	97.1	92.4-99.1	*Plan set B > A: *p*<0.001
	1.5	94.4	89.3-96.6	98.8*	96.2-100	98.7	96.4-100	98.8	96.0-100	*Plan set B > A: *p*<0.001
NTCP rectum	3	2.8	1.4-3.3	11.4*	3.8-30.8	10	0.6-47.1	9.6	3.5-31.9	*Plan set B > A: *p*=0.002
NTCP bladder	3	0	0	0	0	0	0	0	0	
NTCP femoral heads	3	0	0	0	0	0	0	0	0	

Table 3.7 Relative variation rates (%) following a change in TCP parameter by up or down 10% (median (and range))

All results $p<0.001$ using Wilcoxon signed-rank test to compare high α/β with low α/β, and low α/β with very low α/β.

	$\bar{\alpha}$ increased 10%	$\bar{\alpha}$ reduced 10%	Clonogen density increased 10%	Clonogen density decreased 10%	α/β increased 10%	α/β decreased 10%	σ_α increased 10%	σ_α decreased 10%
α/β high (~10Gy)								
Non-DIL Prostate	6.53 (5.01-9.88)	-8.39 (-11.96- -6.67)	-0.34 (-0.52-0)	0.35 (0.11-0.69)	-1.75 (-2.99- -1.22)	1.92 (1.33-3.12)	-2.71 (-2.89- -2.31)	3.02 (2.70- 3.25)
DIL	5.74 (2.39-14.41)	-7.67 (-18.26- -3.85)	-0.23 (-0.76-0)	0.23 (0-0.85)	-1.65 (-5.97- -0.62)	1.76 (0.52-6.83)	-2.54 (-3.26- -1.19)	2.73 (1.71-3.25)
α/β low (~3Gy)								
Non-DIL Prostate	3.28 (2.38-4.76)	-4.55 (-6.64- -3.63)	-0.11 (-0.22-0)	0.11 (0-0.22)	-1.16 (-2.10- -0.83)	1.22 (0.73-1.99)	-2.11 (-2.65- -1.88)	2.11 (1.76-2.65)
DIL	2.55 (0.81-8.33)	-4.16 (-9.93- -2.02)	-0.10 (-0.25-0)	0.10 (0-0.37)	-0.95 (-4.04- -0.20)	1.16 (0.20-4.41)	-1.96 (-2.82- -1.21)	1.77 (0.81-3.31)
α/β very low (~1.5Gy)								
Non-DIL Prostate	2.21 (1.52-3.39)	-3.244 (-4.56- -2.74)	-0.10 (-0.11-0)	0.10 (0-0.21)	-0.82 (-1.38- -0.61)	0.82 (0.41-1.48)	-1.80 (-2.12- -1.52)	1.65 (1.22-2.22)
DIL	1.68 (0-5.26)	-2.98 (-7.39- -1.30)	0 (-0.22-0)	0.05 (0-0.22)	-0.62 (-3.02- -0.10)	0.61 (0-2.46)	-1.53 (-2.80- -1.10)	0.61 (0-2.46)

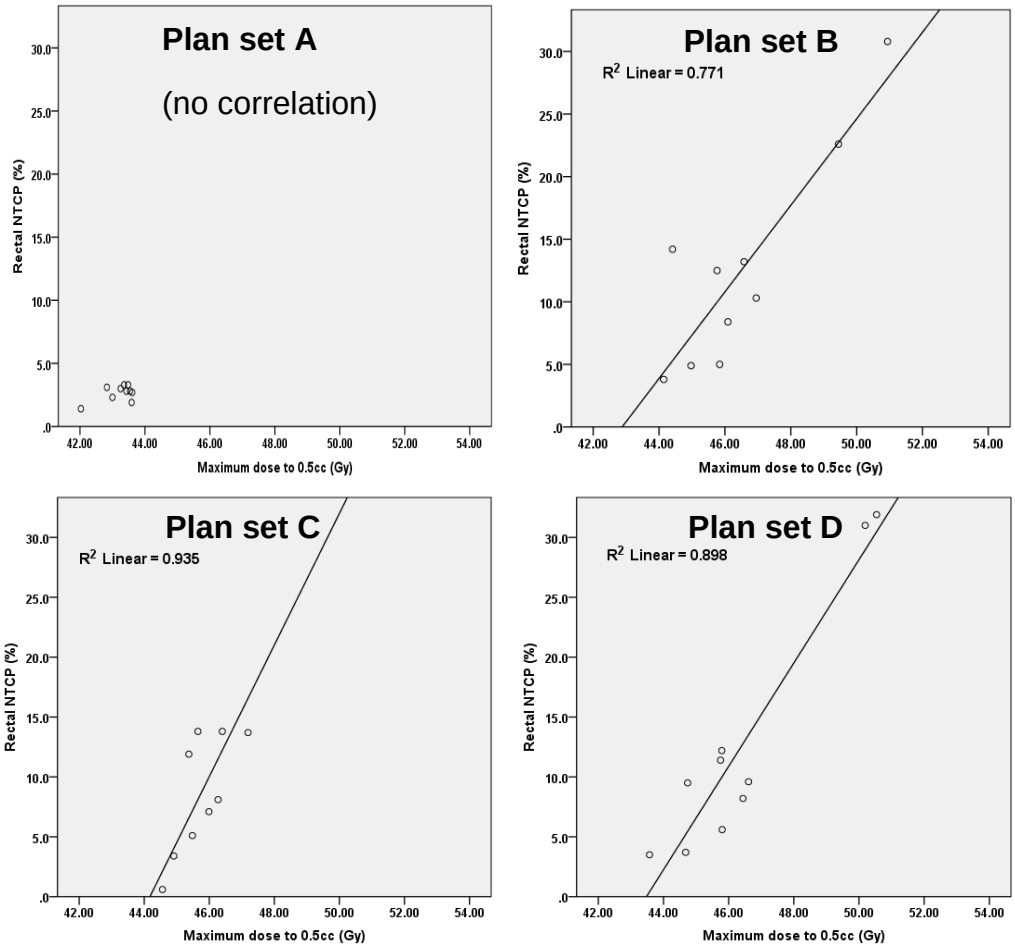
DIL: dominant intra-prostatic lesion, TCP: tumour control probability

Table 3.8 Median sensitivity indices (and ranges) based on changing each TCP parameter up or down by 10%

Numbers closer to zero indicate smaller changes in response to a 10% change in TCP input parameter. Negative numbers indicate a change in the opposite direction to which the TCP input parameter was changed. All results $p<0.001$ using Wilcoxon signed-rank test to compare high α/β with low α/β, and low α/β with very low α/β. DIL: dominant intra-prostatic lesion, TCP: tumour control probability

	$\bar{\alpha}$ increased 10%	$\bar{\alpha}$ reduced 10%	Clonogen density increased 10%	Clonogen density decreased 10%	α/β increased 10%	α/β decreased 10%	σ_α increased 10%	σ_α decreased 10%
α/β high (~10Gy)								
Non-DIL Prostate	0.66 (0.51-0.99)	0.83 (0.66-1.21)	-0.04 (-0.05-0)	-0.03 (-007- -0.01)	-0.19 (-0.32- -0.13)	-0.18 (-0.29- -0.13)	-0.29 (-0.31- -0.25)	-0.28 (-0.30- -0.25)
DIL	0.59 (0.25-1.68)	0.76 (0.37-1.91)	-0.02 (-0.08-0)	-0.02 (-0.08-0)	-0.17 (-0.65- -0.07)	-0.17 (-0.63- -0.05)	-0.27 (-0.35- -0.13)	-0.26 (-0.30- -0.16)
α/β low (~3Gy)								
Non-DIL Prostate	0.33 (0.25-0.49)	0.44 (0.35-0.65)	-0.01 (-0.02-0)	-0.01 (-0.02-0)	-0.12 (-0.22- -0.09)	-0.12 (-0.19- -0.07)	-0.22 (-0.28- -0.20)	-0.20 (-0.25- -0.17)
DIL	0.26 (0.08-0.84)	0.40 (0.19-0.99)	-0.01 (-0.03-0)	-0.01 (-0.03-0)	-0.10 (-0.43- -0.02)	-0.11 (-0.41- -0.02)	-0.21 (-0.30- -0.13)	-0.17 (-0.31- -0.08)
α/β very low (~1.5Gy)								
Non-DIL Prostate	0.23 (0.16-0.35)	0.31 (0.26-0.44)	-0.01 (-0.01-0)	-0.01 (-0.02-0)	-0.09 (-0.15- -0.06)	-0.08 (-0.14- -0.04)	-0.19 (-0.22- -0.16)	-0.16 (-0.21- -0.12)
DIL	0.18 (0-0.54)	0.29 (0.12-0.73)	0 (-0.02-0)	-0.01 (-0.02-0)	-0.06 (-0.32- -0.01)	-0.06 (-0.23-0)	-0.16 (-0.30- -0.12)	-0.13 (-0.26-0)

Figure 3-3 Correlation between the maximum dose received by 0.5cm^3 of rectum and rectal NTCP



NTCP: normal tissue complication probability

Of the five 'worst' rectal NTCP plans, (QUANTEC parameters, i.e. NTCP>15%), three came from one dataset containing two DILs, the larger abutting the rectum, both boosted to 130%. The two other 'worst' plans came from one dataset containing a large PTV_{DIL} (51.6cm^3) prescribed 125%, which overlapped with the rectum. All five cases were re-planned with the aim of delivering the same PTV_{DIL} prescription while respecting the constraints in Table 3.2 and also reducing rectal Dmax0.5cc to <47.1Gy. In four cases the same PTV_{DIL} prescription level was achieved albeit with lower PTV_{DIL} D50%. Rectal NTCP was reduced considerably (from 30.8%, 47.1%, 31.9% and 22.6% to 1.7%, 3.4%, 2.5% and 8.9% respectively), accompanied by small reductions in DIL

TCP (Table 3.9). In one case it was not possible to maintain coverage, respect constraints and lower rectal dose, and so PTV_{DIL} prescription was lowered by 5% to 120%, which resulted in reduced rectal NTCP (31% to 5.6%). Thus rectal NTCP became <15% in all cases.

Results of anorectal NTCP calculations using alternative parameters are shown in Table 3.10. Median values were encouragingly low. Rates of severe rectal bleeding and frequency, and anal incontinence were relatively low when considering PCa patients as a whole (maximum NTCPs of 5.9%, 0.7% and 3.5% for bleeding, frequency and incontinence respectively) and patients with no history of abdominal surgery (maximum NTCP 9.1% and 2.9% for rectal bleeding and anal incontinence respectively). When considering patients with a history of abdominal surgery, the risk of severe anal incontinence remained relatively low (maximum 6.4%) while the risk of severe rectal bleeding was greater than 10% in four plans, all of which had unacceptable NTCP levels according to the QUANTEC parameters. The re-plans described above resulted in reductions in the risk of severe rectal bleeding in the setting of previous abdominal surgery in all cases (from 11.8% to 0.5%, 20.9% to 1.2%, 13.5% to 0.9% and 13.8% to 2.5%). The maximum NTCP levels for severe rectal bleeding for all patients (5.9%), and patients with no history of abdominal surgery (9.1%), mentioned above, also occurred in those plans which were unacceptable according to the QUANTEC parameters, Again, the re-plans resulted in reductions in NTCP in these settings (5.9% to 0.2% and 9.1% to 0.4%).

The risk of severe rectal bleeding was significantly less using ‘no boost’ plans compared to boost plans for all patients and those with and without a history of abdominal surgery. The other statistically significant differences were clinically irrelevant (Table 3.10).

Table 3.9 Impact of re-planning five 'worst' rectal NTCP plans

Dataset	Original boost level (% of PD)	Re-planned boost level (% of PD)	Original maximum dose received by 0.5cm^3 rectum (Gy)	Re-planned maximum dose received by 0.5cm^3 rectum (Gy)	Original rectal NTCP (%)	Re-planned rectal NTCP (%)	Original DIL TCP (%, α/β ratio 1.5Gy and accompanying parameters)	Re-planned DIL TCP (%, α/β ratio 1.5Gy and accompanying parameters)
1	130	130	50.9	42.6	30.8	1.7	98.8 99.8	98.1 99.1
1	130	130	52.6	44.4	47.1	3.4	98.9 99.9	98.0 99.0
1	130	130	50.5	42.7	31.9	2.5	98.8 99.9	98.1 99.1
2	125	125	49.5	46.5	22.6	8.9	96.3	96.2
2	125	120	50.2	45.2	31.0	5.6	96.5	95.1

DIL: dominant intra-prostatic lesion, NTCP: normal tissue complication probability, PD: prescription dose

Table 3.10 Anorectal NTCP (%) calculated using alternative parameters (median and (range))

	Plan set A: No boost to DILs, Prostate alone	Plan set B: Boost to DILs, Prostate alone	Plan set C: Boost to DILs, Proximal seminal vesicles treated to intermediate dose	Plan set D: Boost to DILs, Prostate plus proximal seminal vesicles treated to high dose	*p* value where significant (Plan set B compared with Plan set A, Plan set C compared with Plan set B and Plan set D compared with Plan set C)
Severe[§] rectal bleeding- all patients	0.4 (0.2-0.6)	1.3* (0.7-2.8)	1.3 (0.5-5.9)	1.25 (0.6-4.1)	*p=0.002: plan set B > Plan set A
Severe[§] rectal bleeding- no abdominal surgery	0.5 (0.2-0.7)	1.8* (0.7-4.7)	1.7 (0.6-9.1)	1.6 (0.7-5.6)	*p=0.002: plan set B > Plan set A
Severe[§] rectal bleeding- previous abdominal surgery	1.5 (0.8-2.0)	5.0* (2.1-11.8)	4.6 (1.7-20.9)	4.4 (2.0-13.8)	*p=0.002: plan set B > Plan set A
Severe[§] rectal frequency- all patients	0.3 (0.2-0.4)	0.4 (0.2-0.5)	0.4 (0.3-0.6)	0.5 (0.3-0.7)	
Severe[§] anal incontinence- all patients	1.9 (1.1-3.4)	2.1 (1.1-3.5)	2.0 (1.1-2.8)	2.0 (1.1-3.3)	
Severe[§] anal incontinence- no abdominal surgery	1.9 (1.4-2.9)	2.1 (1.4-2.9)	2.0[†] (1.4-2.5)	2.0 (1.4-2.8)	[†]p=0.031: plan set C < Plan set B
Severe[§] anal incontinence- previous abdominal surgery	2.9 (1.4-6.2)	3.4 (1.4-6.4)	3.2[†] (1.4-4.9)	3.1 (1.4-5.9)	[†]p=0.031: plan set C < Plan set B

NTCP: normal tissue complication probability, [§]Severe symptoms considered as: i) rectal bleeding requiring transfusion or laser treatment, ii) faecal incontinence with the loss of mucus, blood or stools requiring the use of pads more than two times each week and iii) stool frequency of 6 or more episodes per day [222]

3.4 Discussion

This study investigated boosting DILs while maintaining organ at risk constraints in the context of SABR. DIL dose escalation to a median of 125% of the $PTV_{prostate}$ prescription ($EQD2_{1.5}$: 139Gy) was feasible. This resulted in increased TCP in DILs and the non-DIL prostate, likely because of the dose gradients required to deliver boosts. DIL boosting also increased rectal NTCP and, in some cases, rectal NTCP became unacceptable.

Simultaneous EBRT DIL boosts up to 4.1Gy and 2.7Gy per fraction have been delivered in planning and clinical studies respectively, to total doses up to $EQD2_{1.5}$ 220Gy and 114Gy [207,209-219]. The non-DIL prostate has received up to 2.8Gy and 2.7Gy per fraction in planning and clinical settings respectively (up to $EQD2_{1.5}$: 93.5Gy and 81.4Gy) [207,209-219]. Late grade 2+ rectal and bladder toxicity rates up to 15% and 43% are reported clinically [207]. At the time of writing, no other publications were identified which examined TCP and NTCP using SABR to the whole prostate ($EQD2_{1.5}$:92.7Gy) with simultaneous SABR DIL boosts. Previous studies have observed the impact of DIL location on boost feasibility [210,211]. In this current study it was also found that PTV_{DIL} proximity to the rectum and volume of rectal overlap influenced PTV_{DIL} prescription level and PTV_{DIL} D50%. Unlike studies using conventional fractionation, prescribing SABR also requires strict limits for high and intermediate dose spill. These also influenced the boosts that could be achieved.

It was possible to prescribe the same PTV_{DIL} prescriptions and achieve similar PTV_{DIL} median doses when including the proxSV, both when prescribing 32.4Gy and 36.5Gy. This potentially provides a SABR option for intermediate risk PCa patients, at higher risk of SV invasion. Including the proxSV resulted in 'bowing out' of isodoses posteriorly, reflected by increases in CI and R50. Despite this, there was no significant increase in rectal NTCP. The estimation of TCP was limited to that for the prostate and DILs only, and did not consider TCP in terms of disease in the SV as there is little evidence regarding suitable parameters for calculating TCP in this region.

This study has limitations and several factors would have to be addressed before adopting this strategy clinically. Firstly, the optimal method for defining DILs is debated. Existing studies employ multi-parametric MRI, MR spectroscopy, radio-labelled Indium and choline-PET (positron emission tomography). Multi-parametric MRI was used in this study, in-keeping with guidelines [205]. Based on histopathological correlation with prostatectomy specimens, T2-weighted sequences combined with DWI sequences, or DWI combined with DCE sequences, have sensitivities and specificities of 70 to 87% [232,233]. Combining all three sequences results in receiver-operator-curve area under the curve of 0.94 [234]. Secondly, accurate image co-registration is essential. A soft-tissue auto-match with manual correction as necessary was adopted here. Deformable registration might prove superior, as this could deal with alterations is prostate shape and discrepancies in prostate size between imaging modalities more adequately than was possible using rigid registration, but this has not been validated in the setting of DILs. The optimal method of registration might well include models which add additional DIL margins to specifically take account of registration errors, although techniques requiring additional margins may prove difficult to implement without unacceptable increases in NTCP. Uncertainties resulting from DIL definition and registration will reduce the actual TCP benefit achieved from DIL boosting to less than that calculated here. Thirdly, the addition of catheterisation at planning would facilitate reliable identification of the urethra. Although patients in this current study were not catheterised at planning, it would be essential if this strategy were to be adopted clinically.

Fourthly, robust image-guidance together with appropriate CTV-PTV margins are essential. For the $CTV_{prostate}$ and $CTV_{prostate+SV}$, 6mm CTV-PTV margins were used, compatible with daily online fiducial-based image-guidance (without intra-fraction tracking) [186-188]. There is evidence that intra-fraction motion becomes more problematic with increasing daily treatment time, particularly beyond 8 minutes [199]. The plans in this study had average estimated delivery times of 4.2 minutes (maximum 5.9 minutes). Intra-fraction motion, therefore, may not be a major concern [164,198,199]. The use of flattening filter free (FFF) treatments, however, could further reduce delivery times. Five boost plans were re-planned using FFF, and estimated delivery times reduced by 116 seconds on average. While IMRT (rather than VMAT) could potentially achieve similar boosts, the longer delivery times would be more of a concern in the absence of intra-fraction tracking. If intra-fraction motion

tracking was available in conjunction with VMAT techniques, then smaller CTV-PTV margins could be feasible, which in turn might allow further DIL dose escalation, although whether this would indeed be the case, and the resulting impact on TCP and NTCP, would need separate investigation.

Fifthly, the most appropriate CTV-PTV margin for use around a DIL is uncertain. A variety of margins have previously been adopted, ranging from 0 to 8mm [207]. The phase III FLAME trial, which prescribes 77Gy in 35 fractions to the prostate, with or without a 95Gy simultaneous DIL boost, employs 4mm DIL CTV-PTV margins [219]. In this current study 4mm margins were also adopted. The concept of a DIL CTV-PTV margin within a larger (i.e. whole prostate) PTV margin is not consistent with the derivation of margins using the traditional 'van Herk' methods, which are based on the CTV receiving the appropriate dose with standard penumbra of 5mm, and doses falling from 95% at the edge of the PTV to 20% at the edge of the penumbra [235]. In the case of DILs, doses were falling from a median of 125% to around 100%. Furthermore, the dose fall-off around the DILs was relatively shallow, such that each DIL was generally well encompassed within the 95% isodose relevant to that DIL, thus adding additional coverage security to that created by the 4mm CTV-PTV DIL margin, to help account for intra-fraction motion as well as uncertainties in DIL definition and registration.

Adequately addressing the above issues, while relevant in the context of conventional fractionation, is even more important in the context of SABR, where the TCP and NTCP consequences of inaccurate dose delivery are greater.

The optimal organ at risk constraints for prostate SABR are unknown [96]. The same constraints as the HYPO-RT-PC trial, the phase III trial which delivers the same $PTV_{prostate}$ prescription [133] were adopted here, and additional constraints were added. Despite this relatively conservative approach, plans which included DIL boosts were sometimes associated with unacceptable rectal NTCP. The 'acceptable' level of grade 2+ late rectal complications has not been defined. QUANTEC suggests constraints for conventional 3D-CRT which should result in no more than 15% late grade 2+ rectal complications [229]. Most of the plans here satisfied this limit but five did not. Strong correlations between rectal Dmax0.5cc and rectal NTCP were demonstrated. This is

unsurprising as NTCP modelling considered the rectum as a serial structure, thus higher doses have greater impact on NTCP. Re-planning the five 'worst' cases, aiming to reduce rectal Dmax0.5cc yet still deliver the highest possible boost, resulted in considerable reductions in rectal NTCP, and only once was it necessary to reduce the PTV_{DIL} prescription to achieve this.

When considering alternative NTCP parameters for anorectal toxicities, and personalising NTCP based on a history of abdominal surgery, NTCP levels were generally low. Those plans where NTCP levels were highest, based on alternative parameters, were those where rectal NTCP was unacceptable using QUANTEC parameters, and the re-plans predicted acceptable NTCP levels.

In this study, DIL boost doses were escalated until organ at risk constraints were met. The variability in rectal NTCP shows that this strategy cannot be considered isotoxic. True isotoxic planning would involve specifying a maximum level of rectal NTCP and planning to achieve maximal TCP while respecting this. Indeed Azzeroni et al adopted this approach, although not in the context of SABR [210]. Similarly, however, they observed variability in TCP and concluded that maximising TCP for all patients would be limited by the need to maintain rectal NTCP within acceptable limits [210]. The proposed phase II BIOPROP (BIologically Optimised Prostate cancer Radiotherapy Or dose Painting) trial (Clatterbridge Cancer Centre) also plans to adopt an isotoxic approach to prostate planning. A dose of 60Gy in 20 fractions is prescribed to the whole prostate and image defined DILs are escalated up to a maximum median dose of 68Gy in 20 fractions based on fixed NTCP levels (5%) for rectal bleeding and faecal incontinence [236].

The applicability of the modelling approach adopted here in the setting of SABR is uncertain [229]. The TCP and NTCP models employed rely on the LQ-model. There is debate about the appropriateness of this model at high doses per fraction, therefore calling into question the validity of the calculations in this SABR study [237,238]. Two points, however, should be emphasised. Firstly, the concern about the validity of the LQ-model begins at fraction sizes of at least 10Gy [237,238], while the doses in this study were all less than 10Gy per fraction. Secondly, the concern regarding the LQ-model at high doses per fraction is that it over-estimates cell killing, thus over-

estimating NTCP [238]. The potential inaccuracies in the NTCP calculations in this study can therefore be considered safe. Regarding TCP, sensitivity analysis revealed TCPs based on α/β~1.5Gy are most robust to small changes in input parameters. If the 'true' TCP parameters for ultra-hypofractionation are slightly different to those adopted here, and if PCa α/β is ~1.5Gy, then these TCP calculations will be the most reliable. Long term clinical SABR data is required before these issues can be resolved.

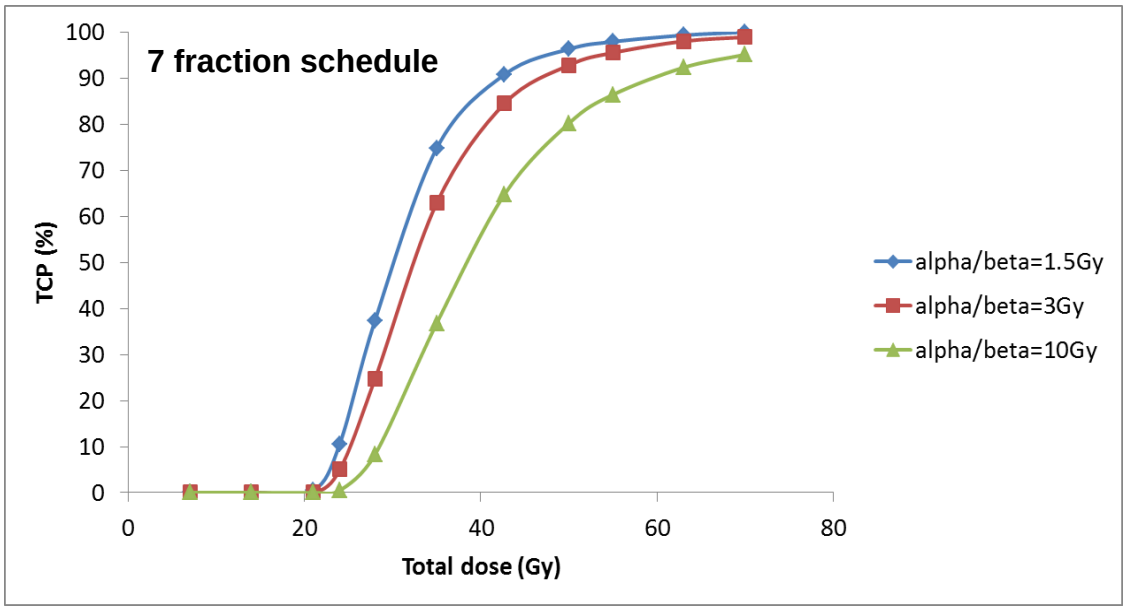
NTCP calculations used total rectal and bladder volumes, rather than structure walls. Total rectal volume is considered a suitable surrogate for the rectal wall if the rectum is empty, as occurred here, thus justifying this approach [239]. The parameters used for bladder NTCP estimation were originally designed using total bladder volume, and so this is how bladder NTCP was calculated here. It has also been suggested that bladder DVHs fit clinical data better than dose-wall histograms [240]. Similar to existing DIL planning studies which examine NTCP in the setting of boosting DILs [210,212,213,216], urethral NTCP was not estimated due to a lack of robust modelling parameters. The urethral constraints, however, were biologically equivalent to those for HDR brachytherapy, and included a maximum dose, which could limit problems similar to those encountered with rectal NTCP in the absence of a maximum dose constraint.

The differences between DILs and the non-DIL prostate are incompletely understood. A higher clonogen density in DILs than the remaining prostate was assumed and therefore the DILs and non-DIL prostate were handled separately. If DILs are the most likely source of local failure, then TCPs calculated for DILs are more relevant. CTVs were used for TCP calculations instead of PTVs, thus avoiding the uncertainties which arise since the CTV-PTV margin contains a lower clonogen density than the CTV. The α/β for PCa is debated. TCP varied with the α/β adopted: α/β=1.5Gy resulted in the highest TCP and the benefit of boosting DILs was least in this setting. Indeed, in non-boost plans, α/β=1.5Gy resulted in TCP greater than 94% and greater than 89% for the non-DIL prostate and DILs respectively. Non-boost plans were also associated with low rectal NTCP, and so, if PCa α/β is ~1.5Gy, then prostate SABR *without* DIL boosting is safe and acceptable. If α/β is higher, then TCP is more limited, even with DIL boosting, and boosting DILs to higher doses in an effort to achieve greater increases in TCP would cause unacceptable increases in rectal NTCP. As mentioned above, the uncertainties associated with DIL definition and registration will result in the realised

TCP from boosting being less than that calculated, thus reinforcing the role of SABR to the whole prostate without DIL boosting, if the α/β of PCa is ~1.5Gy.

The impact of the α/β ratio of PCa on TCP is further illustrated in Figure 3-4. TCPs were calculated in BioSuite using the parameters described in Table 3.3 using 'single dose' fictitious CTV_{DIL} DVHs (in practice, for BioSuite to calculate TCP, it was necessary to create DVHs where a small volume received 0.1Gy above and below the dose under investigation, thus DVHs had three dose levels: *x*Gy received by a $3cm^3$ volume, (*x*-0.1)Gy received by $0.01cm^3$ and (*x*+0.1Gy received by $0.01cm^3$). TCPs were calculated for doses based on a 7 fraction regimen.

Figure 3-4 Impact of prostate cancer α/β ratio and dose on TCP based on a seven fraction schedule



TCP: tumour control probability

As demonstrated from the calculations performed in this study, based on a 7 fraction schedule, differences in TCP with dose depend on the PCa α/β ratio. Based on α/β=1.5Gy, the non-boost prescription dose (42.7Gy in 7 fractions) is approaching the upper plateau of the dose-TCP curve, and so increases in dose have only a small effect on overall TCP. With α/β=10Gy, a dose of 42.7Gy falls on the steep part of the dose-TCP curve, and further increases in dose will initially result in more marked increases in TCP. Doses of above about 60Gy in 7 fractions (i.e. 141% of the prostate

prescription dose) are required before the upper plateau of the dose-TCP curve for α/β=10Gy is approached.

Although this planning study included some patients with higher risk disease than would be envisaged appropriate for treatment with this technique, this approach was justifiable as approximately 43% of patients with low-intermediate risk PCa have DILs identifiable on MRI [241]. Most patients also received neo-adjuvant androgen deprivation which is used less frequently in lower risk patients. If adopted clinically, the impact of hormonal therapy on DIL appearance would need to be considered where relevant [242].

Using BT to boost DILs in the context of whole prostate BT is an alternative option to this external beam technique. This approach has the advantage of removing the impact of prostate motion and, because of the rapid dose fall-off, higher boosts may be achievable while still respecting organ at risk constraints. For both these reasons, it may be that the gain achieved from boosting DILs in the context of BT would be greater than that achieved here. The uncertainties in terms of DIL definition and co-registration, however, still remain and, like the situation here, will reduce any realised TCP gain from boosting to less than any calculated gain.

In the previous chapter it was discussed that when prescribing whole prostate SABR, allowing gentle dose escalation but restricting the maximum point dose to 120% was unlikely to result in excessive urethral toxicity. In Chapter 2 the urethra was not defined and so this could not be confirmed. In this current study, urethras were defined on MRI by an experienced radiologist. In the non-boost plans, where a similar prescribing strategy was used as in Chapter 2, the median D50% dose received by the $PTV_{prostate}$ and prostate was 43.6Gy and 43.9Gy respectively while the doses received by the $PRV_{urethra}$ were well within tolerance (Table 3.11). Thus gentle dose escalation was achieved beyond the prescription dose of 42.7Gy, in keeping with the concept of SABR, while keeping the urethra well within tolerance, which should be reassuring when adopting non-boost whole prostate SABR in a clinical setting, although clinical trials will be required to establish if this strategy results in low levels of urethral toxicity in practice.

Table 3.11 Urethral doses ($PRV_{urethra}$) in non-boost plans (Plan set A)

	Median	Range	Constraint
D50% (Gy)	43.7	43.0-44.9	<50.7
D10% (Gy)	45.0	44.7-47.1	<53.3
Dmax (Gy)	46.3	45.3-48.1	<58.1

Since performing this work, two groups have published planning studies which investigate boosting DILs in the context of SABR. Tree et al published comparisons between Cyberknife™ and RapidArc® VMAT (as a double arc, Varian, USA) when used for SABR DIL boost delivery [243]. TCP and NTCP were not assessed. For a series of fifteen patients, the whole prostate and proximal SV were prescribed 36.25Gy in 5 fractions ($EQD2_{1.5}$=91Gy) while the DIL regions (defined on T2-weighted and DW MRI) were simultaneously boosted to 47.5Gy ($EQD2_{1.5}$=149Gy). For the purposes of a pure dosimetric comparison, plans for both Cyberknife™ and RapidArc® were generated using 5mm CTV-PTV margins in all directions, except for 3mm posteriorly. For DILs, a 0mm CTV-PTV margin was adopted. Based on this comparison, rectal and bladder doses were generally higher for Cyberknife™, although for both technologies, the same number of rectal dose constraints (11 out of 75), and a similar number of bladder dose constraints, were exceeded. The RapidArc® plans were also produced with larger CTV-PTV margins (8mm in all directions except for 5mm posteriorly) around the prostate and proximal SVs, to represent the situation where intra-fraction motion monitoring was not available. Again, a 0mm margin was used around the DILs. Increasing the size of the CTV-PTV margin resulted in increased rectal and bladder doses, and a marked increase in the number of exceeded rectal constraints to 37 out of 75. In addition, at least one constraint was exceeded in 13 out of 15 plans, highlighting the difficulty with larger CTV-PTV margins when a fixed boost level is required [243]. These problems could perhaps have been avoided by adopting an approach similar to the one used in this current study, by varying the boost dose, depending on rectal and bladder doses.

In addition, Udrescu et al recently published a planning study comparing prostate SABR delivering: i) 32.5Gy in 5 fractions to the $PTV_{prostate}$ ($EQD2_{1.5}$=74Gy), ii) 40Gy in 5 fractions to the $PTV_{prostate}$ ($EQD2_{1.5}$=109Gy) and iii) 32.5Gy in 5 fractions to the

$PTV_{prostate}$ with a simultaneous boost of 40Gy to DILs (defined using T2-weighted and DCE MRI sequences) [244]. A 3mm CTV-PTV margin was applied to the prostate and a 5mm margin (3mm posteriorly) was applied to the DILs, based on daily online image guidance of fiducial markers using CBCT and intra-fraction motion tracking. No dose constraints were adopted, except plans were optimised to ensure that the rectum, bladder and femoral head doses were as low as possible while maintaining coverage. A 9-field coplanar IMRT technique was used for planning. Dose escalation to the whole prostate (from 32.5Gy to 40Gy) resulted in increases in all rectal and bladder dose parameters other than maximum rectal dose. Focal dose escalation to the DILs also resulted in increases in all rectal and bladder dose parameters, other than the median bladder dose and the dose received by $25cm^3$ of bladder. The magnitude of the increase in rectal and bladder doses with focal dose escalation, however, was about half of that observed when escalating the whole prostate to 40Gy, and so the group concluded that focal boosting was the preferable option and required validation in clinical trials [244]. The TCP and NTCP consequences of dose escalation were not evaluated, and so the value and harm of this approach cannot be assessed.

3.5 Conclusions

Accepting the limitations and uncertainties discussed above, it is technically feasible to create SABR VMAT plans which boost DILs. This increases TCP. Rectal NTCP also increases and can become unacceptable, although high levels of rectal NTCP can be reduced by minimising maximum rectal doses. TCP is influenced by prostate α/β ratio. The higher the true α/β in PCa, the smaller the gap between doses required for adequate tumour control and acceptable rectal toxicity. Boosting DILs in the context of SABR should be approached with caution. If adopted, strict organ at risk constraints are required, including maximum rectal dose constraints. If PCa α/β is ≤1.5Gy, then for most patients, high TCP can be achieved with low NTCP by delivering one SABR dose to the whole prostate, without DIL boosting, and thereby avoiding the uncertainties associated with the DIL definition and planning process.

3.6 Acknowledgements

Dr Brendan Carey for contouring DILs, urethras and prostates on MRI sequences.

Mr Christopher Thompson for advice on creating the prescription in Monaco® and for transferring images into Monaco®.

Mr John Lilley for reviewing plans.

Mr Joshua Mason for assistance with image co-registration, for providing details of the MRI scanning protocols (contained in first paragraph in Methods section) and for providing the MRI images used in Figure 3-1 of Chapter 3.

Chapter 4 : Impact of flattening filter free mode on prostate stereotactic ablative radiotherapy (SABR) planning

4.1 Introduction

Conventional radiotherapy is delivered with a flattening filter placed within the machine head to compensate for the non-uniform, forward-peaked photon fluence generated from the target, thus creating a flat uniform profile across the full width of the radiotherapy field. With modern planning systems and MLCs which move during treatment, photon fluence can be modulated as required, without the need for the flattening filter. As such, there has been increasing interest in the removal of the flattening filter from the machine head. This has been shown to have several advantages including increased dose rates and reduced out-of-field doses [245].

The feasibility of planning prostate radiotherapy without a flattening filter has not been extensively investigated. Two groups have demonstrated the equivalence of prostate treatment plans using flattening filter free (FFF) and standard (flattened) beams in the setting of conventionally fractionated IMRT planned using Varian (USA) planning systems [246,247]. As well as no significant difference in plan quality, both groups observed a reduction in the number of MU required for treatment delivery using FFF [246,247]. One other group recently compared FFF with standard (flattened) prostate plans in the context of Rapid Arc® VMAT (Varian, USA) and moderate hypofractionation (57Gy in 19 fractions) [248]. Again, using Varian systems, dose distributions were similar for FFF and flattened plans. Compared to standard (flattened) plans, FFF plans had shorter delivery times when a single arc was adopted, while MU requirements were greater [248].

The impact of FFF on prostate planning in the context of SABR has not yet been investigated and, given the evidence above, although equivalence in dose distributions would be expected, this should be confirmed if SABR FFF techniques are considered for clinical implementation. This study therefore aims to compare prostate VMAT

planning for SABR using FFF and standard (flattened) beams. In contrast to the above studies, plans were generated using an Elekta (Sweden) platform with energy-matched flattened and FFF beams. Removal of the flattening filter removes a source of beam hardening and as such the energy of the FFF beam drops compared to the equivalent flattened beam. Elekta systems, however, 'retune' the beam to match the relative dose in water at 10cm deep for a 10x10cm standard 6MV beam, 100cm source-to-surface distance [249].

4.2 Methods

4.2.1 Planning

Fifteen prostate datasets were used for planning. Based on the class solution developed in Chapter 2, plans were generated using a single anterior 210° VMAT arc (255°→105°) with the Agility™ Head (Elekta AB, Sweden) and 6MV standard (flattened) and energy-matched FFF beams. As before, the PD was 42.7Gy in 7 fractions. Planning was performed using Monaco version 3.3 (Elekta AB, Sweden) with a MC calculation, a maximum of 150 control points per arc and 1% MC uncertainty per plan. A 2mm calculation grid was employed for enhanced dosimetric information (in contrast to the 3mm grid employed in Chapter 2). Coverage requirements were based on those used in Chapter 2 with the additional requirement that the volume of CTV receiving 100% of the PD was at least 95% (i.e. CTV V42.7Gy≥95%) (Table 4.1), thus giving the PD a defined role in the prescription. Organ at risk constraints for the rectum, bladder, FHs and bowel were also those adopted in Chapter 2 (Table 4.1).

Table 4.1 Coverage requirements and organ at risk constraints

Volume	Requirement/ Constraints
$CTV_{prostate}$	Minimum dose=40.6Gy (95%)
$CTV_{prostate}$	Volume receiving 42.7Gy (V100%)≥95%
$PTV_{prostate}$	Volume receiving 40.6Gy (V95%)≥95%/ Dose to 95%(D95%)≥40.6Gy (95%)
$PTV_{prostate}$	Dose to 99% (D99%) ≥38.4Gy (90%)
Maximum dose	Dmax<120% (51.2Gy)
Conformity index*	≤1.2
R50**	≤5.5
Maximum dose at 2cm from PTV	≤29.9Gy (70%)
Rectum (recto-sigmoid junction to anus)	V41.4Gy(97%)<3%
	V38.4Gy(90%)≤15%
	V32.0Gy(75%)≤35%
	V28.0Gy(65%)≤45%
	V24.8Gy(58%)<70%
	V19.6Gy(46%)<80%
Bladder	V41.4Gy(97%)<5% V34.7Gy(81%)<25% V29.9Gy(70%)<50%
Femoral heads	Dmax≤29.9Gy (70%)
	V29.9Gy(70%)<50%
Bowel	V29.9Gy(70%)<17cc
Penile bulb†	V29.9Gy(70%)<50% V34.7Gy(81%)<10%

* Conformity index: volume of the 95% isodose/volume of PTV,

**R50: volume of 50% isodose/volume of PTV,

†dose constraints for the penile bulb were for guidance only and did not have to be achieved.

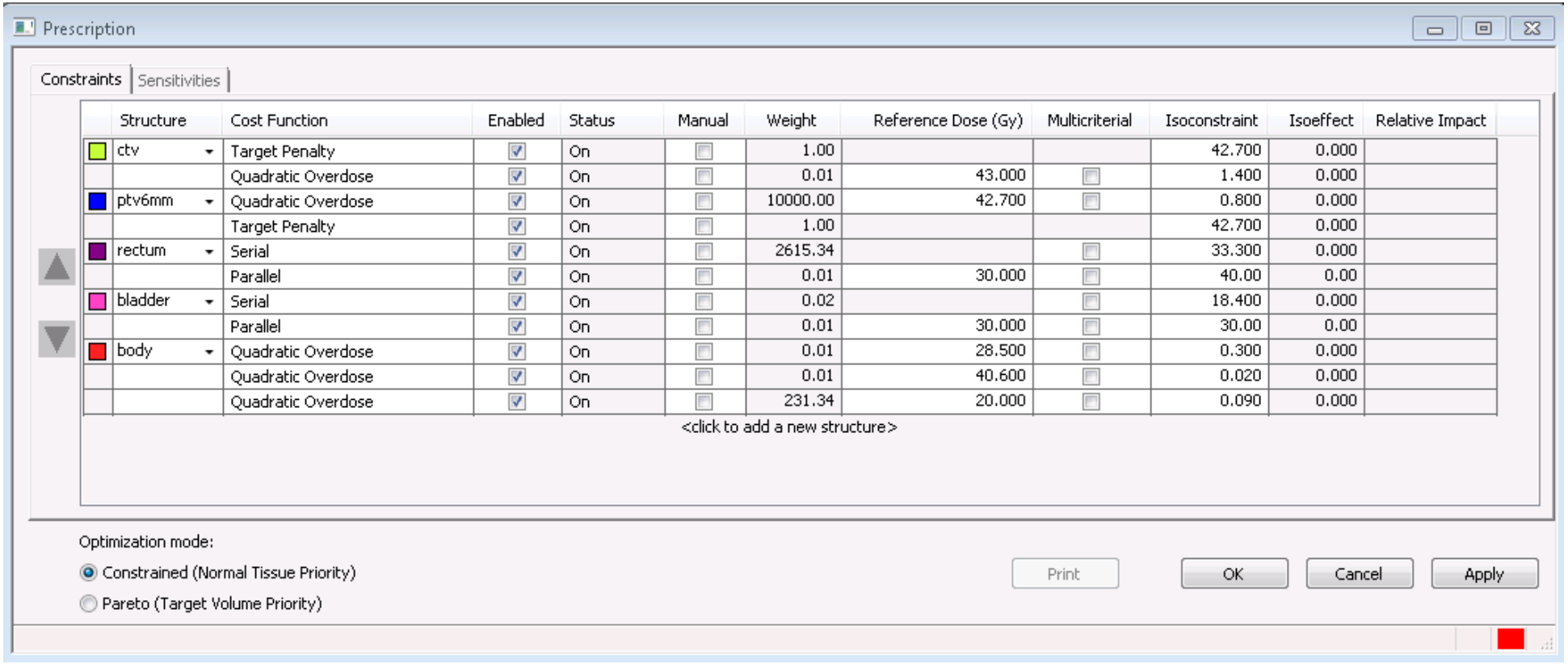
The final prescription is shown in Figure 4-1. Explanations for the various cost functions are those described in Chapter 2. It was found that the ‘Underdose DVH’ was not as necessary using Monaco® version 3.3 as it was when using version 3.2 in Chapter 2, and so this was omitted from the prescription, unless obtaining coverage proved difficult based on the ‘Target penalty’ function alone.

4.2.2 Plan evaluation

Plans were evaluated and compared according to:

- CTV: median dose (D50%), D2%, D98% and volume receiving 100% of the PD (V100%)
- PTV: D50%, D2%, D98% and D95%
- Organ at risk mean doses and D2%
- Volume of rectum and bladder receiving at least 95% (V95%), 80% (V80%), 50% (V50%) and 20% (V20%) of the PD to reflect very high, high, intermediate and low doses respectively
- CI: volume of 95% isodose/PTV volume [195]
- conformation number (CN): (Volume of PTV receiving 95% isodose/PTV volume) x (Volume of PTV receiving 95% isodose/volume of 95% isodose) [195]
- homogeneity index (HI): (D2%-D98%)/D50% [196]
- R50: volume of 50% isodose/PTV volume
- maximum dose 2cm from PTV (Dmax2cm)
- MU per fraction
- estimated delivery time (EDT)

Figure 4-1 Prescription



4.2.3 Statistics

The Wilcoxon signed-rank exact test was used to compare parameters for FFF and standard (flattened) plans as data was not presumed to be normally distributed. Median values and ranges are therefore presented. SPSS v19.0 (IBM Corporation, Armonk, New York, USA) was used for calculations. Tests were two-tailed. As for Chapter 2 part III, $p \leq 0.005$ was considered statistically significant to account for multiple statistical testing (a full Bonferroni correction would be over-conservative as several factors would not be independent of others).

4.2.4 Verification

For one dataset, both the standard (flattened) and FFF plans were verified on a Synergy® linear accelerator (Elekta AB, Sweden) with conventional and high dose rate modes using the Delta4 phantom (ScandiDos AB, Sweden) and using a semi-flex chamber (PTW, Freiburg, Germany) positioned within an in-house solid water IMRT phantom.

4.3 Results

4.3.1 Plans

Plans were successfully generated using standard (flattened) and FFF beams and all mandatory constraints (i.e. rectal, bladder and FH constraints) were met. In addition, fourteen of the fifteen standard (flattened) and corresponding FFF plans met both PB constraints, and doses were well within the desired limits. In the one remaining case, the PTV overlapped with the PB, thus it was not possible to maintain coverage and respect the PB constraints. Target coverage is shown in Table 4.2 and conformity, MU requirements and estimated delivery times are shown in Table 4.3. Doses to organs at risk are shown in Table 4.4.

Target coverage (Table 4.2), conformity and homogeneity (Table 4.3) were equivalent between standard (flattened) and FFF plans other than for a small but statistically significant reduction in the maximum dose at 2cm from the PTV (Dmax2cm) using FFF compared to standard (flattened) beams (median Dmax2cm FFF vs. flattened: 24.8Gy vs. 25.5Gy, p=0.004; Table 4.3).

With regard to organ at risk doses, there was a statistically significant increase in rectal V80% using FFF but this was not clinically relevant (median rectal V80% FFF vs. flattened: 10.2% vs. 10.0%; Table 4.4). There was a small but statistically significant increase in mean PB dose with FFF compared to flattened plans, and there was a significant increase in PB D2% (Table 4.4).

Table 4.2 Plan statistics for FFF plans compared to flattened plans: coverage

Median (and range). $p \leq 0.005$ considered statistically significant

	Standard (Flattened)	FFF	*p* value (if significant)
CTV coverage			
D50% (Gy)	44.4 (43.8-45.0)	44.5 (44.0-45.0)	-
D2% (Gy)	46.1 (43.4-47.0)	46.2 (45.6-47.4)	-
D98% (Gy)	42.8 (42.4-43.4)	42.8 (42.4-43.3)	-
V100% (%)	98.4 (95.6-100)	98.9 (95.7-100)	-
PTV coverage			
D50% (Gy)	43.5 (43.3-43.9)	43.7 (43.3-43.9)	-
D2% (Gy)	45.8 (45.0-46.7)	45.8 (45.3-46.9)	-
D98% (Gy)	40.5 (39.8-41.0)	40.2 (39.8-41.2)	-
D95% (Gy)	41.2 (40.6-41.6)	40.8 (40.7-41.7)	-

FFF: flattening filter free

Table 4.3 Plan statistics for FFF plans compared to flattened plans: dose spread, monitor unit requirements and estimated delivery times

Median (and range). $p \leq 0.005$ considered statistically significant

	Standard (Flattened)	FFF	*p* value (if significant)
Dose spread			
Conformity index*	1.06 (1.00-1.11)	1.04 (1.00-1.15)	-
Conformation number†	0.89 (0.86-0.92)	0.90 (0.86-0.91)	-
Homogeneity index‡	0.12 (0.10-0.15)	0.13 (0.10-0.16)	-
Maximum dose at 2cm (Gy)	25.5 (23.0-29.3)	24.8 (22.6-29.2)	*p*=0.004 FFF<flattened
R50^	3.6 (3.3-3.8)	3.6 (3.4-4.0)	-
Delivery parameters			
Monitor units per fraction	1621 (1422-1818)	1681 (1467-1813)	*p*=0.002 flattened<FFF
Estimated delivery time (seconds)	169.7 (149.8-189.5)	87.5 (78.9-96.7)	*p*<0.001 FFF< flattened

FFF: flattening filter free

* Conformity index: volume of the 95% isodose/volume of PTV

† Conformation number: (Volume of PTV receiving 95% isodose/ volume of PTV) x (Volume of PTV receiving 95% isodose/volume of 95% isodose),

‡ homogeneity index: (D2%-D98%)/D50%,

^R50: volume of 50% isodose/volume of PTV

Table 4.4 Plan statistics for FFF plans compared to flattened plans: organs at risk

Median (and range). $p \leq 0.005$ considered statistically significant

	Standard (flattened)	FFF (flattening filter free)	*p* value (if significant)
Rectal Dmean (Gy)	13.7 (10.2-15.6)	13.8 (10.4-15.6)	-
Rectal D2% (Gy)	41.9 (41.7-42.1)	41.8 (41.5-42.4)	-
Rectal V95% (%)	4.0 (3.3-4.8)	4.1 (3.4-4.8)	-
Rectal V80% (%)	10.0 (6.5-14.4)	10.2 (6.9-14.5)	*p*=0.003 flattened<FFF
Rectal V50% (%)	22.1 (13.9-31.3)	22.6 (14.5-31.2)	-
Rectal V20% (%)	58.3 (43.7-70.4)	59.4 (44.3-71.3)	-
Bladder Dmean (Gy)	7.0 (4.1-10.3)	7.1 (4.2-10.2)	-
Bladder D2% (Gy)	43.0 (39.4-43.7)	42.6 (39.5-43.8)	-
Bladder V95% (%)	3.6 (1.7-5.7)	3.5 (1.8-5.5)	-
Bladder V80% (%)	5.9 (2.9-8.9)	5.9 (3.0-9.0)	-
Bladder V50% (%)	12.6 (6.7-19.0)	12.6 (6.7-19.2)	-
Bladder V20% (%)	22.1 (12.8-41.4)	22.6 (13.5-41.2)	-
Left femoral head Dmean (Gy)	9.8 (0.7-13.0)	10.1 (0.7-13.1)	-
Left femoral head D2% (Gy)	16.1 (1.8-18.3)	16.1 (2.1-19.0)	-
Right femoral head Dmean (Gy)	10.7 (1.5-15.0)	11.0 (1.6-15.2)	-
Right femoral head D2% (Gy)	19.0 (8.7-20.2)	18.7 (9.6-20.1)	-
Bowel Dmean (Gy)	0.6 (0.2-1.7)	0.6 (0.2-1.8)	-
Bowel D2% (Gy)	1.6 (0.6-13.6)	1.7 (0.6-12.2)	-
Penile bulb Dmean (Gy)*	3.1 (1.2-36.2) 3.0 (1.2-9.6)	3.6 (1.2-35.5) 3.5 (1.2-10.6)	*p*=0.004 flattened<FFF *p*=0.001 flattened<FFF
Penile bulb D2% (Gy)*	7.4 (1.7-43.5) 6.3 (1.7-31.5)	9.1 (1.7-43.6) 9.0 (1.7-32.6)	*p*<0.001 flattened<FFF *p*<0.001 flattened<FFF

* lower line of data is with the dataset which failed to meet penile bulb constraints because of overlap with PTV omitted

FFF plans required a statistically significant increase in MU (FFF vs. flattened: 1681 vs. 1621 MU per fraction, p=0.002) and estimated delivery times using FFF were significantly shorter (FFF vs. flattened: 87.5 seconds vs. 169.7 seconds, p=0.001) (Figure 4-2; Table 4.3).

The similarity between standard (flattened) and FFF plans in terms of target coverage and rectal and bladder doses is illustrated in Figure 4-3.

Figure 4-2 Box and whisker comparison of treatment times for flattening filter free (FFF) and standard (flattened) plans

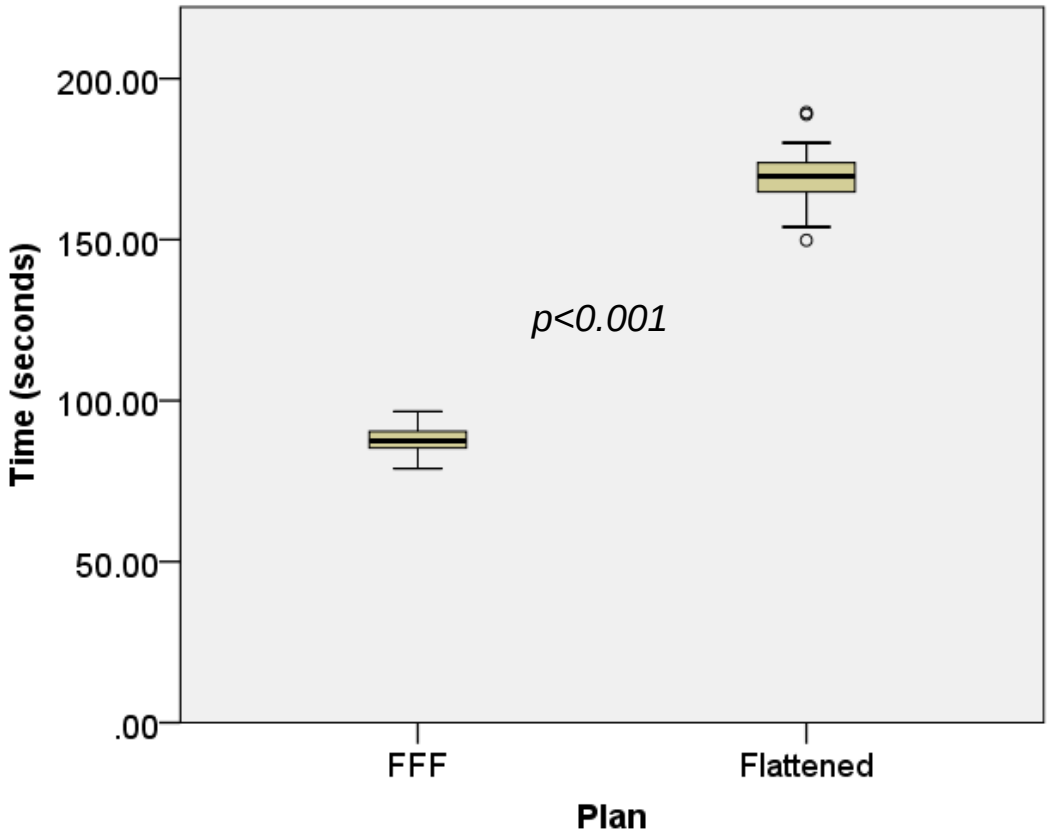
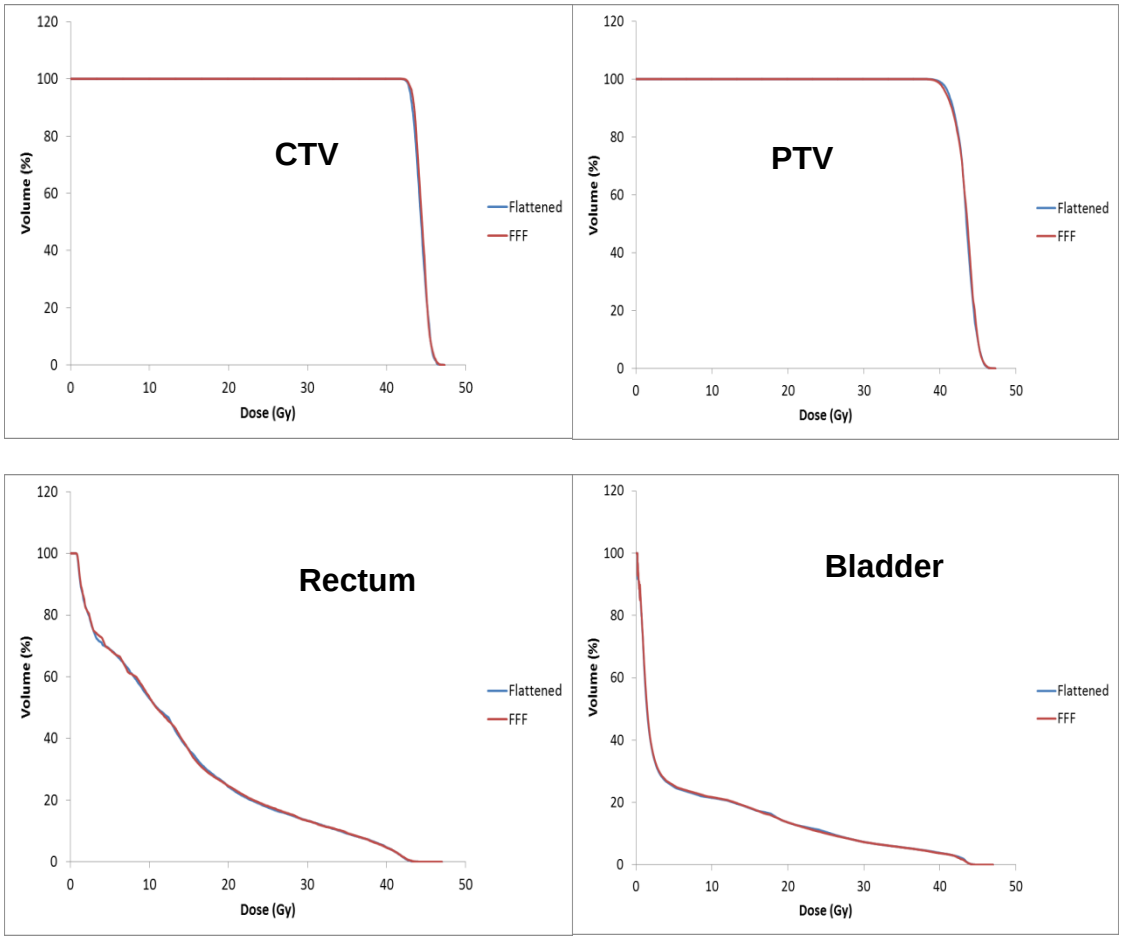


Figure 4-3 Dose-volume histograms for standard (flattened) and flattening filter free (FFF) plans (median values plotted)



It was noted that there were small but statistically significant increases in right FH mean dose compared to left FH mean doses in both FFF and flattened plans (median values, mean dose right FH vs. left FH: 11.0 vs. 10.1Gy, p=0.002 for FFF plans, 10.7 vs. 9.8Gy, p=0.003 for flattened plans). In addition, there were significant increases in right FH D2% compared to left FH D2% in both FFF and flattened plans (median values, D2% right FH vs. left FH: 18.7 vs. 16.1Gy, p=0.001 for FFF plans and 19.0 vs. 16.1Gy, p=0.001 for flattened plans). All FH doses, however, were very well within tolerance (Dmax=29.9Gy and V29.9Gy<50%), making the differences in left and right FH doses of little clinical concern.

4.3.2 Verification

The standard (flattened) and FFF plan both passed the Delta4 verification with scores of 100% at 3%/3mm. For the chamber measurement, there was 0.1% difference in the measured dose from the expected dose for the standard (flattened) plan and, for the FFF plan, there was 0% difference between the measured and expected doses (<3% difference is optimal, <5% difference is mandatory). Measured delivery times for the standard (flattened) and FFF plans were 163 seconds and 84 seconds respectively.

4.4 Discussion

Standard (flattened) and FFF prostate SABR VMAT plans were similar in terms of target coverage and rectal, bladder and FH doses, and both types of plan passed verification well. The largest advantage of FFF over standard (flattened) plans was in terms of more rapid delivery times: median estimated delivery times improved from 170 seconds per fraction to 88 seconds with FFF. The delivery time advantage of FFF was also confirmed during verification.

Faster delivery times offer patient benefits in terms of reducing the opportunity for intra-fraction motion, which has been shown to become increasingly problematic with increasing treatment time [199]. Potentially, faster delivery times could potentially allow smaller CTV-PTV margins to be adopted [164], which could, in turn, facilitate dose escalation and/ or reduced toxicity. Faster delivery times also provide service delivery benefits, allowing greater throughput and efficiency within the Radiotherapy Department.

The equivalence between standard (flattened) and FFF prostate planning has previously been demonstrated in the context of IMRT with conventional fractionation [246,247], as well as in the context of VMAT (RapidArc®) and moderate hypofractionation [248]. The feasibility of prostate radiotherapy planning in the context of SABR VMAT using energy-matched FFF beams and an Elekta platform has not previously been demonstrated, and so this exercise is worthwhile.

An increased number of MU were required for delivery of FFF plans in this study. This is not unexpected in the setting of FFF beams where the centrally peaked non-flattened beam profile means that more MU are required to deliver off-axis doses. Where beams are not energy-matched, then increased MU are also required to compensate for the drop in beam energy resulting from the loss of beam hardening. The two studies which compared standard and FFF prostate planning in the setting of conventional fractionation using Varian systems, however, found that a lower number of MU were required for FFF treatments [246,247]. Despite appearing contradictory, this finding can be explained by the fact that neither of these studies recalibrated the FFF beam MU to match those of the flattened beam, and so simply removing the flattening filter without MU recalibration resulted in an increase in dose per MU for the FFF beam, thus the expected increase in MU for FFF plan delivery was not observed [246,247]. The one study comparing standard and FFF plans in the context of moderate hypofractionation did observe an increase in the number of MU required for FFF treatments [248]. Here the FFF beam MU had been recalibrated to match the flattened beam such that 100MU resulted in 1Gy being delivered to the maximum depth dose [248], as was the case in this current study. To overcome the lower dose off-axis profile of the FFF beam, and the loss of beam energy in the setting of non-energy-matched beams, the increase in MU is as expected.

There was a small dosimetric disadvantage to FFF in terms of PB mean dose and D2%. For all but one dataset, the doses received by the PB were well within the specified PB constraints, and so the small increase in dose resulting from FFF is unlikely to be of clinical significance. In the one remaining case, the PTV overlapped with the PB, and constraints could not be met for either standard or FFF planning. It is acknowledged that the PB itself is not the organ critical for normal erectile function [250,251]. Despite this, a dose-volume relationship between PB dose and risk of erectile dysfunction has been demonstrated and QUANTEC recommends that the mean dose received by 95% of the PB should not exceed 50Gy and that it may be appropriate to also keep the dose received by 70% (i.e. D70%) of the structure to less than 70Gy and the dose received by 90% of the structure (i.e. D90%) to less than 50Gy, although target coverage should not be compromised to achieve these goals [250,251]. If the biologically equivalent doses reported by QUANTEC are recalculated for a 7 fraction schedule, then the mean dose to 95% of the PB should be

<29.9Gy, D70% should be <39.5Gy and D90% should be <29.9Gy. As with the constraints used for planning here, 14 of the standard (flattened) and corresponding FFF plans met the QUANTEC recommendations comfortably. As above, therefore, the significance of the higher PB mean and D2% doses with FFF plans observed here is unlikely to be clinically relevant for the majority of patients.

For both the standard (flattened) and FFF plans, a small amount of asymmetry in terms of FH mean doses and D2% was noted. Doses, however, remained very well within tolerance for all patients and are therefore unlikely to be clinically relevant. Indeed, asymmetry in FH doses but which remain within tolerance, when observed elsewhere, has not been felt to be of clinical concern [252,253].

FFF has also been shown to result in reduced out-of-field doses [245], which potentially could result in a reduction in the risk of radiation-induced second cancers. This will be investigated in Chapter 6.

Since commencing this work one group has reported preliminary outcomes (median follow-up 11 months) for a cohort of 40 low and intermediate risk PCa patients treated with linear accelerator-based SABR delivering a dose of 35Gy in 5 fractions using RapidArc® VMAT with 10MV FFF (one or two full arcs were employed, the CTV contained the prostate and, in cases at higher risk of SV invasion, some or all of the SV were also included and 3-5mm CTV-PTV margins were used) [84]. All plans met the desired constraints. Grade 2 CTCAEv4 acute rectal and GU toxicity was reported in 10% and 40% of cases respectively, and no grade 3 or greater acute toxicities occurred [84]. A spacer gel was used selectively in eight patients to increase the rectal-prostate distance [84]. These initial clinical results, reporting the implementation of FFF beams in prostate SABR are encouraging, but longer clinical follow-up is required to establish efficacy and long-term toxicity.

4.5 Conclusions

In summary, prostate SABR VMAT planning is feasible using FFF, and results in similar target coverage, conformity and rectal, bladder and FH doses. Plans were also deliverable. The biggest advantage of FFF planning was the significant improvement in delivery time, which offers both patient and service delivery benefits.

4.6 Acknowledgements

Mr Christopher Thompson for his assistance in verification of the two plans.

Dr Mitchell Naisbit for producing the median data used to generate DVH curves.

Chapter 5 : Radiation-induced second primary cancers in patients irradiated for prostate cancer: a systematic review of clinical evidence

5.1 Introduction

The development of a radiation-induced second primary cancer (RISPC) is one of the most serious long term consequences of successful cancer treatment. Patients diagnosed with early or locally advanced PCa face a variety of treatment options, several of which involve ionising radiation: EBRT, BT or combination EBRT-BT might be employed. Modern radiotherapy techniques such as IMRT result in changes in dose distribution and scatter which have resulted in theoretical concerns about an increased risk of RISPC [254]. Patients are now diagnosed with PCa at an earlier stage than in the past and so may receive treatment sooner in the course of the disease. In addition, patients now survive for longer following their diagnosis. As such the long term consequences of treatment, including the risk of RISPC, become particularly relevant.

Studies of Atomic bomb survivors demonstrated that there is a latency period of at least five years before the development of solid RISPCs [255]. A second primary cancer (SPC) is generally considered radiation induced if: i) it is diagnosed after a latency period (usually considered to be five years or more) following irradiation, ii) it occurs within the radiation field (for prostate radiotherapy, this includes the rectum, bladder, anus, prostate, soft tissues, bones or joints of the pelvis and pelvic lymphoma), iii) it is a different histological type to the original cancer and iv) the second tumour was not evident at the time of radiotherapy [256,257]. More commonly, PCa patients may develop subsequent SPCs which are not radiotherapy induced, but are the result of genetic and environmental factors. The distinction between RISPC and SPC can become blurred as regions beyond the primary radiation field are exposed to scattered doses of radiation, and theoretically these may increase the risk of RISPCs in out-of-field regions.

When evaluating SPCs in irradiated PCa patients, registry databases provide very large numbers of patients for analysis, and therefore have sufficient power to observe differences between patient groups. The information within registries, however, is less complete than that from institutional series. In depth details regarding treatment are often absent and details of potential confounding factors (e.g. smoking status) are often not recorded. Reaching valid conclusions about the impact of radiation from multivariate models when important information regarding potential cofounders is missing, is therefore challenging. Registries may also suffer from under-reporting of SPCs, particularly in elderly patients.

Institutional data provides more detailed information and so confounding factors may be easier to identify. Patient numbers, however, are smaller and therefore the power to detect real differences in SPC incidences is limited. Institutional data does not come with its own 'normal population' for comparison, and so external comparators must be used. Some institutional studies only report crude rates of SPC, rather than making comparisons with SPC in non-irradiated patients or the general population, thus limiting the usefulness of this data. Series examining survival following prostate irradiation may report numbers of deaths due to SPCs but, again, risk comparisons may not be performed.

This work reviews published registry and institutional data with particular regard to the impact of treatment technique on the risk of second cancers.

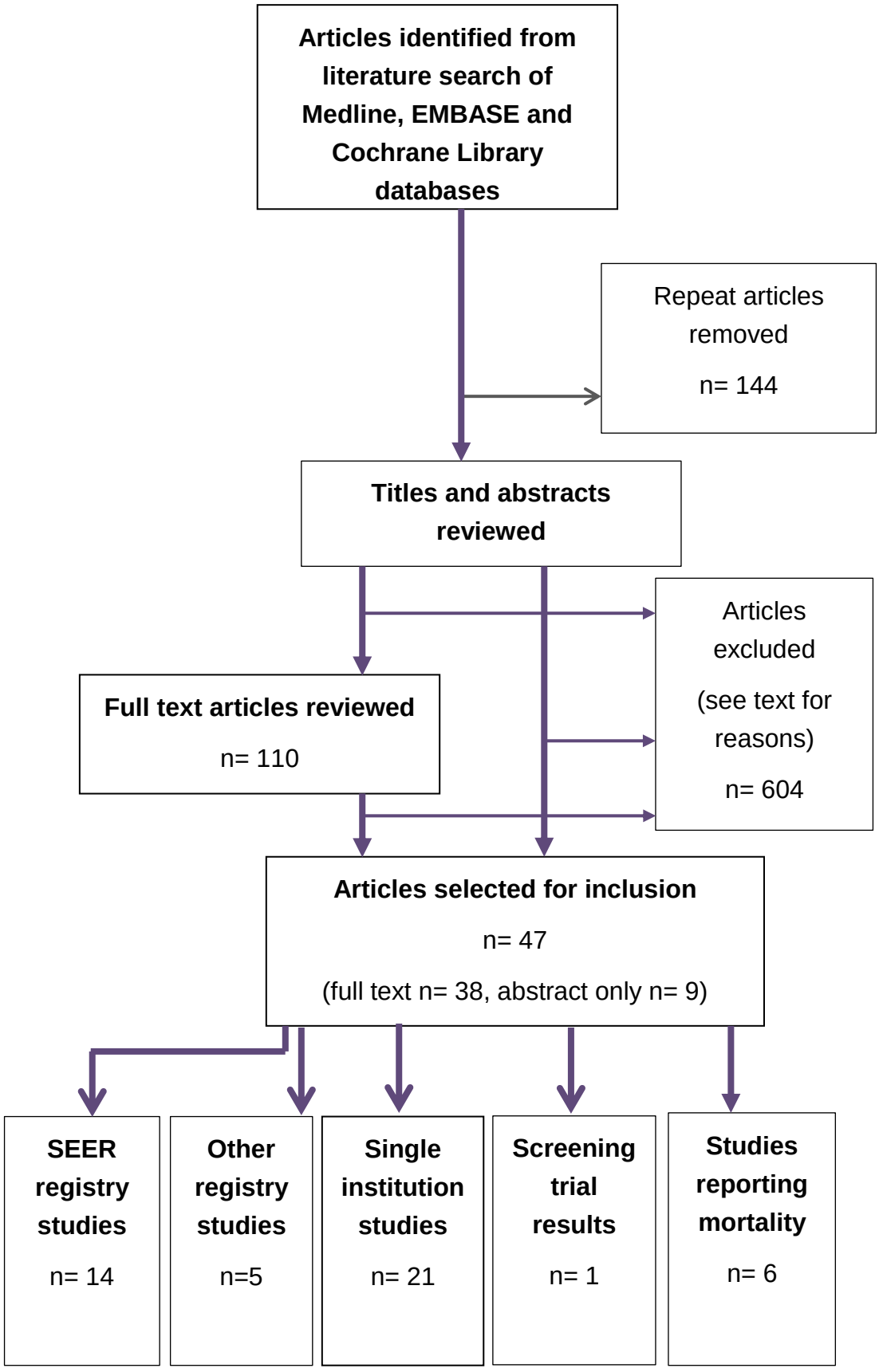
5.2 Objectives

To evaluate SPCs in PCa patients treated with radiotherapy, and to evaluate whether different radiotherapy techniques result in different risks of SPCs.

5.3 Methods

A systematic search of the literature was performed using Medline, EMBASE (Excerpta Medica dataBASE) and the Cochrane Library databases. Search terms were related to SPC and RISPC, and radiotherapy and PCa. The actual search terms are shown in Appendix D. References and “related articles” of relevant articles were also reviewed. Studies in English which reported rates of, or mortality from, SPC overall, or rectal or bladder cancer specifically, following curative irradiation for prostate adenocarcinoma were included. Studies published in full text and abstract form were included. Studies involving radiotherapy for paediatric and non-adenocarcinoma PCa were excluded. Studies examining prostate cancers as a whole, without specifically differentiating between treatment modalities were also excluded (i.e. where SPCs in surgically and irradiated patients were not examined separately). Case studies and series limited to 10 or fewer patients, and studies examining palliative radiotherapy alone, were excluded. The last search was performed on the 10th September 2013. This strategy identified 651 different articles. Reasons for exclusion included articles: not dealing with SPC (n=241), planning studies (n=101), primary tumour not prostate adenocarcinoma (n=74), about management of SPC but not risk (n=3), review articles (n=53), case reports (n=25), not in English language (n=24), patients treated with non-standard therapy (e.g. high dose chemotherapy; n=6), letters/editorials without new data (n=19), studies reporting laboratory based work (n=6), early versions of later full study (n=14), patients treated with palliative therapies alone (n=20), studies examining risks related to concomitant imaging (n=3), studies examining PCa patients as a whole but not examining irradiated PCa patients specifically (n=2), studies examining specific second cancer other than rectal or bladder cancer (n=3) and studies that evaluated risk from radiation but did not specifically evaluate risks from PCa radiation (n=10). In total, 14 SEER (Surveillance, Epidemiology and End Results) registry, 5 other registry and 21 institutional studies were identified, as well one abstract which reported the results of a screening trial that examined second cancers and 6 studies which reported only mortality due to SPC (Figure 5-1).

Figure 5-1 Schema of article selection process



5.4 Results

The majority of evidence addresses SPC and RISPC in patients treated with primary EBRT (mainly in the form of non-conformal and 3D-CRT techniques) which is discussed initially, considering risk of SPC overall, then rectal cancer and then bladder cancer, before evaluating SPCs following other irradiation techniques. Throughout this review, crude rates are stated as such and, wherever available, adjusted risk ratios and comparisons are presented in preference to unadjusted figures.

5.4.1 Overall second cancer risk associated with EBRT for prostate cancer

Compared to the general (i.e. non-prostate cancer) population, 5 out of 5 registry studies did not find irradiated patients to be at any significantly increased risk of SPC, both when considering all durations of follow-up (i.e. beyond any exclusion periods) and also when considering follow-up beyond five years [258-262] (Table 5.1). Although not reaching the threshold for statistical significance, Rapiti et al did conclude that compared to the general population, irradiated PCa patients were at a slight increased risk beyond five years which the group considered to be of "borderline significance" (p=0.056) [262]. Brenner et al found irradiated PCa patients to be at a significantly reduced risk of SPCs (Standardised incidence ratio (SIR): 0.89) compared to the general population, although when patients under the age of 60 were considered alone, no difference in risk was observed [259]. The low SPC incidence observed amongst irradiated PCa patients was attributed to the relatively elderly population evaluated. Bagshaw et al, a single institution study, also found irradiated patients not to be at increased risk of SPC compared to the general population [263].

Comparing irradiated PCa patients with a non-irradiated PCa cohort may be considered more representative than comparisons with the general population, and in this situation different results are observed to those above (Table 5.2). All four registry studies found irradiated patients to be at increased risk of SPC compared to non-irradiated PCa patients [258,259,261,264]. This increased risk began after one year of follow-up in two of these studies [258,264], and was observed after five years of follow-

up in the three studies which specifically examined this time period [259,261,264].Risk increased further beyond 10 years of follow-up in the one study which examined this period [259]. Similarly, data from prostate patients treated within the PLCO (prostate, lung, colorectal and ovarian) screening trial demonstrated that irradiated PCa patients had a significantly increased risk of any second cancer beyond 30 days and beyond 5 years compared to non-irradiated PCa Patients (rate of any SPC: 15.5/1000 person-years in irradiated patients vs. 11.4/1000 person-years in non-irradiated patients) [265].

In terms of single institution studies, Huang et al compared SPC incidence between 2120 irradiated and 2120 surgically treated patients within a matched-pair analysis [266]. Most irradiated patients were treated with EBRT alone (as opposed to with EBRT-BT). Over all durations of follow-up there was no significant increased risk of SPC in irradiated patients, but, in keeping with the registry studies above, after 5 and 10 years there was a significant increase in risk of SPC in irradiated patients. After 10 years this risk was almost five times that of surgical patients [266]. In contrast, Movsas et al, the smallest study examined here, and the study with the shortest median follow-up, found irradiated PCa patients to be at no increased risk of SPC over all durations of follow-up, from 5 to 9.9 years, and beyond 10 years, compared to PCa patients from the SEER database (of whom only 12.5% were irradiated) [267].

Single institution studies reporting crude rates of SPC (Table 5.3) include Johnstone et al who reported a crude SPC rate of 17.5% beyond one year of PCa diagnosis, in a series of 154 irradiated patients after a median follow-up of 10.9 years [268]. This was not significantly different to the rate of non-prostate cancers diagnosed prior to PCa diagnosis (p=0.288). Zilli et al reported a crude rate of SPC of 5.4% beyond six months of follow-up [269].Long term trial results reported by Bolla et al revealed a crude rate of SPCs in irradiated patients of 7.7% over all durations of follow-up [270]. Median follow-up is variable between these studies, and no comparisons with other population groups are performed, limiting the usefulness of these figures. Studies examining mortality in irradiated PCa patients (Table 5.4) reveal that up to 4.1% of patients (crude rates) irradiated with EBRT die from SPCs although, as above, duration of follow-up is different in all studies and so these figures must be interpreted with caution [267,270,271]. In one study, 10% of all deaths were the result of second malignancies [272].

Table 5.1 Studies examining second primary cancers at any site in prostate cancer patients irradiated using external beam radiotherapy compared to general population

Study	Type of data	Period examined	No. patients	Median follow-up (years)	Exclusions	Time period(s) assessed	Risk of second cancer at any site (based on $p<0.05$ or CI not including 1.0)	Magnitude of risk (SIR, 95% CI or p value in parentheses if available)
Pawlish 1997 [258]	Retrospective, SEER registry	1973 -1982	2,087	6.1 (mean FU reported)	<1 year FU	>1 year FU	No difference	1.03 (0.91-1.16)
Brenner 2000 [259]	Retrospective, SEER registry	1973-1993	51,584	4 (mean FU reported)	<2months	> 2 months >5 years >10 years	Reduced Reduced Reduced	0.89* 0.92* 0.96*
Berrington de Gonzalez 2011 [261]	Retrospective, SEER registry	1973-2002	76,363	9.4 (mean FU reported)	<5 years	>5 years	No difference	0.98 (NS*)
Pickles 2002 [260]	Retrospective, British Columbia Tumor Registry	1984-2000	9,890	4.77	<2 months	> 2 months 2 months- 5 years >5 years >10 years	No difference No difference No difference No difference	1.01 (p=0.9) 0.96 (NS*) 1.08 (NS*) 1.12 (NS*)
Rapiti 2008 [262]	Retrospective, Geneva Cancer Registry	1980-1998	264	7.8	<5 years	>5 years 5-9 years ≥10 years	No difference** No difference No difference	1.35 (p=0.056) 1.28 (NS*) 1.55 (NS*)
Bagshaw 1988 [263]	Retrospective, single centre	1956-1985	914	NR	None	All periods	No difference	0.93 (p=0.48)

CI: confidence interval, FU: follow-up, NR: not reported, NS: not significant, SEER: Surveillance, Epidemiology and End Results, SIR: standardised incidence ratio, * p value and/or confidence interval not reported, ** The group concluded irradiated patients were at a slightly increased risk which was “of borderline significance”

Table 5.2 Studies examining second primary cancers at any site in prostate cancer patients irradiated using external beam radiotherapy compared to non-irradiated prostate cancer patients

Continued overleaf.

Study	Type of data	Period	No. patients	Median follow-up (years)†	Exclusions	Time period(s) assessed	Risk of second cancer at any site (based on $p<0.05$ or CI not including 1.0)	Magnitude of risk (Relative risk or other where stated (95% CI and/or p value if available))
Pawlish 1997 [258]	Retrospective, SEER registry	1973 - 1982	2,087 RT 6,390 no RT	6.1 (mean)	<1 year	>1 year	Increased	1.23 (1.06-1.42)
Brenner 2000 [259]	Retrospective, SEER registry	1973-1993	51,584 RT 70,539 no RT	4 (mean)	<2months	 > 2 months >5 years >10 years	 No difference Increased Increased	Percentage increase in risk: 4 (-1-9, p=0.08) 11 (3-20, p=0.007) 27 (9-48, p=0.002)
Abdel-Wahab 2008 [264]	Retrospective, SEER registry	1973-2002	48,400 RT 40,733 no RT	5.3 RT 4.3 no RT	<1 year	>1 year >5 years	Increased Increased	HR: 1.137 (1.087-1.190) HR: 1.263 (1.167-1.367)
Berrington de Gonzalez 2011 [261]	Retrospective, SEER registry	1973-2002	76,363 RT 123,800 no RT	9.4 RT (mean) 10.1 no RT (mean)	<5 years	>5 years	Increased	1.26 (1.21-1.30)

Table 5.2 cont. Studies examining second primary cancers at any site in prostate cancer patients irradiated using external beam radiotherapy compared to non-irradiated prostate cancer patients

Study	Type of data	Period	No. patients	Median follow-up (years)†	Exclusions	Time period(s) assessed	Risk of second cancer at any site (based on $p<0.05$ or CI not including 1.0)	Magnitude of risk (Relative risk or other where stated (95% CI and/or p value if available))
Movsas 1998 [267]	Retrospective, single centre	1973-1993	543 RT 18,135 no RT*	3.9 RT 3.9 no RT (mean)	<2 months	 >2 months >2 months- 9 years 1-4.9 years 5-9.9 years 10+ years	 No difference No difference No difference No difference No difference	Crude rates (RT vs no RT): 5.7% vs 5.8% (p=0.99) 0.74% vs 0.9% (p=0.89) 3.8% vs 3.6% (p=0.95) 4.3% vs 4.4% (p=0.89) 0% vs 8.3% (p=0.56)
Huang 2011 [266]	Retrospective, single centre matched-pair analysis	1984-2005	2,120 RT 2,120 no RT	7.15 RT 6.99 no RT	None	All durations >5 years >10 years	No difference Increased Increased	HR: 1.14 (0.94 to 1.39) HR: 1.86 (1.36-2.55) HR: 4.94 (2.18-11.2)
Black 2013 [265]	Prospective, trial data	1993-2001	3,216 RT 4,263 no RT	6 (mean)	<30 days	>30 days >5 years	Increased Increased	1.25 (1.1-1.5) 1.6 (1.2-2.1)

RT: external beam radiotherapy, HR: hazard ratio, CI: confidence interval, NR: not reported, SEER: Surveillance, Epidemiology and End Results, † if follow-up for each treatment group reported separately, then this is presented, * Non-RT patients from Connecticut Cancer Registry, approximately 12.5% received RT despite being considered as 'no RT' group

Table 5.3 Studies reporting second cancer rates in irradiated prostate cancer patients without comparison to other populations

Study	Type of data	Period	No. patients	Median follow-up (years)	Exclusions	Time period(s) assessed	Crude rate of second cancer at any site	Crude rate of second rectal cancer	Crude rate of second bladder cancer
Johnstone 1998 [268]	Retrospective, single centre	1974-1988	154	10.9	<1 years	>1 year	17.5% (27/154) diagnosed ≥1 year of prostate cancer diagnosis (vs 14.9% (23/154) diagnosed before or within one year of prostate cancer diagnosis (*p*=0.288))	See Table 5.5*	See Table 5.5*
Gardner 2002 [273]	Retrospective single centre (EBRT+ proton boost)	1976-1992	39	13.1	None	All durations of FU	NR	2.6% (1/39)	0% (0/39)
Zilli 2010 [269]	Retrospective single centre	2002 - 2009	276	3.5	<6 months	>6 months	5.4% (15/276)	1.8% (5/276)	1.1% (3/276)
Bolla et al 2010 [270]	Prospective, clinical trial data	1987-1995	415	9.1	None	All durations of FU	7.7% (32/415)	NR	NR

EBRT: external beam radiotherapy, NR: not reported, * risk comparisons with general population performed for rectal and bladder cancers

Table 5.4 Deaths due to second cancers following irradiation in prostate cancer patients

Study	Type of data	No. patients	Period	Median follow-up (years)	Patients dying due to second malignancy (crude rate based on all patients in study or other when specified, actual numbers in parentheses)
External beam radiotherapy					
Movsas 1998 [267]	Retrospective, single centre	543	1973-1993	3.9	2.8% (15/543)
Kannan 2005 [271]	Retrospective, single centre	51	1998-2002	2.7	2.0% (1/51)
Bolla et al 2010 [270]	Prospective, clinical trial data	415	1987-1995	9.1	4.1% (17/415)
Nguyen 2010 [272]	Retrospective, single centre	929	1987-2004	7.5	10% of all deaths due to second cancers
Zelefsky 2012 [274]	Retrospective, single centre	897 (mainly IMRT)	1998-2001	7.5	10-year mortality rate for in-field SPC: 0.12% (95%CI:0-0.36%)* 10-year mortality rate for extra-pelvic SPC: 1.97% (95%CI:1.01-2.92%)*
Post-operative radiotherapy					
Ciezki 2012 [275]	Retrospective, SEER registry	20,545 surgery and PORT	1973-2008	9.5	20-year age-adjusted mortality rate for colorectal cancer: 0.06% 20-year age-adjusted mortality rate for bladder cancer: 0.14%
Bellavita 2011 [276]	Retrospective, single centre	214	1998-2007	4.8	1.9% (4/214)
Brachytherapy studies					
Bittner 2008 [277]	Retrospective, single centre	1,354	1995-2004	5.4	3.0% (41/1354) 7.2% (cumulative hazard of death from second cancer)
Rodriguez 2009 [278]	Retrospective, single centre	150	2003-2006	4.1 (mean)	2.0% (3/150)
Henry 2012 [279]	Retrospective, single centre	1805	1995-2005	6-17 years	0.06% (1/1805) died from rectal cancer 0.2% (3/1805) died from bladder cancer
Zelefsky 2012 [274]	Retrospective, single centre	413	1998-2001	7.7	10-year mortality rate for in-field SPC: 0%* 10-year mortality rate for extra-pelvic SPC: 0.78% (95%CI:0.01-1.67%)*

CI: confidence interval, SEER: Surveillance, Epidemiology and End Results, SPC: second primary cancer, *Based on competing risk analyses to account for other causes of death

Overall, therefore, an increase in SPC has not been consistently demonstrated in irradiated patients compared to the general population. There is more consistent evidence, however, of an increase in SPC risk in comparison to non-irradiated PCa patients, particularly with increasing durations of follow-up. This raises the possibility that PCa patients are different to the general population, and so non-irradiated PCa patients and the general population should not be considered equivalent.

Patient age has an impact on SPC incidence, as illustrated by Brenner et al above [259]. Length of follow-up is also important, and studies with shorter durations of follow-up may not detect all SPCs. Brenner et al and Huang et al illustrated that the relative risk of SPC in irradiated patients increased over time compared to surgically treated patients [259,266]. Brenner et al demonstrated a 6% increase in relative risk of second solid tumour overall, which increased to 15% and 34% beyond 5 and 10 years respectively. In absolute terms, the risk of radiation-associated SPC was 1 in 290 over all durations of follow-up, 1 in 125 beyond 5 years and 1 in 70 for those surviving beyond 10 years [259]. Similarly, Pickles et al reported a crude risk estimate of 1 in 220 over all durations of follow-up, which is not dissimilar [260]. Berrington de Gonzalez et al, more recently, concluded that the number of excess second solid cancers in irradiated PCa patients surviving beyond one year attributable to radiotherapy was 1 in 114, with 10% of all second cancers being attributable to radiotherapy [261].

5.4.2 Second rectal cancer risk associated with EBRT for prostate cancer

Amongst the six SEER registry studies examining rectal cancer in irradiated PCa patients compared to the general population (Table 5.5), three showed no increase in rectal cancer risk, including when follow-up beyond five and eight years was specifically examined [258,280,281], while three demonstrated increased risk [259,261,282]. Two of the studies to demonstrate an increase in rectal cancer risk compared to the general population were the only two studies which examined follow-up beyond 10 years, as well as other time periods and, in both cases, the increased risk of rectal cancer was only present beyond 10 years [259,282]. In the third study which demonstrated increased risk of rectal cancer in irradiated patients compared to the general population, this risk was demonstrated beyond five years [261]. Of the 3

non-SEER registry studies, one found no increase in risk from irradiation beyond 5 years, nor beyond 10 years [262] although the number of irradiated PCa patients was relatively small, while another demonstrated increased risk of rectal cancer following irradiation beyond 6 months and beyond 5 years of follow-up [283], and the third demonstrated an increased risk of colorectal cancer beyond 2 months of follow-up and between 2 months and 5 years of follow-up, but not beyond 5 years or beyond 10 years [260].

Of the two single institution studies examining rectal cancer in irradiated PCa patients compared to the general population, one found no difference in the risk of rectal cancer following irradiation over all durations of follow-up [263], and one found an increased risk within one year of follow-up only [268].

Seven of the ten SEER registry studies comparing second rectal cancer incidence between irradiated and non-irradiated PCa patients demonstrated that irradiated patients were at increased risk (Table 5.6) [259,261,264,281,282,284,285]. This increased risk has mainly been observed after longer durations of follow-up (i.e. beyond 5 and 10 years) and appears to increase with increasing durations of follow-up. For example, the hazard ratios reported by Nieder et al, increase from 1.11 when considering follow-up from 6 months to 5 years (non-significant) to 1.39 (significant) between 5 and 10 years of follow-up to 1.79 (significant) from beyond 10 years [281]. Of the remaining SEER studies, two report no increase in risk of second rectal cancer, one of which examined follow-up beyond 5 years specifically [258,286]. The one remaining SEER study, by Kendall et al, demonstrated that the specific comparator group with which irradiated PCa patients are compared might impact on the relative risk observed: when irradiated PCa patients were compared to patients treated surgically, there was a significantly increased risk of rectal cancer in irradiated patients, while compared to patients who did not receive RT or surgery, the risk of rectal cancer was significantly less, which the group felt was unrealistic [287]. Thus risk ratio was influenced by comparator group. The group therefore suggested an unidentified confounding factor was influencing results and, after further analysis, concluded that there was insufficient evidence to confirm that irradiation for prostate cancer induced rectal cancer [287]. Indeed, Kendal et al's analysis from 2007 did not demonstrate any increase in the risk of second rectal cancer in irradiated patients over all durations of follow-up or beyond five years [286].

Table 5.5 Studies examining second rectal and second bladder cancers in prostate cancer patients irradiated using external beam radiotherapy compared to general population

Continued overleaf.

Study	Type of data	Period	No. patients	Median follow-up (years)	Exclusions	Time period assessed	Risk of second rectal cancer (based on *p*<0.05 or confidence interval not including 1.0)	Magnitude of risk of rectal cancer (SIR (95% CI or *p* value if available)	Risk of second bladder cancer (based on *p*<0.05 or confidence interval not including 1.0)	Magnitude of risk of bladder cancer (SIR (95% CI or *p* value if available)
Neugut 1996 [280]	Retro, SEER registry	1973 - 1990	34,889	NR	<6 months	>6months-5years	Reduced	0.7 (0.5-0.9)	No difference	1.0 (0.8-1.2)
						5-8 years	No difference	0.8 (0.5-1.2)	No difference	1.3 (1.0-1.7)
						>8 years	No difference	0.8 (0.4-1.3)	Increased	1.5 (1.1-2.0)
Pawlish 1997 [258]	Retro, SEER registry	1973 - 1982	2,087	6.1 (mean)	<1 year	>1 year	No difference	0.95 (0.45-1.74)	Increased	1.49 (1.07-2.02)
						>5 years	NR	NR	Increased	1.60 (1.05-2.35)
Brenner 2000 [259]	Retro, SEER registry	1973-1993	51,584	4 (mean)	<2months	> 2 months	Reduced	0.82*	Increased	1.10*
						>5 years	Reduced	0.95*	Increased	1.20*
						>10 years	Increased	1.18*	Increased	1.32*
Nieder 2008 [281]	Retro, SEER registry	1988-2003	93,059	4.1	6 months	>6 months	No difference	0.99 (0.90-1.10)	Increased	1.42 (1.34-1.50)

Table 5.5 cont. Studies examining second rectal and second bladder cancers in prostate cancer patients irradiated using external beam radiotherapy compared to general population. Continued overleaf.

Study	Type of data	Period	No. patients	Median follow-up (years)	Exclusions	Time period assessed	Risk of second rectal cancer (based on $p<0.05$ or confidence interval not including 1.0)	Magnitude of risk of rectal cancer (SIR (95% CI or p value if available)	Risk of second bladder cancer (based on $p<0.05$ or confidence interval not including 1.0)	Magnitude of risk of bladder cancer (SIR (95% CI or p value if available)
Huo 2009 [282]	Retro, SEER registry	1973-2005	211,882	NR	None	All	No difference	1.04 (0.97-1.11)	NR	NR
						<6 months	No difference	0.99 (0.77-1.27)		
						6 months- 5 years	No difference	0.96 (0.88-1.05)		
						>5 to 10 years	No difference	1.06 (0.93-1.20)		
						>10 years	Increased	1.44 (1.22-1.71)		
Berrington de Gonzalez 2011 [261]	Retro, SEER registry	1973-2002	76,363 RT 123,800 no RT	9.4 (mean)	<5 years	>5 years	Increased†	1.12 (p≤0.05)	Increased	1.31 (p≤0.05)
Pickles 2002 [260]	Retro, British Columbia Tumor Registry	1984-2000	9,890	4.8	<2 months	> 2 months	Increased‡	1.21 (p≤0.01)‡	No difference	1.04 (NS*)
						>2 months to 5 years	Increased‡	1.21 (p≤0.05)‡	No difference	0.86 (NS*)
						>5 years	No difference‡	1.24 (NS*)‡	No difference	1.30 (NS*)
						>10 years	No difference‡	1.01 (NS*)‡	No difference	1.64 (NS*)

Table 5.5 cont. Studies examining second rectal and second bladder cancers in prostate cancer patients irradiated using external beam radiotherapy compared to general population. Continued overleaf.

Study	Type of data	Period	No. patients	Median follow-up (years)	Exclusions	Time period assessed	Risk of second rectal cancer (based on $p<0.05$ or confidence interval not including 1.0)	Magnitude of risk of rectal cancer (SIR (95% CI or p value if available)	Risk of second bladder cancer (based on $p<0.05$ or confidence interval not including 1.0)	Magnitude of risk of bladder cancer (SIR (95% CI or p value if available)
Rapiti 2008 [262]	Retro, Geneva Cancer Registry	1980-1998	264	7.8	<5 years	>5 years >5 – 9 years ≥10 years	No difference No difference No difference	2.0 (0.2 to 7.2) 1.2 (0.04-6.9) 5.3 (0.2-29.3)	No difference No difference No difference	1.84 (NS*) 0.80 (NS*) 5.15 (NS*)
Margel 2011 [283]	Retro, Israel Cancer Registry	1982 - 2005	2,163	11.2	<6 months	>6 months >5 years	Increased Increased	1.81 (1.2-2.5) 1.30 (1.05-2.8)	NR	NR
Bagshaw 1988 [263]	Retro, single centre	1956-1985	914	NR	None	All	No difference	0.54 (p=0.21)	No difference	1.08 (p=0.8)
Johnstone 1998 [268]	Retro, single centre	1974-1988	154	10.9	None	<1 year 1-4 years 4-10 years >10 years	Increased No difference No difference No difference	p<0.001** p=0.64** p=0.80** p=0.69**	Increased No difference No difference No difference	p<0.001** p=0.88** p=0.75** p=0.66**

Table 5.5 cont. Studies examining second rectal and second bladder cancers in prostate cancer patients irradiated using external beam radiotherapy compared to general population

Study	Type of data	Period	No. patients	Median follow-up (years)	Exclusions	Time period assessed	Risk of second rectal cancer (based on $p<0.05$ or confidence interval not including 1.0)	Magnitude of risk of rectal cancer (SIR (95% CI or p value if available)	Risk of second bladder cancer (based on $p<0.05$ or confidence interval not including 1.0)	Magnitude of risk of bladder cancer (SIR (95% CI or p value if available)
Chrouser 2005 [288]	Retro, single centre	1980-1998	1,743	7.1 (mean)	<30 days	>30 days	NR	NR	No difference	0.798 (0.511-1.187)
						>30 days to 1 year			No difference	0.292 (0.007-1.619)
						1-4 years			No difference	0.909 (0.469-1.586)
						5-9 years			No difference	0.665 (0.267-1.367)
						10-19 years			No difference	1.37 (0.373-3.507)
Singh 2005 [289]	Retro, single centre	1996-2003	210	NR	<6 months	>6 months	NR	NR	Increased	7.27 (3.132-14.331)

Retro: retrospective, SEER: Surveillance, Epidemiology and End Results, SIR: standardised incidence ratio, CI: confidence interval, NR: not reported, NS: not-significant, * no p value or confidence interval provided, ** SIRs and confidence intervals not reported, [†]includes rectal and rectosigmoid junction cancers, [‡]risk reported is for *colo*rectal cancer

Table 5.6 Studies examining second rectal and bladder cancers in prostate cancer patients irradiated using external beam radiotherapy compared to non-irradiated prostate cancer patients

Continued overleaf.

Study	Type of data	Period	No. patients	Median follow-up (years)[6]	Exclusions	Time period(s) assessed	Risk of second rectal cancer (based on $p<0.05$ or CI not including 1.0)	Magnitude of risk of second rectal cancer (Relative risk or other where stated, (95% CI or p value if available))	Risk of second bladder cancer (based on $p<0.05$ or CI not including 1.0)	Magnitude of risk of second bladder cancer (Relative risk or other where stated, (95% CI or p value if available))
Pawlish 1997 [258]	Retro, SEER registry	1973 - 1982	2,087 RT 6,390 no RT	6.1 (mean)	<1 year	>1 year	No difference	NR	Increased	OR: 1.63 ($p<0.05$)[s]
Brenner 2000 [259]	Retro, SEER registry	1973-1993	51,584 RT 70,539 no RT	4 (mean)	<2months			Percentage increase in risk:		Percentage increase in risk:
						> 2 months	No difference	-2 (-18-18, $p=0.87$)	Increased	15 (2-31, $p=0.02$)
						>5 years	No difference	35 (-1- 86, $p=0.06$)	Increased	55 (24-92, $p<0.01$)
						>10 years	Increased	105 (9-292, $p=0.03$)	Increased	77 (14-163, $p=0.01$)
Baxter 2005 [284]	Retro, SEER registry	1973-1994	30,552 RT 55,263 no RT	7.9 RT 8.3 no RT	<5 years	>5 years	Increased	HR: 1.7 (1.4-2.2)	NR	NR
Kendal 2006 [287]	Retro, SEER registry	1973-2001	33,831 RT 167,607 no RT (surgical patients)	5.1 RT 5.1 no RT	None	All	Increased	2.38 (2.21-2.55)*	NR	NR
						0-10 years	Increased	2.16 (2.00-2.33)		
						>10 years	Increased	15.62 (12.01-19.83)		
Kendal 2006 [287]	Retro, SEER registry	1973-2001	33,831 RT 36,335 no RT (non-surgical and no RT patients)	5.1 RT 3.3 no RT	None	All	Reduced	0.69 (0.64-0.75)[a]	NR	NR
						0-10 years	Reduced	0.66 (0.61-0.71)		
						>10 years	No difference	0.93 (0.64-1.46)		

Table 5.6 cont. Studies examining second rectal and bladder cancers in prostate cancer patients irradiated using external beam radiotherapy compared to non-irradiated prostate cancer patients. Continued overleaf.

Study	Type of data	Period	No. patients	Median follow-up (years)[6]	Exclusions	Time period(s) assessed	Risk of second rectal cancer (based on $p<0.05$ or CI not including 1.0)	Magnitude of risk of second rectal cancer (Relative risk or other where stated, (95% CI or p value if available))	Risk of second bladder cancer (based on $p<0.05$ or CI not including 1.0)	Magnitude of risk of second bladder cancer (Relative risk or other where stated, (95% CI or p value if available))
Moon 2006 [285]	Retro, SEER registry	1973-1999	39,805 EBRT	10	<5 years	> 5years	Increased	OR: 1.60 (1.29-1.99)	Increased	OR: 1.63 (1.44-1.84)
Kendal 2007 [286]	Retro, SEER registry	Not stated	520,780 (RT and no RT)	NR	None	All >5 years	No difference No difference	NR HR: 1.13 (0.98-1.31)	No difference Increased	NR HR: 1.23 (1.15-1.32)
Nieder 2008 [281]	Retro, SEER registry	1988-2003	93,059 RT 109,178 no RT	4.1	6 months	>6 months 6 months- 5 years 5-10 years >10 years	Increased No difference Increased Increased	HR: 1.26 (1.08-1.47) HR: 1.11 (0.90-1.37) HR: 1.39 (1.09-1.79) HR: 1.79 (1.05-3.07)	Increased Increased Increased Increased	HR: 1.88 (1.70-2.08) HR: 1.69 (1.47-1.94) HR: 2.26 (1.89-2.69) HR: 1.83 (1.31-2.55)
Abdel-Wahab 2008 [264]	Retro, SEER registry	1973-2002	48,400 RT 40,733 no RT	5.3 RT 4.3 no RT	<1 year	1-5 years >5 years	Increased[†] Increased[†]	Percentage increase in risk: 0.07%, $p<0.001$[†] 0.16%, $p=0.023$[†]	Increased[†] Increased[†]	Percentage increase in risk: 0.07% $p<0.001$[†] 0.16% $p=0.023$[†]
Huo 2009 [282]	Retro, SEER registry	1973-2005	211,882 RT 424,028 no RT	NR	None	All	Increased	1.91 (1.52-1.89)	NR	NR

Table 5.6 cont. Studies examining second rectal and bladder cancers in prostate cancer patients irradiated using external beam radiotherapy compared to non-irradiated prostate cancer patients. Continued overleaf.

Study	Type of data	Period	No. patients	Median follow-up (years)[6]	Exclusions	Time period assessed	Risk of second rectal cancer (based on $p<0.05$ or CI not including 1.0)	Magnitude of risk of second rectal cancer (Relative risk or other where stated, (95% CI or p value if available))	Risk of second bladder cancer (based on $p<0.05$ or CI not including 1.0)	Magnitude of risk of second bladder cancer (Relative risk or other where stated, (95% CI or p value if available))
Singh 2010 [290]	Retro, SEER registry	1973-2005	124,141 RT 163,111 no RT	5.3 RT 4.0 No RT	None	All >6months >5years >10years	NR	NR	Increased Increased Increased Increased	HR: 1.19 (1.11-1.28) HR: 1.33 (1.23-1.44) HR: 1.58 (1.38-1.81) HR: 1.91 (1.40-2.62)
Berrington de Gonzalez 2011 [261]	Retro, SEER registry	1973-2002	76,363 RT 123,800 no RT	9.4 RT (mean) 10.1 no RT (mean)	<5 years	5-9 years 10-14 years ≥15 years	Increased‡ Increased‡ Increased‡	1.39 (1.29-1.50)‡ 1.59 (1.41-1.80)‡ 1.91 (1.53-2.38)‡	Increased‡ Increased‡ Increased‡	1.39 (1.29-1.50)‡ 1.59 (1.41-1.80)‡ 1.91 (1.53-2.38)‡
Pickles 2002 [260]	Retro, British Columbia Tumor Registry	1984-2000	9,890 RT 29,371 no RT	4.77 RT 1.7 no RT	<2 months	> 2 months	Increased (colorectal)	1.21 (p=0.03)	No difference	NR (NS)
Boorjian 2007 [291]	Retro, CaPSURE Disease Registry	1989-2003	2,471 RT 4,608 no RT	3.25	<30 days	>30 days	No difference	NR (p=0.14)	Increased	HR: 1.96 (1.12-3.45)
Bhojani 2010 [292]	Retro, Quebec Health Plan database	1983-2003	9,390 RT 8,455 no RT	NR	< 5years	>5 years >10years	Increased No difference	HR: 1.9 (p=0.01) HR: 1.6 (p=0.5)	Increased No difference	HR: 1.5 (p=0.01) HR: 2.0 (p=0.1)

Table 5.6 cont. Studies examining second rectal and bladder cancers in prostate cancer patients irradiated using external beam radiotherapy compared to non-irradiated prostate cancer patients

Study	Type of data	Period	No. patients	Median follow-up (years)[6]	Exclusions	Time period assessed	Risk of second rectal cancer (based on *p*<0.05 or CI not including 1.0)	Magnitude of risk of second rectal cancer (Relative risk or other where stated, (95% CI or *p* value if available))	Risk of second bladder cancer (based on *p*<0.05 or CI not including 1.0)	Magnitude of risk of second bladder cancer (Relative risk or other where stated, (95% CI or *p* value if available))
Movsas 1998 [267]	Retro, single centre	1973-1993	543 RT 18,135 'no RT'**	3.9 RT 3.9 no RT (mean)	<2 months	>2 months	NR	NR	No difference	NR
Singh 2005 [289]	Retro, single centre	1996-2003	210 RT 416 no RT	NR	<6 months	>6 months	NR	NR	No difference	NR (No difference based on overlapping confidence intervals for SIRs for RT vs general population and no RT vs general population
Huang 2011 [266]	Retro, single centre matched-pair analysis	1984-2005	2,120 RT 2,120 no RT	6.99 RT 7.15 no RT	None	All >5 years >10 years	No difference No difference No difference	HR: 0.91 (0.39-2.14) HR: 1.98 (0.36-10.83) *p*=0.31[¥]	Increased Increased Increased	HR: 2.02 (1.2-3.41) HR: 4.49 (1.70-11.85) HR: 9.70 (1.23-76.57)
Black 2013 [265]	Prosp, trial data	1993-2001	3,216 RT 4,263 no RT	6 (mean)	>30 days	>30 days	No difference (colorectal)	1.5 (0.9-2.4)	No difference	1.6 (0.9-2.8)

CaPSURE: University of California, San Francisco Cancer of the Prostate Strategic Urology Research Endeavor, CI: confidence interval, HR: hazard ratio, NR: not reported, OR: odds ratio, Prosp: prospective, Retro: retrospective, SEER: Surveillance, Epidemiology and End Results,*HR for all time periods also available: 2.42 (95%CI: 2.08-2.81), ** Non-RT patients from Connecticut Cancer Registry, approximately 12.5% received RT despite being considered as 'no RT' group, [†]ratio reported for any 'primary pelvic' second cancer, considered as rectum, bladder, anus, anal canal, anorectum, prostate and other cancer from the bones, joints and lymphomas, and based on comparison of age adjusted estimates only, not full Cox model, [‡] ratio reported for organs considered to be in 'high dose' (>5Gy) sites, includes rectum and bladder, [¥] hazard ratio not calculated as too few events, [§] Relative risk also reported: 1.59 (95%CI: 1.09-232), [6] if follow-up for each treatment group reported separately, then this is presented, ¤HR for all time periods also available: 0.69 (95%CI: 0.58-0.82)

Of the three non-SEER registry studies comparing second rectal cancer risk in irradiated PCa patients and non-irradiated patients, all of which contain fewer patients than the SEER studies, two demonstrate an increase in risk in irradiated patients, in one from two months onwards, and in the other, beyond five years [260,292]. The third non-SEER registry study demonstrated no increase in risk of second rectal cancer in irradiated patients from 30 days [291].

The one single institution study which compared second rectal cancer risk between irradiated and non-irradiated patients, did so in the context of a matched-pair analysis. Patient numbers were smaller than in the above registry studies. No increase in risk in irradiated PCa patients was observed, both when considering risk from early on in the follow-up period, and after longer time periods [266]. Similarly, results of the PLCO trial found irradiated PCa patients to be at no increased risk of second colorectal cancers beyond 30 days compared to non-irradiated patients [265].

Two studies report crude rates of rectal cancer in irradiated PCa patients without comparison to other population groups. Crude rates of 2.6% after a median follow-up of 13.1 years are reported in one series, and of 1.8% after a median follow-up of 3.5 years in another [269,273] (Table 5.3).

Clearly there are discrepancies between studies. There is a suggestion, however, that where an increased risk of rectal cancer is observed, this is mainly when follow-up beyond 5 or 10 years is included in the evaluated time period. Beyond five years, cancers may be considered radiation induced [259,281-285,287,292]. Trials with shorter durations of follow-up, or few patients with follow-up beyond 5 or 10 years, therefore may not detect all the second rectal cancers that develop and therefore underestimate the true rate. Indeed, the study by Rapiti et al demonstrated that the median time to rectal cancer was 8.8 years, while median follow-up was only 7.4 years, which was therefore insufficient to detect all second rectal cancers [262]. One study revealed an increase in rectal cancer within one year of follow-up but not beyond [268]. This could be attributed to surveillance bias, whereby patients with rectal symptoms following radiotherapy are investigated and incidental rectal cancers are detected [268].

The increased risk of second rectal cancer is more consistently observed when irradiated PCa patients are compared to non-irradiated patients, as opposed to when irradiated patients are compared to the general population, again highlighting that there are differences between comparator groups. Differences in length of follow-up between treatment groups may contribute to these discrepancies. Since the risk of developing SPC increases with time, failure to adequately correct for duration of follow-up, may result in inaccurate conclusions. This particular criticism was levelled at Moon et al (who demonstrated an increased risk of second rectal cancer in irradiated patients compared to non-irradiated PCa patients) [285] by Kendal et al (who, after correcting for duration of follow-up, demonstrated no increase in risk in irradiated patients) [286]. Subsequent studies which have also adjusted for length of follow-up, however, have demonstrated an increase in rectal cancer risk compared to non-irradiated patients [261,281,282,292].

Another important factor is selection bias: although detailed information from registries is generally not available, it is possible that surgically treated patients as a whole have less co-morbidity than patients treated with radiotherapy. These patients may also have fewer risk factors for rectal cancer. Age also impacts on the risk of rectal SPC [284,287], and the majority of the studies have tried to adjust for this [258-260,262,267,280-287,291,292]. Indeed, Berrington de Gonzalez et al demonstrated that the risk of developing a second cancer within a region irradiated to high dose (>5Gy, includes the rectum and bladder) lessened with an increasing age at diagnosis of PCa, to become non-significant for patients diagnosed with PCa aged 75 years or greater [292].

In terms of absolute risks, Baxter et al reported the risk of second rectal cancer over 10 years (from 5 to 15 years) as 5.1 per 1000 for surgically treated patients and 10 per 1000 for patients treated with radiotherapy [284]. Over a median of 10 years (beginning from 6 months of PCa diagnosis), Margel et al calculated that the absolute increase in rectal cancer risk as a result of irradiation was 13 per 1000 [283].

5.4.3 Second bladder cancer risk associated with EBRT for prostate cancer

All five SEER studies which compared the risk of bladder cancer in irradiated PCa patients with the general population (Table 5.5) report increased risk in irradiated patients, albeit over different periods of follow-up: three report increased risk beginning from early in the follow-up period and, where examined, persisting beyond 5 and 10 years [258,259,281], while one study reports increased risk beginning after 8 years and not before [280], and the other demonstrated increased risk beyond 5 years and did not examine any other end points [261]. The two non-SEER registries comparing risk of second bladder cancer in irradiated patients compared to the general population report no difference in risk within 5 years, beyond 5 years and beyond 10 years of follow-up, although the study by Rapiti et al is relatively small [260,262]. Amongst the four single institution studies comparing risk in irradiated patients with the general population, two show no increase in the risk of bladder cancer in irradiated patients over all the follow-up periods examined (including 10-19 years in one study) [263,288]. Of the other two institutional studies, one demonstrated increased risk within one year of follow-up, but no increase in risk beyond this period [268], and the other showed increased risk beyond six months [289].

All but one of the 11 registry studies which compare the risk of second bladder cancer with non-irradiated PCa patients, show a consistently increased risk of second bladder cancer [258,259,261,264,281,285,286,290-292] (Table 5.6). The increased risk is often seen from early on in the follow-up period and frequently persists and increases beyond 5 and, if assessed, beyond 10 years. The one study which demonstrates no increased risk is that by Pickles et al who examined risk from two months and did not specifically examine longer time periods [260].

Of the three single institution studies comparing the risk of second bladder cancer in irradiated PCa patients compared to non-irradiated PCa patients, two show no difference in risk from early in the follow-up period [267,289], while the remaining study shows increased risk in irradiated patients over all durations of follow-up and beyond 5 and beyond 10 years [266] (Table 5.6). Results for irradiated PCa patients from the

PLCO trial suggest no difference in the risk of second bladder cancer beyond 30 days in irradiated and non-irradiated patients [265].

In terms of single institution studies reporting crude rates of second bladder cancers (Table 5.3), Zilli et al reported a crude rate of 1.1% in a series of 276 patients with median follow-up of 3.5 years, and Gardner et al reported no cases of bladder cancer in a series of 39 patients followed up for a median of 13.1 years [269,273]. In both studies, risk comparisons were not performed.

Overall therefore, there does appear to be an increase in the risk of second bladder cancer in irradiated PCa patients, particularly when compared to non-irradiated PCa patients. As was observed when considering second rectal cancer, the increased risk of second bladder cancer from irradiation is less consistently observed when comparisons are made with the general population. In the case of institutional data, small patient numbers may be the reason for these discrepancies. Amongst registry data, there may be fundamental differences in comparator populations, duration of follow-up or how adequately differences in follow-up are corrected. Selection bias between surgical and irradiated patients may also have an impact. Of great importance when considering bladder cancer, is smoking history and the potential confounding impact this may have. If more smokers are refused surgery due to co-morbidities, then there will be excess smokers in irradiated patient cohorts. Registry data frequently does not contain information regarding smoking status. By comparing the proportion of smokers amongst PCa patients treated with surgery and RT in an earlier case-control study, Brenner et al suggested that it was unlikely there were excess smokers in the irradiated patient cohort examined, and therefore concluded that smoking was unlikely to be a confounding factor [259]. The University of California, San Francisco Cancer of the Prostate Strategic Urology Research Endeavor (CaPSURE) disease registry, however, contains data about smoking, and Bhojani et al used this to demonstrate that both smoking and irradiation were independent risk factors for second bladder cancer and that patients treated with RT who were also smokers were more than three and a half times more likely to develop bladder cancer than non-smoking patients who did not receive RT (Hazard ratio (HR): 3.65; 95%CI:1.45 to 9.16; [292]).

The increased risk of bladder cancer is frequently reported as beginning within five years of follow-up in the above studies and so radiation is not the likely cause of these early bladder tumours. Surveillance bias, as a result of regular oncological or urological follow-up may play a part in this, while the impact of smoking may also be involved in early (i.e. less than five years from RT) and late (i.e. beyond five years of RT) bladder cancer development. Beyond five years the risk of bladder cancer appears to increase further, and radiation may be attributed to this although the factors mentioned above should also be considered.

5.4.4 Impact of treatment technique: older treatments

The studies discussed above have evaluated SPC incidences in cohorts where all patients, or the vast majority of patients, received EBRT. Many of the SEER analyses have included patients treated in the 1970s and early 1980s when large pelvic fields and cobalt machines were often employed [258,259,261,264,280,282,284,285,287]. SPC risks from these treatments may therefore be different to those observed with more contemporary techniques. Some studies have adjusted for the year or era of diagnosis to try to take different treatment techniques into consideration although date of treatment did not appear to impact SPC risk [261,281,282,284].

5.4.5 Impact of treatment technique: 3D-conformal radiotherapy and IMRT

It is not possible to separate the impact of more conformal EBRT techniques and older large field treatments from most studies. Initial indications of potential reductions in SPC risk with more contemporary treatment techniques were demonstrated by Rapiti et al, who found a reduction in colorectal cancer incidence in patients irradiated to higher doses (68 to 80Gy) compared to those treated to less than 67Gy (Relative risk (RR):0.2; 95% CI: 0.04 to 0.91 [262]. This reduction in risk was attributed to the introduction of smaller volume conformal radiotherapy techniques which accompanied dose escalation. Significance was lost, however, after adjustment for socio-economic status [262]. In addition, the study by Pickles et al, which excluded patients treated with cobalt and included fewer patients treated with large pelvic fields, found no increase in the incidence of SPC overall in irradiated patients compared to the general

population [260]. The group suggested that it was the increased use of smaller fields that resulted in no difference in SPC overall or bladder SPC, although a significant increase in colorectal tumours was observed [260]. Two other studies also evaluated SPC in more contemporary irradiated populations, however, and these have demonstrated increased bladder SPC risk compared to the general population and non-irradiated patients [281,291]. One of these studies also revealed an increase in rectal cancer beyond five years in irradiated compared to non-irradiated patients [281].

Huang et al was the first institutional study to specifically evaluate differences in EBRT treatment technique [266] (Table 5.7). Using a matched-pair analysis comparing irradiated and surgically treated patients in an effort to minimise confounding factors, they demonstrated that patients treated with 2D conventional RT were at increased risk of any SPC (HR: 1.76; 95% CI: 1.32 to 2.35) and bladder cancers (HR: 2.97; 95% CI: 1.50-5.89) . There was no difference in the risk of rectal cancer. In contrast, patients treated with 3D-CRT or intensity-modulated radiotherapy (IMRT), had no increase in the incidence of SPCs overall, nor in rectal or bladder cancer. The group acknowledged that the numbers of patients in each RT subset was relatively small (769 in the 2D conventional RT subset and 616 in 3D-CRT/ IMRT) and that the median follow-up in the 3DCRT/ IMRT group was relatively short (4.96 years) in comparison to the 2D conventional RT group (9.26 years) [266]. Unfortunately numbers were too small to analyse SPC in patients treated with 3D-CRT and IMRT separately. Some radiotherapy planning studies, however, have raised theoretical concerns that increased low dose irradiation and leakage (because of increased monitor unit requirements) with IMRT might increase SPC incidence [254,293-298].

Zelefsky et al reported outcomes for a series of 897 patients treated predominantly with IMRT [299]. After a median follow-up of seven years, compared to the general population, there was no significant increase in the development of any second malignancy beyond one and five years [299] (Table 5.7). Similarly, compared with the general population (and excluding non-melanoma skin cancers), there was no significant increase in risk of second in-field and out-of-field malignancies beyond one and beyond five years. Within the analysis the group also compared the risk of any second malignancy between patients receiving IMRT (the majority) and 3D-CRT (number of patients not reported), and no significant difference was found (p=0.59) [299].

Table 5.7 Studies examining second primary cancers at any site, rectal cancers and bladder cancers in prostate cancer patients irradiated using modern external beam techniques compared to general population and compared to surgical prostate cancer patients

Study	Type of data	Period	No. patients	Median follow-up (years)	Exclusions	Time period assessed	Risk of any second cancer based on *p*<0.05 or confidence interval not including 1.0 (magnitude, and (95% CI))	Risk of second rectal cancer based on *p*<0.05 or confidence interval not including 1.0 (magnitude, and (95% CI))	Risk of second bladder cancer based on *p*<0.05 or confidence interval not including 1.0 (magnitude, and (95% CI))
Compared to general population									
Zelefsky 2012 [299]	Retrospective, single centre	1998-2001	897 (mainly IMRT)	7	<1 years	>1 year >5 years	No difference (SIR: 0.881 (0.701-1.082)) No difference (SIR: 0.937 (0.673-1.295))	No difference (SIR: 1.179 (0.739-1.720))* No difference (SIR: 1.336 (0.611-2.339))*	No difference (SIR: 1.179 (0.739-1.720))* No difference (SIR: 1.336 (0.611-2.339))*
Compared to surgically treated patients									
Huang 2011 [266]	Retrospective, single centre matched-pair analysis	1984-2005	616 3D-CRT/ IMRT 616 surgery	4.96 RT 4.90 surgery	None	All durations	No difference (HR: 0.81 (0.55-1.21, *p*=0.30))	No difference (HR: 0.24 (0.03-2.18))	No difference (HR: 0.83 (0.25-2.72))
Zelefsky 2012 [274]	Retrospective, single centre	1998-2001	897 RT (mainly IMRT) 1348 surgery	7.5 RT 9.4 surgery	None	0-10 years	No difference (Multivariate analysis: no significant difference between techniques)	No difference (10-year likelihood RT vs. surgery: 4% vs. 3% (NS))*	No difference (10-year likelihood RT vs. surgery: 4% vs. 3% (NS))*

CI: confidence interval, HR: hazard ratio, NS: not significant, SIR: standardised incidence ratio, * figures shown are for any second in-field/pelvic cancer which includes rectal and bladder cancers

In a second publication, including the same irradiated population with slightly longer follow-up (7.5 years), Zelefsky et al compared SPC risks with 1348 patients treated with radical prostatectomy (median FU 9.4 years) and 413 patients treated with BT (median follow-up 7.7 years; Table 5.7) [274]. There was no significant difference in the rates of second rectal or bladder cancer with treatment type (10-year actuarial likelihood of pelvic second malignancy: 3%, 4% and 2% for patients treated with surgery, EBRT and BT, p=0.29). Multivariate Cox regression revealed that only age and smoking history were significant predictors of SPC, while treatment type (i.e. surgery, BT or EBRT) was not [274]. Survival following SPC diagnosis was also no different between irradiated and surgically treated patients [274].

5.4.6 Impact of treatment technique: Brachytherapy

Since the introduction of prostate BT, studies examining the impact of BT on SPC have been published. Four studies have compared SPC incidence after BT with that in the general population [281,299-301] (Table 5.8). Two single institution studies, have examined the risk of any SPC compared to the general population, and neither have shown any increase in risk in patients treated with BT, including when follow-up beyond five years is examined specifically [299,300]. The risk of rectal cancer has also been shown to be no greater than that in the general population over various time points, including beyond five years, in both SEER and single institution studies [281,300]. In terms of bladder cancer, one SEER analysis found patients treated with EBRT-BT to be at increased risk of second bladder cancer beyond six months compared to the general population, while patients treated with BT monotherapy were not at any increased risk [281]. Liauw et al, a single institution study, demonstrated more than double an increase in bladder cancer in patients treated with BT or EBRT-BT over all durations of follow-up compared to the general population. The risk was maintained over longer periods of follow-up (and was equivalent to an absolute excess risk of 35 per 10,000), but did not reach statistical significance [301]. Hinnen et al, also a single institution study, found an increased risk of second bladder cancer in patients treated with BT in years 1 to 4 of follow-up but not over all durations of follow-up, nor between 5 and 15 years. An increased risk in BT patients aged less than 60 was also observed (SIR: 5.84, 95% CI: 2.14-12.71) [300]. In addition, Zelefsky et al, a third single institution study, found no difference in the risk of any in-field cancer, which includes

rectal and bladder cancers, in BT treated patients compared to the general population, beyond one and beyond five years of follow-up [299].

Four studies, one registry and three single institution, have compared the incidence of any SPC in patients irradiated with BT or EBRT-BT with non-irradiated PCa patients (Table 5.9) [264,266,274,300]. Three of the four, all single institution studies, suggested no increased risk of any SPC following BT or EBRT-BT [266,274,300]. The fourth study, importantly, is the largest to examine SPC in patients managed with BT and the only one to specifically examine longer periods of follow-up [264]. On multivariate analysis there was no difference in risk for SPC beyond one year for patients treated with BT or EBRT-BT compared to non-irradiated patients (Table 5.9) [264]. The hazard ratios for 'late' SPCs (i.e. SPC developing beyond five years) in patients treated with BT alone, however, increased over time (0.721 at five years, 0.930 at seven years and 1.2 at nine years) but did not reach significance. Similarly, the hazard ratios for patients treated with EBRT-BT increased over time and only became significant at nine years (HR of 1.317; 95%CI: 1.053 to 1.647). Amongst patients treated with BT, however, the median time to develop 'late' SPC was 6.9 years while the median follow-up amongst BT patients without SPC was only 6.3 years, thus the duration of follow-up was insufficient [264]. With regard to RISPC specifically (defined in this study as cancers developing after five years in any primary pelvic site, including rectal and bladder tumours), no significant difference in risk was observed amongst patients treated with BT or EBRT-BT compared to patients receiving neither surgery nor RT [264] (Table 5.10).

None of the studies, with one exception, which compare the risk of second rectal or second bladder cancer in patients managed with BT or EBRT-RT with non-irradiated PCa patients (Table 5.10) demonstrate an increased risk in patients managed with BT or EBRT-BT [264,266,274,285,300]. The time periods examined are variable, but follow-up beyond five years is examined in two of these studies [264,285]. The one exception is the study by Nieder et al, the largest study and the only one to specifically examine risk beyond 10 years. Patients treated with EBRT-BT were found to be at increased risk of second rectal cancer beyond 10 years (patients treated with BT monotherapy were at no increased risk). In addition, patients treated with BT or EBRT-BT were at increased risk of second bladder cancer from 6 months, between 6 months and 5 years and between 5 and 10 years [281]. Significance was lost beyond 10 years although fewer patients were followed up for this length of time.

Table 5.8 Studies examining second primary cancers at any site, second rectal cancers and second bladder cancers in prostate cancer patients irradiated using brachytherapy compared to general population

Continued overleaf.

Study	Type of data	Period	No. patients	Median follow-up (years)[†]	Exclusions	Time period(s) assessed	Risk of second cancer at any site based on *p*<0.05 or confidence interval not including 1.0 (SIR and (95% CI))	Risk of second rectal cancer based on *p*<0.05 or confidence interval not including 1.0 (SIR and (95% CI))	Risk of second bladder cancer based on *p*<0.05 or confidence interval not including 1.0 (SIR and (95% CI))
Nieder 2008 [281]	Retro, SEER registry	1988-2003	22,889 BT	4.1	<6 months	>6 months	NR	Reduced (0.68 (0.49-0.93))	No difference (1.10 (0.92-1.31))
Nieder 2008 [281]	Retro, SEER registry	1988-2003	17,956 EBRT-BT	4.1	<6 months	>6 months	NR	No difference (0.86 (0.65-1.14))	Increased (1.39 (1.19-1.64))
Liauw 2006 [301]	Retro, single centre	1987 - 1994	348 (125 BT, 223 EBRT-BT)	11.4 BT 10.2 EBRT-BT	None	All durations 0-1 years 1.1-5 years 5.1-10 years 10.1-20 years >5 years	NR	NR	Increased (2.34 (1.26-3.42)) No difference 0 No difference (2.80 (0.73-4.87)) No difference (2.33 (0.60-4.06)) No difference (2.35 (0.05-4.66)) No difference (2.34 (0.95-3.72))

Table 5.8 cont. Studies examining second primary cancers at any site, second rectal cancers and second bladder cancers in prostate cancer patients irradiated using brachytherapy compared to general population

Study	Type of data	Period	No. patients	Median follow-up (years)†	Exclusions	Time period(s) assessed	Risk of second cancer at any site based on *p*<0.05 or confidence interval not including 1.0 (SIR and (95% CI))	Risk of second rectal cancer based on *p*<0.05 or confidence interval not including 1.0 (SIR and (95% CI))	Risk of second bladder cancer based on *p*<0.05 or confidence interval not including 1.0 (SIR and (95% CI))
Hinnen 2011 [300]	Retro, single centre	1989-2005	1,187 BT	7.1	None	All durations	No difference (0.94 (0.78-1.12))	No difference (0.90 (0.41-1.72))	No difference (1.69 (0.98 to 2.70))
						1-4 years	No difference (1.03 (0.80-1.30))	No difference (0.41 (0.05 to 1.48))	Increased (2.14 (1.03 to 3.94))
						5-15 years	No difference (0.78 (0.56-1.04))	No difference (1.78 (0.71 to 3.67))	No difference (0.92 (0.25 to 2.35))
Zelefsky 2012 [299]	Retro, single centre	1998-2001	413 (322 BT, 91 EBRT (IMRT)-BT)	7.5	<1 year	>1 year	No difference (0.821 (0.565-1.124))	No difference (0.753 (0.276-1.465))*	No difference (0.753 (0.276-1.465))*
						>5 years	No difference (0.635 (0.304-1.085))	No difference (0.944 (0.195-2.274))*	No difference (0.944 (0.195-2.274))*

BT: brachytherapy, CI: confidence interval, EBRT-RT: combination external beam radiotherapy and brachytherapy, IMRT: intensity-modulated radiotherapy, NR: not reported, Retro: retrospective, SEER: Surveillance, Epidemiology and End Results, †if follow-up for each treatment group reported separately, then this is presented, *: SIR quoted is for any in-field cancer, which includes rectal and bladder cancers

Table 5.9 Studies examining second primary cancers at any site in prostate cancer patients irradiated using brachytherapy compared to non-irradiated prostate cancer patients

Continued overleaf.

Study	Type of data	Period	No. patients	Median follow-up (years)	Exclusions	Time period(s) assessed	Risk of second cancer at any site (based on $p<0.05$ or CI not including 1.0)	Magnitude of risk (HR or other where stated (95% confidence interval))
Abdel-Wahab 2008 [264]	Retrospective, SEER database	1973-2002	10,223 BT 40,733 no RT	3.3 BT 4.3 no RT	<1 year	>1 year 5 years 7 years 9 years	No difference No difference No difference No difference	0.958 (0.869-1.057) 0.721 (0.435-1.197) 0.930 (0.575-1.504) 1.200 (0.736-1.956)
Abdel-Wahab 2008 [264]	Retrospective, SEER database	1973-2002	9,096 EBRT-BT 40,733 no RT	3.8 EBRT-BT 4.3 no RT	<1 year	>1 year 5 years 7 years 9 years	No difference No difference No difference Increased	1.012 (0.920-1.112) 0.920 (0.699-1.211) 1.101 (0.910-1.331) 1.317 (1.053-1.647)
Hinnen 2011 [300]	Retrospective, Single centre	1989-2005	1,187 BT 701 no RT	7.1 BT 8.7 no RT	None	All durations of FU	No difference	0.87 (0.64-1.18)
Huang 2011 [266]	Retrospective, single centre matched-pair analysis	1984-2005	333 BT 333 no RT	6.67 BT 6.62 no RT	None	All durations of FU	No difference	0.53 (0.28-1.01)
Huang 2011 [266]	Retrospective, single centre matched-pair analysis	1984-2005	402 EBRT-BT 402 no RT	8.81 EBRT-BT 8.87 no RT	None	All durations of FU	No difference	0.83 (0.50-1.38)

Table 5.9 cont. Studies examining second primary cancers at any site in prostate cancer patients irradiated using brachytherapy compared to non-irradiated prostate cancer patients

Study	Type of data	Period	No. patients	Median follow-up (years)	Exclusions	Time period(s) assessed	Risk of second cancer at any site (based on $p<0.05$ or CI not including 1.0)	Magnitude of risk (HR or other where stated (95% confidence interval))
Zelefsky 2012 [274]	Retrospective, single centre	1998-2001	413 BT (322 BT, 91 EBRT (IMRT)-BT) 1,348 no RT	7.7 BT 9.4 no RT	None	0-10 years	No difference	10 year second cancer actuarial likelihood BT vs. surgery: 13% vs. 11% (p=0.37). HR non-significant on multivariate analysis

BT: brachytherapy, CI: confidence interval, EBRT-BT: combination external beam radiotherapy and brachytherapy, HR: hazard ratio, IMRT: intensity-modulated radiotherapy, SEER: Surveillance, Epidemiology and End Results

Table 5.10 Studies examining second rectal and bladder cancers in prostate cancer patients irradiated using brachytherapy compared to non-irradiated prostate cancer patients

Continued overleaf.

Study	Type of data	Period	No. patients	Median follow-up[¥] (years)	Exclusions	Time period(s) assessed	Risk of second rectal cancer (based on *p*<0.05 or confidence interval not including 1.0)	Magnitude of risk of second rectal cancer (RR or other where stated, 95% CI or p value if available)	Risk of second bladder cancer (based on *p*<0.05 or confidence interval not including 1.0)	Magnitude of risk of second bladder cancer (RR or other where stated, 95% CI or p value if available)
Moon 2006 [285]	Retro, SEER registry	1973-1999	1285 BT 94,541 no RT	10	<5 years	>5 years	No difference	OR: 0.3 (NS*)	No difference	OR: 1.4 (NS*)
Moon 2006 [285]	Retro, SEER registry	1973-1999	2219 EBRT-BT 94,541 no RT	10	<5 years	>5 years	No difference	OR: 1.59 (NS*)	No difference	OR: 1.08 (NS*)
Abdel-Wahab 2008 [264]	Retro, SEER registry	1973-2002	10,223 BT 40,733 no RT	3.3 RT 4.3 no RT	<1 year	1-4.9 years ≥5 years	No difference** No difference**	0.01% difference in risk (NS)** 0.17% difference in risk (NS)**	No difference** No difference**	0.01% difference in risk (NS)** 0.17% difference in risk (NS)**
Abdel-Wahab 2008 [264]	Retro, SEER registry	1973-2002	9,096 EBRT-BT 40,733 no RT	3.8 RT 4.3 no RT	<1 year	1-4.9 years ≥5 years	No difference** No difference**	0.09% difference in risk (NS)** 0.05% difference in risk (NS)**	No difference** No difference**	0.09% difference in risk (NS)** 0.05% difference in risk (NS)**

Table 5.10 cont. Studies examining second rectal and bladder cancers in prostate cancer patients irradiated using brachytherapy compared to non-irradiated prostate cancer patients. Continued overleaf.

Study	Type of data	Period	No. patients	Median follow-up[¥] (years)	Exclusions	Time period assessed	Risk of second rectal cancer (based on *p*<0.05 or confidence interval not including 1.0)	Magnitude of risk of second rectal cancer (RR or other where stated, 95% CI or *p* value if available)	Risk of second bladder cancer (based on *p*<0.05 or confidence interval not including 1.0)	Magnitude of risk of second bladder cancer (RR or other where stated, 95% CI or *p* value if available)
Nieder 2008 [281]	Retro, SEER registry	1988-2003	22,889 BT 109,178 no RT	4.1	6 months	>6 months	No difference	HR: 1.08 (0.77-1.54)	Increased	HR: 1.52 (1.24-1.87)
						6 months- 5 years	No difference	HR: 0.96 (0.63-1.44)	Increased	HR: 1.48 (1.17-1.86)
						5-10 years	No difference	HR: 1.49 (0.75-2.94)	Increased	HR: 1.64 (1.03-2.62)
						>10years	No difference	HR: 1.13 (0.15-8.42)	No difference	HR: 0.47 (0.06-3.38)
Nieder 2008 [281]	Retro, SEER registry	1988-2003	17,956 EBRT-BT 109,178 no RT	4.1	6 months	>6 months	No difference	HR: 1.21 (0.89-1.65)	Increased	HR: 1.85 (1.54-2.22)
						6 months- 5 years	No difference	HR: 1.05 (0.71-1.55)	Increased	HR: 1.81 (1.46-2.25)
						5-10 years	No difference	HR: 1.26 (0.69-2.29)	Increased	HR: 1.80 (1.22-2.67)
						>10years	Increased	HR: 3.25 (1.25-8.44)	No difference	HR: 1.64 (0.75-3.59)
Hinnen 2011 [300]	Retro, Single centre	1989-2005	1,187 BT 701 no RT	7.1 BT 8.7 no RT	None	All durations of FU	No difference[†]	HR: 0.96 (*p*=0.92)[†]	No difference[§]	HR: 1.13 (*p*=0.75)[§]

Table 5.10 cont. Studies examining second rectal and bladder cancers in prostate cancer patients irradiated using brachytherapy compared to non-irradiated prostate cancer patients

Study	Type of data	Period	No. patients	Median follow-up[¥] (years)	Exclusions	Time period assessed	Risk of second rectal cancer (based on *p*<0.05 or confidence interval not including 1.0)	Magnitude of risk of second rectal cancer (RR or other where stated, 95% CI or *p* value if available)	Risk of second bladder cancer (based on *p*<0.05 or confidence interval not including 1.0)	Magnitude of risk of second bladder cancer (RR or other where stated, 95% CI or *p* value if available)
Huang 2011 [266]	Retro, single centre matched-pair analysis	1984-2005	333 BT 333 no RT	6.67 BT 6.62 no RT	None	All durations of FU	No difference	HR: NR (too few events to analyse), *p*=0.32	No difference	HR: 0.66 (0.11-3.95)
Huang 2011 [266]	Retro, single centre matched-pair analysis	1984-2005	402 EBRT-BT 402 no RT	8.81 EBRT-BT 8.87 no RT	None	All durations of FU	No difference	HR: 1.00 (0.14-7.06)	No difference	HR: 2.98 (0.31-28.7)
Zelefsky 2012 [274]	Retro, single centre	1998-2001	413 BT (322 BT, 91 EBRT (IMRT)-BT) 1,348 no RT	7.7 BT 9.4 no RT	None	0-10 years	No difference[‡]	10 year actuarial risk BT vs. surgery: 2% vs. 3% (NS)[‡]	No difference[‡]	10 year actuarial risk BT vs. surgery: 2% vs. 3% (NS)[‡]

BT: brachytherapy, CI: confidence interval, EBRT-BT: combination external beam radiotherapy and brachytherapy, HR: hazard ratio, IMRT: intensity-modulated radiotherapy, NR: Not reported, NS: not significant, OR: odds ratio, Retro: retrospective, RR: relative risk, SEER: Surveillance, Epidemiology and End Results, *no *p* value or confidence interval reported, ** difference in any 'primary' pelvic second primary cancer (includes rectum and bladder) based on comparisons of age-adjusted estimates and not on multivariate Cox regression, [†]risk of second cancer in any location in digestive tract, [‡]risk of any second pelvic tumour reported, [¥] if follow-up for each treatment group reported separately, then this is presented, [§]risk of second cancer in any location in urinary tract

Three studies have compared patients treated with BT with patients treated with EBRT (Table 5.11) [264,274,302]. One of these studies, a SEER analysis, suggested that between 1 and 15 years of follow-up, patients treated with BT or EBRT-BT were at reduced risk of any SPC compared to patients irradiated using EBRT [264]. When follow-up beyond 5 years was examined specifically, however, no differences in risk were observed [264]. Neither of the other two studies, both single institution studies, have demonstrated any difference in the risk of any SPC between patients irradiated with BT compared to patients irradiated using EBRT [274,302]. Similarly, no difference in the risk of second pelvic/ primary pelvic SPC has been observed between patients treated with BT and EBRT-BT compared to those treated with EBRT (in the two studies which assessed this) [264,274]. While these results are encouraging overall, it should be remembered that the patient numbers are often lower than in similar studies which have examined risks in EBRT patients, and the duration of follow-up may not always be sufficient.

Gutman et al examined the frequency of colorectal cancers before and after BT or EBRT-BT [303] (Table 5.12)**.** After a median follow-up of 4.6 years, no differences in the frequency of colorectal cancers were observed, nor were there any differences in the geographical location of second colorectal primaries. In addition, the addition of supplemental EBRT (i.e. EBRT-BT) did not increase the risk of colorectal cancer compared to using BT alone [303].

Of the eight single institution studies examining SPC following BT without comparisons to other population groups (Table 5.12), crude rates range from 0% for any SPC, rectal and bladder cancer up to 11.1%, 0.8% and 1.2% for any SPC, second rectal and second bladder cancers respectively [279,303-309]. It is likely that some studies have insufficient follow-up to detect all SPCs and most single institution studies contain a relatively small number of patients. The age of the patient population may also have an impact. For example, Yagi et al reported no cases of SPC in patients aged less than 60 but a crude rate of 7.6% in patients aged over 60, after median follow-up of 4.3 years [308].

Table 5.11 Studies examining second primary cancers at any site in prostate cancer patients irradiated using brachytherapy compared to patients irradiated using external beam radiotherapy

Continued overleaf.

Study	Type of data	Period	No. patients	Median follow-up (years)	Exclusions	Time period assessed	Risk of any second cancer based on $p<0.05$ or confidence interval not including 1.0 (magnitude of risk)	Risk of second rectal cancer based on $p<0.05$ or confidence interval not including 1.0 (magnitude of risk)	Risk of second bladder cancer based on $p<0.05$ or confidence interval not including 1.0 (magnitude of risk)
Abdel-Wahab 2008 [264]	Retrospective, SEER database	1973-2002	10,223 BT 48,400 EBRT	3.3 BT 5.3 EBRT	<1 year	1-15 years	Reduced (0.28% reduction in risk, $p=0.025$)†	NR	NR
						1-5 years	No difference (0.15% difference in risk, NS)†	No difference (0.08% difference in risk, NS)*	No difference (0.08% difference in risk, NS)*
						>5 years	No difference (0.49% difference in risk, NS)†	No difference (0.004% difference in risk, NS)*	No difference (0.004% difference in risk, NS)*
Abdel-Wahab 2008 [264]	Retrospective, SEER database	1973-2002	9,096 EBRT-BT 48,400 EBRT	3.8 EBRT-BT 5.3 EBRT	<1 year	1-15 years	Reduced (0.28% reduction in risk, $p=0.025$)†	NR	NR
						1-5 years	No difference (0.2% difference in risk, NS)†	No difference (0.03% difference in risk, NS)*	No difference (0.03% difference in risk, NS)*
						>5 year	No difference (0.33% difference in risk, NS)†	No difference (0.12% difference in risk, NS)*	No difference (0.12% difference in risk, NS)*

Table 5.11 cont. Studies examining second primary cancers at any site in prostate cancer patients irradiated using brachytherapy compared to patients irradiated using external beam radiotherapy

Study	Type of data	Period	No. patients	Median follow-up (years)	Exclusions	Time period assessed	Risk of any second cancer based on *p*<0.05 or confidence interval not including 1.0 (magnitude of risk)	Risk of second rectal cancer based on *p*<0.05 or confidence interval not including 1.0 (magnitude of risk)	Risk of second bladder cancer based on *p*<0.05 or confidence interval not including 1.0 (magnitude of risk)
Reddy 2010 [302]	Retrospective, single centre	1996 - 2008	1,758 EBRT 2,317 BT	5.7 EBRT 2.8 BT	None	All durations of follow-up	No difference (Multivariate analysis OR: 1.226 (0.887-1.695))	NR	NR
Zelefsky 2012 [274]	Retrospective, single centre	1998-2001	413 BT (322 BT, 91 EBRT (IMRT)-BT) 897 EBRT	7.7 BT 7.5 EBRT	None	0-10 years	No difference (HR on multivariate analysis NS)	No difference (10 year actuarial risk (BT vs EBRT): 2% vs 4% (NS))**	No difference (10 year actuarial risk (BT vs EBRT): 2% vs 4% (NS))**

EBRT: external beam radiotherapy, BT: brachytherapy, EBRT-BT: combination EBRT and BT, IMRT: intensity-modulated radiotherapy, NR: not reported, NS: non-significant, HR: hazard ratio, OR: odds ratio, SEER: Surveillance, Epidemiology and End Results, * risks shown for any second 'primary' pelvic second cancer (includes rectum and bladder) and are based on are based on comparisons of age-adjusted estimates and not on multivariate Cox regression, ** risks shown for any pelvic second cancer (includes rectal and bladder cancer), † based on comparisons of age-adjusted estimates and not on multivariate Cox regression

Table 5.12 Studies reporting second cancer rates in patients treated with brachytherapy or combination external beam radiotherapy and brachytherapy without comparison

Study	Type of data	Period examined	No. patients	Median follow-up (years)	Exclusions	Crude rate of any second cancer	Crude rate of second rectal cancer	Crude rate of second bladder cancer
Gutman 2006 [303]	Retrospective, single centre	1995-2004	652 BT 699 EBRT-BT	4.6	None	NR	0.3% (n=4) post-radiation vs 0.2% (n=3) pre-radiation	NR
Swartz 2010 [304]	Prospective, single centre	1997 - 1999	86 BT or EBRT-BT	Minimum FU 10 years	None	0	0	0
Wilcox 2011 [306]	Retrospective, single centre	Not stated	431 BT or EBRT-BT	6.9	None	<1%*	NR	NR
Henry 2012 [279]	Retrospective, single centre	1995-2005	1,805 BT	6-17 years	NR	11.1% (201/1805)	0.6% (11/1805)	1.2% (21/1805)
Laing 2012 [305]	Prospective, single centre	1999-2011	121 (all <55 years) BT or EBRT-BT	Minimum FU >3 years	NR	0	0	0
Lilleby 2012 [307]	Prospective, single centre	2004-2009	275 EBRT-BT (mainly high risk patients)	3.7	None	1.1% (3/275; all colorectal cancers)	0.4% (1/275)	0
Yagi 2012 [308]	Retrospective, single centre	2005-2008	86 BT aged <60 685 BT aged >60	4.3	NR	Patients aged<60: 0 Patients aged>60: 7.6% (52/685)	Patients aged<60: 0 Patients aged>60: 1.3% (9/685; bladder or rectal cancers)	Patients aged<60: 0 Patients aged>60: 1.3% (9/685; bladder or rectal cancers)
Buckstein 2013 [309]	Retrospective, single centre	1990-2002	102 BT 29 EBRT-BT (all <60 years)	11.5 (minimum FU 10 years)	None	3.1% (4/131)	0.8% (1/131)	0.8% (1/131)

BT: brachytherapy, EBRT-BT: combination external beam and brachytherapy, FU: follow-up, NR: not reported, *<1% “rate of possible radiation-induced cancer” (not defined further)

Studies examining survival following BT suggest that up to 3% of patients may die from SPC following BT or EBRT-BT (crude rate, Table 5.4) [277-279]. The cumulative hazard of death due to a SPC was found to be 7.2% in one study of 1354 patients treated with either BT or EBRT-BT after 12 years [277]. In another series, based on competing analysis to take into account other causes of death, the 10 year risks of death from second malignancy following BT was 0.8% for out-of-field SPC and 0% for in-field SPC in a series of 413 patients, and this was not significantly different to mortality rates following EBRT (or surgery) [274].

Overall, evidence from patients treated with BT or EBRT-BT is encouraging, and is less suggestive of an increased risk of SPCs as has been observed in studies evaluating patients treated with EBRT. Three studies have suggested an increase in bladder cancer risk beginning in the first few years of follow-up, which could be at least partly attributed to surveillance bias [281,300,301]. Importantly, there is a suggestion from two of the largest cohorts, that the risk of a SPC, although low, may increase with time and so it is likely that follow-up in general has been insufficient to detect all potential late increases in SPC incidence [264,281].

5.4.7 Impact of treatment technique: Proton therapy

Protons result in high doses of radiation being delivered to the target with rapid dose fall off beyond the target. Entrance doses from protons are lower than when using photon radiation, and exit doses are minimal, both of which result in reduced normal tissue irradiation compared to photon radiotherapy [293]. Given these differences in dose distribution, planning studies have suggested that proton therapy should result in lower risks of second cancer compared to photon radiotherapy [295,310-313]. Only one study was identified which reported SPC rates in patients treated with proton therapy for PCa [273]. Treatment consisted of a photon 4-field box delivering 50.4Gy in 28 fractions followed by a 27Gy conformal perineal proton boost. After a median follow-up of 13.1 years, one of the 39 patients (2.6%) developed rectal cancer [273]. Clearly no comparisons to other populations have been performed and this series is too small to draw any firm conclusions. Furthermore, the relative contribution of the EBRT and proton components cannot be assessed. Larger numbers of patients treated with

proton monotherapy will be required before any conclusion can be drawn regarding the impact of proton therapy on SPC incidence in PCa patients.

5.4.8 Post-operative radiotherapy

Four registry studies and one single institution study have examined SPC risk in patients treated with post-operative radiotherapy (PORT) following prostatectomy [275,288,290,291,314] (Table 5.13).

Chrouser et al included a subset of 184 PCa patients managed with PORT in their single institution analysis and compared bladder cancer incidence to the general population [288]. No increased risk of bladder cancer was observed in patients receiving PORT over several time points.

Compared to patients treated with radical surgery alone, Abdel-Wahab et al, using a SEER registry, demonstrated that there was a significantly increased risk of a 'primary pelvic' SPC (i.e. tumour likely to arise within the irradiated field: bladder, rectum, anus, anal canal and anorectum) in patients who received PORT beyond one year and beyond five years of follow-up [314]. There was no increase in the risk of 'secondary' pelvic tumours (recto-sigmoid, penis, small intestine, ureter, other urinary primaries, male genital organs, testes and pelvic lymphoma) or non-pelvic tumours beyond one and beyond five years [314]. Overall the group estimated that radiation increased the risk of a pelvic RISPC by an age-adjusted rate of 374 per 100,000 [314]. Ciezki et al, another SEER analysis, used 20-year competing risk regression to compare second rectal and bladder cancers between patients treated with surgery and PORT and patients treated with surgery alone [275]. At 20 years, the cumulative incidence of second rectal cancer was 0.74% and 1.06% in patients treated with surgery alone and surgery followed by PORT respectively. The cumulative incidence of second bladder cancer at 20 years was 1.7% and 2.7% in patients treated with surgery alone and surgery plus PORT respectively. Multivariate analysis revealed a significantly increased risk of second rectal and bladder cancers amongst irradiated patients. Older age was also a significant predictor of second bladder cancer (HR: 1.01, p=0.003) [275].

Table 5.13 Risk of second rectal and bladder cancers following post-operative radiotherapy for prostate cancer compared to the general population and compared to non-irradiated patients

Continued overleaf.

Study	Type of data	Period	No. patients	Median follow-up (years)	Exclusions	Time period assessed	Risk of second rectal cancer based on $p<0.05$ or confidence interval not including 1.0 (magnitude and (95% confidence interval))	Risk of second bladder cancer based on $p<0.05$ or confidence interval not including 1.0 (magnitude and (95% confidence interval))
Compared to general population								
Chrouser 2005 [288]	Retrospective, Single centre	1980-1998	184	7.1 (mean for whole study population)	None	All durations <1 year 1-4 years 5-9 years 10-19 years	NR	No difference (SIR:2.345 (0.943-4.832)) No difference (SIR:0 (0-15.18)) No difference (SIR:3.643 (0.990-9.312)) No difference (SIR:1.799 (0.218-6.475)) No difference (SIR:1.890 (0.048-10.53))
Compared to prostate patients managed in other ways								
Abdel-Wahab 2009 [314]	Retrospective, SEER registry	1973-2002	5,044 surgery and PORT 80,157 surgery	NR	<1 year	>1 year >5 years	Increased* (HR:1.53 (1.22- 1.90)) Increased* (HR:1.82 (1.36-2.43))	Increased* (HR:1.53 (1.22- 1.90)) Increased* (HR:1.82 (1.36-2.43))

Table 5.13 cont. Risk of second rectal and bladder cancers following post-operative radiotherapy for prostate cancer compared to the general population and compared to non-irradiated patients

Study	Type of data	Period	No. patients	Median follow-up (years)	Exclusions	Time period assessed	Risk of second rectal cancer based on *p*<0.05 or confidence interval not including 1.0 (magnitude and (95% confidence interval))	Risk of second bladder cancer based on *p*<0.05 or confidence interval not including 1.0 (magnitude and (95% confidence interval))
Compared to prostate patients managed in other ways								
Singh 2010 [290]	Retrospective, SEER registry	1973-2005	32,744 surgery and PORT 163,111 no surgery, no RT	7.8 PORT 4.0 No surgery, no RT	None (simultaneous diagnoses excluded)	All time periods >6months >5years >10years	NR	Increased (HR:1.18 (1.07-1.29)) Increased (HR:1.28 (1.15-1.42)) Increased (HR:1.52 (1.30-1.78)) Increased (HR:1.94 (1.40-2.67))
Ciezki 2012 [275]	Retrospective, SEER registry	1973-2008	20,545 surgery and PORT 127,189 surgery alone	9.5 surgery and PORT 9.2 surgery alone	<3 years	20 years	Increased (HR: 1.45 (1.23-1.71))	Increased (HR:1.72 (1.55-1.91))
Boorjian 2007 [291]	Retrospective, CaPSURE Disease Registry	1989-2003	232 surgery and PORT 4339 surgery alone	3.25 for whole study population	<30 days	>30 days	NR	No difference (HR: NR, *p*=0.12)

HR: hazard ratio, NR: not reported, PORT: post-operative radiotherapy, SEER: Surveillance, Epidemiology and End Results, SIR: standardised incidence ratio, * ratio reported for any 'primary pelvic' second cancer considered as rectum, bladder, anus, anal canal, anorectum and other cancer from the bones, joints and lymphomas involving the pelvis

Singh et al, also using SEER data, observed that patients treated with surgery and PORT had an increased risk of second bladder cancers overall as well as beyond six months of follow-up (HR: 1.28) compared to patients treated with neither surgery, nor RT [290]. The risk increased beyond five years and increased further beyond 10 years of follow-up (HRs: 1.52 and 1.94 respectively). The duration of follow-up in the PORT group was almost twice that in the comparator group (median 93.6 months and 48.4 months respectively) and so it is possible that the incidence of bladder cancer was lower in the reference group as a result of insufficient follow-up [290].

In a small subset of patients within the CaPSURE disease registry, Boorjian et al did not find patients receiving PORT to be at increased risk of second bladder cancer beyond 30 days compared to patients treated with surgery alone [291].

One series of 214 patients treated with PORT reported death due to second malignancy in 1.9% of patients after median follow-up of 4.8 years (crude rate) [276] while Ciezki et al reported very low age-adjusted mortality rates from second colorectal or bladder cancers [275] (Table 5.4).

Compared to surgically treated PCa patients who do not receive PORT, there is, therefore, a reasonably consistent suggestion of an increased risk of second bladder/rectal cancers following PORT, and this risk appears to increase with time but may also be present early on in the follow-up period. Compared to the general population the same increase in risk has not been observed, although the number of patients in this particular analysis was small [288].

5.5 Discussion

There is much heterogeneity in the above studies, in terms of methods, comparisons and results, which makes it difficult to draw firm conclusions. Increases in SPC have been observed in irradiated PCa patients in some studies, more so when compared to non-irradiated PCa patients, and less consistently when compared to the general population. The majority of the evidence suggests that the risk of SPC increases over time, particularly for SPCs occurring within the radiation field and, if these occur beyond five years, they may be considered RISPCs.

Solid second primary cancers which occur within five years of irradiation are not generally considered RISPCs. Other explanations for an excess of early SPCs must therefore be sought. Surveillance bias is one explanation, as patients presenting with both bladder and bowel symptoms following RT may be investigated and incidental SPCs may be identified. Alternatively, there may be genetic or environmental factors which are common to PCa and other cancers, and therefore patients with PCa are likely to develop other cancers, within five years of prostate irradiation or beyond. This is one possible reason for increased cancer rates which have at times been observed when comparing irradiated PCa patients to the general population. If this were the case, then the same increased risk should be observed when comparing non-irradiated PCa patients to the general population. In practice, this is not consistently the case, and non-irradiated PCa patients have been shown to have similar (or even reduced) rates of second malignancy compared to the general population in terms of cancer overall, and in terms of rectal and bladder cancer specifically [258,259,262,280,283,300]. Surveillance bias is perhaps, therefore, a better explanation for increased early SPCs in irradiated patients. Beyond five years, radiation for in-field SPCs, and genetic or environmental factors for either in-field or out-of-field SPCs, may potentially contribute.

Differences in comparator group are important to consider when evaluating relative SPC risks. As well as the general population, comparisons have been made with non-irradiated PCa patients. This patient group might consist of surgically treated patients, PCa patients treated with neither surgery nor RT, or a mixture of surgically treated patients and patients treated with neither surgery, nor-RT. Although differences

between these non-irradiated groups were not analysed in detail here, it should not be assumed that any of these PCa patients are pure surrogates for the general population or that they are equivalent to each other. While all these non-irradiated patients have PCa, and therefore common factors contributing to this, there are likely variations in genetic or environmental factors in each of these patient groups that may contribute to or reduce the risk of other cancers.

If the non-irradiated comparator group consists of purely surgically treated patients, selection bias may contribute to differences in SPC risk between surgically treated and irradiated patients. Patients who are fit enough to undergo an operation may have fundamental differences to patients who are only deemed well enough to undergo radiotherapy, and as such surgically treated patients may lack risks factors for certain SPCs.

If the non-irradiated comparator group is patients treated with neither surgery nor RT, many of these patients may have significant co-morbidities which render them unfit for either definitive treatment. Again, this population of patients will have different risks of SPC to PCa patients overall. Furthermore, these patients may not be as thoroughly followed up or investigated for possible second malignancy compared to fitter healthier patients, thus creating additional bias in comparisons and under-reporting of SPC rates.

When the non-irradiated comparator group is a mixture of surgically treated patients as well as those who receive no definitive therapy, a mixed population is potentially created, consisting of surgically fit patients and patients unfit for any definitive therapy, leading to further difficulties in making non-biased comparisons.

It has been suggested that comparing irradiated patients to surgically treated patients results in fewer confounding factors than comparisons to the general population or other non-irradiated PCa patients [266]. Certainly, in clinical practice, if patients are fit enough to consider surgery or RT, then it can be argued that this is the most relevant comparison.

The length of follow-up between comparator groups is also important, and where this is insufficient in any group or not adequately corrected for, reported outcomes may be inaccurate in that group.

Smoking is an important potential confounding factor, especially when considering bladder and lung cancer. As discussed above, smokers may be refused surgery and therefore cohorts of patients treated with radiotherapy may contain a higher proportion of smokers, which in turn will increase the risk of SPCs. PCa patients treated with radiotherapy may also be older than surgically treated patients and this too may have an impact on risks of SPC. Indeed, age at PCa diagnosis has been shown to be another important factor: increasing age has been associated with a reduced risk of second cancers within high dose (>5Gy) regions [261], while increasing age has been shown to be a significant predictor of bladder SPC [290,291]. Most studies have adjusted for age when calculating risks [258-262,264-267,274,275,280-292,299,300,314]. Similarly most studies have adjusted for race and grade of tumour. It is possible that other confounding factors exist which are more common in irradiated than non-irradiated PCa patients, and these may also contribute to SPC risk within or beyond five years.

A recently identified potential confounding factor is visceral adiposity [269]. Zilli et al intended to investigate the impact of total abdominal adiposity on clinical and pathological PCa features [269]. Incidentally they observed that increased visceral adiposity was an independent significant predictor of SPCs (HR: 1.014; p=0.0001).

While many of the studies have included patients treated with now out of date techniques, the registry studies by Nieder et al and Boorjian et al which included patients from 1988/1989 to 2003, are considered more contemporary EBRT populations, and so the risks observed in these studies may be considered more relevant to today's PCa patients [281,291]. It is worth noting, therefore, that both of these studies found the risk of bladder cancer to be increased in irradiated patients [281,291], and one demonstrated an increased risk of rectal cancer as well [281]. Insufficient follow-up (mean approximately four years) may explain the absence of increased rectal cancer risk from EBRT in the other of these studies [291]. .

Studies including patients from the 1970s and early 1980s would have included patients diagnosed before the routine use of PSA. As such a greater proportion of patients would be diagnosed with locally advanced disease and so would have inferior survival compared to patients in today's society where many more patients are diagnosed at an earlier stage. A significant proportion of patients from the past may therefore have died prior to developing SPC, and so the relative risks of SPC reported from these studies may actually be lower than what would be expected from modern day PCa patients [281].

With the advent of more conformal treatments, it was hoped that SPC risk might reduce, although the clinical evidence to support this is based on limited evidence from only two relatively small populations irradiated with IMRT/3D-CRT [266,274,299] and on extrapolated evidence from two other studies [260,262]. Longer follow-up and larger numbers of patients will be required. Studies examining the impact of BT or EBRT-BT on SPC risk appear promising, although, once again, longer follow-up will be required before definitive conclusions can be drawn.

5.6 Conclusions

Given the multiple factors involved, and heterogeneity among studies, it is very difficult to tease out definitive answers regarding irradiation and the risk of SPCs. Putting all the potential confounders and biases aside, however, it must be acknowledged that a small increased risk of SPC and RISPC in irradiated PCa patients has been observed in several studies. The risk of RISPC appears small, in the range of 1 in 220 to 1 in 290 over all durations of follow-up, based on older external beam radiation techniques. Importantly, the risk appears to increase with time, and beyond five years, SPCs in the region of the original field may be considered RISPCs. To date there is insufficient clinical data to draw firm conclusions about the impact of more modern RT techniques, although limited evidence is encouraging. As PCa survival improves, the risk of second malignancy becomes more relevant, especially when treating younger patients. Second primary cancer risks must therefore be borne in mind when considering which patients to irradiate and which technique to employ.

5.7 Update at time of thesis write-up

The search strategy was re-run at the time of thesis compilation (last search date 1st July 2014). This revealed an additional 71 records, including 8 repeats. Of the remaining 63 new articles, reasons for exclusion included: initial primary cancer not PCa (n=9), not dealing with new primary cancer (n=11), case reports (n=5), review/ commentary (n=9), planning studies (n=12), letters not containing new data (n=3), laboratory or biomarker based studies (n=5), imaging study (n=1), not specifically dealing with irradiated PCa patients (n=1) and not in English language (n=2). Five additional studies were therefore identified that could be added, one of which was a full paper which had previously been included in abstract form only. The outcomes from all five studies are largely in-keeping with findings from the studies reviewed earlier, and are discussed below.

Nam et al used the Ontario Cancer Registry to retrospectively compare complications following either prostatectomy or radiotherapy treatment for PCa [315]. Patients received treatment between 2002 and 2009. In total, 15,870 patients were included who received surgery and 16,595 patients who received radiotherapy (without surgery). Patients who received surgery were younger and had less co-morbidity than those who received radiotherapy. Patients with less than five years follow-up were excluded from the second malignancy analysis. The maximum duration of follow-up was nine years. Compared to the general population, and in keeping with studies discussed earlier, patients receiving radiotherapy aged 65 to 90 were at no increased risk of second cancer at any site (SIR: 0.8, 95%CI:0.7-1.0). When patients aged between 40 to 65 were examined specifically, however, an increased risk of SPC was observed (SIR:3.5, 95%CI:2.3-4.7), which influenced the overall SIR such that when considering all patients, there appeared to be an increased risk of SPC in irradiated patients compared to the general population (SIR:2.0, 95%CI:1.7-2.3). When irradiated patients were compared to surgically treated patients within a Cox proportional hazards model, irradiated patients were found to be at increased risk of second cancers from five to nine years (HR:2.08, 95%CI:1.48-2.91, p<0.0001). Increasing age and greater co-morbidity were also identified as risk factors for second malignancy. Although the data were not provided, the group reported that when the analysis was restricted to only those irradiated patients who received ‘contemporary’ radiotherapy (i.e. 3D planning),

the hazard ratio for any SPC for radiotherapy versus surgery was maintained. An unadjusted numerical comparison (i.e. not within a Cox model) of the number of patients developing GI and GU cancers also found these tumours to be more common in irradiated patients compared to surgically treated patients (p<0.0001) [315]. This study has been criticised for issues including selection bias, the manner in which radically treated patients were identified from the database, the relatively short follow-up and the lack of inclusion of potential confounders in the Cox model (including PCa stage, Gleason score and smoking history (although this is frequently not available in registry data)) [316-319]. At least 40% of the SPCs identified occurred outside the treatment field, including tumours at sites with known links to smoking, and so the impact of smoking was felt to be of particular importance. Issues with selection bias are difficult to avoid when performing retrospective analyses such as this, and some of the criticisms raised to this study, could also be applied to the earlier registry studies, as discussed before.

Okajima et al evaluated SPCs in a single institution study of 150 patients irradiated for PCa [320]. After a median follow-up of 48 months (range 12 to 142 months), 16 patients (11%) developed SPCs more than two months from the PCa diagnosis, including two cases of bladder cancer but no cases of rectal cancer. The median time to develop a SPC was 44 months (range 13 to 83 months), and so several of these tumours would not be considered radiation-induced. Compared to the expected incidence in the general population, there was no significant increase in the risk of any SPC (SIR at four years post-treatment: 1.21, p=0.501, SIR at five years post treatment: 0.96, p=non-significant), nor bladder cancer specifically (SIR at four years post-treatment: 4.55, p=0.072, SIR at five years post treatment: 3.57, p=0.110). As with similar single institution studies, this study is limited by a small sample size and relatively short follow-up.

Musunuru et al provided a full report of the single institution BT data previously included in abstract form [279,321]. The risk of SPC at any site, or rectal or bladder cancer specifically, did not appear to be higher in BT treated patients compared to the general population. In a series of 1574 patients with a median follow-up of 8 years (interquartile range 6 to 10 years, patients with <1 year of follow-up excluded, 31% of patients had greater than 10 years of follow-up), the SIR for SPC at any site was 0.70 (95%CI:0.57-0.84) over all durations of follow-up, 0.92 ((95%CI:0.71-1.18) for follow-up

between one and four years, and 0.55 (95%CI:0.42-0.74) for follow-up beyond five years. For rectal cancer, the SIR was 0.83 (95%CI:0.46-1.53) over all durations of follow-up, 1.30 (95%CI:0.64-2.68) for follow-up between one to four years, and 0.45 (95%CI:0.16-1.31) for follow-up beyond five years. For bladder cancer, SIR was 1.54 (95%CI:0.96-2.46) over all durations of follow-up, 1.69 (95%CI:0.87-3.34) for between one and four years of follow-up and 1.42 (95%CI:0.75-2.7) for follow-up beyond five years. The group concluded that there was a potentially increased risk of second bladder cancer in BT treated patients compared to the general population, although this did not reach statistical significance. The effect was mostly observed in the early follow-up period where it was attributed to increased surveillance rather than radiotherapy. As before, it is only those BT studies with larger patient numbers and longer durations of follow-up that suggest that there could be an increased risk of SPC following BT, and so larger patient numbers and longer follow-up are still required in this and similar studies before a firm conclusions regarding SPC following BT can be drawn.

Roach et al performed a post hoc analysis of SPCs in 1979 irradiated PCa patients from the RTOG 9408 trial [322]. Patients were treated between 1994 and 2001. Rates of SPC were compared between patients irradiated using whole pelvic radiotherapy (WPRT) and patients who received prostate only radiotherapy. No significant difference was identified in the risk of second cancer at 10 years (19.1% for WPRT vs. 16.9% for prostate only radiotherapy, p=0.87). There was, however, a trend towards increased death from SPC following WPRT (9.1% for WPRT vs. 4.2% for prostate only radiotherapy at 10 years) although this did not reach statistical significance (p=0.061). The group concluded that this observation required further work to determine its clinical significance and validity.

Ferrer et al examined toxicity following pelvic VMAT (48.6Gy in 27 fractions) with a hypofractionated whole prostate boost (67.5Gy in 27 fractions) in a series of 28 high risk PCa patients treated between June 2010 and November 2012 [323]. After a median follow-up of six months, one patient was diagnosed and died from a second cancer (crude death rate: 4%). Given the relatively short follow-up in this series, this cancer was unlikely to have been radiation-induced.

Thus none of these studies alter the conclusions reached in the main text. Problems can be encountered both when using large, potentially incomplete registry data, as well as when trying to draw conclusions from relatively small studies or studies with short durations of follow-up. As before, there remains a suggestion that EBRT can result in an increase in SPC compared to non-irradiated PCa patients, while the evidence concerning BT remains encouraging but too immature to draw firm conclusions.

Chapter 6 : Radiation-induced second primary cancer risks from modern external beam radiotherapy for early prostate cancer: impact of stereotactic ablative radiotherapy (SABR), volumetric modulated arc therapy (VMAT) and flattening filter free (FFF) radiotherapy

6.1 Introduction

One the most serious long-term consequences of successful radiotherapy treatment is the development of a RISPC. As treatment techniques improve along with survival, the development of RISPC becomes a more significant clinical issue. As discussed in the previous chapter, there is clinical evidence that suggests that PCa patients treated with EBRT, compared to patients treated surgically, are at increased risk of developing RISPC, and that this risk increases over time. The vast majority of the clinical literature concerning RISPC in PCa patients, however, consists of patients treated with older radiotherapy techniques. Theoretical concerns have been raised that modern techniques such as IMRT may increase RISPC risk [254]. The clinical evidence concerning patients treated with more modern techniques is currently too immature to determine if these concerns are warranted. Until more clinical data is available, planning studies can be used to estimate RISPC risks. In PCa, such planning data exists in terms of comparisons of IMRT with 3D-conformal radiotherapy [294,297,324-327]. Studies comparing IMRT and 3D-CRT at equivalent energies have consistently demonstrated an increase in RISPC risk from IMRT [294,297,324,325]. The magnitude of the increase in risk depends on the models and methods used for RISPC calculation but, in absolute terms, the increase in risk can be very small. Those studies which have directly compared 6MV IMRT with higher energy 3D-CRT treatments, as are often employed clinically, however, do not demonstrate an increase in risk from IMRT [326,327]. The RISPC risk from IMRT compared to 3D-CRT, therefore, may not be as high as has perhaps been historically presumed. Little data exist concerning techniques such as SABR (although it has been postulated that this should reduce RISPC risk [328]) and VMAT. It has previously been demonstrated that the use of FFF

in PCa treatment results in a reduction in out-of-field doses [329], although quantification and comparisons of RISPC risk in in-field, close-to-field and out-of-field organs have not been widely performed.

This study aims to compare the RISPC risks from modern radiation techniques used to treat early PCa using doses, fractionations and beam energies that are employed in day to day clinical practice. Conventionally fractionated schedules delivered using 10MV 3D-conformal radiotherapy (3D-CRT), 6MV 5-field IMRT, 6MV VMAT with standard (flattened) and energy-matched 6MV FFF beams are evaluated together with SABR delivered using 6MV VMAT with standard (flattened) and energy-matched FFF beams. Schneider's concept of Organ Equivalent Dose (OED) [330], which considers the effects of fractionation, has been employed. In addition, the impact of in-field and out-of-field dose is included (as opposed to out-of-field dose in isolation). For organs in close proximity to the treatment field (where the majority of RISPCs have been shown to develop [261]), RISPC risk has been estimated using DVH data, while for organs further from the treatment volume, chamber measurements were used to assess RISPC risk.

6.2 Methods

6.2.1 Contouring

Three prostate datasets were selected which were typical for patients diagnosed with low risk, localised PCa. The CTV was defined as the prostate alone and was expanded by 6mm in all directions to create the PTV, a margin compatible with daily online image guidance with fiducial markers in situ [186-188]. The rectum (recto-sigmoid junction to anus), bladder and femoral heads were contoured as organs at risk. All pelvic bones were also contoured and used to represent the dose received by bones. A 5mm shrink margin was created within the bladder and the subtraction of this structure from the whole bladder structure was used to represent the bladder wall. The patients' rectums were empty at the time of the planning scan and so the whole rectal volume was taken to represent the dose received by the rectum, as has been previously shown to be acceptable [239].

6.2.2 Advanced radiotherapy planning

Five external beam treatment plans were produced for each dataset using Monaco® v3.3 (Elekta AB, Sweden) with a MC algorithm, 6MV photons, a 2mm calculation grid and the Agility™ head (Elekta AB, Sweden). A 5-field step and shoot IMRT plan was produced, delivering 78Gy in 39 fractions, with a standard (flattened) 6MV beam with the following beam angles: 180° (posterior), 252°, 324°, 36° and 108°. Two VMAT plans delivering 78Gy in 39 fractions were produced using one 240° arc (240° to 120°, 30° sectors), one with a standard (flattened) 6MV beam and one with an energy-matched 6MV FFF beam. Two SABR plans delivering 42.7Gy in 7 fractions were produced, also using one 240° VMAT arc (240° to 120°, 30° sectors), one with a standard (flattened) 6MV beam and one with energy-matched 6MV FFF. (As before, 'energy-matched' means the FFF beam energy was re-tuned to match the relative dose in water at 10cm deep for a 10x10cm standard 6MV beam, 100cm source-to-surface distance [249]). For all VMAT plans, a 240° arc was used instead of the 210° arc adopted in earlier chapters as the manufacturer suggested that adopting an even number of sectors (i.e. 8 x 30° sectors as opposed to 7 x 30° sectors) might facilitate a more symmetrical plan in terms of femoral head dose.

In all plans, doses were prescribed so that at least 95% of the PTV received at least 95% of the prescription dose and the median dose was within 1Gy of the prescription dose. Organ at risk constraints for the conventionally fractionated schedules for the rectum and femoral heads were those used in the 78Gy in 39 fraction arm of the Hypo-RT-PC trial [133] and, for the bladder, were those used in the RTOG 0126 trial (79.2Gy in 44 fractions vs. 70.2Gy in 39 fractions using IMRT or 3D-CRT) [331] (Table 6.1). For SABR schedules, rectal constraints were those used in the HYPO-RT-PC trial [133] with additional constraints for the high and low dose regions, as defined in Chapter 2, and for the bladder, were biologically equivalent for a seven fraction schedule to those used in the 74Gy in 37 fraction arm of the UK Phase III CHHiP trial [191], as defined in Chapter 2 (Table 6.1). Femoral head doses were those used both in the HYPO-RT-PC trial [133] and biologically equivalent for a seven fraction schedule to those used in the UK Phase III CHHiP trial [191].

Table 6.1 Organ at risk constraints

Volume	78Gy in 39 fraction constraints	Source	SABR constraints	Source
Rectum	V70Gy(90%)<15% V59Gy(76%)<35% V51Gy(65%)<45%	HYPO-RT-PC trial [133]	V41.4Gy(97%)<3% V38.4Gy(90%)≤15% V32.0Gy(75%)≤35% V28.0Gy(65%)≤45% V24.8Gy(58%)<70% V19.6Gy(46%)<80%	HYPO-RT-PC trial [133] plus biologically equivalent constraints to 74Gy arm of CHHiP trial for high and low dose regions [191]
Bladder	V80Gy(103%)<15% V75Gy(96%)<25% V70Gy(90%)<35% V65Gy(83%)<50%	RTOG 0126 [331]	V41.4Gy(97%)<5% V34.7Gy(81%)<25% V29.9Gy(70%)<50%	Biologically equivalent constraints to 74Gy arm of CHHiP trial [191]
Femoral heads	Dmax≤55Gy(70%)	HYPO-RT-PC trial [133]	Dmax≤29.9Gy(70%) V29.9Gy(70%)<50%	HYPO-RT-PC trial [133] and biologically equivalent constraints to 74Gy arm of CHHiP trial regions [191]

CHHiP: Conventional versus Hypofractionated High-dose intensity-modulated radiotherapy for Prostate Cancer,
RTOG: Radiation Therapy Oncology Group

6.2.3 3D-conformal planning

3D-conformal radiotherapy (3D-CRT) plans cannot be produced using Monaco® v3.3. A 10MV 3D-CRT 4-field (anterior, posterior, left and right lateral) was therefore produced for each dataset using Oncentra® MasterPlan (Elekta AB, Sweden) delivering 78Gy in 39 fractions with a standard (flattened) beam and using a 1cm mulitleaf collimator head. In terms of energy, 10MV was selected for the 3D-CRT plan as 6MV photons are less commonly used in this setting, thus 10MV was considered to produce the most clinically relevant data for comparison.

For the 3D-CRT plans, the prescription dose was normalised to the centre of the PTV, and the PTV was encompassed by the 95% isodose, aiming for 100% coverage and accepting ≥95% coverage. Organ at risk constraints were those described in Table 6.1. The final plans were then transferred to Monaco® prior to DVH export so that DVHs for all six techniques were produced in the same way.

The threshold for neutron production, which contributes to second malignancy risk, begins at 10MV. It has previously been demonstrated that the contribution of neutron contamination at 10MV is minimal and so this was neglected from all calculations for the 10MV plan [297,325].

6.2.4 In-field and close-to-field RISPC risk assessment

Differential DVHs for the rectum, bladder wall, pelvic bones and pelvic soft tissue (total volume minus bones and prostate) for all three datasets were exported from Monaco® using 0.01Gy bin widths and used to calculate Organ Equivalent Doses (OED) and excess absolute risks (EAR) for second rectal and bladder cancers as well as for pelvic bone and soft tissue sarcomas, as described below. Average values from the three datasets are presented with the range of values obtained.

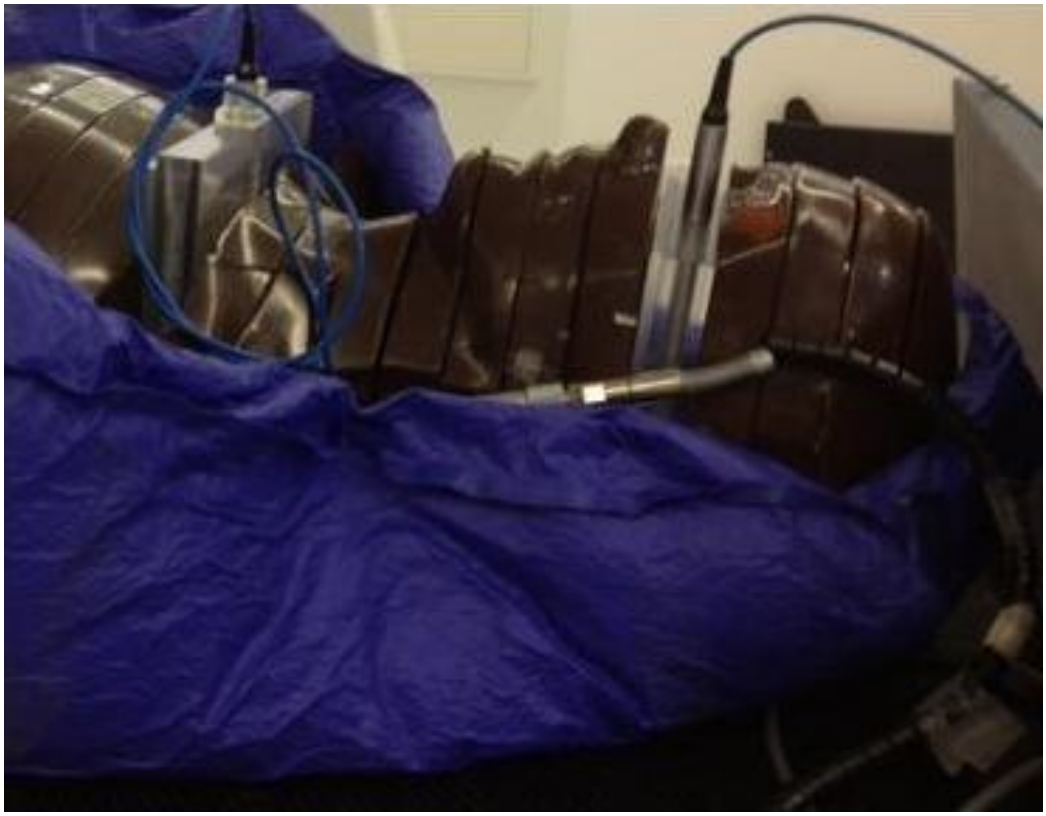
6.2.5 Out-of-field RISPC risk assessment

As little variation in out-of-field dose is likely between datasets for each radiotherapy technique, only one of the three datasets was used to deliver each of the six techniques to the RANDO® phantom (The Phantom Laboratory, USA) in order to measure out-of-field dose. Plans were delivered on a Synergy® linear accelerator (Elekta, AB Sweden) with the Agility™ head and with and without FFF high dose rate mode. As the Agility™ head was not available for planning within MasterPlan, the 10MV 78Gy in 39 fraction 3D-CRT plan was approximated and delivered as a 6x6cm 4-field QA (Quality Assurance) plan, created within Monaco.

For conventionally fractionated treatments three fractions of 2Gy were delivered, while for each of the SABR plans, one fraction of 6.1Gy was delivered. The RANDO® phantom is an anthropomorphic phantom consisting of 35 slices each of 2.5cm, and one slice of 8cm at the base. For treatment delivery the isocentre was positioned 1.75cm from the base of slice 32 (approximately at the level of the upper symphysis pubis). Chamber measurements were performed in the midline of the phantom at increasing distances from the isocentre (5cm, 10cm, 15cm, 20cm, 25cm, 30cm, 40cm, 50cm, 60cm and 70cm) by substituting each relevant slice of the phantom for a 2.5cm tall perspex block with a chamber holder centred at 1.75cm from the base of the block (Figure 6-1). A 20x20cm wide and deep block was used in torso region and a 10x10cm wide and deep block was used in the head and neck region. Measurements were taken at a depth corresponding approximately to the midline of the phantom. Doses at specific distances from the isocentre were taken to represent doses received by organs located at approximately those distances from the isocentre (a homogenous dose distribution was assumed within each out-of-field organ; Table 6.2).

Figure 6-1 Experimental set-up for assessment of out-of-field dose

Perspex slice holding chamber was substituted for various slices in the RANDO® phantom.



Chamber measurements were performed using a semi-flex ionisation chamber (PTW GmbH, Germany) previously calibrated for 6MV flattened, 6MV FFF and 10MV beams. Chamber readings were corrected for leakage, temperature and pressure. To estimate the impact of chamber drift on measurements, on the first full day of measurements, a second semi-flex chamber was positioned at 70cm from the isocentre and doses were recorded here at the same time as recording measurements at points closer to the isocentre (Figure 6-1). At 70cm, where the impact of drift was assumed to be greatest, the average standard deviation was 2.57% of the mean reading at 70cm. Drift was therefore not considered likely to have a major impact on measured dose for the majority of readings, and would therefore be adequately encompassed within the 5% error assigned (below).

Table 6.2 Source of dosimetric data and parameters for RED and EAR calculations

(Parameters from [332]) Continued overleaf.

Site	**Source of dose data**	**Position of chamber from isocentre (cm)†**	**Mechanistic model**		**Bell-shaped model**	**Plateau model**	**β‡**	**γ_e (years)**	**γ_a (years)**
			α (Gy^{-1})	**R**	**α (Gy^{-1})**	**α (Gy^{-1})**	(for calculation of EAR for mechanistic, bell-shaped, plateau and linear models)		
Rectum	DVH	-	0.033	0.56	0.031	0.065	0.73	-0.056	6.9
Bladder	DVH	-	0.219	0.06	0.213	0.633	3.8	-0.024	2.38
Bone sarcoma	DVH	-	Separate sarcoma model: α=0.067 based on intermediate repopulation (R=0.5), β‡=0.20					-0.013	-0.56
Soft tissue sarcoma	DVH	-	Separate sarcoma model: α=0.060, based on intermediate repopulation (R=0.5), β‡=0.60					-0.013	-0.56
Colon§	Chamber	20§	-	-	-	-	7.4	-0.056	6.9
Liver	Chamber	25	-	-	-	-	2.4	-0.021	3.6
Stomach	Chamber	30	-	-	-	-	5.2	-0.002	1.9

Table 6.2 cont. Source of dosimetric data and parameters for RED and EAR calculations (Parameters from [332])

Site	Source of dose	Position of chamber from isocentre (cm)†	Mechanistic model		Bell-shaped model	Plateau model	β‡	γ_e (years)	γ_a (years)
Lung	Chamber	Average of readings at 40 and 50	-	-	-	-	8.0	0.002	4.23
Oesophagus	Chamber	Average of readings at 40, 50 and 60	-	-	-	-	3.2	-0.002	1.9
Thyroid	Chamber	60	-	-	-	-	0.40	-0.046	0.6
Salivary gland	Chamber	60	-	-	-	-	0.73	-0.024	2.38
Mouth	Chamber	70	-	-	-	-	0.73	-0.024	2.38
Brain and CNS	Chamber	70	-	-	-	-	0.70	-0.024	2.38

DVH: dose-volume histogram, EAR: excess absolute risk, OED: Organ Equivalent Dose, RED: risk equivalent dose, † Positions based on work of Blais et al [333] and Scalzetti et al [334], ‡ β excess cases (10,000 person-years Gray)$^{-1}$, based on A-bomb survivors exposed at 30 years and surviving to 70 years, and modified for a UK population (See Schneider et al 2011 [332] for further detail). Note this β is used for EAR calculation only. β within the α/β ratio is calculated from α based on α/β=3Gy for all tissues. §Point considered representative of dose received by transverse colon

Traditionally thermoluminescent dosimeters (TLDs) have been used for out-of-field dose measurements given their relative energy independence. Recently, it has been demonstrated that at about 10 to 20cm from the field edge, the mean energy spectra of photon beams is in the region of 200KeV, and in this region the energy spectra appear to plateau [329]. In addition, chamber measurements have been performed up to 22cm from the field edge with similar readings to those obtained from TLDs [329]. Energies down to 200keV were within the range of the chamber used here, thus providing confidence in the suitability of chamber measurements for out-of-field regions both up to and beyond 20cm. In keeping with out-of-field chamber measurements performed by others, a 5% uncertainty was assumed for all out-of-field measurements to account for potential inaccuracies resulting from the MV calibrated chamber, as well inaccuracies in positioning [329].

6.2.6 Assessment of head leakage and scatter

To assess the proportion of out-of-field dose resulting from head leakage and head scatter, out-of-field chamber measurements were performed at increasing distances from the isocentre (10cm, 15cm, 20cm, 25cm, 30cm, 40cm, 50cm, 60cm and 70cm) as described above but with the phantom pelvis removed (slices 30 to 35 removed). The vast majority of any measured dose would therefore be the result of head leakage and head scatter. As before, 5% uncertainty was assumed for inaccuracies in chamber measurements and positioning.

6.2.7 Second malignancy risk assessment

The optimal method for predicting RISPC risk is unknown. A variety of models exist. These include the linear model which is considered appropriate for use in low dose out-of-field regions (up to about 4Gy of conventionally fractionated radiotherapy [254,326]), the plateau model which suggests that risk increases initially in a linear fashion as dose increases, before levelling off (due to cell sterilisation at higher doses with full normal tissue repair) and the bell-shaped

model, which suggests that risk increases in a linear fashion with dose before decreasing (also due to cell sterilisation at higher doses but without any normal tissue repair or repopulation). Schneider's concept of OED states that two different dose distributions which result in the same RISPC risk have the same OED [330,332]. This model takes into account the effects of fractionation, and is designed to include the impact of the primary beam as well as out-of-field doses, and can employ linear, bell-shaped and plateau models as well as a mechanistic model (which incorporates an individual tissue specific repair and repopulation constants and therefore lies between the extremes of the plateau (assuming full repair) and bell-shaped (neglecting repair and repopulation) models. The OED concept is discussed in detail elsewhere [330,332], but in summary:

$$OED = \frac{1}{V_T}\sum_i V_{D_i} RED_{D_i}$$

where V_T is the total volume of the structure under consideration, V_D is the volume of the dose bin *i* which receives dose D_i and the *RED* is the risk equivalent dose for the dose bin receiving dose D_i. *RED* is calculated according to:

i) $RED_D = D$

when a linear model is applied, as is appropriate for low dose out-of-field regions

and

ii) $RED_D = \frac{e^{-\alpha' D}}{\alpha' R}\left(1 - 2R + R^2 e^{\alpha' D} - (1-R)^2 e^{-\frac{\alpha' R}{1-R}D}\right)$

according to Schneider's mechanistic model which incorporates *R,* a tissue specific repair/ repopulation parameter [332]. Here, and in subsequent models, the impact of fractionation is also considered according to α':

$$\alpha' = \alpha + \beta d = \alpha + \beta \frac{D}{D_T} d_T$$

where *d* is the dose per fraction, D_T is the dose prescribed to the target and d_T is the prescribed dose per fraction to the target. *α* and *R* were defined by Schneider et al by fitting the models to clinical data from Atomic bomb survivors and patients irradiated for Hodgkin's disease [332]. β is such that α/β=3Gy.

To illustrate the possible OED in the extreme scenarios of no repair/ repopulation, and full repair/ repopulation, RED and thus OED can also be calculated according to:

iii) $RED_D = D\exp\left(-\alpha' D\right)$,

a bell-shaped model where the effect of repopulation or repair is neglected (*R*=0)

and

iv) $RED_D = \frac{1-\exp\left(-\alpha' D\right)}{\alpha'}$,

a linear plateau model where the full repair/ repopulation is presumed (*R*=1).

All of the above models approach a linear model at low doses.

When considering radiation-induced sarcoma, RED is calculated according to Schneider's mechanistic sarcoma model [332]:

$$RED = \frac{e^{-\alpha' D}}{\alpha' R}\left(1-2R+R^2 e^{\alpha' D}-(1-R)^2 e^{-\frac{\alpha' R}{1-R}D}-\alpha' RD\right)$$

RED can also be used to calculate the excess absolute risk (EAR) of developing an RISPC in an organ with volume V_T after exposure to dose RED at one age (*agex*) and attaining a greater age (*agea*), according to [332]:

$$EARorg = \frac{1}{V_T}\sum_i V_{D_i} \bullet RED_{D_i} \bullet \beta \bullet \mu(agex, agea)$$

where β is the initial slope for the dose response curve for RISPC, V_D is the volume of the DVH bin receiving dose D_i and RED is the RED_D for that bin and μ is a modifying factor which adjusts for age at exposure (*agex*) and attained age (*agea*), calculated according to:

μ (*agex, agea*) = $exp(\gamma_e(age\text{-}30) + \gamma_a \times ln(agea/70))$

where γ_e and γ_a are age modifying factors and where β was originally calculated for persons exposed at age 30 years and attaining age 70 years [332].

All EAR calculations in this study were calculated for patients irradiated at age 60 years and attaining 80 years.

The parameters used with each model and for calculation of EAR are shown in Table 6.2.

OED is directly proportional to RISPC risk and so the ratio of OED from one technique to the OED from a different technique produces a relative risk ratio for RISPC [332].

For tissues within the CT planning scan volume and in the in-field or close-to-field region (i.e. rectum, bladder wall, pelvic bone and pelvic soft tissue), where the dose-risk relationship is not assumed to be linear (as pure linear models have not been shown to be the best fit to clinical data in higher dose regions), the OED concept was used to calculate the risks of rectal and bladder cancer, and pelvic bone and soft tissue sarcoma. For the rectum and bladder, OED was calculated using i) Schneider's mechanistic model, ii) a bell-shaped model and iii) a plateau model. To estimate the risks of pelvic bone and soft tissue sarcoma, OED was calculated using Schneider's mechanistic sarcoma model. For low dose out-of-field regions, where dose-response is considered linear, the OED concept was used with a linear model.

All absolute doses, OEDs, relative risks and EARs are based on the total dose delivered over the whole treatment course.

6.2.8 Integral dose assessment

To investigate the relationship between integral dose and RISPC risk, integral dose was calculated for each tissue (as before, pelvic soft tissue consisted of the whole pelvic volume minus pelvic bones and prostate). Integral dose, which reflects the energy absorbed by the normal tissues, may be calculated using a differential DVH according to [335]:

$$ID = \sum_i v_i D_i \rho_i$$

where *v* is the volume of DVH bin *i* multiplied by the total dose received by that bin, D_i, multiplied by the density, ρ_i, of that bin (assuming consistent density throughout each dose bin), and is measured in Gy-litres [335]. Since different fractionation schedules were adopted in this study, all doses were corrected to 2Gy fraction equivalent, and so integral dose in 2Gy fraction equivalent (IDEQD2) was calculated according to [335,336]:

$$IDEQD2 = \sum_i v_i D_i \left(\frac{d_i + \alpha/\beta}{2 + \alpha/\beta} \right) \rho_i$$

Where v_i, D_i and ρ_i are as above, and d_i is the dose per fraction received by dose bin *i*, and α/β was taken as 3Gy.

Volumes for rectum, bladder wall, pelvic tissue soft tissue and pelvic bones were taken from the DVH data. For out-of-field organs, volumes were established from typical male volumes as described in ICRP (International Commission on Radiation Protection) Publication 89 [337]. Density was taken as 1 gcm^{-3} for all tissues other than bone and lung where values of 1.3 g/cm^3 [337] and 0.26 gcm^{-3} [338] were used respectively.

Pearson's correlation (*r*) was used to investigate any linear relationship between integral dose and OED. In view of multiple statistical testing (where several of the examined correlations would not be independent of others thus making a full Bonferroni correction over-conservative), a pragmatic approach was adopted, and a *p* value of <0.005 was considered statistically significant. SPSS version 19.0 (IBM Corporation, Armonk, New York, USA) was used for calculations.

6.3 Results

6.3.1 Plans

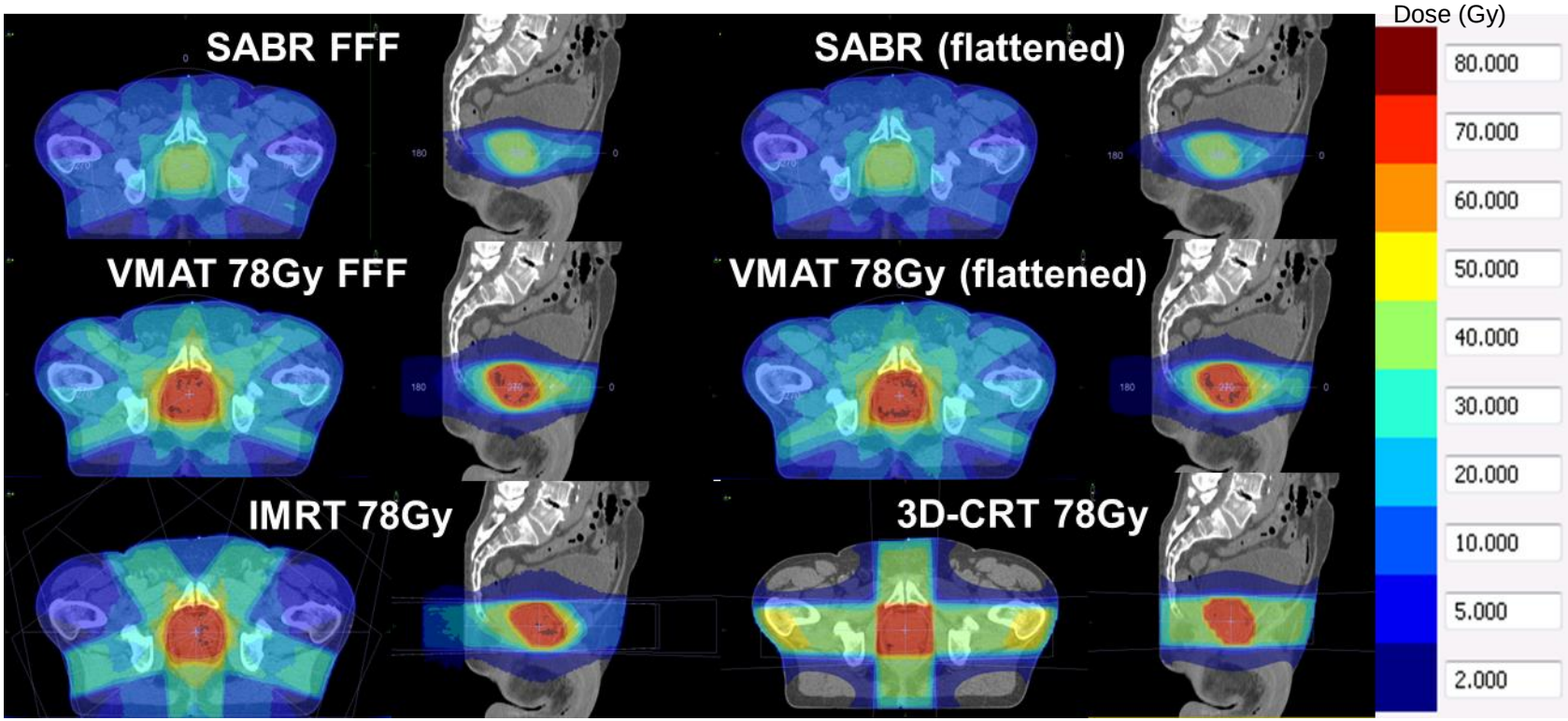
Plans were created for all three datasets for each technique according to the criteria described above (Table 6.1, Figure 6-2). The total number of monitor units (MU) required to deliver all the fractions and beam-on times per fraction for the delivered plans are shown in Table 6.3.

Table 6.3 Monitor units and beam on time for delivered plan

Plan	Total Monitor Units per plan	Beam-on time per fraction (seconds)
SABR FFF	13,446	118
SABR	13,010	225
VMAT 78Gy FFF	25,2775	52
VMAT 78Gy	24,040	76
IMRT 78Gy	13,623	190 (338 including gantry motion between beams)
3D-CRT 78Gy	10,429	54 (170 including gantry motion between beams)

3D-CRT: 3-dimensional conformal radiotherapy, FFF: flattening filter free,
IMRT: intensity-modulated radiotherapy, SABR: stereotactic ablative radiotherapy,
VMAT: volumetric modulated arc therapy

Figure 6-2 Comparison of physical dose distributions for different techniques



3D-CRT: 3-dimensional conformal radiotherapy, FFF: flattening filter free, IMRT: intensity-modulated radiotherapy, SABR: stereotactic ablative radiotherapy, VMAT: volumetric modulated arc therapy

6.3.2 In-field or close-to-field RISPC risks

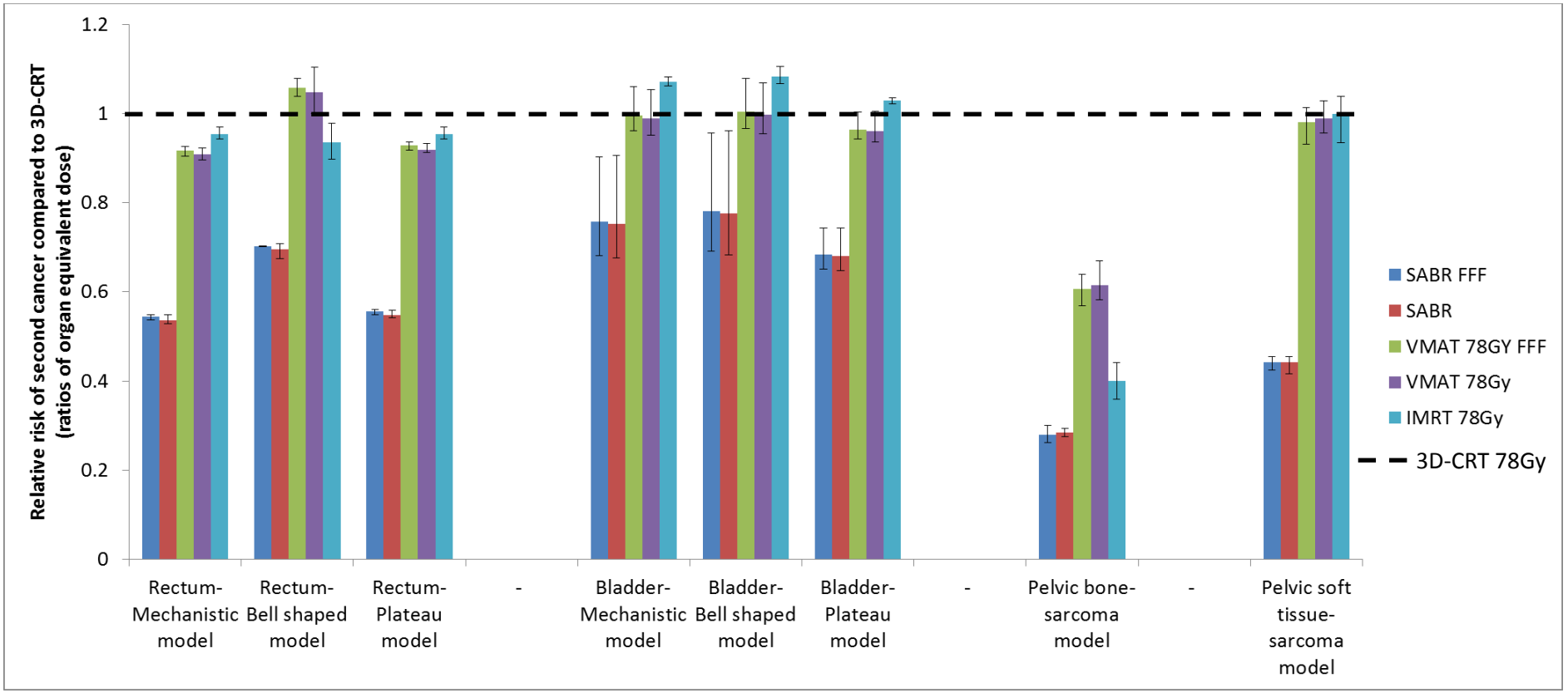
Ratios of OED, thus relative risks of second rectal and bladder cancers and pelvic bone and soft tissue sarcoma for each alternative technique relative to 3D-CRT, calculated using mechanistic, bell-shaped and plateau models, and averaged over three datasets, are shown in Figure 6-3. Actual OEDs are shown in Table 6.4a-c. Despite the variation in OEDs between individual datasets (maximum difference from average: 1.28Gy, largest standard deviation: 0.91Gy), there was much smaller variation between individual datasets in terms of relative risks (maximum difference from average: 0.18, largest standard deviation: 0.13).

SABR techniques, both FFF and standard (flattened), resulted in the lowest OEDs for in-field and close-to-field tissues, and thus resulted in the greatest risk reductions relative to 3D-CRT, regardless of the model used.

Considering all alternative 78Gy techniques relative to 3D-CRT, and all models, relative risks of rectal and bladder cancer or soft tissue sarcoma were within 9%, 8% and 2% of that for 3D-CRT respectively. Risk of bone sarcoma was lower using all alternative techniques compared to 3D-CRT.

When comparing FFF with the equivalent flattened technique, for in-field and close-to-field tissues, there was minimal difference in risk (average relative risks for FFF consistently within 2% of flattened techniques).

Figure 6-3 Relative risks of second malignancy in in-field or close-to-field tissues relative to 3D-conformal radiotherapy for whole treatment course



3D-CRT: 3-dimensional conformal radiotherapy (shown as black dashed line), FFF: flattening filter free, IMRT: intensity-modulated radiotherapy, SABR: stereotactic ablative radiotherapy, VMAT: volumetric modulated arc therapy.
Error bars display range of relative risks for the three datasets used for planning

Table 6.4 Organ equivalent doses averaged over three datasets in in-field or close-to-field organs for whole treatment course (Gy): a) rectum

	Rectum					
	Mechanistic model	Range	Bell-shaped model	Range	Plateau model	Range
SABR FFF	4.279	3.623-4.647	3.291	2.814-3.599	4.157	3.524-4.516
SABR	4.221	3.498-4.583	3.264	2.702-3.619	4.102	3.401-4.462
VMAT 78Gy FFF	7.217	6.114-7.841	4.959	4.230-5.519	6.941	5.886-7.553
VMAT 78Gy	7.142	6.093-7.773	4.920	4.180-5.645	6.873	5.862-7.512
IMRT78Gy	7.503	6.396-8.178	4.368	3.924-4.750	7.128	6.096-7.765
3D-CRT 78Gy	7.877	6.601-8.669	4.688	4.011-5.116	7.486	6.283-8.231

3D-CRT: 3-dimensional conformal radiotherapy, FFF: flattening filter free, IMRT: intensity-modulated radiotherapy, SABR: stereotactic ablative radiotherapy, VMAT: volumetric modulated arc therapy

Table 6.4 Organ equivalent doses averaged over three datasets in in-field or close-to-field organs for whole treatment course (Gy): b) bladder

	Bladder					
	Mechanistic model	Range	Bell-shaped model	Range	Plateau model	Range
SABR FFF	0.672	0.621-0.767	0.649	0.603-0.727	0.757	0.648-0.938
SABR	0.667	0.616-0.770	0.645	0.598-0.730	0.753	0.641-0.938
VMAT 78Gy FFF	0.886	0.876-0.901	0.842	0.820-0.861	1.064	0.932-1.267
VMAT 78Gy	0.880	0.866-0.895	0.835	0.813-0.860	1.061	0.930-1.267
IMRT78Gy	0.954	0.920-0.972	0.909	0.840-0.948	1.132	1.021-1.289
3D-CRT 78Gy	0.891	0.850-0.912	0.840	0.760-0.888	1.100	0.987-1.262

3D-CRT: 3-dimensional conformal radiotherapy, FFF: flattening filter free, IMRT: intensity-modulated radiotherapy, SABR: stereotactic ablative radiotherapy, VMAT: volumetric modulated arc therapy.

Table 6.4 Organ equivalent doses averaged over three datasets in in-field or close-to-field organs for whole treatment course (Gy): c) pelvic bone and soft tissue

	Pelvic bone		Pelvic soft tissue	
	Sarcoma model*	Range	Sarcoma model*	Range
SABR FFF	0.313	0.244-0.409	0.172	0.149-0.215
SABR	0.320	0.253-0.430	0.171	0.151-0.211
VMAT 78Gy FFF	0.679	0.546-0.886	0.381	0.330-0.472
VMAT 78Gy	0.693	0.520-0.923	0.386	0.326-0.484
IMRT 78Gy	0.445	0.357-0.560	0.388	0.341-0.473
3D-CRT 78Gy	1.133	0.893-1.557	0.392	0.332-0.507

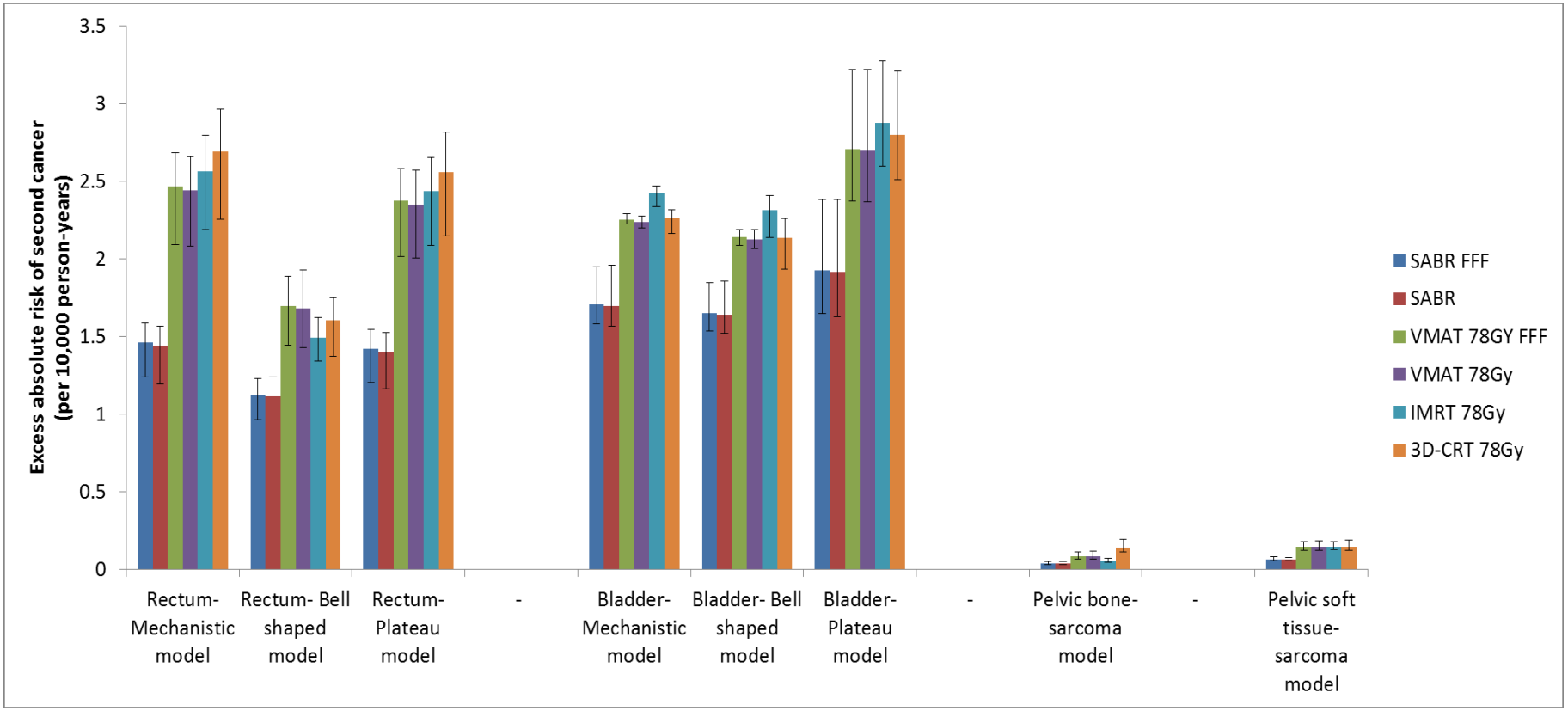
3D-CRT: 3-dimensional conformal radiotherapy, FFF: flattening filter free, IMRT: intensity-modulated radiotherapy, SABR: stereotactic ablative radiotherapy, VMAT: volumetric modulated arc therapy. *assuming intermediate repopulation and repair

The EARs for in-field or close-to-field second cancers are shown in Figure 6-4. Excess absolute risks of in-field or close-to-field second cancers were low using all techniques and using all models. According to the mechanistic model, for the different techniques evaluated, the average EAR for rectal cancer ranged from 1.44 to 2.69 per 10,000 person-years (PY). For bell-shaped and plateau models, the average EAR for second rectal cancer ranged from 1.12 to 1.70 and 1.40 to 2.56 per 10,000 PY respectively. For second bladder cancer, average EAR according to the mechanistic model ranged from 1.70 to 2.42 per 10,000 PY, and according to the bell-shaped and plateau models, ranged from 1.64 to 2.31 and from 1.91 to 2.88 per 10,000 PY respectively. Within each model, absolute differences in risk between radiotherapy techniques were also low, at most 1.25 per 10,000 PY in terms of rectal cancer (mechanistic model, based on average results for three datasets) and 0.96 per 10,000 PY in terms of bladder cancer (plateau model). For each in-field or close-to-field site, absolute differences between models were also low: the greatest differences between models was observed for rectal cancers where differences ranged from 0.33 per 10,000 PY (SABR (flattened): bell-shaped model to mechanistic model) to 1.09 per 10,000 PY (3D-CRT: bell-shaped model to mechanistic model; based on average results for all three datasets). For the bladder, difference between models ranged from 0.27 per 10,000 PY (SABR FFF: bell-shaped model to plateau model) to 0.66 per 10,000 PY (3D-CRT: bell-shaped model to plateau model).

Comparing FFF with equivalent flattened techniques, differences in EAR were clinically irrelevant (largest difference between average EARs: 0.025 per 10,000 PY).

When comparing all conventionally fractionated techniques, the absolute differences between techniques were also small, at most 0.25 per 10,000 PY in terms of rectal cancer (mechanistic model) and 0.19 per 10,000 PY in terms of bladder cancer (bell-shaped model).

Figure 6-4 Excess absolute risks of second malignancy in in-field or close-to-field tissues for whole treatment course



3D-CRT: 3-dimensional conformal radiotherapy, FFF: flattening filter free, IMRT: intensity-modulated radiotherapy, SABR: stereotactic ablative radiotherapy, VMAT: volumetric modulated arc therapy
Error bars display range of excess absolute risks for the three datasets used for planning

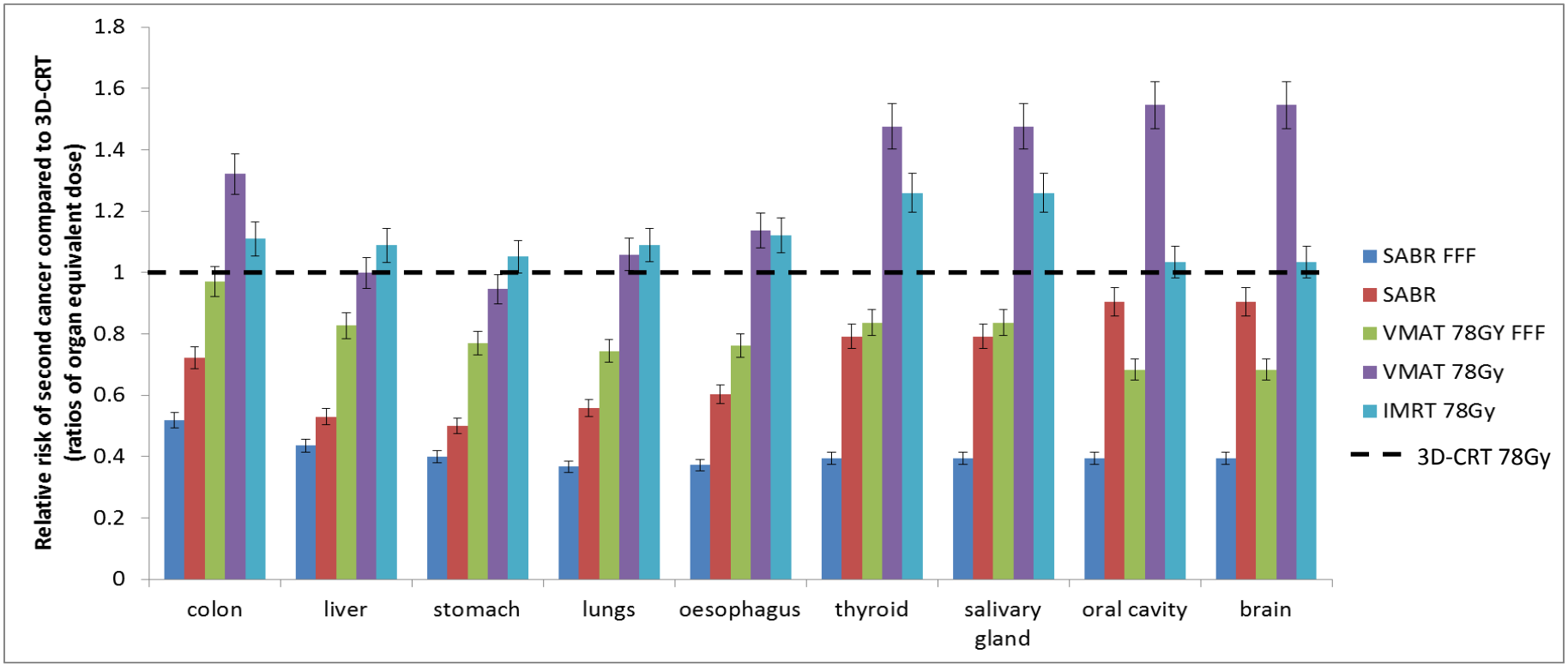
6.3.3 Out-of-field RISPC risks

RISPC risks in out-of-field organs relative to 3D-CRT (linear model) are shown in Figure 6-5. Actual OEDs for out-of-field organs are shown in Table 6.5. As for in-field or close-to-field tissues, SABR (both FFF and standard (flattened)) resulted in reduced RISPC risks relative to 3D-CRT in out-of-field organs. In contrast to in-field or close-to-field tissues, FFF, in comparison to the equivalent flattened technique, resulted in relative RISPC risk reductions in out-of-field organs. The impact of FFF in reducing relative risk increased at greater distances from the treatment field. For example, in the region of the stomach (measured at 30cm from the isocentre), SABR FFF resulted in a 20% risk reduction relative to SABR flattened, and VMAT 78Gy FFF resulted in a 19% risk reduction relative to VMAT 78Gy flattened. In the region of the oral cavity (measured at 70cm from the isocentre), both SABR FFF and VMAT 78Gy FFF resulted in 56% risk reductions relative to equivalent flattened techniques.

In all out-of-field organs, IMRT resulted in increased RISPC risks relative to 3D-CRT, although the increases in risk were frequently small. At most, a 26% risk increase was observed in the region of the salivary gland and thyroid using IMRT relative to 3D-CRT. Similarly, VMAT 78Gy using a standard (flattened) beam resulted in increased RISPC risks in the majority of out-of-field organs of up to 55% relative to 3D-CRT. Increased risks of out-of-field RISPC, relative to 3D-CRT, however, were not observed when using VMAT 78Gy with FFF.

The EARs for second cancers in out-of-field organs are shown in Figure 6-6. These are low for all sites and all techniques. At greater distances from the field, where the relative impact of FFF was greatest, in absolute terms, risks were very small. For example, in the region of the oral cavity, the 56% risk reduction observed for FFF relative to the equivalent flattened technique, equated to an absolute reduction of 0.002 per 10,000 PY (from 0.004 to 0.002 per 10,000 PY for VMAT 78Gy flattened vs. VMAT 78Gy FFF). For SABR, EAR reduced by 0.0014 per 10,000 PY (from 0.0025 to 0.0011 per 10,000 PY for SABR flattened vs. SABR FFF).

Figure 6-5 Relative risks of second malignancy in out-of-field tissues relative to 3D-conformal radiotherapy (linear model) for whole treatment course



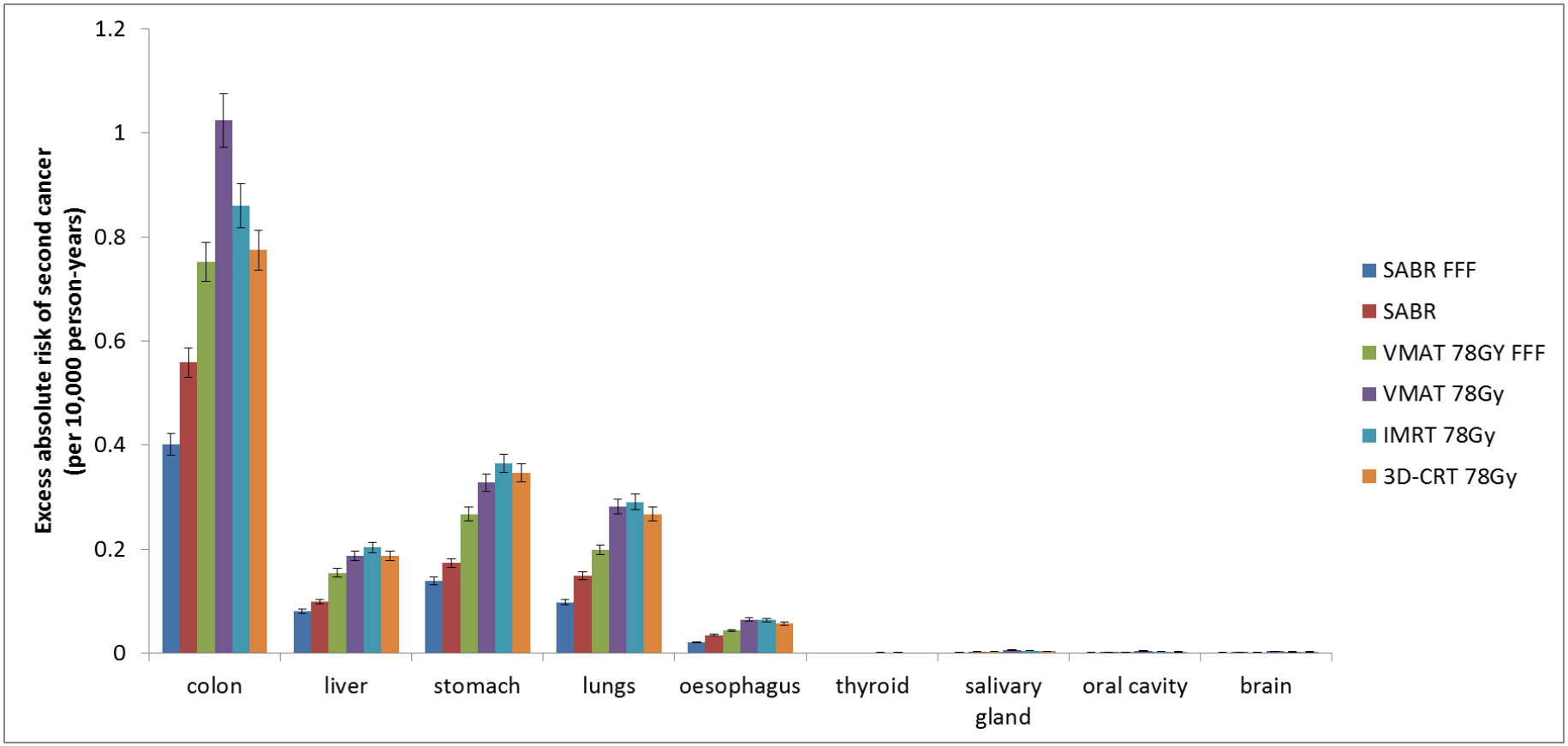
3D-CRT: 3-dimensional conformal radiotherapy (shown as black dashed line), FFF: flattening filter free, IMRT: intensity-modulated radiotherapy, SABR: stereotactic ablative radiotherapy, VMAT: volumetric modulated arc therapy
5% error bars shown to account for dosimetric uncertainty

Table 6.5 Organ equivalent doses in out-of-field organs for whole treatment course (Gy)

	colon	liver	stomach	lungs	oesophagus	thyroid	salivary gland	oral cavity	brain
SABR FFF	0.116	0.039	0.022	0.007	0.005	0.003	0.003	0.002	0.002
SABR	0.161	0.048	0.027	0.010	0.009	0.007	0.007	0.005	0.005
VMAT 78GY FFF	0.217	0.075	0.042	0.013	0.011	0.007	0.007	0.004	0.004
VMAT 78Gy	0.295	0.090	0.052	0.019	0.017	0.012	0.012	0.009	0.009
IMRT 78Gy	0.248	0.098	0.058	0.019	0.016	0.010	0.010	0.006	0.006
3D-CRT 78Gy	0.224	0.090	0.055	0.018	0.015	0.008	0.008	0.006	0.006

3D-CRT: 3-dimensional conformal radiotherapy, FFF: flattening filter free, IMRT: intensity-modulated radiotherapy, SABR: stereotactic ablative radiotherapy, VMAT: volumetric modulated arc therapy

Figure 6-6 Excess absolute risks of second malignancy in out-of-field organs (linear model) for whole treatment course



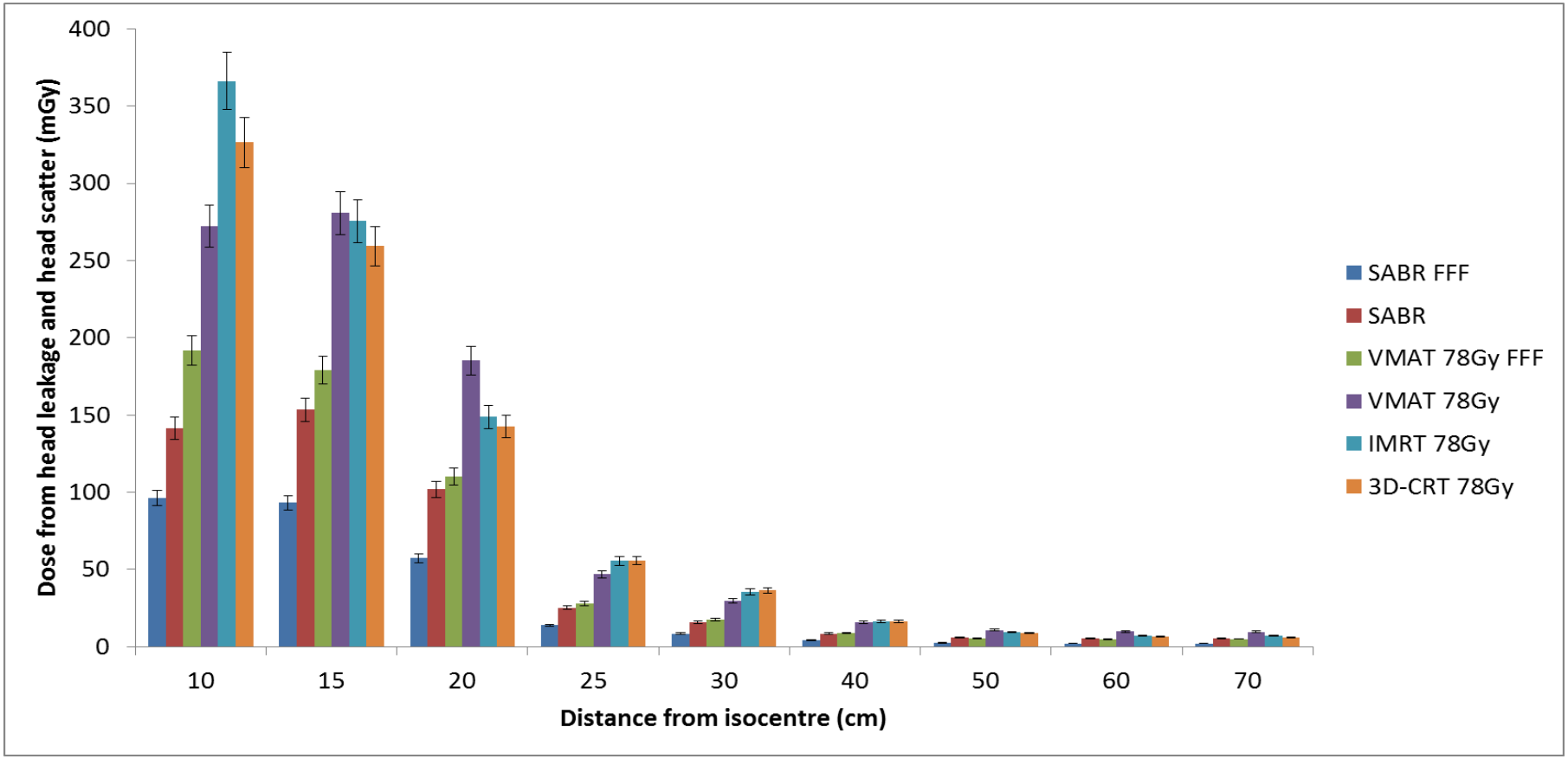
3D-CRT: 3-dimensional conformal radiotherapy, FFF: flattening filter free, IMRT: intensity-modulated radiotherapy, SABR: stereotactic ablative radiotherapy, VMAT: volumetric modulated arc therapy
5% error bars shown to account for dosimetric uncertainty

In absolute terms, the increased risk from IMRT relative to 3D-CRT was also small: the 26% relative risk increase observed amounted to an EAR increase from 0.0041 per 10,000 PY using 10MV 3D-CRT to 0.0051 per 10,000 PY using 6MV IMRT for salivary gland cancer, and from 0.0009 to 0.0011 per 10,000 PY in terms of thyroid cancer. Similarly the 55% risk increase in the region of the oral cavity and brain with VMAT 78Gy (flattened) relative to 3D-CRT, amounted to absolute increases from 0.0028 to 0.0043 and 0.0027 to 0.0041 per 10,000 PY for oral cavity and CNS cancers going from 3D-CRT to VMAT 78Gy respectively.

6.3.4 Dose from machine head and machine scatter

For all techniques, it was confirmed that the radiotherapy field edge (defined here as the 50% isodose) was contained within the phantom pelvis (slices 30 to 35), so that when the pelvis was removed, recorded doses would predominantly be the result of head scatter and leakage. Out-of-field measurements performed following removal of the phantom pelvis revealed that FFF resulted in reduced out-of-field doses due to head scatter and leakage compared to equivalent flattened techniques (Figure 6-7).

Figure 6-7 Out-of-field dose resulting from head leakage and head scatter



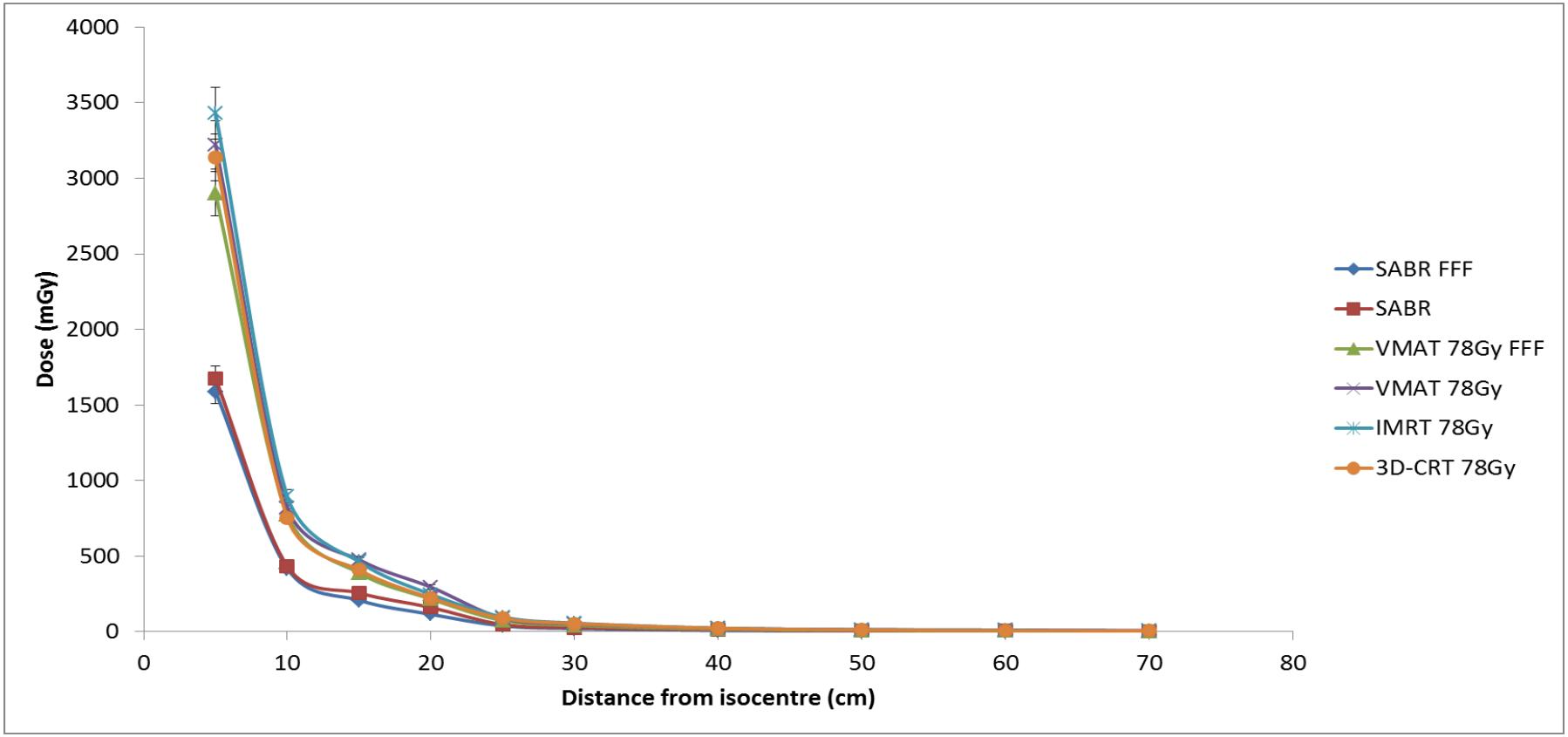
3D-CRT: 3-dimensional conformal radiotherapy, FFF: flattening filter free, IMRT: intensity-modulated radiotherapy,
SABR: stereotactic ablative radiotherapy, VMAT: volumetric modulated arc therapy
5% error bars shown to account for dosimetric uncertainty

6.3.5 Components of dose and distance

Dose fall-off with increasing distance from the isocentre with different techniques is illustrated in Figure 6-8. Figure 6-9 illustrates dose fall-off for out-of-field dose resulting from head leakage and scatter and Figure 6-10 illustrates dose fall-off for within patient scatter (total dose minus dose due to head leakage/scatter). As expected, total doses were lowest for SABR treatments although beyond 25cm doses were low for all techniques. Total out-of-field doses resulting from head leakage and head scatter were lower for FFF techniques compared to the equivalent flattened technique. A slight increase in dose from within patient scatter was observed with FFF compared to the equivalent flattened beam, but this was outweighed by the reduction in dose due to reduced head leakage/scatter with FFF, resulting in lower total doses with FFF compared to the equivalent flattened technique.

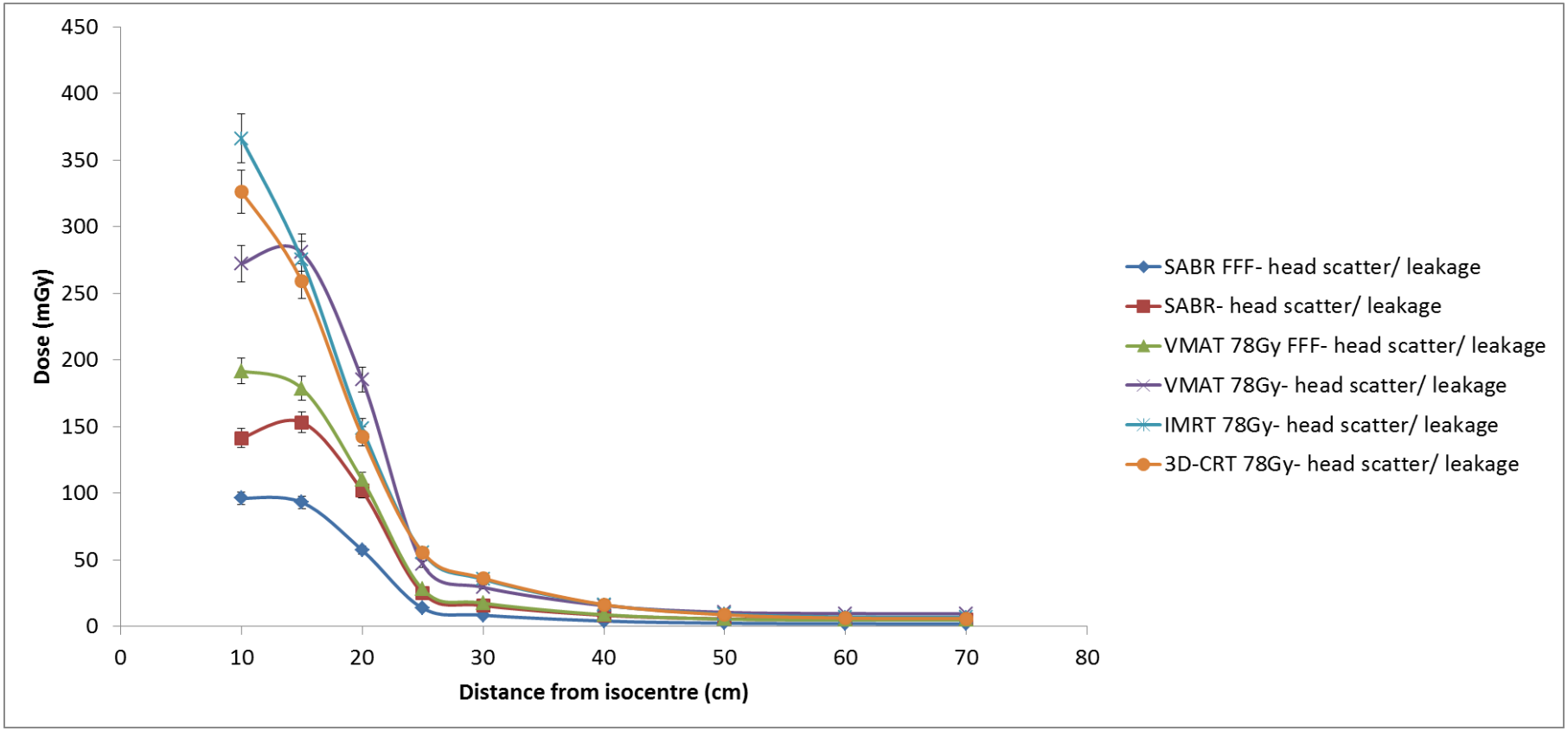
Very small peaks in head leakage/scatter dose were observed at 15cm from the isocentre for both the VMAT 78Gy (flattened) and SABR (flattened) techniques which could be the result of treatment head geometry in flattened rotational modes [339]. The peaks in dose were, however, small and encompassed within the assumed 5% uncertainty (i.e. error bars overlapped for doses at 10 and 15cm for these techniques).

Figure 6-8 Total dose for whole treatment course with increasing distance from isocentre



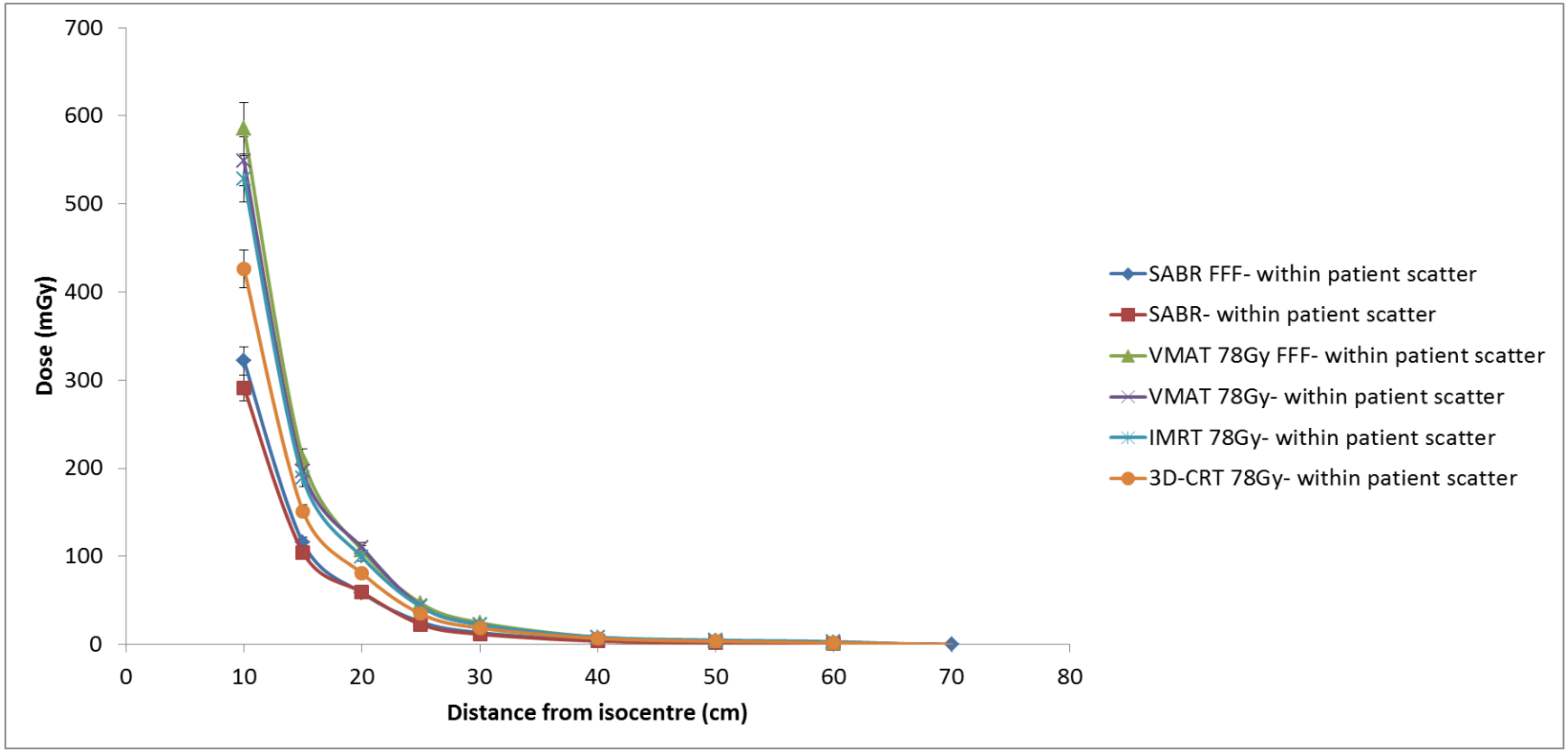
3D-CRT: 3-dimensional conformal radiotherapy, FFF: flattening filter free, IMRT: intensity-modulated radiotherapy, SABR: stereotactic ablative radiotherapy, VMAT: volumetric modulated arc therapy
5% error bars shown to account for dosimetric uncertainty

Figure 6-9 Out-of-field dose for whole treatment course resulting from head leakage and head scatter with increasing distance from isocentre



3D-CRT: 3-dimensional conformal radiotherapy, FFF: flattening filter free, IMRT: intensity-modulated radiotherapy, SABR: stereotactic ablative radiotherapy, VMAT: volumetric modulated arc therapy
5% error bars shown to account for dosimetric uncertainty

Figure 6-10 Out-of-field dose for whole treatment course resulting from within patient scatter (total dose minus dose from head leakage/ scatter) with increasing distance from isocentre



3D-CRT: 3-dimensional conformal radiotherapy, FFF: flattening filter free, IMRT: intensity-modulated radiotherapy, SABR: stereotactic ablative radiotherapy, VMAT: volumetric modulated arc therapy
5% error bars shown to account for dosimetric uncertainty

6.3.6 Relationship between RISPC risk and integral dose

Integral doses in 2Gy fraction equivalent (IDEQD2) for individual organs are shown in Table 6.6. Correlations with OED are shown in Table 6.7. As would be predicted from the models, a strong linear correlation was observed between IDEQD2 and OED for all out-of-field organs (r=1.000 and p<0.001 for each out-of-field organ). In terms of both pelvic bone sarcoma and pelvic soft tissue sarcoma, significant correlations were also observed, while for rectal and bladder cancers, no significant relationships were observed at the p<0.005 level. If a less conservative significance level of p<0.05 was selected, significance correlations between rectal IDEQD2 and rectal OED would be observed according to the mechanistic and plateau models. Similarly for the bladder, a significant correlation would be observed between bladder IDEQD2 and OED according to the plateau model. Figure 6-11 displays the correlation between rectal IDEQD2 and OED according to the mechanistic model and demonstrates the weakness of this correlation in comparison to that seen for out-of-field organs (represented by the perfect correlation between stomach IDEQD2 and OED (Figure 6-11b)). Figure 6-12 displays the significant correlations observed between IDEQD2 and OED for pelvic bone and soft tissue sarcomas. Although these correlations are stronger in comparison to those observed for the rectum and bladder, they remain weaker than that observed for out-of-field organs.

Table 6.6 Integral doses in 2Gy fraction equivalent (Gy-litres)

	SABR FFF	SABR	VMAT 78Gy FFF	VMAT 78Gy	IMRT 78Gy	3D-CRT 78Gy
Rectum *	1.0985	1.0726	1.3737	1.3799	1.7475	1.8726
Bladder*	0.6836	0.6895	0.8562	0.8701	0.9012	1.0939
Pelvic bone*	8.4177	8.4299	11.4092	11.4958	8.4476	20.0963
Pelvic soft tissue*	43.3331	42.2862	57.3973	58.0679	57.7826	58.4318
Colon	0.0210	0.0292	0.0391	0.0533	0.0448	0.0403
Liver	0.0427	0.0519	0.0808	0.0976	0.1064	0.0978
Stomach	0.0020	0.0025	0.0038	0.0047	0.0052	0.0049
Lungs	0.0072	0.0109	0.0145	0.0207	0.0213	0.0195
Oesophagus	0.0001	0.0002	0.0003	0.0004	0.0004	0.0004
Thyroid	0.0000	0.0001	0.0001	0.0001	0.0001	0.0001
Salivary gland	0.0002	0.0003	0.0004	0.0006	0.0005	0.0004
Oral cavity	0.0002	0.0005	0.0003	0.0008	0.0005	0.0005
Brain	0.0020	0.0045	0.0034	0.0077	0.0051	0.0050

3D-CRT: 3-dimensional conformal radiotherapy, FFF: flattening filter free, IMRT: intensity-modulated radiotherapy, SABR: stereotactic ablative radiotherapy, VMAT: volumetric modulated arc therapy, *Averaged values for three datasets

Table 6.7 Correlations between integral dose in 2Gy fraction equivalent (IDEQD2) and organ equivalent dose

Organ	Model	Pearson's correlation (*r*)	*p* value
Rectum	Mechanistic model	0.549	0.018
	Bell-shaped model	0.297	0.231
	Plateau model	0.536	0.022
Bladder	Mechanistic model	0.464	0.053
	Bell-shaped model	0.392	0.108
	Plateau model	0.542	0.020
Pelvic bone	**Sarcoma model**	**0.889**	**<0.001**
Pelvic soft tissue	**Sarcoma model**	**0.769**	**<0.001**
Colon	**Linear model**	**1.000**	**<0.001**
Liver	**Linear model**	**1.000**	**<0.001**
Stomach	**Linear model**	**1.000**	**<0.001**
Lungs	**Linear model**	**1.000**	**<0.001**
Oesophagus	**Linear model**	**1.000**	**<0.001**
Thyroid	**Linear model**	**1.000**	**<0.001**
Salivary glands	**Linear model**	**1.000**	**<0.001**
Oral cavity	**Linear model**	**1.000**	**<0.001**
Brain	**Linear model**	**1.000**	**<0.001**

Figure 6-11 Correlations between integral dose in 2Gy fraction equivalent (IDEQD2) and Organ Equivalent Dose (OED) for a) the rectum (rectal organ equivalent dose calculated according to mechanistic model, *p*=0.018, not significant at selected significance level) and b) the stomach (representative of all out-of-field organs, *p*<0.001)

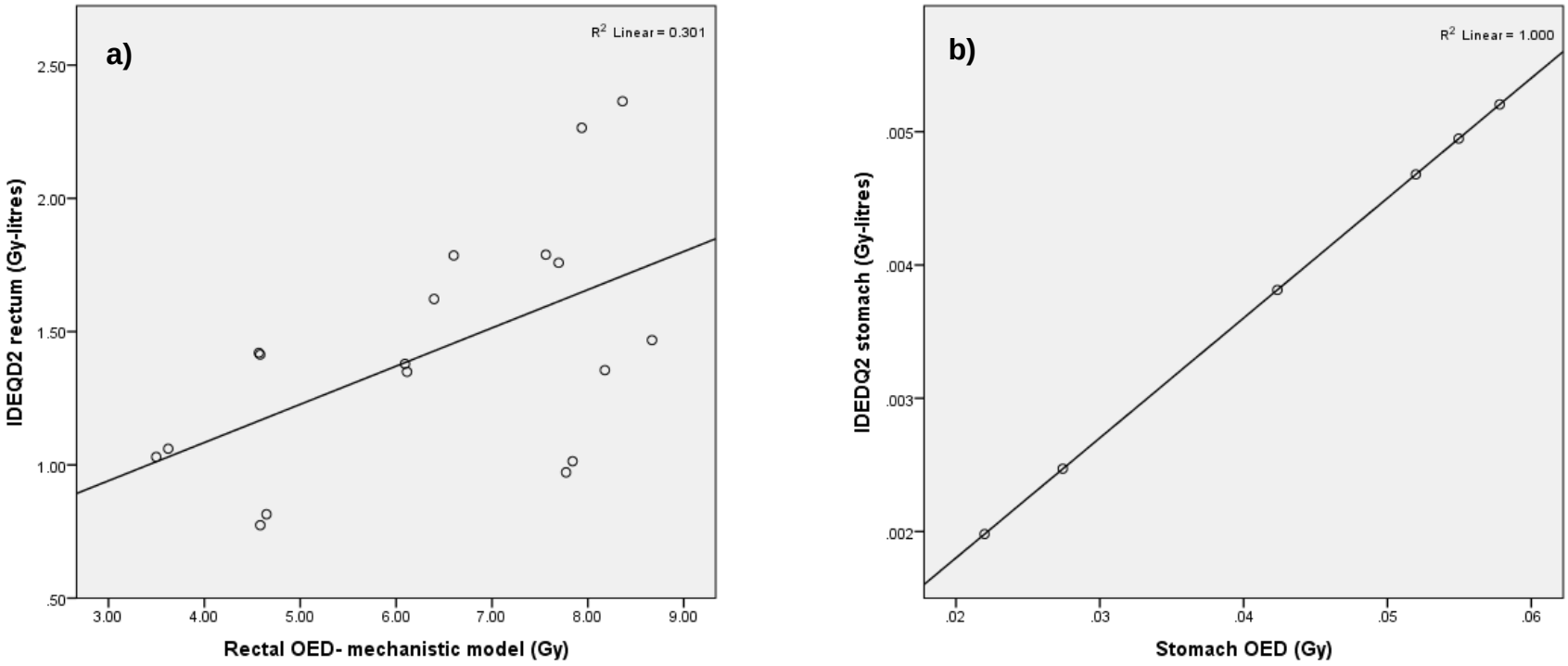
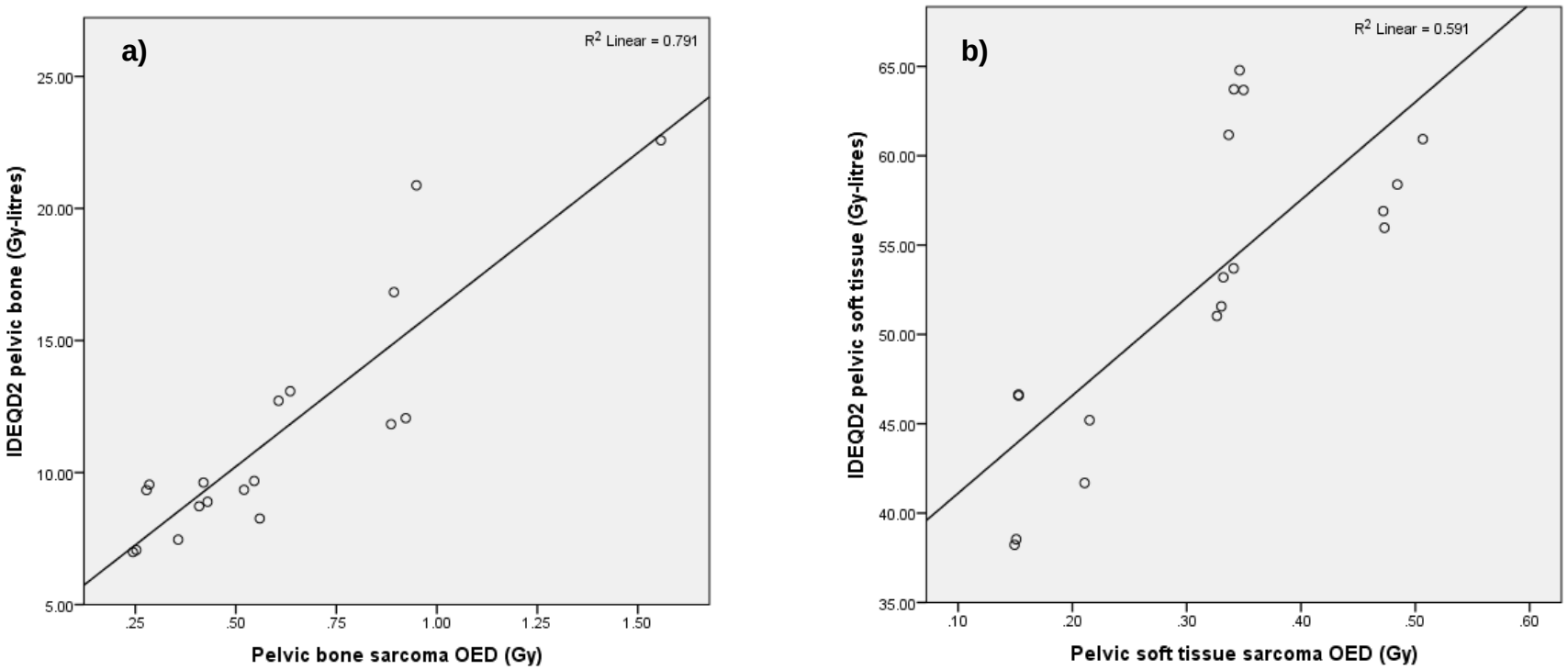


Figure 6-12 Correlations between integral dose in 2Gy fraction equivalent (IDEQD2) and Organ Equivalent Dose (OED) for a) pelvic bone sarcoma (p<0.001) and b) pelvic soft tissue sarcoma (p<0.001)



6.3.7 Femoral head doses

As mentioned above, a 240° arc was used to investigate if using an even number of sectors resulted in the right and left femoral head receiving more similar doses than using a 210° arc. There were no statistically significant differences between doses received by the left and right FHs in SABR (FFF or flattened) or VMAT 78Gy (FFF or flattened) plans (Table 6.8), suggesting that the 240° arc may improve the symmetry in FH doses. Only a small number of plans, however, were analysed in respect of FH doses here. A larger number of datasets would need to be investigated for firmer conclusions to be drawn regarding the impact of a 240° arc on FH dose symmetry. Most importantly, using a 210° arc as in earlier chapters, or 240° arc as in this current chapter, resulted in FH doses which were very well within tolerance and lower than what would be achieved using 3-field or 4-field 3D-CRT. In addition, when the dose per fraction received by femoral heads is also considered, the differences in dose in terms of BED, or EQD2, are small. Bearing both these factors in mind, the differences in dose between right and left FHs are, therefore, unlikely to be of clinical concern in adult male patients.

Table 6.8 Left and right femoral head doses using 240° arc (median values (and range))

	Left FH SABR plans	Right FH SABR plans	*p* value	Left FH VMAT 78Gy plans	Right FH VMAT 78Gy plans	*p* value
Mean dose (Gy)	6.73 (6.12-7.17)	6.16 (5.31-7.82)	0.463	13.70 (10.74-14.99)	12.93 (9.63-16.30)	0.116
D2% (Gy)	16.11 (15.11-17.10)	13.60 (13.38-17.04)	0.345	27.96 (26.98-29.93)	28.64 (22.71-33.41)	0.753

FH: femoral head, SABR: stereotactic ablative radiotherapy, VMAT: volumetric modulated arc therapy

6.4 Discussion

This study assessed risks of radiation-induced second malignancy following modern prostate radiotherapy techniques used in day to day practice. For all techniques, the EARs of second malignancy were low for the population examined. SABR techniques, however, conferred a consistently lower risk of second malignancy in in-field, close-to-field, and out-of-field organs, while techniques employing FFF conferred lower second malignancy risks in out-of-field organs only, with the greatest relative impact being observed at greater distances from the field edge, where the absolute benefits were very small.

Prostate SABR delivers a lower physical dose compared to conventionally fractionated treatments, and so, particularly in low dose out-of-field regions where the dose risk relationship is considered linear, and where the impact of fractionation is neglected, it is not really unexpected to observe a lower risk of radiation-induced malignancy following SABR treatments. For organs within and close to the radiotherapy field, both the lower physical dose and the impact of hypofractionation have an impact, and both these factors will have contributed to the lower second malignancy risk observed in these regions. Doses were not formally re-scaled in order to isolate the impact of fractionation (e.g. to compare second malignancy risk from the same physical dose delivered using 2Gy per fraction and using a higher dose per fraction) as this is not how these doses are used in clinical practice. It can be deduced from the models used above that a higher dose per fraction with result in a larger value of α', which, in turn, will result in lower values for RED according to all non-linear models, and thus lower second malignancy risk. The theoretical benefit of hypofractionation in terms of reduced second malignancy risk has previously been discussed elsewhere [328].

While other groups have assessed the relative impact of FFF on out-of-field doses in the treatment of PCa [340,341], as a result of reduced head scatter and leakage [245], attempts to quantify the absolute size of the benefit have not been made. It is relevant to consider any relative risk alongside the absolute risk when considering absolute clinical benefit, although it is acknowledged that the calculation of EAR, by virtue of how it is derived (i.e. as an extension of OED calculation), introduces uncertainties

additional to those already involved in the calculation of relative risk (i.e. age modifying factors and the initial slope of the dose-risk curve). Despite this, the observed absolute benefit from FFF at large distances from the isocentre was very small for this population. In the situation where patients are irradiated for PCa at a younger age, the benefit of FFF in terms of absolute reduction in second cancer risk will become more valuable (while relative risk reductions will be maintained). Thinking clinically, however, most patients irradiated for PCa are about the age range considered here, making the absolute risks calculated here relevant for the majority.

The impact of FFF in PCa has also not been previously investigated in the setting of energy-matched FFF and standard (flattened) beams. Kry et al, however, evaluated non-energy matched FFF beams [341]. An increase in total out-of-field dose was observed at 3-15cm from the field edge which was attributed to the lower energy FFF beams resulting in increased within patient scatter, potentially increasing RISPC risks. Using energy-matched FFF beams, no such increase in total out-of-field dose was observed in this region, and the slight increase observed in within patient scatter was outweighed by the substantial reduction in head leakage/scatter.

The impact of linear accelerator-based SABR techniques on second malignancy risk has not been widely examined and only one other group was identified who evaluated the absolute size of the benefit from prostate SABR techniques [342]. Dasu et al quantified risks of second rectal and bladder cancer following 42.7Gy in 7 fractions or 78Gy in 39 fractions, both delivered using 3D-CRT [342]. Risks were calculated from exported DVHs using the competition model (which incorporates the effects of fractionation and predicts maximum cancer induction at doses of about 4Gy). Overall predicted risks of second cancers were low, and PTV margin size had a larger impact on risk than fractionation schedule. The group concluded that the risks of second rectal and bladder cancers were similar between conventionally fractionated and ultra-hypofractionated regimens (numerically, in fact, the hypofractionated regimen resulted in a very small increase in the mean risk of second bladder and rectal cancer although standard deviations were wide and overlapping) [342]. Thus the potential in-field benefits of SABR that were observed in this current study were not observed in Dasu et al's work. This likely reflects the differences in the modelling processes used: the competition model used predicts a maximum second cancer effect at around 4Gy [342,343], which is not entirely supported by clinical evidence [261]. According to

the OED model and accompanying parameters, however, risks may become maximal at higher doses [332]. In addition, while both models incorporate fractionation, fractionation is incorporated into each model differently. Furthermore, the competition model incorporates risks coefficients directly into the calculation of risk, while calculating ratios of OED avoids this parameter, thus avoiding this potential source of uncertainty in relative risk assessment. Recalculating the risk of second bladder and rectal cancers for the datasets in this current study using the competition model and the same parameters as used by Dasu et al (Table 6.9), also resulted in broadly similar risks of second cancers between hypofractionated and all conventionally fractionated techniques (Table 6.10). Dasu et al, also acknowledged that there was a potential benefit from SABR in terms of RISPC risk in out-of-field organs as a result of the lower physical doses delivered, although they restricted their RISPC assessments to the bladder and rectum only [342].

Table 6.9 Competition model calculation and parameters

From Dasu et al [342]

Effect calculation (%)	Parameter	Rectum	Bladder
Effect for bin *i* of DVH = $\left(\alpha_1 D_i + \frac{\beta_1 D_i^2}{n}\right) \bullet \exp\left[-\left(\alpha_2 D_i + \frac{\beta_2 D_i^2}{n}\right)\right]$	α_1 (Gy^{-1})	0.00984	0.00328
	α_2 (Gy^{-1})	0.25	0.25
	β_1 (Gy^{-2})	0.00182	0.000437
Total effect over all bins in structure = $\frac{\sum_i \left(v_i \bullet Effect\left(D_i\right)\right)}{\sum_i v_i}$	β_2 (Gy^{-2})	0.046	0.033
	α/β (Gy)	5.4	7.5
D_i =Dose received by bin *i*			
n= number of fractions			
v_i= volume of DVH bin *i*			

Table 6.10 Predicted percentage risks (%) of second rectal and bladder cancers based on competition model averaged for three datasets

	Rectum		Bladder	
	Average	Range	Average	Range
SABR FFF	0.57	0.55 - 0.59	0.22	0.20 - 0.25
SABR	0.58	0.55 - 0.61	0.22	0.20 - 0.25
VMAT 78Gy FFF	0.58	0.54 - 0.64	0.25	0.24 - 0.26
VMAT 78Gy	0.58	0.55 - 0.63	0.25	0.24 - 0.26
IMRT78Gy	0.54	0.51 - 0.61	0.27	0.24 - 0.29
3D-CRT	0.47	0.43 - 0.55	0.25	0.22 - 0.27

3D-CRT: 3-dimensional conformal radiotherapy, FFF: flattening filter free,
IMRT: intensity-modulated radiotherapy, SABR: stereotactic ablative radiotherapy,
VMAT: volumetric modulated arc therapy

Few groups have evaluated RISPC risk in PCa following VMAT compared to other external beam photon techniques. Blais et al, however, compared RISPC in PCa following rotational IMRT (an approximation of VMAT) and 7-field IMRT using a plateau model which saturated at 4Gy [333]. Overall lifetime risks were calculated according to ICRP 103 risk coefficients and weightings [189]. No clinically significant difference in RISPC risks were observed using rotational-IMRT or IMRT. In the simple geometry case (where PTV did not overlap with the rectum or the bladder), risk was very slightly higher using IMRT at 4.78% compared to 4.56% with rotational IMRT, although the difference was considered clinically irrelevant. The small difference was attributed to increased MU requirements for the IMRT plan. In the complex geometry case, where there was overlap of the PTV with the rectum and bladder, a situation more close to day to day clinical practice, the difference in risk was minimal: risk was 5.73% using IMRT and 5.74% using rotational IMRT [333]. Alvarez Moret et al examined RISPC risk from quasiIMAT, a pseudo-rotational technique employing 36 equally spaced step and shoot beams to simulate an arc, and thus also an approximation of VMAT [344]. Estimates were calculated for quasiIMAT and IMRT using 36 and 72 segments. The OED concept was used, employing plateau and bell-shaped models. OED was similar using both models. For both IMRT and quasiIMAT, a higher number of segments resulted in higher OED in regions beyond the scanned volume. Total body OED was

similar with 36 segment quasiIMAT and IMRT. When 72 segments were used there was a small increase in total body OED with quasiIMAT which was attributed to increased MU requirements but this was considered insignificant [344]. Despite the increase in volume of normal tissue irradiated to a low dose due to the large number of beams with quasiIMAT, overall, therefore, quasiIMAT did not significantly increase SPC risk [344].

Rechner et al principally compared risks of bladder and rectal RISPC from VMAT with proton arc therapy [345]. Excess relative risks were calculated and ratios of excess relative risks were used for comparisons (another modelling process which incorporates the effects of fractionation and reports risk relative to that in an non-irradiated population [346-348]). DVH data provided details of the therapeutic dose for VMAT and protons. For VMAT, DVH data were also used to estimate secondary radiation doses (i.e. dose resulting from head leakage and scatter and additional within patient scatter). Monte Carlo simulations and previously published data were used to estimate secondary radiation doses resulting from proton arc therapy. Proton arc therapy, resulting in low entrance doses and minimal exit doses, predicted significantly lower risks of second bladder or rectal cancer according to bell-shaped and plateau models compared to VMAT while there was no significant difference in second rectal or bladder cancer risk when using a linear model. The group also compared calculated excess relative risks of second bladder and rectal from VMAT with those previously estimated from IMRT by another group [311]. Numerically, VMAT resulted in lower risks of second bladder and rectal cancer compared to IMRT (excess relative risk for bladder RISPC: 5.25 with VMAT and 8.88 with IMRT, excess relative risk for rectal RISPC: 2.09 with VMAT and 3.32 for IMRT) [345]. These risks, however, were calculated using a linear model, which is often considered inappropriate in higher dose regions [254,326]. The use of a different model may also explain why greater differences were observed between IMRT and VMAT by Rechner et al than what was observed in this current piece of work.

Comparisons of the data presented here with those of other groups are difficult, not least, as mentioned above, because of the lack of similar comparisons with the specific techniques evaluated in this work, and also as a result of the different models used, but also because several studies calculate whole body risk, rather than individual organ risks as presented here. While parameters are available for calculating whole body risk

using the methods adopted in this study, caution is urged in carrying this out in situations of inhomogeneous dose distributions across the whole body, i.e. situations other than mantle radiotherapy [332]. Only individual organ risks were therefore calculated in this study. Patil et al also used the concept of OED and calculated EAR for second bladder and rectal cancers following radiotherapy for PCa using 6MV IMRT [349]. Calculations were based on DVH data from the Eclipse® (Varian, USA) planning system. The EAR for rectal cancer was slightly higher than what was observed here at 3.42 per 10,000 PY while that calculated for the bladder was lower at 0.1 per 10,000 PY. The differences between these results and the results in this current study could be attributed to differences in the volumes irradiated, CTV to PTV margins, planning systems, beam arrangements and parameters used for risk calculations.

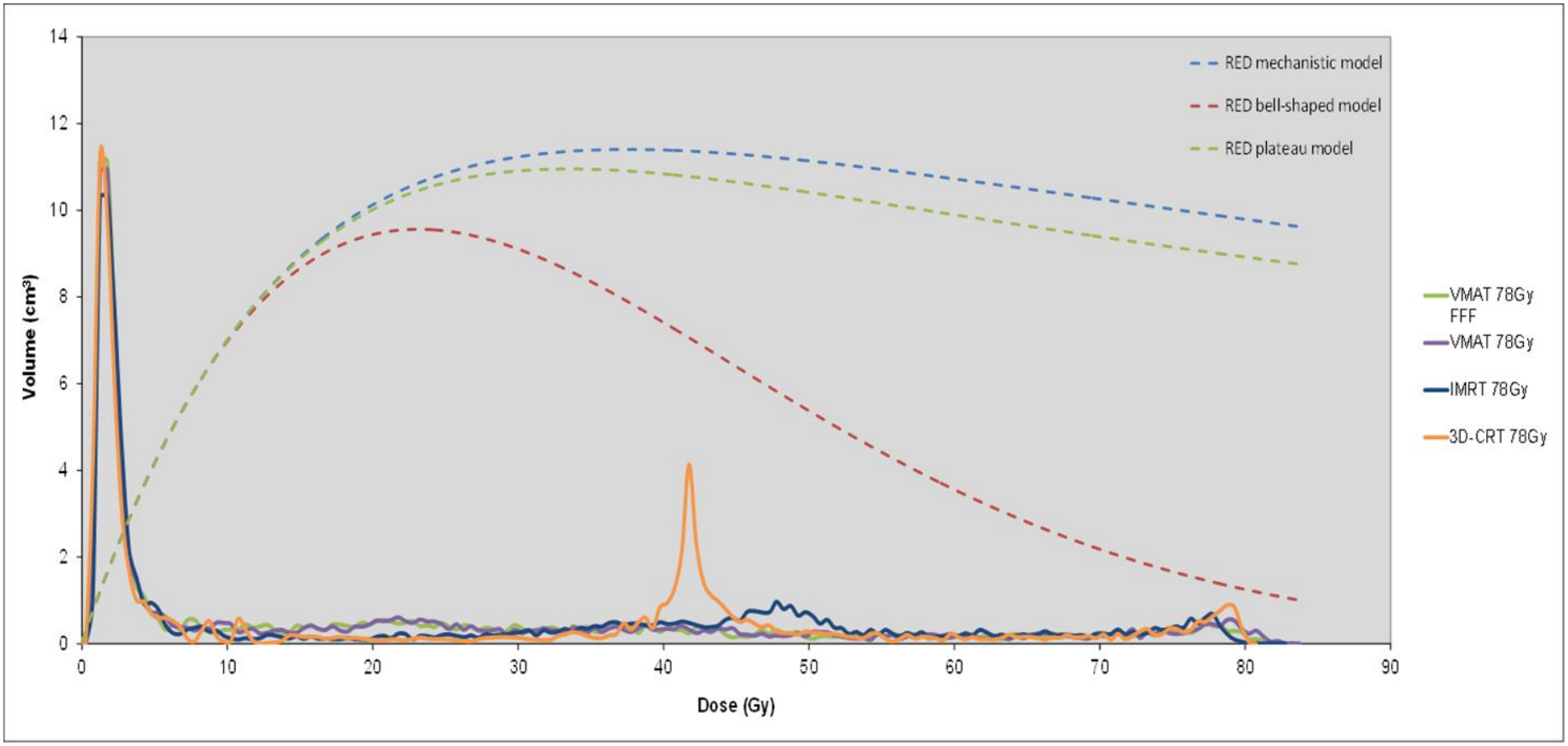
Theoretical concerns have been raised regarding a potential large (at times >100%) increase in RISPC risk using IMRT compared to 3D-CRT [254,294,297,298,324]. Some of these studies have been criticised for neglecting the impact of the primary beam in risk evaluation and/ or the methods used in calculating risk [293,350]. More recent papers have suggested that any increased risk from 6MV IMRT would only be very small, particularly when compared to higher energy 3D-CRT (as often employed clinically) [326,327]. The theoretical increase in risk from IMRT is often attributed to two things: i) increased MU requirements for IMRT, resulting in increased head leakage, thus contributing to out-of-field dose, and ii) the change in dose distribution, resulting in an increased volume of normal tissue receiving low doses. Increased risks from 6MV IMRT and VMAT 78Gy (flattened) were observed here relative to 10MV 3D-CRT in out-of-field organs of up to 26% and 55% respectively, likely the result of increased MU. In absolute terms, however, where the greatest relative risk increases were observed, absolute increases were very small. The addition of FFF to VMAT 78Gy, despite an increase in MU compared to 3D-CRT, however, did not result in any increase in second cancer risk in out-of-field organs compared to 3D-CRT, and relative risks were, in fact, reduced. Again, however, in absolute terms, the differences in second cancer risk in in-field and out-of-field organs between 78Gy IMRT, VMAT 78Gy or VMAT 78Gy FFF were small, although the smallest absolute risks were observed for VMAT 78Gy FFF.

When considering individual in-field or close-to-field tissues, the impact of a change in dose distribution when moving from 3D-CRT to IMRT did not translate into clinically relevant increases in RISPC risk according to the models and margins employed here.

Dose-volume histograms for all 78Gy treatments for one dataset are plotted in Figure 6-13 to Figure 6-16. The relationship between dose and RED according to Schneider's models has also been superimposed onto the DVH curves. Note that the values for RED are not shown, but the dose-RED curves are plotted purely to illustrate the shape of the dose-risk relationship.

A Visual inspection of differential DVHs for the rectum for all 78Gy treatments (Figure 6-13) are not suggestive that the rectum receives a greater proportion of low dose irradiation with IMRT, and dose distributions are largely similar between 3D-CRT and IMRT until around 40Gy where there is a peak in the 3D-CRT DVH. For IMRT, a smaller peak is seen around 48Gy. In Schneider's model for rectal cancer induction, the risk peaks at about 23Gy using the bell-shaped model, and at about 35Gy according to the mechanistic and plateau models. The 40-50Gy region is therefore in the region of decreasing risk and the small 48Gy peak in the IMRT DVH falls in a lower risk portion of the curve compared to the larger 40Gy peak for the 3D-CRT curve. This may contribute to the slightly reduced risk observed in the risk of rectal cancer using IMRT relative to 3D-CRT (although in absolute terms the difference in risk is very small). Considering the VMAT treatments, a slightly higher proportion of rectal tissue receives doses in the 15 to 25Gy range compared to IMRT and 3D-CRT. This dose region falls in the highest risk portion of the bell-shaped model, thus resulting in the slightly increased risk of rectal cancer using VMAT relative to 3D-CRT and IMRT using this model. Considering the competition model, which predicts maximum effect at around 4Gy, IMRT and VMAT treatments display a slightly higher volume of tissue receiving doses in the 3 to 4Gy region compared to 3D-CRT, resulting in the slightly higher risks seen with IMRT and VMAT according to this model.

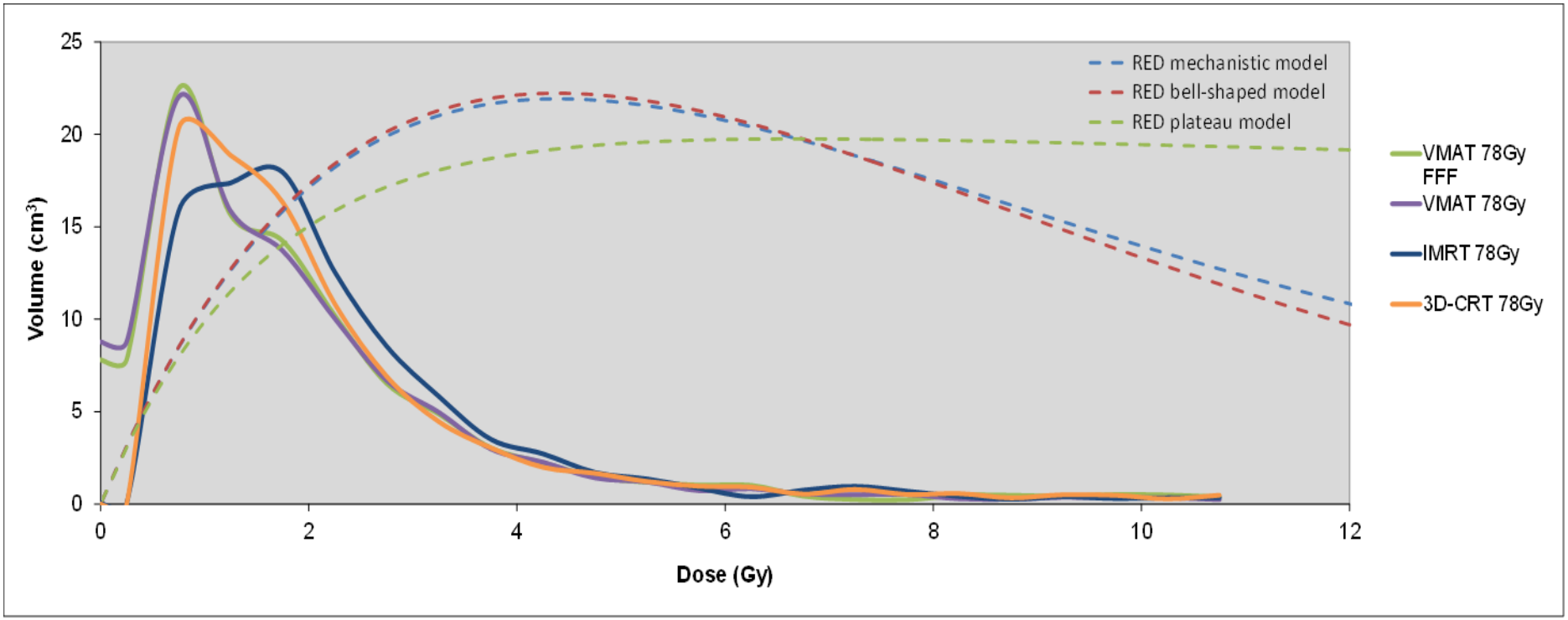
Figure 6-13 Differential dose-volume histograms comparing 78Gy techniques: rectum



3D-CRT: 3-dimensional conformal radiotherapy, FFF: flattening filter free, IMRT: intensity-modulated radiotherapy, RED: risk equivalent dose, VMAT: volumetric modulated arc therapy

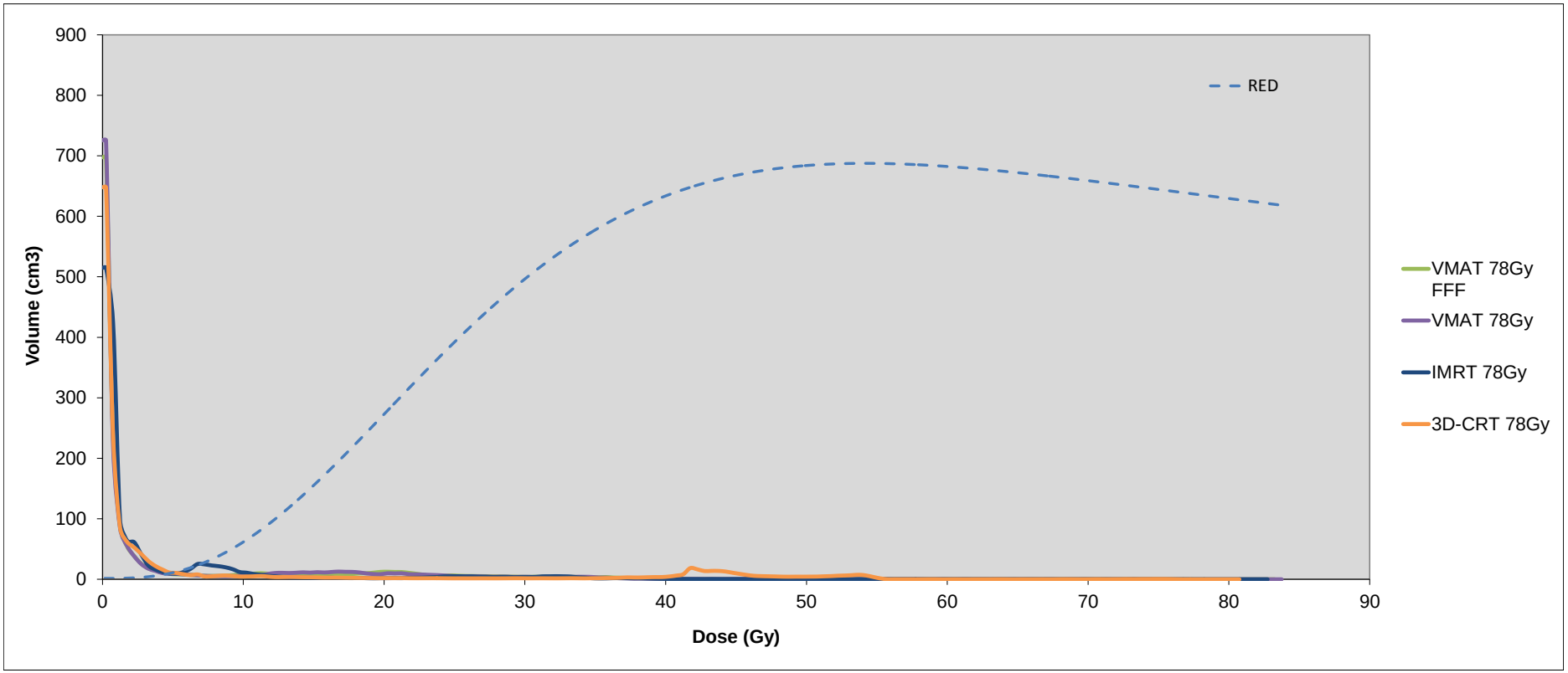
Figure 6-14 Differential dose-volume histograms comparing 78Gy techniques: bladder

(only first 10.5Gy shown to allow differences to be more clearly observed)



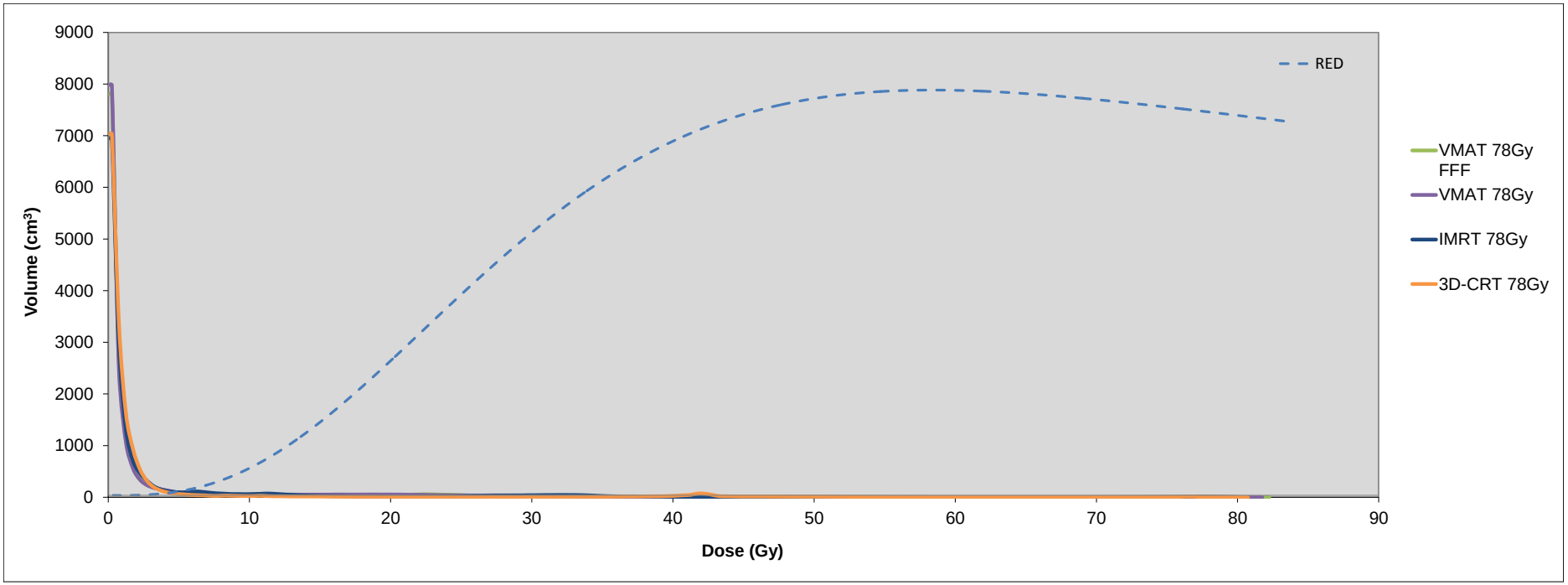
3D-CRT: 3-dimensional conformal radiotherapy, FFF: flattening filter free, IMRT: intensity-modulated radiotherapy, RED: risk equivalent dose, VMAT: volumetric modulated arc therapy

Figure 6-15 Differential dose-volume histograms comparing 78Gy techniques: pelvic bones



3D-CRT: 3-dimensional conformal radiotherapy, FFF: flattening filter free, IMRT: intensity-modulated radiotherapy, RED: risk equivalent dose, VMAT: volumetric modulated arc therapy

Figure 6-16 Differential dose-volume histograms comparing 78Gy techniques: pelvic soft tissues



3D-CRT: 3-dimensional conformal radiotherapy, FFF: flattening filter free, IMRT: intensity-modulated radiotherapy, RED: risk equivalent dose, VMAT: volumetric modulated arc therapy

In the case of the bladder DVHs (Figure 6-14), IMRT appears to result in a slight increase in the volume of tissue receiving 2 to 5Gy, which encompasses the area of maximal effect according to Schneider's bladders models, thus resulting in the slightly higher relative risk of second bladder cancers from IMRT compared to 3D-CRT. For both VMAT treatments, a smaller volume of tissue receives doses in the region of 1 to 2Gy compared to 3D-CRT, and similar volumes of tissues receive doses of 3 to 5Gy compared to 3D-CRT, thus resulting in only very slight second bladder cancer risk reductions using VMAT. These differences in dose distributions between techniques also explain the slight increase in second bladder cancer risk observed using IMRT compared to 3D-CRT, and similarities in risk between VMAT and 3D-CRT, according to the competition model.

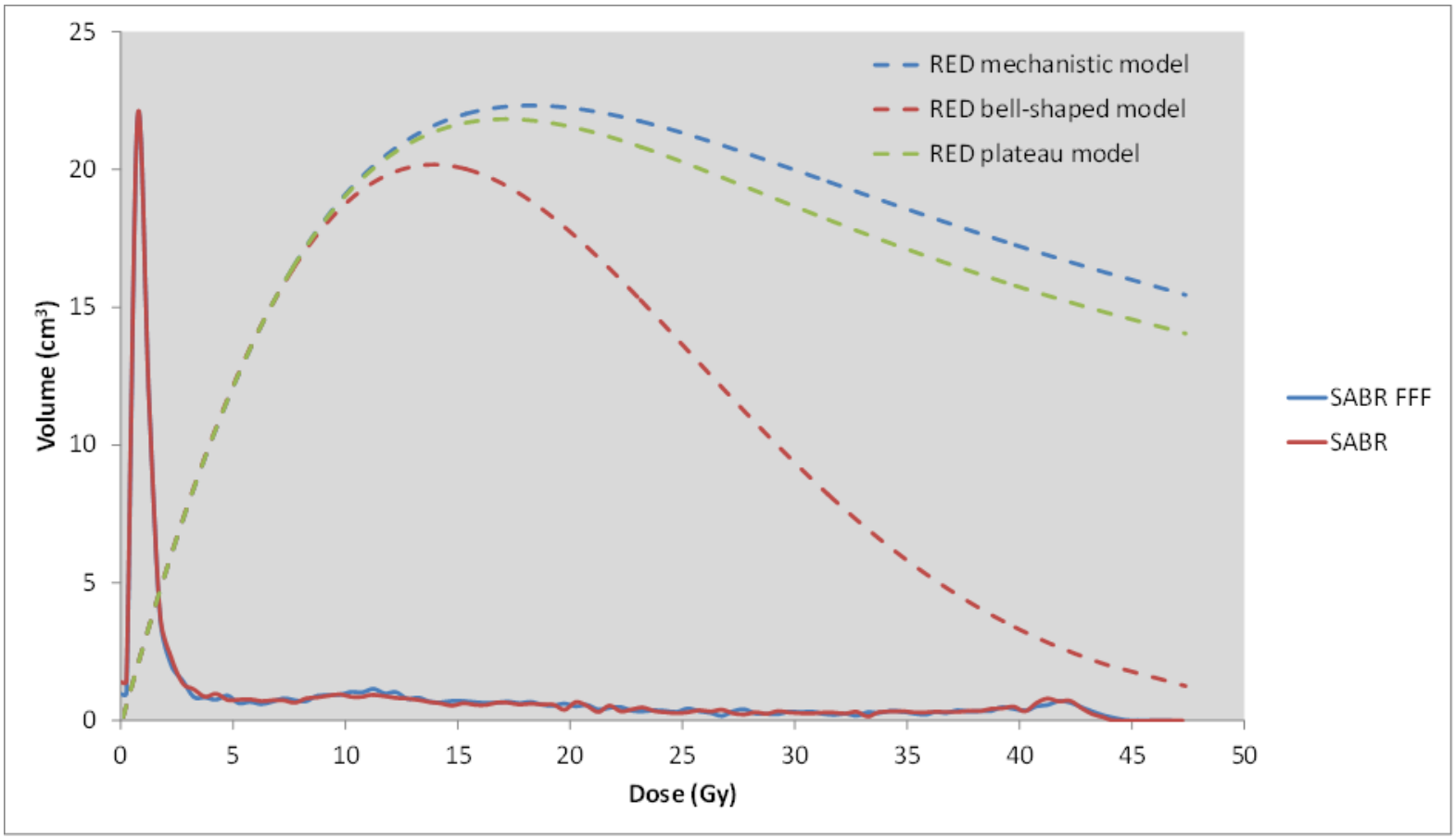
Considering the pelvic bone DVHs (Figure 6-15), VMAT results in a larger volume of tissue receiving very low doses (<1Gy) and IMRT results in a slight increased volume of tissue receiving doses around 2Gy and around 6-10Gy compared to 3D-CRT. Schneider's model, however, predicts a peak in RISPC risk at around 54Gy. A small peak in dose is seen for the 3D-CRT plan at just above 40Gy, thus falling in the higher risk region of the dose-RED curve, and contributing to the increased relative risk of second bone sarcoma observed for 3-DRT compared to all other techniques, while the increased volume of bone receiving lower doses from IMRT and VMAT fall on a much lower risk part of the dose-risk curve, and thus contribute little to the calculated risk.

In terms of the soft tissue DVHs (Figure 6-16), where perhaps one might expect to see the biggest impact of an increased volume of tissue receiving a lower dose of radiation with IMRT or VMAT techniques, it can be seen that VMAT, as with the pelvic bone DVHs, results in a higher volume of tissues receiving very low doses (i.e. <1Gy), while 3D-CRT results in a slightly larger volume of tissue receiving 2-3 Gy. Schneider's model predicts maximum effect at around 58Gy and so it is doses in this region which will have the largest impact on risk. In the 50-60Gy region, the DVH is largely similar for all techniques, and there is only a very slight peak at about 42Gy for 3D-CRT. Overall, therefore, calculated risks for pelvic soft tissue sarcoma are similar for all four techniques, and the traditional concern that IMRT/VMAT techniques result in a larger volume of normal tissue receiving lower (and thus more cancer inducing) doses appears to contribute little to the overall calculated risk, according to the model used here.

Figure 6-17 to Figure 6-20 display DVHs for rectum, bladder, pelvic bone and pelvic soft tissue for the SABR FFF and standard (flattened) SABR techniques for one dataset. Once again, a graph of RED is plotted against dose (without vertical units for RED) to display the shape of the dose-RED relationship. Note, given the impact of fractionation, the dose-RED relationship peaks at a different point to that for conventionally fractionated treatments and the magnitude of RED is also different. It can be seen that for the rectum, bladder wall, pelvic bone and pelvic soft tissues, DVHs for the FFF and standard (flattened) treatments are very similar, thus resulting in similar RISPC risks for these techniques.

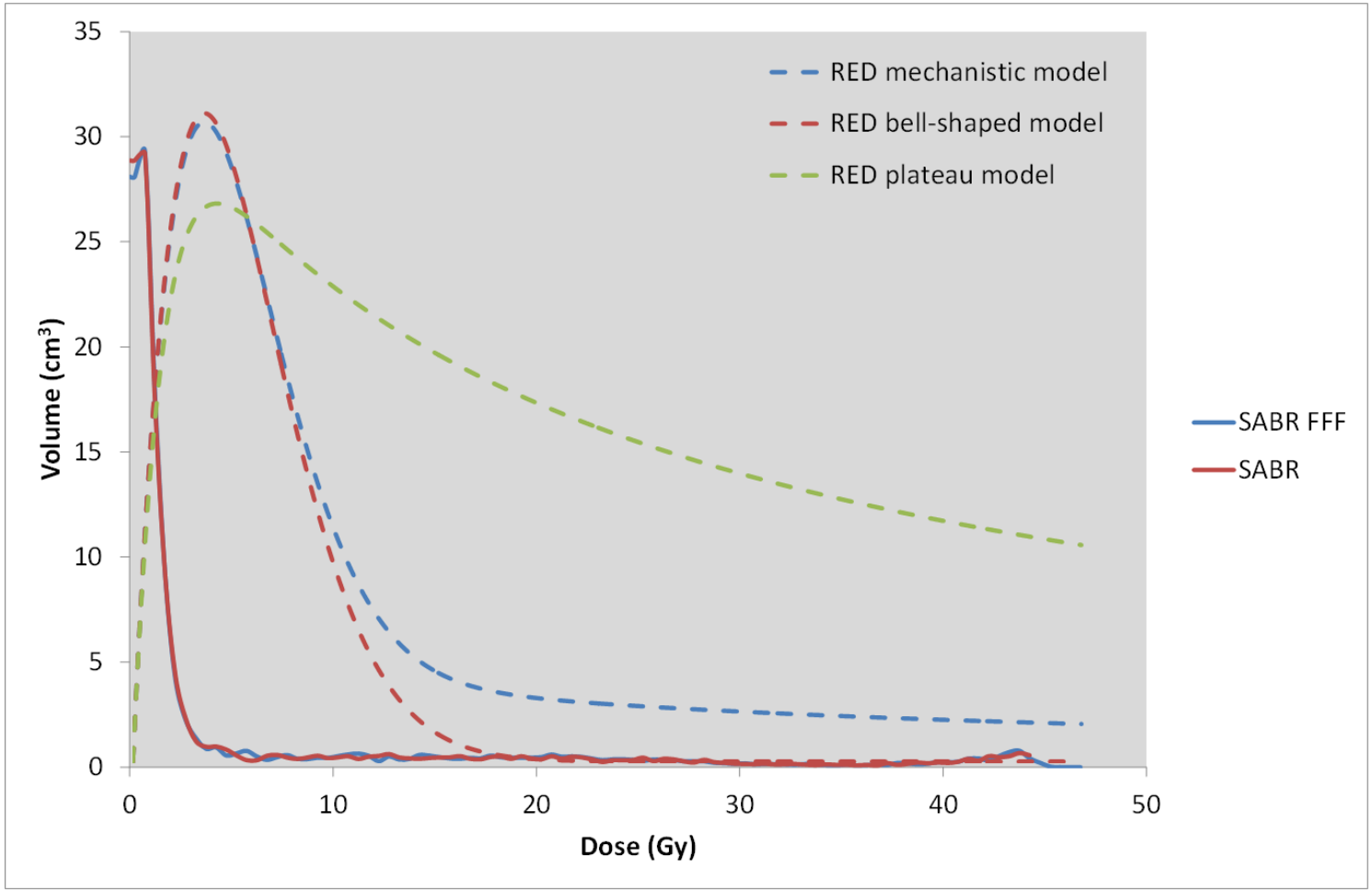
Historically, it has on occasion been assumed that IMRT results in an increase in normal tissue integral dose, and thus an increase in second malignancy risk. More recent work has, however, suggested that integral dose is not necessarily higher following IMRT compared to 3D-CRT [326,351,352]. Caution should be exercised in using integral dose as a relative indicator of second malignancy risk [293]. While a correlation will be observed between integral dose and RISPC risk in the low dose out-of-field regions, where a linear model can be applied, in the in-field and close-to-field regions, where non-linear models are considered more realistic, then the same assumption cannot be made [293]. Indeed, strong correlations were demonstrated between integral dose and OED for all out-of-field organs here. For the rectum and bladder, however, where most second cancers are reported clinically following prostate radiotherapy, such correlations were not apparent. Similarly, integral dose has been found to be a poor estimator of second malignancy risk in the context of lung cancer [336].

Figure 6-17 Differential dose-volume histograms comparing SABR techniques: rectum



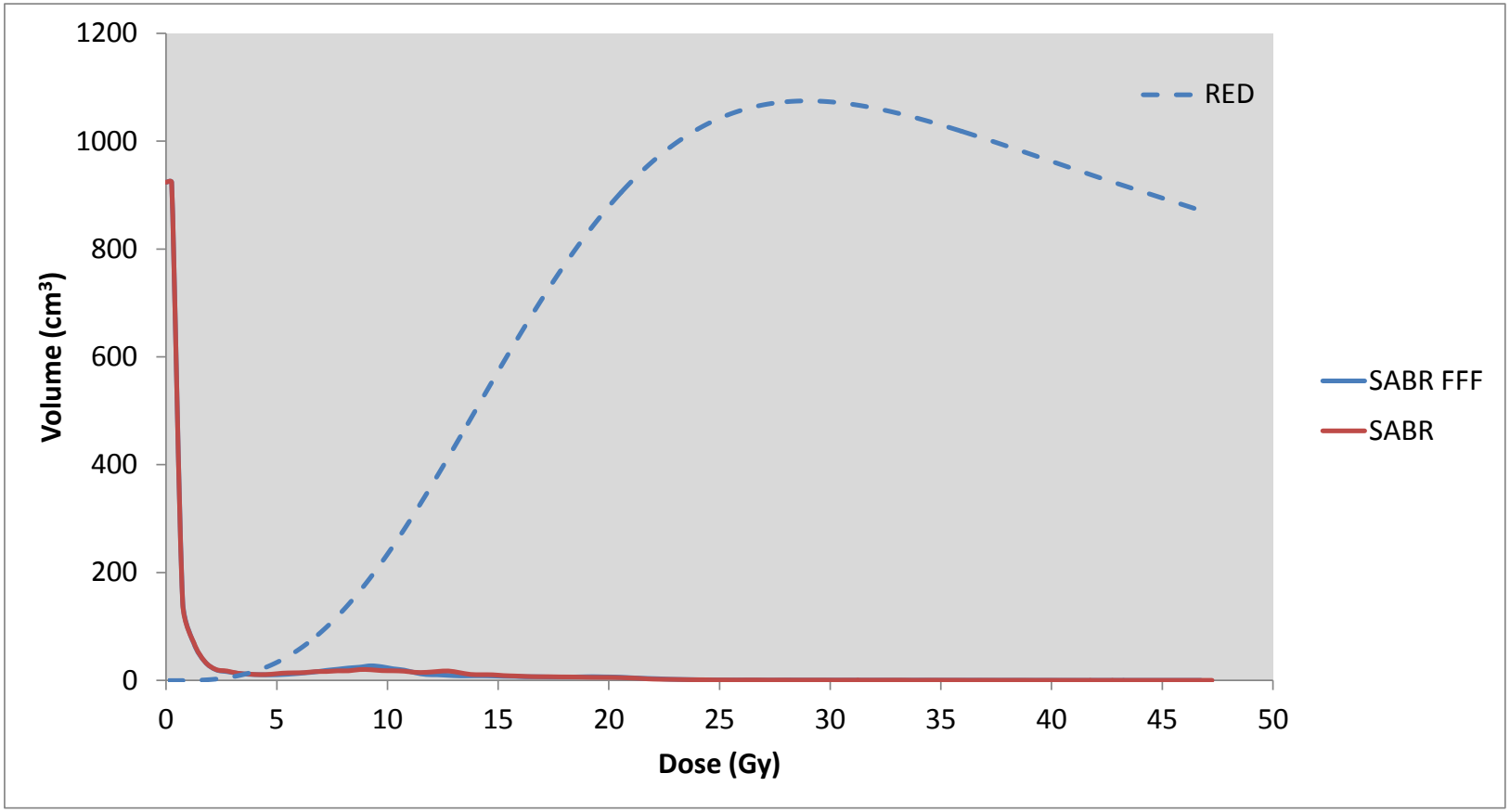
FFF: flattening filter free, RED: risk equivalent dose, SABR: stereotactic ablative radiotherapy

Figure 6-18 Differential dose-volume histograms comparing SABR techniques: bladder



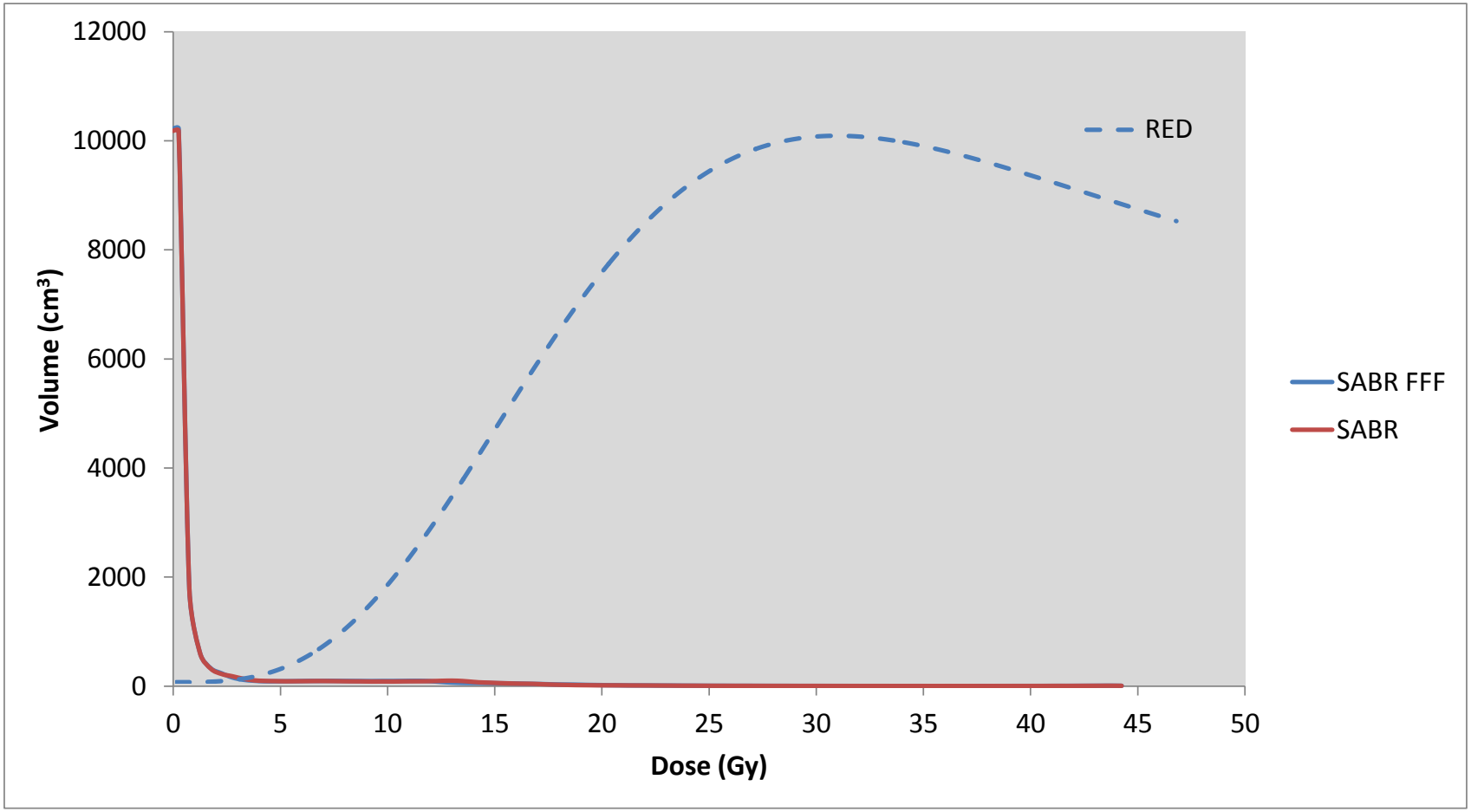
FFF: flattening filter free, RED: risk equivalent dose, SABR: stereotactic ablative radiotherapy

Figure 6-19 Differential dose-volume histograms comparing SABR techniques: pelvic bones



FFF: flattening filter free, RED: risk equivalent dose, SABR: stereotactic ablative radiotherapy

Figure 6-20 Differential dose-volume histograms comparing SABR techniques: pelvic soft tissue



FFF: flattening filter free, RED: risk equivalent dose, SABR: stereotactic ablative radiotherapy

There are a number of limitations in this work. Firstly, there are uncertainties in all of the models and parameters which can be used to estimate second malignancy risk, including the models adopted here. Schneider's concept of OED was employed as this incorporates fractionation, which is relevant for current practice. In addition, when used with Schneider's mechanistic model, individual tissue repair and repopulation parameters are included: intuitively it seems likely that tissues exposed to radiation will undergo a degree of repair and repopulation, the extent of which may vary with tissue type and dose received. To illustrate the range of possible outcomes, however, based on scenarios of no repair and no repopulation, and full repair and repopulation, rectal and bladder cancer risk was also assessed based on bell-shaped and plateau models. All models suggested benefit from SABR in in-field or close-to-field tissues, which is where the majority of radiation-induced tumours are observed [261]. Similarly, all models predicted broadly comparable second rectal and bladder cancer risks from 3D-CRT, 5-field IMRT and VMAT 78Gy (FFF or standard). For out-of-field organs, where it is generally accepted that a linear model is appropriate for risk assessment, a 5% uncertainty was assumed to account for dosimetric and positioning issues. As with higher dose regions, however, underlying uncertainties in the parameters and models used for calculation will remain. It should also be acknowledged that the second cancer induction models used in this study are based on mutation induction only, and do not take into account other potential factors, such as changes in the microenvironment following irradiation and inflammation, which may have independent dose-response relationships and different temporal patterns in second cancer induction.

Secondly, the appropriateness of using these models for high dose per fraction treatments such as SABR could also be questioned. The SABR prescription, however, was 6.1Gy per fraction, within the 10Gy per fraction range in which the LQ-model is considered reliable [238]. In addition, most normal tissues received doses far below the prescription dose, and therefore a considerably lower dose per fraction. A further concern could be the use of a model incorporating repair and repopulation factors, in the setting of an ablative treatment. Although the ultra-hypofractionated regimens investigated here are termed SABR, and thus ablative, this and other prostate SABR regimens deliver doses per fraction much lower than those employed for ablative treatments in other sites such as small primary lung cancer and brain metastases. It is unclear exactly how much ablation is achieved from doses of 6.1Gy per fraction as

used here. If full ablation were to be achieved, then the risks calculated according the bell-shaped model would be perhaps most relevant. That said, however, as most of the normal tissues irradiated receive doses far below the high dose per fraction delivered to the target, a mechanistic model, which allows a degree of repair and repopulation, may be more appropriate. Only clinical evidence, once available, will be able to address this issue fully.

Thirdly, a calibrated MV chamber was used for out-of-field measurements. TLDs have often been used given their relative energy independence. The concern regarding chamber out-of-field measurements is the lower energy spectra in this region. As mentioned earlier, it has been demonstrated that the mean energy spectra out to 20cm from the field edge are in the kilovoltage range, within the range of the chamber [329]. Chamber measurements up to 22cm from the field edge have been shown to have good correlation with TLD readings although it should be acknowledged that TLDs can prove difficult in terms of accuracy and reproducibility, with uncertainties of up to 10% being quoted [329]. At 10-20cm from the field edge, it appears the energy spectra are plateauing or at worst decreasing only very slowly, thus allowing chamber measurements to be taken at distances of 20cm and beyond, accepting 5% uncertainty [329]. In the situation that the chamber readings were inaccurate, presuming such an error was of a similar proportion for all techniques at each measurement point, then calculated relative risks will be maintained. Indeed, the out-of-field relative risk reductions observed using FFF in this study, and the increasing impact of FFF at increasing distances from the treatment field, have been demonstrated elsewhere based on TLD measurements and Monte Carlo modelling [341,353]. Furthermore, in the case of EAR calculations, chamber measured doses would need to be considerably different to ‘true’ doses if the low EARs calculated here were, in reality, much higher. For example, in the region of the stomach (30cm from the isocentre), the calculated EAR was 0.34 per 10,000 PY using 3D-CRT 78Gy. The measured dose would need to have been ‘out’ by a factor of about three if the true risk was 1 per 10,000 PY. For the same plan, in the region of the oral cavity (70cm from the isocentre), calculated EAR was 0.0028 per 10,000 PY for the 3D-CRT 78Gy plan. The measured dose would need to be ‘out’ by a factor of about 350 if the true EAR was as high as 1 per 10,000 per year. In addition, while there are undoubtedly uncertainties arising from the measured doses in this study, much larger uncertainties arise from the models used for risk calculation.

Fourthly, in this study 6MV was adopted for all arc therapies and 10MV was used for 3D-CRT as these are the energies commonly adopted clinically. The photo-neutron effect begins at around 10MV. The impact of neutron contamination on malignancy risks for the 10MV plan was not assessed here, but it has previously been demonstrated that this effect is minimal at 10MV [297,325].

Fifthly, only three datasets were used to compare second malignancy risks in in-field and close-to-field organs amongst the six investigated irradiation techniques (i.e. 18 plans in total), and only one dataset was used for out-of-field dose assessment. While three is a very low number, most existing planning studies which examine second malignancy risk following prostate radiotherapy do so using only one to three datasets [297,326,333,340,341,345], as it is generally the differences in radiation techniques that are the subject of interest rather than inter-patient variation in risk. While inter-patient variations in the bladder and rectum are likely, the position of the prostate in relation to the surrounding anatomy is likely to be more constant than other primary tumours which can adopt a variety of anatomical locations (and thus varying proximities to surrounding normal tissues), thus potentially resulting in a greater variation in relative risks from different irradiation techniques. In the case of the three prostate datasets used here, risk ratios were similar, thus supporting the suggestion of relative anatomical constancy for the prostate and surrounding tissues. For out-of-field dose measurements, doses are likely to be similar between patients, and so only one dataset was used for point dose measurements.

Sixthly, the parameters adopted here were based on Atomic bomb survivors and patients irradiated for Hodgkin's disease treated with radiotherapy. Some of these patients also received chemotherapy and it could be postulated that the risk of second malignancy may be partly influenced by the use of chemotherapy. This has been previously examined, and any impact resulting from the addition of chemotherapy to radiotherapy has not been found to be significant [332,354].

Lastly, for out-of-field organs it was assumed that the point dose measured was representative of the dose received by the whole organ. This is a reasonable approach for the majority of out-of-field organs where relatively homogenous doses are likely to

be received. This approach, however, is likely to be least satisfactory for the colon which covers a large geographical area at a variety of distances from the treatment field. The calculated OED and EAR for the colon should therefore be viewed with the greatest caution out of all the out-of-field organ results. The point chosen to measure the dose received by the colon was in the approximate location of the central portion of the transverse colon, and as such the OED and EAR calculated are perhaps best regarded as relating to this region only. A more accurate assessment of OED and EAR for the ascending and descending segments of the colon would have either required a series of point dose measurements toward the sides of the phantom and at increasing distances from the field. Alternatively, a DVH for the whole colon could be exported from the planning system, although in the case of the patients examined here, the planning scans did not contain the complete colon volume making this approach infeasible.

The impact of image-guided radiotherapy (IGRT) on RISPC risk was not included in this study as this will vary with the IGRT technique employed. The CTV-PTV margin was intended for daily online IGRT with fiducial markers. Thus conventionally fractionated regimens will require at least 39 images while SABR will require at least seven images. If automatic couch adjustments are used, and treatment time is sufficiently fast, then further imaging following shifts or post-treatment would be unnecessary. The need for fewer images with ultra-hypofractionated regimens potentially adds additional RISPC benefit to SABR techniques. Of note, all the techniques evaluated in this study employed the same CTV-PTV margins. Advances in image-guided radiotherapy (IGRT) have facilitated CTV-PTV margin reduction, and the impact of CTV-PTV margin reduction on normal tissue irradiation and RISPC risk would require separate investigation. It has previously been suggested (based on the Competition model), however, that tighter margins result in less normal tissue high dose irradiation which in turn results in increased normal tissue exposure to lower, potentially RISPC-inducing, doses [342].

Different hardware and software combinations as well as treatment margins may all contribute to differences in second cancer risk [326,342]. These were minimised as far as possible in this study by delivering all plans on the same machine, by creating plans using the same planning system where possible, and by using the same CTV-PTV

margin. Differences in risks observed in this study should therefore largely be due to the doses, fractionations and planning techniques under evaluation.

Proton therapy, TomoTherapy® (Accuray®, USA) and Cyberknife™ (Accuray®, USA) are other early PCa external beam techniques. Other groups have demonstrated very low RISPC risks from protons [295,310-313,345]. Risks from TomoTherapy® and Cyberknife™ have not been as widely evaluated. Hälg et al, however, measured out-of-field doses for a variety of techniques including TomoTherapy® and Cyberknife™ [340]. TomoTherapy® resulted in out-of-field doses largely similar to 3D-CRT and IMRT while Cyberknife™, despite delivering a SABR dose (thus lower physical dose), resulted in higher out-of-field doses, attributed to non-coplanar beams and increased MU: compared to 3D-CRT, in regions receiving <0.5Gy, Cyberknife™ resulted in 2.7 times the dose [340]. Absolute RISPC risks were not quantified, but would likely be very low in this region.

The clinical data regarding second malignancy risk following prostate radiotherapy is largely based on older and often larger field techniques (Chapter 5). In terms of small field 3D-CRT techniques there are fewer data, and in terms of IMRT even less data are available. The clinical evidence that is available regarding modern techniques, however, is encouraging, and suggests that IMRT does not result in the large increased risk of second malignancy as has been historically presumed [266,274,299]. This data, however, is relatively immature and the patient numbers involved are relatively small. No clinical data has been reported which specifically examines second malignancy risk following VMAT, SABR or FFF in PCa. Until more clinical data is available, then planning data in conjunction with appropriate models must be used as a surrogate.

6.5 Conclusions

In summary, RISPC risks were compared following contemporary clinically relevant radiotherapy techniques for early PCa. SABR techniques resulted in reduced relative RISPC risks in all organs, while FFF techniques resulted in reduced RISPC risks in out-of-field organs relative to equivalent flattened techniques, particularly at greater distances from the treatment field. Overall, SABR FFF offered the greatest benefits in terms of RISPC risk reduction. Although large differences in relative risk were sometimes observed between techniques, in absolute terms, RISPC risks were low overall and absolute differences between techniques were also small. Until clinical data regarding RISPC in irradiated prostate patients treated with contemporary techniques matures, data from this and other planning studies should be considered when selecting appropriate radiation techniques for individual patients.

6.6 Acknowledgements

John Lilley for producing the 3D-conformal radiotherapy plans and for reviewing the VMAT and IMRT plans.

Christopher Thompson for assistance with treatment delivery and creating the 3D-conformal QA plan for delivery.

Steve Weston for training me as a linear accelerator operator.

Chapter 7 : Summary and Future Work

7.1 Summary

Prostate cancer is the most common cancer in UK males [1]. External beam radiotherapy is one of several treatment options for men presenting with localised disease. Stereotactic ablative radiotherapy offers patients the theoretical benefits of hypofractionation, including the potential for increased cure, together with the convenience of a treatment which involves a small number of out-patient visits. This project aimed to investigate linear accelerator-based prostate SABR with the ultimate aim of optimising outcomes for PCa patients.

A class solution was developed for prostate SABR prescribing. A single partial anterior VMAT arc was found to be optimal as this resulted in highly conformal plans with reduced rectal doses compared to a full arc arrangement. Most patients also benefited from the partial arc arrangement in terms of reduced estimated delivery times and monitor unit requirements. A 6mm CTV-PTV margin, compatible with daily online image guidance of fiducial markers was preferred as this margin resulted in lower organ at risk doses compared to a larger CTV-PTV margin which would be more appropriate for CBCT soft tissue matching. Including the proxSV within the CTV was possible but also resulted in increased organ at risk doses.

Boosting dominant intra-prostatic lesions was feasible in the context of whole prostate SABR, and a median boost of 125% of the prescription dose was possible while maintaining organ at risk constraints. Boosting dominant lesions resulted in an increase in TCP but this benefit was offset by marked increases in NTCP. The TCP benefit of DIL boosting was greatest in the setting of a prostate α/β ratio of 10Gy and least in the setting of a prostate α/β ratio of 1.5Gy. Indeed, if prostate α/β ratio is 1.5Gy, then high levels of TCP and low levels of NTCP can be achieved by whole prostate SABR without DIL boosting.

Creating prostate SABR plans using energy-matched FFF beams resulted in no clinically relevant dosimetric disadvantages compared to planning with the flattening filter in situ. The major advantage of FFF was reduced estimated delivery times. Plan verification showed both the FFF and conventional flattened plans to be deliverable, and confirmed the time advantage of FFF treatment delivery.

There is clinical evidence which suggests that PCa patients treated with radiotherapy are at increased risk of second cancers, particularly when compared to non-irradiated PCa patients. The risk of second cancer appears to increase over time. This evidence is largely based on studies which include patients treated with older radiation techniques and so may not be applicable to patients treated with more modern conformal techniques. The clinical evidence regarding more modern radiotherapy techniques such as IMRT or brachytherapy is encouraging, but patient numbers are too few and follow-up too short to draw firm conclusions about the RISPC risk in patients treated with these modern techniques.

In the absence of clinical evidence with regard to second cancer risk, planning studies and models of second malignancy induction must be used to give estimations of RISPC risk following more modern radiotherapy techniques, including prostate SABR. SABR techniques reduced the risk of RISPC in in-field and out-of-field organs compared to 78Gy in 39 fractions 3D-CRT. FFF techniques, compared to flattened techniques, reduced RISPC risks in out-of-field organs. 78Gy IMRT and 78Gy VMAT delivered using a flattened beam resulted in increased RISPC risk in several out-of-field organs compared to 3D-CRT. Although relative risk increases were at times marked, the absolute risk of second cancers was low and the absolute differences in risk between techniques were low. Overall, however, SABR with FFF resulted in the lowest risk of second cancers out of all the techniques evaluated.

In summary, therefore, whole prostate SABR delivered using a single partial anterior VMAT arc results in highly conformal plans with rapid delivery times, particularly when delivered using FFF beams. High levels of TCP and low levels of NTCP are predicted from this technique, and risks of radiation-induced second cancers are also estimated to be low. Phase III clinical trials are required to investigate this technique in practice.

7.2 Future work

As above, Phase III trials are required to evaluate prostate SABR in clinical practice and in comparison to conventionally fractionated radiation techniques. Long term follow-up of such patients is the only way to draw definitive conclusions in terms of prostate SABR efficacy, toxicity and appropriate organ at risk constraints, and long term second malignancy risk. Both the ongoing Phase III HYPO-RT-PC trial and the recently opened PACE trial will ultimately provide some of this evidence in comparison to 78Gy in 39 fraction schedules [133,134]. In addition, the PACE trial may provide additional information regarding the relative benefits, if any, of Cyberknife™ SABR prescribing compared to linear accelerator-based prescribing. The platform used for SABR delivery, however, is not randomised within the PACE trial, and so it could prove difficult to come to a firm conclusion about the optimal means of SABR delivery. An additional challenge that occurs in phase III trials examining radical treatments for patients with low and intermediate-risk PCa is the long time that it takes to reach meaningful clinical end-points [355]. For example, it takes many years (i.e. in excess of 10 years) to obtain accurate outcomes in terms of PSA failure, particularly in patients with low-risk disease, and late toxicity also takes several years of follow-up for an accurate picture to develop [355,356]. In addition, where the anticipated differences in outcome from different treatment arms are small, or where treatments are considered likely to be equivalent (i.e. a non-inferiority trial), then very large patient numbers must be recruited and followed-up, again adding to the long duration required to reach a definitive outcome. The role of androgen deprivation in the setting of SABR should also be evaluated in randomised trials, although the same challenges will arise as mentioned above.

Motion and image-guidance is one area which should be investigated specifically in the context of SABR delivered using VMAT. The 6mm CTV-PTV margin which was used throughout this project as compatible with daily online imaging of fiducial markers was based on work by others, and is the same as the margin used in the IGRT sub-study within the CHHiP trial [192]. The evidence used to support this margin was, however, not necessarily derived in the setting of SABR, nor in the setting of the rapid delivery times achievable with VMAT or VMAT with FFF [186-188]. This margin was

conservative and would be adequate in the setting in which it was used, based on: i) evaluation of a 20 fraction regimen of prostate IMRT with intra-fraction motion monitoring, where it was demonstrated that a 6mm homogenous margin was required to limit the reduction in prostate D99% to 1% or less in all patients in the absence of intra-fraction motion monitoring [187], ii) portal imaging of fiducial markers before each beam in a 4-field box arrangement during a 39 to 41 fraction course of radiotherapy where, using a 0mm action threshold, margins of 4.3mm, 4.9mm and 4.8mm in the left-right, superior-inferior and anterior-posterior directions were found to be necessary to account for intra-fraction motion as well as set-up and interobserver variability [188] (these were based on the Van Herk margin 'recipe' which is designed to ensure that 90% of patients receive a dose to the CTV that is at least 95% of the prescribed dose [235], and so the slightly larger 6mm margins defined above allow improved coverage in a greater proportion of patients), and iii) evaluation of a five fraction IMRT SABR regimen with pre-treatment and post-treatment portal imaging of fiducials, where margins of 1.4mm, 4.4mm and 5.2mm in the left-right, superior-inferior and anterior-posterior directions were found to be adequate to account for intra-fraction motion [186] (again based on the Van Herk margin 'recipe' [235]). It should be remembered that margin calculations for SABR should also consider the errors resulting from delineation, residual set up uncertainty and the impact of a very small number of fractions [235].

With the rapid delivery times achievable with VMAT and VMAT with FFF, it is likely that prostate intra-fraction motion will become less of a problem, allowing CTV-PTV margin reduction. The Royal College of Radiologists 'On Target' publication recommends that each centre should determine what the appropriate margins are for that centre [357] and so, in the context of prostate SABR VMAT, margins need to be formally evaluated. While pre-treatment and post-treatment CBCT or portal images will give some indication of intra-fraction motion, once kilovoltage intra-fraction motion monitoring during VMAT becomes more widely available [173], then obtaining a more accurate picture of intra-fraction motion will become possible to more fully inform margin calculation. In addition, kilovoltage intra-fraction motion monitoring during VMAT may also eventually facilitate tracking during treatment delivery, again facilitating margin reduction.

Another exciting area in the field of radiotherapy is the advent of MRI-only planning in conjunction with the development of the MRI-linear accelerator [358,359]. Contouring on MRI provides enhanced soft tissue discrimination compared to contouring on planning CT and being able to contour and plan using the MRI alone, removes the uncertainty that is currently introduced from co-registration of MRI and planning CT images [358]. In addition, online image-guidance and intra-fraction motion monitoring, using MRI in the setting of an MRI-linear accelerator, would provide far enhanced soft tissue images compared to what is currently achievable using CBCT or portal images, and without the need for fiducial marker insertion [359]. This could facilitate further margin reduction and, in turn, allow safe dose escalation to the whole prostate [359]. There could also be potential to boost DILs to higher doses with fewer uncertainties than are currently associated with the process, particularly if functional MRI sequences such as DCE sequences could be used for planning and image-guidance. In this setting, the TCP benefit and NTCP detriment of boosting DILs would have to be re-assessed. The use of MRI for planning and image-guidance also removes the additional radiation that is currently received from planning CTs and CBCT or portal images thus, potentially, reducing radiation-induced second malignancy risk [358,359].

While the MRI-linear accelerator is not currently ready for clinical implementation, an MRI-cobalt-60 system is now in clinical use (ViewRay System, ViewRay Incorporated, USA) [360]. This system incorporates a ring gantry with three cobalt-60 sources, each with MLCs and a 0.35-Tesla MRI, allowing MRI-based treatment planning, simple to complex (i.e. IMRT) plan delivery and MRI imaging for online set-up and intra-fraction motion monitoring and tracking. The system can also perform on-couch dose calculations based on the patient's MRI images on each treatment day and, if necessary, a plan can be rapidly re-optimised (while the patient remains on the couch) to create an improved plan specific for the patient's anatomy on that day (i.e. adaptive radiotherapy) [360]. Such a system could well deliver safe and accurate prostate SABR with small CTV-PTV margins, although this requires specific clinical investigation.

Chapter 8 : References

[1] Cancer Research UK. *Prostate cancer- UK incidence statistics* [Internet]. 2014. [updated 2014 June 11; cited 2014 September 29]. Available from: http://info.cancerresearchuk.org/cancerstats/types/prostate/incidence

[2] Westlake S, Cooper N. Cancer incidence and mortality: trends in the United Kingdom and constituent countries, 1993 to 2004. *Health Stat Q* 2008;38:33-46.

[3] Potosky AL, Kessler L, Gridley G, Brown CC, Horm JW. Rise in prostatic cancer incidence associated with increased use of transurethral resection. *J Natl Cancer Inst* 1990;82:1624-1628.

[4] Potosky AL, Miller BA, Albertsen PC, Kramer BS. The role of increasing detection in the rising incidence of prostate cancer. *JAMA* 1995;273:548-552.

[5] Surveillance Epidemiology and End Results. *Statistics stratified by cancer site* [Internet]. 2011. [cited 2012 October 26]. Available from: http://seer.cancer.gov/fhanaststats/selections.php

[6] Moore AL, Dimitropoulou P, Lane A, et al. Population-based prostate-specific antigen testing in the UK leads to a stage migration of prostate cancer. *BJU Int* 2009;104:1592-1598.

[7] Hanks GE, Lee WR, Schultheiss TE. Clinical and biochemical evidence of control of prostate cancer at 5 years after external beam radiation. *J Urol* 1995;154:456-459.

[8] Zietman AL, Coen JJ, Dallow KC, Shipley WU. The treatment of prostate cancer by conventional radiation therapy: an analysis of long-term outcome. *Int J Radiat Oncol Biol Phys* 1995;32:287-292.

[9] Brundage M, Lukka H, Crook J, et al. The use of conformal radiotherapy and the selection of radiation dose in T1 or T2 low or intermediate risk prostate cancer - a systematic review. *Radiother Oncol* 2002;64:239-250.

[10] Koper PC, Stroom JC, van Putten WL, et al. Acute morbidity reduction using 3DCRT for prostate carcinoma: a randomized study. *Int J Radiat Oncol Biol Phys* 1999;43:727-734.

[11] Dearnaley DP, Khoo VS, Norman AR, et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. *Lancet* 1999;353:267-272.

[12] Pollack A, Zagars GK, Starkschall G, et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002;53:1097-1105.

[13] Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005;294:1233-1239.

[14] Peeters ST, Heemsbergen WD, Koper PC, et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol* 2006;24:1990-1996.

[15] Dearnaley DP, Sydes MR, Graham JD, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007;8:475-487.
[16] Pollack A, Zagars GK, Starkschall G, et al. Conventional vs. conformal radiotherapy for prostate cancer: preliminary results of dosimetry and acute toxicity. *Int J Radiat Oncol Biol Phys* 1996;34:555-564.
[17] Dearnaley DP, Hall E, Lawrence D, et al. Phase III pilot study of dose escalation using conformal radiotherapy in prostate cancer: PSA control and side effects. *Br J Cancer* 2005;92:488-498.
[18] Kuban D, Pollack A, Huang E, et al. Hazards of dose escalation in prostate cancer radiotherapy. *Int J Radiat Oncol Biol Phys* 2003;57:1260-1268.
[19] Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:67-74.
[20] Zelefsky MJ, Fuks Z, Hunt M, et al. High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. *Int J Radiat Oncol Biol Phys* 2002;53:1111-1116.
[21] Sharma NK, Li T, Chen DY, Pollack A, Horwitz EM, Buyyounouski MK. Intensity-modulated radiotherapy reduces gastrointestinal toxicity in patients treated with androgen deprivation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2011;80:437-444.
[22] Cahlon O, Zelefsky MJ, Shippy A, et al. Ultra-high dose (86.4 Gy) IMRT for localized prostate cancer: toxicity and biochemical outcomes. *Int J Radiat Oncol Biol Phys* 2008;71:330-337.
[23] Alicikus ZA, Yamada Y, Zhang Z, et al. Ten-year outcomes of high-dose, intensity-modulated radiotherapy for localized prostate cancer. *Cancer* 2011;117:1429-1437.
[24] Palma DA, Verbakel WF, Otto K, Senan S. New developments in arc radiation therapy: a review. *Cancer Treat Rev* 2010;36:393-399.
[25] Wolff D, Stieler F, Welzel G, et al. Volumetric modulated arc therapy (VMAT) vs. serial tomotherapy, step-and-shoot IMRT and 3D-conformal RT for treatment of prostate cancer. *Radiother Oncol* 2009;93:226-233.
[26] Palma D, Vollans E, James K, et al. Volumetric modulated arc therapy for delivery of prostate radiotherapy: comparison with intensity-modulated radiotherapy and three-dimensional conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;72:996-1001.
[27] Zhang P, Happersett L, Hunt M, Jackson A, Zelefsky M, Mageras G. Volumetric modulated arc therapy: planning and evaluation for prostate cancer cases. *Int J Radiat Oncol Biol Phys* 2010;76:1456-1462.
[28] Davidson MT, Blake SJ, Batchelar DL, Cheung P, Mah K. Assessing the role of volumetric modulated arc therapy (VMAT) relative to IMRT and helical tomotherapy in the management of localized, locally advanced, and post-operative prostate cancer. *Int J Radiat Oncol Biol Phys* 2011;80:1550-1558.
[29] Ost P, Speleers B, De Meerleer G, et al. Volumetric arc therapy and intensity-modulated radiotherapy for primary prostate radiotherapy with simultaneous integrated boost to intraprostatic lesion with 6 and 18 MV: a planning comparison study. *Int J Radiat Oncol Biol Phys* 2011;79:920-926.

[30] Tsai CL, Wu JK, Chao HL, Tsai YC, Cheng JC. Treatment and dosimetric advantages between VMAT, IMRT, and helical tomotherapy in prostate cancer. *Med Dosim* 2011;36:264-271.
[31] Hardcastle N, Tome WA, Foo K, Miller A, Carolan M, Metcalfe P. Comparison of prostate IMRT and VMAT biologically optimised treatment plans. *Med Dosim* 2011;36:292-298.
[32] Ma L, Yu CX, Earl M, et al. Optimized intensity-modulated arc therapy for prostate cancer treatment. *Int J Cancer* 2001;96:379-384.
[33] Rao M, Yang W, Chen F, et al. Comparison of Elekta VMAT with helical tomotherapy and fixed field IMRT: plan quality, delivery efficiency and accuracy. *Med Phys* 2010;37:1350-1359.
[34] Brenner DJ, Martinez AA, Edmundson GK, Mitchell C, Thames HD, Armour EP. Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue. *Int J Radiat Oncol Biol Phys* 2002;52:6-13.
[35] Fowler JF. The radiobiology of prostate cancer including new aspects of fractionated radiotherapy. *Acta Oncol* 2005;44:265-276.
[36] Dasu A. Is the alpha/beta value for prostate tumours low enough to be safely used in clinical trials? *Clin Oncol (R Coll Radiol)* 2007;19:289-301.
[37] Miralbell R, Roberts SA, Zubizarreta E, Hendry JH. Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: alpha/beta = 1.4 (0.9-2.2) Gy. *Int J Radiat Oncol Biol Phys* 2012;82:e17-24.
[38] Fowler JF, Ritter MA, Chappell RJ, Brenner DJ. What hypofractionated protocols should be tested for prostate cancer? *Int J Radiat Oncol Biol Phys* 2003;56:1093-1104.
[39] Marks LB, Carroll PR, Dugan TC, Anscher MS. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. *Int J Radiat Oncol Biol Phys* 1995;31:1257-1280.
[40] Viswanathan AN, Yorke ED, Marks LB, Eifel PJ, Shipley WU. Radiation dose-volume effects of the urinary bladder. *Int J Radiat Oncol Biol Phys* 2010;76:S116-122.
[41] Brenner DJ. Fractionation and late rectal toxicity. *Int J Radiat Oncol Biol Phys* 2004;60:1013-1015.
[42] Dale RG, Hendry JH, Jones B, Robertson AG, Deehan C, Sinclair JA. Practical methods for compensating for missed treatment days in radiotherapy, with particular reference to head and neck schedules. *Clin Oncol (R Coll Radiol)* 2002;14:382-393.
[43] Liao Y, Joiner M, Huang Y, Burmeister J. Hypofractionation: what does it mean for prostate cancer treatment? *Int J Radiat Oncol Biol Phys* 2010;76:260-268.
[44] Livsey JE, Cowan RA, Wylie JP, et al. Hypofractionated conformal radiotherapy in carcinoma of the prostate: five-year outcome analysis. *Int J Radiat Oncol Biol Phys* 2003;57:1254-1259.
[45] Lukka H, Hayter C, Julian JA, et al. Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. *J Clin Oncol* 2005;23:6132-6138.
[46] Yeoh EE, Holloway RH, Fraser RJ, et al. Hypofractionated versus conventionally fractionated radiation therapy for prostate carcinoma: updated

results of a phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2006;66:1072-1083.
[47] Kupelian PA, Willoughby TR, Reddy CA, Klein EA, Mahadevan A. Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: Cleveland Clinic experience. *Int J Radiat Oncol Biol Phys* 2007;68:1424-1430.
[48] Arcangeli S, Strigari L, Soete G, et al. Clinical and dosimetric predictors of acute toxicity after a 4-week hypofractionated external beam radiotherapy regimen for prostate cancer: results from a multicentric prospective trial. *Int J Radiat Oncol Biol Phys* 2009;73:39-45.
[49] Leborgne F, Fowler J. Late outcomes following hypofractionated conformal radiotherapy vs. standard fractionation for localized prostate cancer: a nonrandomized contemporary comparison. *Int J Radiat Oncol Biol Phys* 2009;74:1441-1446.
[50] Zilli T, Jorcano S, Rouzaud M, et al. Twice-weekly hypofractionated intensity-modulated radiotherapy for localized prostate cancer with low-risk nodal involvement: toxicity and outcome from a dose escalation pilot study. *Int J Radiat Oncol Biol Phys* 2011;81:382-389.
[51] Khoo VS, Dearnaley DP. Question of dose, fractionation and technique: ingredients for testing hypofractionation in prostate cancer--the CHHiP trial. *Clin Oncol (R Coll Radiol)* 2008;20:12-14.
[52] Dearnaley D, Syndikus I, Sumo G, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. *Lancet Oncol* 2012;13:43-54.
[53] Martin A, Gaya A. Stereotactic body radiotherapy: a review. *Clin Oncol (R Coll Radiol)* 2010;22:157-172.
[54] National Cancer Action Team. *National Radiotherapy Implementation Group Report. Stereotactic Body Radiotherapy Clinical Review of the Evidence for SBRT* [Internet]. 2010. [updated 2010 December; cited 2012 August 16]. Available from: http://www.ncat.nhs.uk/sites/default/files/clinical%20evidence%20review%20Dec%2010%20-%20Final%20J11.pdf
[55] ICRU. *Report 50. Prescribing, recording and repoting photon beam therapy*. Bethesda, 1993.
[56] Sahgal A, Roberge D, Schellenberg D, et al. The Canadian Association of Radiation Oncology scope of practice guidelines for lung, liver and spine stereotactic body radiotherapy. *Clin Oncol (R Coll Radiol)* 2012;24:629-639.
[57] Fuller DB, Naitoh J, Lee C, Hardy S, Jin H. Virtual HDR CyberKnife treatment for localized prostatic carcinoma: dosimetry comparison with HDR brachytherapy and preliminary clinical observations. *Int J Radiat Oncol Biol Phys* 2008;70:1588-1597.
[58] Mantz CA, Fernandez E, Zucker I, Harison S. A Phase II Trial of Real-time Target Tracking SBRT for Low-Risk Prostate Cancer Utilizing the Calypso 4D Localization System: Patient Reported Health-related Quality of Life and Toxicity Outcomes [abstract]. *Int J Radiat Oncol Biol Phys* 2010;87:S57.
[59] Bolzicco G, Favretto MS, Satariano N, Scremin E, Tambone C, Tasca A. A single-center study of 100 consecutive patients with localized prostate cancer treated with stereotactic body radiotherapy. *BMC Urol* [Internet]. 2013 [cited

2014 July 18]; 13:49. Available from: http://www.biomedcentral.com/content/pdf/1471-2490-13-49.pdf.
[60] Aluwini S, van Rooij P, Hoogeman M, Kirkels W, Kolkman-Deurloo IK, Bangma C. Stereotactic body radiotherapy with a focal boost to the MRI-visible tumor as monotherapy for low- and intermediate-risk prostate cancer: early results. *Radiat Oncol* [Internet]. 2013 [cited 2014 July 18]; 8:84. Available from: http://www.ro-journal.com/content/pdf/1748-717X-8-84.pdf.
[61] King CR, Brooks JD, Gill H, Presti JC, Jr. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;82:877-882.
[62] Hossain S, Xia P, Chuang C, et al. Simulated real time image guided intrafraction tracking-delivery for hypofractionated prostate IMRT. *Med Phys* 2008;35:4041-4048.
[63] Macdougall ND, Dean C, Muirhead R. Stereotactic body radiotherapy in prostate cancer: is rapidarc a better solution than cyberknife? *Clin Oncol (R Coll Radiol)* 2014;26:4-9.
[64] Collins CD, Lloyd-Davies RW, Swan AV. Radical external beam radiotherapy for localised carcinoma of the prostate using a hypofractionation technique. *Clin Oncol (R Coll Radiol)* 1991;3:127-132.
[65] Corner C, Rojas AM, Bryant L, Ostler P, Hoskin P. A Phase II study of high-dose-rate afterloading brachytherapy as monotherapy for the treatment of localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;72:441-446.
[66] Yoshioka Y, Konishi K, Sumida I, et al. Monotherapeutic high-dose-rate brachytherapy for prostate cancer: five-year results of an extreme hypofractionation regimen with 54 Gy in nine fractions. *Int J Radiat Oncol Biol Phys* 2011;80:469-475.
[67] Demanes DJ, Martinez AA, Ghilezan M, et al. High-dose-rate monotherapy: safe and effective brachytherapy for patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2011;81:1286-1292.
[68] Friedland JL, Freeman DE, Masterson-McGary ME, Spellberg DM. Stereotactic body radiotherapy: an emerging treatment approach for localized prostate cancer. *Technol Cancer Res Treat* 2009;8:387-392.
[69] Meier R, Beckman A, Kaplan I, et al. Stereotactic radiotherapy for organ-confined prostate cancer: early toxicity and quality of life outcomes from a multi-institutional trial [abstract]. *Int J Radiat Oncol Biol Phys* 2010;78:S57.
[70] Kang JK, Cho CK, Choi CW, et al. Image-guided stereotactic body radiation therapy for localized prostate cancer. *Tumori* 2011;97:43-48.
[71] Townsend NC, Huth BJ, Ding W, et al. Acute toxicity after cyberknife-delivered hypofractionated radiotherapy for treatment of prostate cancer. *Am J Clin Oncol* 2011;34:6-10.
[72] Jabbari S, Weinberg VK, Kaprealian T, et al. Stereotactic body radiotherapy as monotherapy or post-external beam radiotherapy boost for prostate cancer: technique, early toxicity, and PSA response. *Int J Radiat Oncol Biol Phys* 2012;82:228-234.
[73] McBride SM, Wong DS, Dombrowski JJ, et al. Hypofractionated stereotactic body radiotherapy in low-risk prostate adenocarcinoma: preliminary results of a multi-institutional phase 1 feasibility trial. *Cancer* 2012;118:3681-3690.

[74] Lee YH, Son SH, Yoon SC, et al. Stereotactic body radiotherapy for prostate cancer: a preliminary report. *Asia Pac J Clin Oncol* 2012;10:e46-53.
[75] Katz AJ, Santoro M, Diblasio F, Ashley R. Stereotactic body radiotherapy for localized prostate cancer: disease control and quality of life at 6 years. *Radiat Oncol* [Internet]. 2013 May 13 [cited 2014 July 18]; 8(1):118. Available from: http://www.ro-journal.com/content/pdf/1748-717X-8-118.pdf.
[76] Chen LN, Suy S, Uhm S, et al. Stereotactic body radiation therapy (SBRT) for clinically localized prostate cancer: the Georgetown University experience. *Radiat Oncol* [Internet]. 2013 [cited 2013 May 24]; 8:58. Available from: http://www.ro-journal.com/content/pdf/1748-717X-8-58.pdf.
[77] Tree A, Ostler P, Hoskin P, Dankulchai P, Khoo V, Van As N. First UK cohort of prostate stereotactic body radiotherapy (SBRT): acute toxicity and early PSA outcomes [abstract]. *Clin Oncol (R Coll Radiol)* 2014;26:e7.
[78] Oliai C, Lanciano R, Sprandio B, et al. Stereotactic body radiation therapy for the primary treatment of localized prostate cancer. *J Radiat Oncol* 2013;2:63-70.
[79] Mantz CA, Fernandez E, Harrison S, Zucker I. A phase II trial of Triology-based prostate SBRT: initial report of favourable acute toxicity outcomes [abstract]. *Int J Radiat Oncol Biol Phys* 2007;69:S334.
[80] Pham HT, Song G, Badiozamani K, Corman J, His RA, Madsen B. Five year outcomes of stereotactic accurate radiotherapy of the prostate (SHARP) for patients with low-risk prostate cancer [abstract]. *Int J Radiat Oncol Biol Phys* 2010;78:S58.
[81] Quon HC, Cheung W, Chu D, et al. Phase I/II Study of Extreme Hypofractionation for Localized Prostate Cancer: Acute Toxicity and Quality of Life [abstract]. *Radiother Oncol* 2011;100:S48.
[82] Loblaw A, Cheung P, D'Alimonte L, et al. Prostate stereotactic ablative body radiotherapy using a standard linear accelerator: toxicity, biochemical, and pathological outcomes. *Radiother Oncol* 2013;107:153-158.
[83] Boike TP, Lotan Y, Cho LC, et al. Phase I dose-escalation study of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer. *J Clin Oncol* 2011;29:2020-2026.
[84] Alongi F, Cozzi L, Arcangeli S, et al. Linac based SBRT for prostate cancer in 5 fractions with VMAT and flattening filter free beams: preliminary report of a phase II study. *Radiat Oncol* [Internet]. 2013 Jul 8 [cited 2014 June 9]; 8(1):171. Available from: http://www.ro-journal.com/content/pdf/1748-717X-8-171.pdf.
[85] Macias VA, Blanco ML, Perez-Romasanta LA. Initial experience with stereotactic body radiation therapy for localized prostate cancer using helical tomotherapy. *Clin Transl Oncol* 2014;16:380-385.
[86] Katz AJ, Santoro M, Ashley R, Diblasio F, Witten M. Stereotactic body radiotherapy as boost for organ-confined prostate cancer. *Technol Cancer Res Treat* 2010;9:575-582.
[87] Miralbell R, Molla M, Rouzaud M, et al. Hypofractionated boost to the dominant tumor region with intensity modulated stereotactic radiotherapy for prostate cancer: a sequential dose escalation pilot study. *Int J Radiat Oncol Biol Phys* 2010;78:50-57.
[88] Oermann EK, Slack RS, Hanscom HN, et al. A pilot study of intensity modulated radiation therapy with hypofractionated stereotactic body radiation

therapy (SBRT) boost in the treatment of intermediate- to high-risk prostate cancer. *Technol Cancer Res Treat* 2010;9:453-462.
[89] Ju AW, Wang H, Oermann EK, et al. Hypofractionated stereotactic body radiation therapy as monotherapy for intermediate-risk prostate cancer. *Radiat Oncol* [Internet]. 2013 [cited 2014 May 24]; 8:30. Available from: http://www.ro-journal.com/content/pdf/1748-717X-8-30.pdf.
[90] Katz A, Kang J. Stereotactic Body Radiotherapy as Treatment for Organ Confined Low and Intermediate Risk Prostate Carcinoma, a Seven Year Study. *Front Oncol* [Internet]. 2014 [cited 2014 July 30]; 4:240. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4150980/pdf/fonc-04-00240.pdf.
[91] King CR, Freeman D, Kaplan I, et al. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiother Oncol* 2013;109:217-221.
[92] Davis BJ, Horwitz EM, Lee WR, et al. American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy. *Brachytherapy* 2012;11:6-19.
[93] Yamada Y, Rogers L, Demanes DJ, et al. American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy. *Brachytherapy* 2012;11:20-32.
[94] Radiation Therapy Oncology Group. *RTOG 0815 Trial Protocol: A phase III prospective randomized trial of dose-escalated radiotherapy with or without short-term androgen deprviation therapy for patients with intermediate-risk protate cancer. Version May 2012* [Internet]. 2012. [updated 2014 June 2; cited 2014 September 29]. Available from: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0815
[95] Madsen BL, Hsi RA, Pham HT, Fowler JF, Esagui L, Corman J. Stereotactic hypofractionated accurate radiotherapy of the prostate (SHARP), 33.5 Gy in five fractions for localized disease: first clinical trial results. *Int J Radiat Oncol Biol Phys* 2007;67:1099-1105.
[96] Grimm J, LaCouture T, Croce R, Yeo I, Zhu Y, Xue J. Dose tolerance limits and dose volume histogram evaluation for stereotactic body radiotherapy. *J Appl Clin Med Phys* [Internet]. 2011 [cited 2014 July 18]; 12(2):3368. Available from: http://www.jacmp.org/index.php/jacmp/article/viewFile/3368/2170.
[97] Al-Mamgani A, van Putten WL, Heemsbergen WD, et al. Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;72:980-988.
[98] Kupelian PA, Potters L, Khuntia D, et al. Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy > or =72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;58:25-33.
[99] Potters L, Klein EA, Kattan MW, et al. Monotherapy for stage T1-T2 prostate cancer: radical prostatectomy, external beam radiotherapy, or permanent seed implantation. *Radiother Oncol* 2004;71:29-33.
[100] Martinez AA, Gonzalez JA, Chung AK, et al. A comparison of external beam radiation therapy versus radical prostatectomy for patients with low risk prostate carcinoma diagnosed, staged, and treated at a single institution. *Cancer* 2000;88:425-432.
[101] Aizer AA, Yu JB, Colberg JW, McKeon AM, Decker RH, Peschel RE. Radical prostatectomy vs. intensity-modulated radiation therapy in the

management of localized prostate adenocarcinoma. *Radiother Oncol* 2009;93:185-191.
[102] Grimm PD, Blasko JC, Sylvester JE, Meier RM, Cavanagh W. 10-year biochemical (prostate-specific antigen) control of prostate cancer with (125)I brachytherapy. *Int J Radiat Oncol Biol Phys* 2001;51:31-40.
[103] Zelefsky MJ, Hollister T, Raben A, Matthews S, Wallner KE. Five-year biochemical outcome and toxicity with transperineal CT-planned permanent I-125 prostate implantation for patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2000;47:1261-1266.
[104] Hoskin PJ, Rojas AM, Bownes PJ, Lowe GJ, Ostler PJ, Bryant L. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother Oncol* 2012;103:217-222.
[105] Galalae RM, Martinez A, Mate T, et al. Long-term outcome by risk factors using conformal high-dose-rate brachytherapy (HDR-BT) boost with or without neoadjuvant androgen suppression for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;58:1048-1055.
[106] Tselis N, Tunn UW, Chatzikonstantinou G, et al. High dose rate brachytherapy as monotherapy for localised prostate cancer: a hypofractionated two-implant approach in 351 consecutive patients. *Radiat Oncol* [Internet]. 2013 [cited 2014 August 5]; 8:115. Available from: http://www.ro-journal.com/content/pdf/1748-717X-8-115.pdf.
[107] Meier R, Kaplan I, Beckham A, et al. Stereotactic Body Radiation Therapy for Intermediate-risk Organ-confined Prostate Cancer: Interim Toxicity and Quality of Life Outcomes From a Mulit-institutional Study [abstract]. *Int J Radiat Oncol Biol Phys* 2012;84:S147.
[108] Katz AJ, Santoro M, Ashley R, Diblasio F. Stereotactic Body Radiation Therapy for Low- and Low-Intermediate-Risk Prostate Cancer: Is there a Dose Effect? *Front Oncol* [Internet]. 2011 [cited 2014 July 18]; 1:49. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3356012/pdf/fonc-01-00049.pdf.
[109] Vu CC, Haas JA, Katz AE, Witten MR. Prostate-specific antigen bounce following stereotactic body radiation therapy for prostate cancer. *Front Oncol* [Internet]. 2014 [cited 2014 July 30]; 4:8. Available from: http://journal.frontiersin.org/Journal/10.3389/fonc.2014.00008/full.
[110] Caloglu M, Ciezki J. Prostate-specific antigen bounce after prostate brachytherapy: review of a confusing phenomenon. *Urology* 2009;74:1183-1190.
[111] Pinkawa M, Fischedick K, Asadpour B, et al. Toxicity profile with a large prostate volume after external beam radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:83-89.
[112] Peeters ST, Hoogeman MS, Heemsbergen WD, et al. Volume and hormonal effects for acute side effects of rectum and bladder during conformal radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2005;63:1142-1152.
[113] Peeters ST, Heemsbergen WD, van Putten WL, et al. Acute and late complications after radiotherapy for prostate cancer: results of a multicenter randomized trial comparing 68 Gy to 78 Gy. *Int J Radiat Oncol Biol Phys* 2005;61:1019-1034.

[114] Tanaka N, Asakawa I, Anai S, et al. Periodical assessment of genitourinary and gastrointestinal toxicity in patients who underwent prostate low-dose-rate brachytherapy. *Radiat Oncol* [Internet]. 2013 [cited 2014 July 18]; 8:25. Available from: http://www.ro-journal.com/content/pdf/1748-717X-8-25.pdf.
[115] Viani GA, Pellizzon AC, Guimaraes FS, Jacinto AA, dos Santos Novaes PE, Salvajoli JV. High dose rate and external beam radiotherapy in locally advanced prostate cancer. *Am J Clin Oncol* 2009;32:187-190.
[116] Arscott WT, Chen LN, Wilson N, et al. Obstructive voiding symptoms following stereotactic body radiation therapy for prostate cancer. *Radiat Oncol* [Internet]. 2014 Jul 24 [cited 2014 July 29]; 9(1):163. Available from: http://www.ro-journal.com/content/pdf/1748-717X-9-163.pdf.
[117] Kim DW, Cho LC, Straka C, et al. Predictors of rectal tolerance observed in a dose-escalated phase 1-2 trial of stereotactic body radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2014;89:509-517.
[118] Freeman DE, King CR. Stereotactic body radiotherapy for low-risk prostate cancer: five-year outcomes. *Radiat Oncol* [Internet]. 2011 [cited 2013 February 3]; 6:3. Available from: http://www.ro-journal.com/content/pdf/1748-717X-6-3.pdf.
[119] Yu JB, Cramer LD, Herrin J, Soulos PR, Potosky AL, Gross CP. Stereotactic body radiation therapy versus intensity-modulated radiation therapy for prostate cancer: comparison of toxicity. *J Clin Oncol* 2014;32:1195-1201.
[120] D'Amico AV. Stereotactic body radiation therapy versus intensity-modulated radiation therapy for prostate cancer: less cost at the expense of more genitourinary toxicity is a concerning but testable hypothesis. *J Clin Oncol* 2014;32:1183-1185.
[121] King CR, Collins S, Fuller D, et al. Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: results from a multi-institutional consortium of prospective trials. *Int J Radiat Oncol Biol Phys* 2013;87:939-945.
[122] Chen LN, Suy S, Wang H, et al. Patient-reported urinary incontinence following stereotactic body radiation therapy (SBRT) for clinically localized prostate cancer. *Radiat Oncol* [Internet]. 2014 [cited 2014 July 18]; 9:148. Available from: http://www.ro-journal.com/content/pdf/1748-717X-9-148.pdf.
[123] Bhattasali O, Chen LN, Woo J, et al. Patient-reported outcomes following stereotactic body radiation therapy for clinically localized prostate cancer. *Radiat Oncol* [Internet]. 2014 [cited 2014 July 18]; 9:52. Available from: http://www.ro-journal.com/content/pdf/1748-717X-9-52.pdf.
[124] Woo JA, Chen LN, Bhagat A, et al. Clinical characteristics and management of late urinary symptom flare following stereotactic body radiation therapy for prostate cancer. *Front Oncol* [Internet]. 2014 [cited 2014 July 18]; 4:122. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4033266/pdf/fonc-04-00122.pdf.
[125] Dash C, Demas K, Uhm S, et al. Low incidence of fatigue after hypofractionated stereotactic body radiation therapy for localized prostate cancer. *Front Oncol* [Internet]. 2012 [cited 2014 July 18]; 2:142. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3473362/pdf/fonc-02-00142.pdf.
[126] Wiegner EA, King CR. Sexual function after stereotactic body radiotherapy for prostate cancer: results of a prospective clinical trial. *Int J Radiat Oncol Biol Phys* 2010;78:442-448.

[127] Obayomi-Davies O, Chen LN, Bhagat A, et al. Potency preservation following stereotactic body radiation therapy for prostate cancer. *Radiat Oncol* [Internet]. 2013 [cited 2014 July 24]; 8:256. Available from: http://www.ro-journal.com/content/pdf/1748-717X-8-256.pdf.
[128] Quon HC, Loblaw DA, Cheung P, et al. Dose Escalation of 5-Fraction Radiation Therapy for Prostate Cancer: Quality of Life Comparison of 2 Prospective Trials [abstract]. *Int J Radiat Oncol Biol Phys* 2012;84:S148.
[129] Katz A, Ferrer M, Suarez JF. Comparison of quality of life after stereotactic body radiotherapy and surgery for early-stage prostate cancer. *Radiat Oncol* [Internet]. 2012 [cited 2014 July 18]; 7:194. Available from: http://www.ro-journal.com/content/pdf/1748-717X-7-194.pdf.
[130] Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* 2008;358:1250-1261.
[131] Hodges JC, Lotan Y, Boike TP, Benton R, Barrier A, Timmerman RD. Cost-effectiveness analysis of stereotactic body radiation therapy versus intensity-modulated radiation therapy: an emerging initial radiation treatment option for organ-confined prostate cancer. *J Oncol Pract* 2012;8:e31s-37s.
[132] Sher DJ, Parikh R, Mays-Jackson S, Punglia RS. Cost-effectiveness Analysis of SBRT Versus IMRT for Low-risk Prostate Cancer. *Am J Clin Oncol* 2012;37:215-221.
[133] Franzen L, Widmark A. *HYPO-RT-PC trial protocol. Phase III study of hypofractionated radiotherapy of intermediate risk localised prostate cancer. Version 6.0. ISRCTN45905321* [Internet]. 2011. [cited 2011 November 10]. Available from: http://www.controlled-trials.com/ISRCTN45905321
[134] van As N. *The PACE Study: International Randomized Study of Laparoscopic Prostatectomy vs Robotic Radiosurgery and Conventionally Fractionated Radiotherapy vs Radiosurgery for Early Stage Organ-Confined Prostate Cancer. Protocol version 1 (November 2011)* [Internet]. 2011. [cited 2012 June 7]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01584258
[135] van As N. *The PACE Trial (Prostate Advances in Comparative Evidence): International randomized study of laparoscopic prostatectomy vs stereotactic body radiotherapy (SBRT) and conventionally fractionated radiotherapy vs SBRT for early stage organ-confined prostate cancer. Protocol version 5 (August 2014)* [Internet]. 2014. [cited 2014 September 3]. Available from: http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=12628
[136] Lai PP, Pilepich MV, Krall JM, et al. The effect of overall treatment time on the outcome of definitive radiotherapy for localized prostate carcinoma: the Radiation Therapy Oncology Group 75-06 and 77-06 experience. *Int J Radiat Oncol Biol Phys* 1991;21:925-933.
[137] Thames HD, Kuban D, Levy LB, et al. The role of overall treatment time in the outcome of radiotherapy of prostate cancer: an analysis of biochemical failure in 4839 men treated between 1987 and 1995. *Radiother Oncol* 2010;96:6-12.
[138] Zelefsky MJ, Crean D, Mageras GS, et al. Quantification and predictors of prostate position variability in 50 patients evaluated with multiple CT scans during conformal radiotherapy. *Radiother Oncol* 1999;50:225-234.

[139] Miralbell R, Ozsoy O, Pugliesi A, et al. Dosimetric implications of changes in patient repositioning and organ motion in conformal radiotherapy for prostate cancer. *Radiother Oncol* 2003;66:197-202.
[140] Frank SJ, Dong L, Kudchadker RJ, et al. Quantification of prostate and seminal vesicle interfraction variation during IMRT. *Int J Radiat Oncol Biol Phys* 2008;71:813-820.
[141] Kupelian PA, Langen KM, Willoughby TR, Zeidan OA, Meeks SL. Image-guided radiotherapy for localized prostate cancer: treating a moving target. *Semin Radiat Oncol* 2008;18:58-66.
[142] Wong JR, Gao Z, Uematsu M, et al. Interfractional prostate shifts: review of 1870 computed tomography (CT) scans obtained during image-guided radiotherapy using CT-on-rails for the treatment of prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;72:1396-1401.
[143] Mutanga TF, de Boer HC, van der Wielen GJ, Hoogeman MS, Incrocci L, Heijmen BJ. Margin evaluation in the presence of deformation, rotation, and translation in prostate and entire seminal vesicle irradiation with daily marker-based setup corrections. *Int J Radiat Oncol Biol Phys* 2011;81:1160-1167.
[144] Xie Y, Djajaputra D, King CR, Hossain S, Ma L, Xing L. Intrafractional motion of the prostate during hypofractionated radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;72:236-246.
[145] Lebesque JV, Bruce AM, Kroes AP, Touw A, Shouman RT, van Herk M. Variation in volumes, dose-volume histograms, and estimated normal tissue complication probabilities of rectum and bladder during conformal radiotherapy of T3 prostate cancer. *Int J Radiat Oncol Biol Phys* 1995;33:1109-1119.
[146] Melian E, Mageras GS, Fuks Z, et al. Variation in prostate position quantitation and implications for three-dimensional conformal treatment planning. *Int J Radiat Oncol Biol Phys* 1997;38:73-81.
[147] Kupelian PA, Langen KM, Zeidan OA, et al. Daily variations in delivered doses in patients treated with radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2006;66:876-882.
[148] Pinkawa M, Asadpour B, Gagel B, Piroth MD, Holy R, Eble MJ. Prostate position variability and dose-volume histograms in radiotherapy for prostate cancer with full and empty bladder. *Int J Radiat Oncol Biol Phys* 2006;64:856-861.
[149] Chen L, Paskalev K, Xu X, et al. Rectal dose variation during the course of image-guided radiation therapy of prostate cancer. *Radiother Oncol* 2010;95:198-202.
[150] Engels B, Soete G, Verellen D, Storme G. Conformal arc radiotherapy for prostate cancer: increased biochemical failure in patients with distended rectum on the planning computed tomogram despite image guidance by implanted markers. *Int J Radiat Oncol Biol Phys* 2009;74:388-391.
[151] de Crevoisier R, Tucker SL, Dong L, et al. Increased risk of biochemical and local failure in patients with distended rectum on the planning CT for prostate cancer radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;62:965-973.
[152] Heemsbergen WD, Hoogeman MS, Witte MG, Peeters ST, Incrocci L, Lebesque JV. Increased risk of biochemical and clinical failure for prostate patients with a large rectum at radiotherapy planning: results from the Dutch trial of 68 GY versus 78 Gy. *Int J Radiat Oncol Biol Phys* 2007;67:1418-1424.

[153] Schallenkamp JM, Herman MG, Kruse JJ, Pisansky TM. Prostate position relative to pelvic bony anatomy based on intraprostatic gold markers and electronic portal imaging. *Int J Radiat Oncol Biol Phys* 2005;63:800-811.
[154] Dehnad H, Nederveen AJ, van der Heide UA, van Moorselaar RJ, Hofman P, Lagendijk JJ. Clinical feasibility study for the use of implanted gold seeds in the prostate as reliable positioning markers during megavoltage irradiation. *Radiother Oncol* 2003;67:295-302.
[155] Shirato H, Harada T, Harabayashi T, et al. Feasibility of insertion/implantation of 2.0-mm-diameter gold internal fiducial markers for precise setup and real-time tumor tracking in radiotherapy. *Int J Radiat Oncol Biol Phys* 2003;56:240-247.
[156] van der Heide UA, Kotte AN, Dehnad H, Hofman P, Lagenijk JJ, van Vulpen M. Analysis of fiducial marker-based position verification in the external beam radiotherapy of patients with prostate cancer. *Radiother Oncol* 2007;82:38-45.
[157] Haverkort MA, van de Kamer JB, Pieters BR, et al. Position verification for the prostate: effect on rectal wall dose. *Int J Radiat Oncol Biol Phys* 2011;80:462-468.
[158] Henry AM, Wilkinson C, Wylie JP, Logue JP, Price P, Khoo VS. Trans-perineal implantation of radio-opaque treatment verification markers into the prostate: an assessment of procedure related morbidity, patient acceptability and accuracy. *Radiother Oncol* 2004;73:57-59.
[159] Moman MR, van der Heide UA, Kotte AN, et al. Long-term experience with transrectal and transperineal implantations of fiducial gold markers in the prostate for position verification in external beam radiotherapy; feasibility, toxicity and quality of life. *Radiother Oncol* 2010;96:38-42.
[160] Poggi MM, Gant DA, Sewchand W, Warlick WB. Marker seed migration in prostate localization. *Int J Radiat Oncol Biol Phys* 2003;56:1248-1251.
[161] Smitsmans MH, de Bois J, Sonke JJ, et al. Residual seminal vesicle displacement in marker-based image-guided radiotherapy for prostate cancer and the impact on margin design. *Int J Radiat Oncol Biol Phys* 2011;80:590-596.
[162] Nichol AM, Brock KK, Lockwood GA, et al. A magnetic resonance imaging study of prostate deformation relative to implanted gold fiducial markers. *Int J Radiat Oncol Biol Phys* 2007;67:48-56.
[163] Willoughby TR, Kupelian PA, Pouliot J, et al. Target localization and real-time tracking using the Calypso 4D localization system in patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2006;65:528-534.
[164] Curtis W, Khan M, Magnelli A, Stephans K, Tendulkar R, Xia P. Relationship of imaging frequency and planning margin to account for intrafraction prostate motion: analysis based on real-time monitoring data. *Int J Radiat Oncol Biol Phys* 2013;85:700-706.
[165] Zeng GG, McGowan TS, Larsen TM, et al. Calcifications are potential surrogates for prostate localization in image-guided radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;72:963-966.
[166] Nijkamp J, Pos FJ, Nuver TT, et al. Adaptive radiotherapy for prostate cancer using kilovoltage cone-beam computed tomography: first clinical results. *Int J Radiat Oncol Biol Phys* 2008;70:75-82.

[167] Ost P, De Gersem W, De Potter B, Fonteyne V, De Neve W, De Meerleer G. A comparison of the acute toxicity profile between two-dimensional and three-dimensional image-guided radiotherapy for postoperative prostate cancer. *Clin Oncol (R Coll Radiol)* 2011;23:344-349.
[168] Langen KM, Zhang Y, Andrews RD, et al. Initial experience with megavoltage (MV) CT guidance for daily prostate alignments. *Int J Radiat Oncol Biol Phys* 2005;62:1517-1524.
[169] White EA, Brock KK, Jaffray DA, Catton CN. Inter-observer variability of prostate delineation on cone beam computerised tomography images. *Clin Oncol (R Coll Radiol)* 2009;21:32-38.
[170] Weiss E, Wu J, Sleeman W, et al. Clinical evaluation of soft tissue organ boundary visualization on cone-beam computed tomographic imaging. *Int J Radiat Oncol Biol Phys* 2010;78:929-936.
[171] Moseley DJ, White EA, Wiltshire KL, et al. Comparison of localization performance with implanted fiducial markers and cone-beam computed tomography for on-line image-guided radiotherapy of the prostate. *Int J Radiat Oncol Biol Phys* 2007;67:942-953.
[172] Barney BM, Lee RJ, Handrahan D, Welsh KT, Cook JT, Sause WT. Image-guided radiotherapy (IGRT) for prostate cancer comparing kV imaging of fiducial markers with cone beam computed tomography (CBCT). *Int J Radiat Oncol Biol Phys* 2011;80:301-305.
[173] Ng JA, Booth JT, Poulsen PR, et al. Kilovoltage intrafraction monitoring for prostate intensity modulated arc therapy: first clinical results. *Int J Radiat Oncol Biol Phys* 2012;84:e655-661.
[174] Teh BS, McGary JE, Dong L, et al. The use of rectal balloon during the delivery of intensity modulated radiotherapy (IMRT) for prostate cancer: more than just a prostate gland immobilization device? *Cancer J* 2002;8:476-483.
[175] Teh BS, Dong L, McGary JE, Mai WY, Grant W, 3rd, Butler EB. Rectal wall sparing by dosimetric effect of rectal balloon used during intensity-modulated radiation therapy (IMRT) for prostate cancer. *Med Dosim* 2005;30:25-30.
[176] Patel RR, Orton N, Tome WA, Chappell R, Ritter MA. Rectal dose sparing with a balloon catheter and ultrasound localization in conformal radiation therapy for prostate cancer. *Radiother Oncol* 2003;67:285-294.
[177] van Lin EN, Kristinsson J, Philippens ME, et al. Reduced late rectal mucosal changes after prostate three-dimensional conformal radiotherapy with endorectal balloon as observed in repeated endoscopy. *Int J Radiat Oncol Biol Phys* 2007;67:799-811.
[178] Jones BL, Gan G, Diot Q, Kavanagh B, Timmerman RD, Miften M. Dosimetric and deformation effects of image-guided interventions during stereotactic body radiation therapy of the prostate using an endorectal balloon. *Med Phys* 2012;39:3080-3088.
[179] Jones BL, Gan G, Kavanagh B, Miften M. Effect of endorectal balloon positioning errors on target deformation and dosimetric quality during prostate SBRT. *Phys Med Biol* 2013;58:7995-8006.
[180] Hatiboglu G, Pinkawa M, Vallee JP, Hadaschik B, Hohenfellner M. Application technique: placement of a prostate-rectum spacer in men undergoing prostate radiation therapy. *BJU Int* 2012;110:e647-652.

[181] Gez E, Cytron S, Yosef RB, et al. Application of an interstitial and biodegradable balloon system for prostate-rectum separation during prostate cancer radiotherapy: a prospective multi-center study. *Radiat Oncol* [Internet]. 2013 [cited 2014 August 1]; 8:96. Available from: http://www.ro-journal.com/content/pdf/1748-717X-8-96.pdf.
[182] Miften M, Kavanagh B, Timmerman R, Diot Q, Papiez L. *Volumetric modulated arc therapy for the stereotactic body radiation therapy of the prostate. Poster 3453 presented ASTRO 2011* [Internet]. 2011. [cited 2011 November 8]. Available from: http://astro2011.abstractsnet.com/handouts/011567_Prostate_SBRT_ASTRO_2011.pdf
[183] Agazaryan N, Ten S, Chow P, et al. *Volumetric arc therapy treatment protocol for hypo-fractionated stereotactic body radiotherapy for localised prostate cancer. Poster 3431 presented ASTRO 2010* [Internet]. 2011. [cited 2011 November 8]. Available from: http://astro2010.abstractsnet.com/handouts/011553_Agazaryan_Poster_ASTRO_2010_Final.pdf
[184] D'Ambrosio DJ, Pollack A, Harris EE, et al. Assessment of external beam radiation technology for dose escalation and normal tissue protection in the treatment of prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:671-677.
[185] Wade A, Koutoumanou E. *Non-parametric tests. Wilcoxon signed rank test.* [Internet]. 2010. [cited 2015 March 8]. Available from: https://epilab.ich.ucl.ac.uk/coursematerial/statistics/non_parametric/wilcoxon.html
[186] Quon H, Loblaw DA, Cheung PC, et al. Intra-fraction motion during extreme hypofractionated radiotherapy of the prostate using pre- and post-treatment imaging. *Clin Oncol (R Coll Radiol)* 2012;24:640-645.
[187] Adamson J, Wu Q, Yan D. Dosimetric effect of intrafraction motion and residual setup error for hypofractionated prostate intensity-modulated radiotherapy with online cone beam computed tomography image guidance. *Int J Radiat Oncol Biol Phys* 2011;80:453-461.
[188] Beltran C, Herman MG, Davis BJ. Planning target margin calculations for prostate radiotherapy based on intrafraction and interfraction motion using four localization methods. *Int J Radiat Oncol Biol Phys* 2008;70:289-295.
[189] ICRP. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103. *Ann ICRP* 2007;37:1-332.
[190] Buyyounouski MK, Price RA, Jr., Harris EE, et al. Stereotactic body radiotherapy for primary management of early-stage, low- to intermediate-risk prostate cancer: report of the American Society for Therapeutic Radiology and Oncology Emerging Technology Committee. *Int J Radiat Oncol Biol Phys* 2010;76:1297-1304.
[191] Dearnaley D. *CHHIP Trial Physics Plan Assessment Form* [Internet]. 2006. [cited 2012 June 26]. Available from: http://rttrialsqa.dnsalias.org/chhip/CHHIP%20Physics%20Plan%20Assessment%20Form%20v4%5B1%5D.0.pdf
[192] Dearnaley DP. *CHHiP Trial Protocol: Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer. Protocol version 9. Protocol number: ICR-CTSU/2006/10007* [Internet]. 2010. [cited

2011 October 26]. Available from: http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=1281
[193] Niemierko A, Goitein M. Dose-volume distributions: a new approach to dose-volume histograms in three-dimensional treatment planning. *Med Phys* 1994;21:3-11.
[194] Niemierko A. Reporting and analyzing dose distributions: a concept of equivalent uniform dose. *Med Phys* 1997;24:103-110.
[195] Feuvret L, Noel G, Mazeron JJ, Bey P. Conformity index: a review. *Int J Radiat Oncol Biol Phys* 2006;64:333-342.
[196] ICRU. Report 83. Chapter 3: Special considerations regarding absorbed-dose and dose–volume prescribing and reporting in IMRT. *J ICRU* 2010;10:27-41.
[197] Seisen T, Drouin SJ, Phe V, et al. Current role of image-guided robotic radiosurgery (Cyberknife((R))) for prostate cancer treatment. *BJU Int* 2013;111:761-766.
[198] Cramer AK, Haile AG, Ognjenovic S, et al. Real-time prostate motion assessment: image-guidance and the temporal dependence of intra-fraction motion. *BMC Med Phys* [Internet]. 2013 [cited 2014 June 18]; 13(1):4. Available from: http://www.biomedcentral.com/content/pdf/1756-6649-13-4.pdf.
[199] Langen KM, Willoughby TR, Meeks SL, et al. Observations on real-time prostate gland motion using electromagnetic tracking. *Int J Radiat Oncol Biol Phys* 2008;71:1084-1090.
[200] Senan S, Palma DA, Lagerwaard FJ. Stereotactic ablative radiotherapy for stage I NSCLC: Recent advances and controversies. *J Thorac Dis* 2011;3:189-196.
[201] UK SABR Consortium. *Stereotactic ABlative Body Radiotherapy (SABR): A resource. Version 4.1, April 2014* [Internet]. 2014. [updated 2014 April; cited 2014 July 7]. Available from: http://www.actionradiotherapy.org/wp-content/uploads/2014/05/UKSABRConsortiumGuidellinesv41.pdf
[202] Aluwini S, van Rooij P, Hoogeman M, et al. CyberKnife stereotactic radiotherapy as monotherapy for low- to intermediate-stage prostate cancer: early experience, feasibility, and tolerance. *J Endourol* 2010;24:865-869.
[203] Lin YW, Lin KH, Ho HW, et al. Treatment plan comparison between stereotactic body radiation therapy techniques for prostate cancer: Non-isocentric CyberKnife versus isocentric RapidArc. *Phys Med* 2014;30:544-661.
[204] Bolzicco G, Favretto MS, Scremin E, Tambone C, Tasca A, Guglielmi R. Image-guided stereotactic body radiation therapy for clinically localized prostate cancer: preliminary clinical results. *Technol Cancer Res Treat* 2010;9:473-477.
[205] Barentsz JO, Richenberg J, Clements R, et al. ESUR prostate MR guidelines 2012. *Eur Radiol* 2012;22:746-757.
[206] Cellini N, Morganti AG, Mattiucci GC, et al. Analysis of intraprostatic failures in patients treated with hormonal therapy and radiotherapy: implications for conformal therapy planning. *Int J Radiat Oncol Biol Phys* 2002;53:595-599.
[207] Bauman G, Haider M, Van der Heide UA, Menard C. Boosting imaging defined dominant prostatic tumors: A systematic review. *Radiother Oncol* 2013;107:274-281.
[208] Pucar D, Hricak H, Shukla-Dave A, et al. Clinically significant prostate cancer local recurrence after radiation therapy occurs at the site of primary

tumor: magnetic resonance imaging and step-section pathology evidence. *Int J Radiat Oncol Biol Phys* 2007;69:62-69.
[209] Niyazi M, Bartenstein P, Belka C, Ganswindt U. Choline PET based dose-painting in prostate cancer--modelling of dose effects. *Radiat Oncol* [Internet]. 2010 [cited 2014 May 24]; 5:23. Available from: http://www.ro-journal.com/content/pdf/1748-717X-5-23.pdf.
[210] Azzeroni R, Maggio A, Fiorino C, et al. Biological optimization of simultaneous boost on intra-prostatic lesions (DILs): Sensitivity to TCP parameters. *Phys Med* 2012;29:592-598.
[211] Housri N, Ning H, Ondos J, et al. Parameters favorable to intraprostatic radiation dose escalation in men with localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2011;80:614-620.
[212] Seppala J, Seppanen M, Arponen E, Lindholm P, Minn H. Carbon-11 acetate PET/CT based dose escalated IMRT in prostate cancer. *Radiother Oncol* 2009;93:234-240.
[213] Nutting CM, Corbishley CM, Sanchez-Nieto B, Cosgrove VP, Webb S, Dearnaley DP. Potential improvements in the therapeutic ratio of prostate cancer irradiation: dose escalation of pathologically identified tumour nodules using intensity modulated radiotherapy. *Br J Radiol* 2002;75:151-161.
[214] Xia P, Pickett B, Vigneault E, Verhey LJ, Roach M, 3rd. Forward or inversely planned segmental multileaf collimator IMRT and sequential tomotherapy to treat multiple dominant intraprostatic lesions of prostate cancer to 90 Gy. *Int J Radiat Oncol Biol Phys* 2001;51:244-254.
[215] Pickett B, Vigneault E, Kurhanewicz J, Verhey L, Roach M. Static field intensity modulation to treat a dominant intra-prostatic lesion to 90 Gy compared to seven field 3-dimensional radiotherapy. *Int J Radiat Oncol Biol Phys* 1999;44:921-929.
[216] Chang JH, Lim Joon D, Lee ST, et al. Intensity modulated radiation therapy dose painting for localized prostate cancer using (1)(1)C-choline positron emission tomography scans. *Int J Radiat Oncol Biol Phys* 2012;83:e691-696.
[217] Maggio A, Fiorino C, Mangili P, et al. Feasibility of safe ultra-high (EQD(2)>100 Gy) dose escalation on dominant intra-prostatic lesions (DILs) by Helical Tomotheraphy. *Acta Oncol* 2011;50:25-34.
[218] van Lin EN, Futterer JJ, Heijmink SW, et al. IMRT boost dose planning on dominant intraprostatic lesions: gold marker-based three-dimensional fusion of CT with dynamic contrast-enhanced and 1H-spectroscopic MRI. *Int J Radiat Oncol Biol Phys* 2006;65:291-303.
[219] Lips IM, van der Heide UA, Haustermans K, et al. Single blind randomized phase III trial to investigate the benefit of a focal lesion ablative microboost in prostate cancer (FLAME-trial): study protocol for a randomized controlled trial. *Trials* [Internet]. 2011 [cited 2014 May 24]; 12:255. Available from: http://www.trialsjournal.com/content/pdf/1745-6215-12-255.pdf.
[220] Pollack A. *A Phase III Trial of Hypofractionated External Beam Image-Guided Highly Targeted Radiotherapy: The HEIGHT Trial* [Internet]. 2014. [updated 2014 August 12; cited 2014 September 7]. Available from: http://clinicaltrials.gov/show/NCT01411332

[221] Tofts PS, Brix G, Buckley DL, et al. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging* 1999;10:223-232.
[222] Peeters ST, Hoogeman MS, Heemsbergen WD, Hart AA, Koper PC, Lebesque JV. Rectal bleeding, fecal incontinence, and high stool frequency after conformal radiotherapy for prostate cancer: normal tissue complication probability modeling. *Int J Radiat Oncol Biol Phys* 2006;66:11-19.
[223] Nahum A, Sanchez-NIeto B. Tumour control probability modelling: basic principles and applications in treatment planning. *Phys Med* 2001;17(Suppl 2):13-23.
[224] Uzan J, Nahum AE. Radiobiologically guided optimisation of the prescription dose and fractionation scheme in radiotherapy using BioSuite. *Br J Radiol* 2012;85:1279-1286.
[225] Fowler J, Chappell R, Ritter M. Is alpha/beta for prostate tumors really low? *Int J Radiat Oncol Biol Phys* 2001;50:1021-1031.
[226] Pedicini P, Strigari L, Benassi M. Estimation of a self-consistent set of radiobiological parameters from hypofractionated versus standard radiation therapy of prostate cancer. *Int J Radiat Oncol Biol Phys* 2013;85:e231-237.
[227] Lyman JT. Complication probability as assessed from dose-volume histograms. *Radiat Res Suppl* 1985;8:S13-19.
[228] Kutcher GJ, Burman C. Calculation of complication probability factors for non-uniform normal tissue irradiation: the effective volume method. *Int J Radiat Oncol Biol Phys* 1989;16:1623-1630.
[229] Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. *Int J Radiat Oncol Biol Phys* 2010;76:S123-129.
[230] Burman C, Kutcher GJ, Emami B, Goitein M. Fitting of normal tissue tolerance data to an analytic function. *Int J Radiat Oncol Biol Phys* 1991;21:123-135.
[231] Mouida A, Alaa N. Sensitivity Analysis of TSEB Model by One-Factor-At-A-Time in irrigated olive orchard. *International Journal of Computer Science Issues* 2011;8:369-377.
[232] Tan CH, Wei W, Johnson V, Kundra V. Diffusion-weighted MRI in the detection of prostate cancer: meta-analysis. *AJR Am J Roentgenol* 2012;199:822-829.
[233] Kozlowski P, Chang SD, Jones EC, Berean KW, Chen H, Goldenberg SL. Combined diffusion-weighted and dynamic contrast-enhanced MRI for prostate cancer diagnosis--correlation with biopsy and histopathology. *J Magn Reson Imaging* 2006;24:108-113.
[234] Selnaes KM, Heerschap A, Jensen LR, et al. Peripheral zone prostate cancer localization by multiparametric magnetic resonance at 3 T: unbiased cancer identification by matching to histopathology. *Invest Radiol* 2012;47:624-633.
[235] van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;47:1121-1135.
[236] Baker C. *Prostate radiotherapy: BIOPROP. Predicting radiotherapy outcome and funtionally optimising treatment* [Powerpoint presentation]. The

British Institute of Radiology: Biological optimisation of radiotherapy treatment planning meeting; March 13; Stewart House, London 2014.
[237] Kirkpatrick JP, Brenner DJ, Orton CG. Point/Counterpoint. The linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery. *Med Phys* 2009;36:3381-3384.
[238] Nahum AE, Uzan J. (Radio)biological optimization of external-beam radiotherapy. *Comput Math Methods Med* [Internet]. 2012 [cited 2013 October 16]; 2012:329214. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3508750/pdf/CMMM2012-329214.pdf.
[239] Fiorino C, Valdagni R, Rancati T, Sanguineti G. Dose-volume effects for normal tissues in external radiotherapy: pelvis. *Radiother Oncol* 2009;93:153-167.
[240] Cheung MR, Tucker SL, Dong L, et al. Investigation of bladder dose and volume factors influencing late urinary toxicity after external beam radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2007;67:1059-1065.
[241] Fonteyne V, Villeirs G, Speleers B, et al. Intensity-modulated radiotherapy as primary therapy for prostate cancer: report on acute toxicity after dose escalation with simultaneous integrated boost to intraprostatic lesion. *Int J Radiat Oncol Biol Phys* 2008;72:799-807.
[242] Groenendaal G, van Vulpen M, Pereboom SR, et al. The effect of hormonal treatment on conspicuity of prostate cancer: implications for focal boosting radiotherapy. *Radiother Oncol* 2012;103:233-238.
[243] Tree A, Jones C, Sohaib A, Khoo V, van As N. Prostate stereotactic body radiotherapy with simultaneous integrated boost: which is the best planning method? *Radiat Oncol* [Internet]. 2013 [cited 2013 December 19]; 8(1):228. Available from: http://www.ro-journal.com/content/pdf/1748-717X-8-228.pdf.
[244] Udrescu C, Rouviere O, Enachescu C, et al. Potential interest of developing an integrated boost dose escalation for stereotactic irradiation of primary prostate cancer. *Phys Med* 2014;30:320-325.
[245] Cashmore J. The characterization of unflattened photon beams from a 6 MV linear accelerator. *Phys Med Biol* 2008;53:1933-1946.
[246] Vassiliev ON, Kry SF, Kuban DA, Salehpour M, Mohan R, Titt U. Treatment-planning study of prostate cancer intensity-modulated radiotherapy with a Varian Clinac operated without a flattening filter. *Int J Radiat Oncol Biol Phys* 2007;68:1567-1571.
[247] Stathakis S, Esquivel C, Gutierrez A, Buckey CR, Papanikolaou N. Treatment planning and delivery of IMRT using 6 and 18MV photon beams without flattening filter. *Appl Radiat Isot* 2009;67:1629-1637.
[248] Zwahlen DR, Lang S, Hrbacek J, et al. The use of photon beams of a flattening filter-free linear accelerator for hypofractionated volumetric modulated arc therapy in localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;83:1655-1660.
[249] Paynter D, Weston SJ, Cosgrove VP, Evans JA, Thwaites DI. Beam characteristics of energy-matched flattening filter free beams. *Med Phys* [Internet]. 2014 May [cited 2014 May 15]; 41(5):052103. Available from: http://www.jacmp.org/index.php/jacmp/article/view/4053/2917.

[250] Roach M, 3rd, Nam J, Gagliardi G, El Naqa I, Deasy JO, Marks LB. Radiation dose-volume effects and the penile bulb. *Int J Radiat Oncol Biol Phys* 2010;76:S130-134.
[251] Rivin del Campo E, Thomas K, Weinberg V, Roach M, 3rd. Erectile dysfunction after radiotherapy for prostate cancer: a model assessing the conflicting literature on dose-volume effects. *Int J Impot Res* 2013;25:161-165.
[252] Wang C, Dai J, Hu Y. Optimization of beam orientations and beam weights for conformal radiotherapy using mixed integer programming. *Phys Med Biol* 2003;48:4065-4076.
[253] Chow JC, Jiang R. Prostate volumetric-modulated arc therapy: dosimetry and radiobiological model variation between the single-arc and double-arc technique. *J Appl Clin Med Phys* [Internet]. 2013 [cited 2014 May 20]; 14(3):4053. Available from: http://www.jacmp.org/index.php/jacmp/article/viewFile/4053/2908.
[254] Hall EJ, Wuu CS. Radiation-induced second cancers: The impact of 3D-CRT and IMRT. *Int J Radiat Oncol Biol Phys* 2003;56:83-88.
[255] Li CI, Nishi N, McDougall JA, et al. Relationship between radiation exposure and risk of second primary cancers among atomic bomb survivors. *Cancer Research* 2010;70:7187-7198.
[256] Cahan WG, Woodard HQ, et al. Sarcoma arising in irradiated bone; report of 11 cases. *Cancer* 1948;1:3-29.
[257] Sale KA, Wallace DI, Girod DA, Tsue TT. Radiation-induced malignancy of the head and neck. *Otolaryngol Head Neck Surg* 2004;131:643-645.
[258] Pawlish KS, Schottenfeld D, Severson R, Montie JE. Risk of multiple primary cancers in prostate cancer patients in the Detroit metropolitan area: A retrospective cohort study. *Prostate* 1997;33:75-86.
[259] Brenner DJ, Curtis RE, Hall EJ, Ron E. Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. *Cancer* 2000;88:398-406.
[260] Pickles T, Phillips N. The risk of second malignancy in men with prostate cancer treated with or without radiation in British Columbia, 1984-2000. *Radiother Oncol* 2002;65:145-151.
[261] Berrington de Gonzalez A, Curtis RE, Kry SF, et al. Proportion of second cancers attributable to radiotherapy treatment in adults: A cohort study in the US SEER cancer registries. *Lancet Oncol* 2011;12:353-360.
[262] Rapiti E, Fioretta G, Verkooijen HM, et al. Increased risk of colon cancer after external radiation therapy for prostate cancer. *Int J Cancer* 2008;123:1141-1145.
[263] Bagshaw MA, Cox RS, Ray GR. Status of radiation treatment of prostate cancer at Stanford University. *NCI Monographs* 1988;7:47-60.
[264] Abdel-Wahab M, Reis IM, Hamilton K. Second primary cancer after radiotherapy for prostate cancer--a seer analysis of brachytherapy versus external beam radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;72:58-68.
[265] Black A, Pinsky PF, Grubb RL, et al. Second cancers following radiotherapy in prostate cancer patients in the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial [abstract]. *J Urology* 2013;189:e135.
[266] Huang J, Kestin LL, Ye H, Wallace M, Martinez AA, Vicini FA. Analysis of second malignancies after modern radiotherapy versus prostatectomy for localized prostate cancer. *Radiother Oncol* 2011;98:81-86.

[267] Movsas B, Hanlon AL, Pinover W, Hanks GE. Is there an increased risk of second primaries following prostate irradiation? *Int J Radiat Oncol Biol Phys* 1998;41:251-255.
[268] Johnstone PAS, Powell CR, Riffenburgh R, Rohde DC, Kane CJ. Second primary malignancies in t1-3n0 prostate cancer patients treated with radiation therapy with 10-year followup. *J Urology* 1998;159:946-949.
[269] Zilli T, Chagnon M, Van Nguyen T, et al. Influence of abdominal adiposity, waist circumference, and body mass index on clinical and pathologic findings in patients treated with radiotherapy for localized prostate cancer. *Cancer* 2010;116:5650-5658.
[270] Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol* 2010;11:1066-1073.
[271] Kannan V, Sathiyanarayanan VK, Sagde S, et al. Three dimensional conformal radiation therapy in prostate adenocarcinoma: survival and rectal toxicity. *J Cancer Res Ther* 2005;1:34-37.
[272] Nguyen Q, Levy LB, Lee AK, et al. Risk factors predicting failure and prostate cancer mortality in high risk prostate cancer patients treated with definitive external beam radiation therapy [abstract]. *Int J Radiat Oncol Biol Phys* 2010;1:S125.
[273] Gardner BG, Zietman AL, Shipley WU, Skowronski UE, McManus P. Late normal tissue sequelae in the second decade after high dose radiation therapy with combined photons and conformal protons for locally advanced prostate cancer. *J Urology* 2002;167:123-126.
[274] Zelefsky MJ, Pei X, Teslova T, et al. Secondary cancers after intensity-modulated radiotherapy, brachytherapy and radical prostatectomy for the treatment of prostate cancer: incidence and cause-specific survival outcomes according to the initial treatment intervention. *BJU Int* 2012;110:1696-1701.
[275] Ciezki JP, Reddy CA, Angermeier K, et al. Twenty-year competing risk analysis of secondary malignancies after external beam radiation for postoperative treatment of prostate cancer patients from the SEER database [abstract]. *Int J Radiat Oncol Biol Phys* 2012;84:S16-S17.
[276] Bellavita R, Massetti M, Arcidiacono F, et al. Postoperative high dose conformal radiotherapy in patients with high risk prostate cancer [abstract]. *Radiother Oncol* 2011;99:S386-S387.
[277] Bittner N, Merrick GS, Galbreath RW, et al. Primary Causes of Death After Permanent Prostate Brachytherapy. *Int J Radiat Oncol Biol Phys* 2008;72:433-440.
[278] Rodriguez A, Duarte OJ, Romero OJ, Medina-Polo J, Castellano D, Ots A, Cabello E, Lanzos E, Cabeza M. Survival free of disease and chronic toxicity for localised prostate cancer treated with low dose I 125 permanent prostate brachytherapy [abstract]. *Urology* 2009;74:S123.
[279] Henry A, Musunuru HB, Mason M, et al. Second primary cancers occuring after I-125 brachytherapy as monotherapy for early prostate cancer [abstract]. *Int J Radiat Oncol Biol Phys* 2012;84:S16.
[280] Neugut AI, Ahsan H, Robinson E, Ennis RD. Bladder carcinoma and other second malignancies after radiotherapy for prostate carcinoma. *Cancer* 1997;79:1600-1604.

[281] Nieder AM, Porter MP, Soloway MS. Radiation therapy for prostate cancer increases subsequent risk of bladder and rectal cancer: a population based cohort study. *J Urology* 2008;180:2005-2009.
[282] Huo D, Hetzel JT, Roy H, Rubin DT. Association of colorectal cancer and prostate cancer and impact of radiation therapy. *Cancer Epidem Biomar* 2009;18:1979-1985.
[283] Margel D, Baniel J, Wasserberg N, Bar-Chana M, Yossepowitch O. Radiation therapy for prostate cancer increases the risk of subsequent rectal cancer. *Ann Surg* 2011;254:947-950.
[284] Baxter NN, Tepper JE, Durham SB, Rothenberger DA, Virnig BA. Increased risk of rectal cancer after prostate radiation: a population-based study. *Gastroenterology* 2005;128:819-824.
[285] Moon K, Stukenborg GJ, Keim J, Theodorescu D. Cancer incidence after localized therapy for prostate cancer. *Cancer* 2006;107:991-998.
[286] Kendal W, Eapen L, Nicholas G. Second primary cancers after prostatic irradiation: Ensuring an appropriate analysis [letter]. *Cancer* 2007;109:164.
[287] Kendal WS, Eapen L, Macrae R, Malone S, Nicholas G. Prostatic irradiation is not associated with any measurable increase in the risk of subsequent rectal cancer. *Int J Radiat Oncol Biol Phys* 2006;65:661-668.
[288] Chrouser K, Leibovich B, Bergstralh E, Zincke H, Blute M. Bladder cancer risk following primary and adjuvant external beam radiation for prostate cancer. *J Urology* 2005;174:107-110.
[289] Singh A, Kinoshita Y, Rovito Jr PM, et al. Higher than expected association of clinical prostate and bladder cancers. *J Urology* 2005;173:1526-1529.
[290] Singh AK, Mashtare TL, McCloskey SA, Seixas-Mikelus SA, Kim HL, May KS. Increasing age and treatment modality are predictors for subsequent diagnosis of bladder cancer following prostate cancer diagnosis. *Int J Radiat Oncol Biol Phys* 2010;78:1086-1094.
[291] Boorjian S, Cowan JE, Konety BR, et al. Bladder cancer incidence and risk factors in men with prostate cancer: results from Cancer of the Prostate Strategic Urologic Research Endeavor. *J Urology* 2007;177:883-887.
[292] Bhojani N, Capitanio U, Suardi N, et al. The rate of secondary malignancies after radical prostatectomy versus external beam radiation therapy for localized prostate cancer: a population-based study on 17,845 patients. *Int J Radiat Oncol Biol Phys* 2010;76:342-348.
[293] Schneider U. Modelling the risk of second malignancies after radiotherapy. *Genes* [Internet]. 2011 [cited 2013 June 11]; 2:17. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3927608/pdf/genes-02-01033.pdf.
[294] Stathakis S, Li J, Ma CCM. Monte Carlo determination of radiation-induced cancer risks for prostate patients undergoing intensity- modulated radiation therapy. *J Appl Clin Med Phys* [Internet]. 2007 [cited 2014 May 2]; 8(4):2685. Available from: http://www.jacmp.org/index.php/jacmp/article/view/2685/1351.
[295] Schneider U, Lomax A, Pemler P, et al. The impact of IMRT and proton radiotherapy on secondary cancer incidence. *Strahlenther Onkol* 2006;182:647-652.

[296] Stathakis S, Roland T, Papanikolaou N, Li J, Ma C. A prediction study on radiation-induced second malignancies for IMRT treatment delivery. *Technol Cancer Res Treat* 2009;8:141-148.
[297] Kry SF, Salehpour M, Followill DS, et al. The calculated risk of fatal secondary malignancies from intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2005;62:1195-1203.
[298] Kry SF, Followill D, White RA, Stovall M, Kuban DA, Salehpour M. Uncertainty of calculated risk estimates for secondary malignancies after radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;68:1265-1271.
[299] Zelefsky MJ, Housman DM, Pei X, et al. Incidence of secondary cancer development after high-dose intensity-modulated radiotherapy and image-guided brachytherapy for the treatment of localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;83:953-959.
[300] Hinnen KA, Schaapveld M, Van Vulpen M, et al. Prostate brachytherapy and second primary cancer risk: A competitive risk analysis. *J Clin Oncol* 2011;29:4510-4515.
[301] Liauw SL, Sylvester JE, Morris CG, Blasko JC, Grimm PD. Second malignancies after prostate brachytherapy: Incidence of bladder and colorectal cancers in patients with 15 years of potential follow-up. *Int J Radiat Oncol Biol Phys* 2006;66:669-673.
[302] Reddy C, Ciezki JP, Klein EA. Second malignancies after definitive radiotherapy for prostate cancer [abstract]. *Brachytherapy* 2010;9:S78.
[303] Gutman SA, Merrick GS, Butler WM, et al. Temporal relationship between prostate brachytherapy and the diagnosis of colorectal cancer. *Int J Radiat Oncol Biol Phys* 2006;66:48-55.
[304] Swartz D, Terk M, Vashi A, Cesaretti J, Hickson R, Nurani R. Brachytherapy for localized prostate cancer: Outcome results with 10 years minimum follow-up [abstract]. *J Urology* 2010;1:e675.
[305] Laing R, Chadwick E, Javed S, Langley SEM. Low dose rate brachytherapy is an excellent treatment option for young men with localised prostate cancer [abstract]. *Radiother Oncol* 2012;103:S93.
[306] Wilcox BN, Senzer N, Filardo DG, Reynolds J, Zielsdorf L, Adams JPP. Thirteen-year biochemical progression free survival in clinical stage T1-T2 prostate cancer patients treated with permanent seed implantation: Baylor university medical center experience [abstract]. *Brachytherapy* 2011;10:S53-S54.
[307] Lilleby W, Tafjord G, Raabe NK. Implementation of high-dose-rate brachytherapy and androgen deprivation in patients with prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;83:933-939.
[308] Yagi Y, Ashikari A, Namitome R, et al. Brachytherapy for young prostate cancer patients. What is different from elder patients [abstract]? *Radiother Oncol* 2012;103:S69-S70.
[309] Buckstein M, Carpenter TJ, Stone NN, Stock RG. Long-term outcomes and toxicity in patients treated with brachytherapy for prostate adenocarcinoma younger than 60 years of age at treatment with minimum 10 years of follow-up. *Urology* 2013;81:364-368.
[310] Schneider U, Lomax A, Besserer J, Pemler P, Lombriser N, Kaser-Hotz B. The impact of dose escalation on secondary cancer risk after radiotherapy of prostate cancer. *Int J Radiat Oncol Biol Phys* 2007;68:892-897.

[311] Fontenot JD, Lee AK, Newhauser WD. Risk of secondary malignant neoplasms from proton therapy and intensity-modulated x-ray therapy for early-stage prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;74:616-622.
[312] Fontenot JD, Bloch C, Followill D, Titt U, Newhauser WD. Estimate of the uncertainties in the relative risk of secondary malignant neoplasms following proton therapy and intensity-modulated photon therapy. *Phys Med Biol* 2010;55:6987-6998.
[313] Yoon M, Ahn SH, Kim J, et al. Radiation-induced cancers from modern radiotherapy techniques: intensity-modulated radiotherapy versus proton therapy. *Int J Radiat Oncol Biol Phys* 2010;77:1477-1485.
[314] Abdel-Wahab M, Reis IM, Wu J, Duncan R. Second Primary Cancer Risk of Radiation Therapy After Radical Prostatectomy for Prostate Cancer: An Analysis of SEER Data. *Urology* 2009;74:866-871.
[315] Nam RK, Cheung P, Herschorn S, et al. Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study. *Lancet Oncol* 2014;15:223-231.
[316] Bece A, Hruby G. Complications of prostate cancer treatment [letter]. *Lancet Oncol* 2014;15:e149-150.
[317] Chen RC, Hamstra DA, Sandler HM, Zietman AL. Complications of prostate cancer treatment [letter]. *Lancet Oncol* 2014;15:e150.
[318] Linton KD, Woo HH. Complications of prostate cancer treatment [letter]. *Lancet Oncol* 2014;15:e150-151.
[319] Halperin R, Maas B, Pickles T. Complications of prostate cancer treatment [letter]. *Lancet Oncol* 2014;15:e151-152.
[320] Okajima K, Ishikawa K, Matsuura T, et al. Multiple primary malignancies in patients with prostate cancer: increased risk of secondary malignancies after radiotherapy. *Int J Clin Oncol* 2013;18:1078-1084.
[321] Musunuru H, Mason M, Murray L, et al. Second primary cancers occurring after I-125 brachytherapy as monotherapy for early prostate cancer. *Clin Oncol (R Coll Radiol)* 2014;26:210-215.
[322] Roach M, 3rd, Hunt D, Jones CU, et al. Radiation oncology Therapy Group (RTOG) 9408: A secondary Analysis of the Risk of Death From Second Cancers Comparing Whole Pelvic (WP) Radiation Therapy (RT) to Prostate Only (PO) RT and Neoadjuvant Hormonal Therapy (NHT) + RT to RT Alone [abstract]. *Int J Radiat Oncol Biol Phys* 2013;87:S357.
[323] Ferrer F, Boladeras A, Pineiro R, et al. Early Toxicity Assessment of Pelvic Volumetric Modulated Arc Therapy (VMAT) With Hypofractionated Simultaneous Integrated Boost to Prostate for High-Risk Prostate Cancer [abstract]. *Int J Radiat Oncol Biol Phys* 2013;87:S388.
[324] Followill D, Geis P, Boyer A. Estimates of whole-body dose equivalent produced by beam intensity modulated conformal therapy. *Int J Radiat Oncol Biol Phys* 1997;38:667-672.
[325] Kry SF, Salehpour M, Followill DS, et al. Out-of-field photon and neutron dose equivalents from step-and-shoot intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2005;62:1204-1216.
[326] Ruben JD, Davis S, Evans C, et al. The effect of intensity-modulated radiotherapy on radiation-induced second malignancies. *Int J Radiat Oncol Biol Phys* 2008;70:1530-1536.

[327] Bednarz B, Athar B, Xu XG. A comparative study on the risk of second primary cancers in out-of-field organs associated with radiotherapy of localized prostate carcinoma using Monte Carlo-based accelerator and patient models. *Med Phys* 2010;37:1987-1994.
[328] Schneider U, Besserer J, Mack A. Hypofractionated radiotherapy has the potential for second cancer reduction. *Theor Biol Med Model* [Internet]. 2010 [cited 2013 February 3]; 7:4. Available from: http://www.tbiomed.com/content/pdf/1742-4682-7-4.pdf.
[329] Kragl G, Baier F, Lutz S, et al. Flattening filter free beams in SBRT and IMRT: dosimetric assessment of peripheral doses. *Z Med Phys* 2011;21:91-101.
[330] Schneider U, Zwahlen D, Ross D, Kaser-Hotz B. Estimation of radiation-induced cancer from three-dimensional dose distributions: Concept of organ equivalent dose. *Int J Radiat Oncol Biol Phys* 2005;61:1510-1515.
[331] Radiation Therapy Oncology Group. *RTOG 0126 Trial Protocol: A Phase III Randomized Study of High Dose 3D-CRT/IMRT Versus Standard Dose 3D-CRT/IMRT in Patients Treated for Localised Prostate Cancer. Version June 2014* [Internet]. 2014. [updated 2014 July 28; cited 2014 September 29]. Available from: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0126
[332] Schneider U, Sumila M, Robotka J. Site-specific dose-response relationships for cancer induction from the combined Japanese A-bomb and Hodgkin cohorts for doses relevant to radiotherapy (and associated erratum). *Theor Biol Med Model* [Internet]. 2011 [cited 2014 May 2]; 8:27. Available from: http://www.tbiomed.com/content/pdf/1742-4682-8-27.pdf.
[333] Blais AR, Lederer E, Oliver M, Leszczynski K. Static and rotational step-and-shoot IMRT treatment plans for the prostate: a risk comparison study. *Med Phys* 2012;39:1069-1078.
[334] Scalzetti EM, Huda W, Bhatt S, Ogden KM. A method to obtain mean organ doses in a RANDO phantom. *Health Phys* 2008;95:241-244.
[335] D'Souza WD, Rosen, II. Nontumor integral dose variation in conventional radiotherapy treatment planning. *Med Phys* 2003;30:2065-2071.
[336] D'Arienzo M, Masciullo SG, de Sanctis V, Osti MF, Chiacchiararelli L, Enrici RM. Integral dose and radiation-induced secondary malignancies: comparison between stereotactic body radiation therapy and three-dimensional conformal radiotherapy. *Int J Environ Res Public Health* 2012;9:4223-4240.
[337] ICRP. Basic anatomical and physiological data for use in radiological protection: reference values. A report of age- and gender-related differences in the anatomical and physiological characteristics of reference individuals. ICRP Publication 89. *Ann ICRP* 2002;32:(3-4).
[338] Saito AI, Li JG, Liu C, Olivier KR, Dempsey JF. Accurate heterogeneous dose calculation for lung cancer patients without high-resolution CT densitites. *J Appl Clin Med Phys* 2009;10:93-104.
[339] Ruben JD, Lancaster CM, Jones P, Smith RL. A comparison of out-of-field dose and its constituent components for intensity-modulated radiation therapy versus conformal radiation therapy: implications for carcinogenesis. *Int J Radiat Oncol Biol Phys* 2011;81:1458-1464.
[340] Halg RA, Besserer J, Schneider U. Systematic measurements of whole-body dose distributions for various treatment machines and delivery techniques in radiation therapy. *Med Phys* 2012;39:7662-7676.

[341] Kry SF, Vassiliev ON, Mohan R. Out-of-field photon dose following removal of the flattening filter from a medical accelerator. *Phys Med Biol* 2010;55:2155-2166.
[342] Dasu A, Toma-Dasu I, Franzen L, Widmark A, Nilsson P. Secondary malignancies from prostate cancer radiation treatment: a risk analysis of the influence of target margins and fractionation patterns. *Int J Radiat Oncol Biol Phys* 2011;79:738-746.
[343] Dasu A, Toma-Dasu I, Olofsson J, Karlsson M. The use of risk estimation models for the induction of secondary cancers following radiotherapy. *Acta Oncol* 2005;44:339-347.
[344] Alvarez Moret J, Koelbl O, Bogner L. Quasi-IMAT technique and secondary cancer risk in prostate cancer. *Strahlenther Onkol* 2009;185:248-253.
[345] Rechner LA, Howell RM, Zhang R, Etzel C, Lee AK, Newhauser WD. Risk of radiogenic second cancers following volumetric modulated arc therapy and proton arc therapy for prostate cancer. *Phys Med Biol* 2012;57:7117-7132.
[346] Sachs RK, Brenner DJ. Solid tumor risks after high doses of ionizing radiation. *Proc Natl Acad Sci USA* 2005;102:13040-13045.
[347] Shuryak I, Hahnfeldt P, Hlatky L, Sachs RK, Brenner DJ. A new view of radiation-induced cancer: integrating short- and long-term processes. Part I: approach. *Radiat Environ Biophys* 2009;48:263-274.
[348] Shuryak I, Hahnfeldt P, Hlatky L, Sachs RK, Brenner DJ. A new view of radiation-induced cancer: integrating short- and long-term processes. Part II: second cancer risk estimation. *Radiat Environ Biophys* 2009;48:275-286.
[349] Patil VM, Kapoor R, Chakraborty S, Ghoshal S, Oinam AS, Sharma SC. Dosimetric risk estimates of radiation-induced malignancies after intensity modulated radiotherapy. *J Cancer Res Ther* 2010;6:442-447.
[350] Schneider U. Calculated risk of fatal secondary malignancies from intensity-modulated radiotherapy: in regard to Kry et al [letter]. *Int J Radiat Oncol Biol Phys* 2006;64:1290.
[351] Aoyama H, Westerly DC, Mackie TR, et al. Integral radiation dose to normal structures with conformal external beam radiation. *Int J Radiat Oncol Biol Phys* 2006;64:962-967.
[352] Della Biancia C, Hunt M, Amols H. A Comparison of the Integral Dose from 3D Conformal and IMRT Techniques in the Treatment of Prostate Cancer [abstract]. *Med Phys* 2002;29:1216.
[353] Cashmore J, Ramtohul M, Ford D. Lowering whole-body radiation doses in pediatric intensity-modulated radiotherapy through the use of unflattened photon beams. *Int J Radiat Oncol Biol Phys* 2011;80:1220-1227.
[354] Dores GM, Metayer C, Curtis RE, et al. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. *J Clin Oncol* 2002;20:3484-3494.
[355] Silberstein JL, Pal SK, Lewis B, Sartor O. Current clinical challenges in prostate cancer. *Transl Androl Urol* 2013;2:122-136.
[356] Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. *JAMA* 2005;293:2095-2101.

[357] Royal College of Radiologists, Society and College of Radiographers, Institute of Physics and Engineering in Medicine. *On target: ensuring geometric accuracy in radiotherapy*. London: The Royal College of Radiologists, 2008.
[358] Lambert J, Greer PB, Menk F, et al. MRI-guided prostate radiation therapy planning: Investigation of dosimetric accuracy of MRI-based dose planning. *Radiother Oncol* 2011;98:330-334.
[359] Lagendijk JJ, Raaymakers BW, Raaijmakers AJ, et al. MRI/linac integration. *Radiother Oncol* 2008;86:25-29.
[360] Mutic S, Dempsey JF. The ViewRay system: magnetic resonance-guided and controlled radiotherapy. *Semin Radiat Oncol* 2014;24:196-199.
[361] Choi C, Cho C, Kim G, et al. Stereotactic radiation therapy of localised prostate cancer using Cyberknife [abstract]. *Int J Radiat Oncol Biol Phys* 2007;69:S375.
[362] Pawlicki T, Kim GY, Hsu A, et al. Investigation of linac-based image-guided hypofractionated prostate radiotherapy. *Med Dosim* 2007;32:71-79.
[363] King CR, Brooks JD, Gill H, Pawlicki T, Cotrutz C, Presti JC, Jr. Stereotactic body radiotherapy for localized prostate cancer: interim results of a prospective phase II clinical trial. *Int J Radiat Oncol Biol Phys* 2009;73:1043-1048.

Appendix A: Definitions of biochemical failure used in prostate cancer

ASTRO definition of biochemical failure: biochemical failure occurs after three consecutive rises in PSA after the post treatment nadir. The date of failure is at the midpoint between the nadir date and the first rise [1].

Phoenix definition of biochemical failure: biochemical failure occurs when the PSA reaches the post treatment nadir + 2ng/ml [2].

References

[1] Cox J. Girignon D KR, Parsons J, Schellhammer P. Consensus statement: guidelines for PSA following radiation therapy. *Int J Radiat Oncol, Biol Phys* 1997;37:1035-1041.

[2] Roach M, 3rd, Hanks G, Thames H, Jr., et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006;65:965-974.

Appendix B: Risk groups in prostate cancer

Based on National Comprehensive Cancer Network® (NCCN [1]) and D'Amico [2] risk classifications:

Low risk prostate cancer: clinical stage (c)T1-T2a and Gleason score ≤6 and PSA<10

Intermediate risk prostate cancer: cT2b-T2c and/or Gleason score 7 and/or PSA10-20

High risk prostate cancer: cT3-T4 or Gleason score 8-10 or PSA>20

Note: T2c disease is considered high rather than intermediate risk in the D'Amico classifications and two or more intermediate risk features may be considered high risk according to NCCN criteria.

Intermediate risk prostate cancer can also be subdivided into low-intermediate and high-intermediate risk [3].

Low-intermediate risk can be considered:

Gleason score 6 with PSA>10, or Gleason score 3+4 with PSA<10

High-intermediate risk can be considered:

Gleason score 3+4 with PSA 10-20, or Gleason score 4+3

References

[1] National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline) Prostate Cancer version 2.2014* [Internet]. 2014 [updated 2014 April 1; cited 2014 August 1]; Available from: http://www.tri-kobe.org/nccn/guideline/urological/english/prostate.pdf

[2] D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280:969-974.

[3] Katz A, Kang J. Stereotactic Body Radiotherapy as Treatment for Organ Confined Low and Intermediate Risk Prostate Carcinoma, a Seven Year Study. *Front Oncol* [Internet]. 2014 [cited 2014 July 30]; 4:240. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4150980/pdf/fonc-04-00240.pdf.

Appendix C: Clinical evidence for prostate SABR

Table C1. Clinical studies delivering prostate SABR using the Cyberknife™

Table C2. Clinical studies delivering prostate SABR using a linear accelerator

Table C3. Clinical studies delivering prostate SABR as a boost following conventional fractionation

Table C4. Toxicity from prostate SABR Cyberknife™ studies

Table C5. Toxicity from prostate SABR linear accelerator studies

Table C6. Toxicity from prostate studies which delivered conventionally fractionated radiotherapy and a prostate SABR boost

(References contained in full reference list (Chapter 8))

Table C1 Clinical studies delivering prostate SABR using the Cyberknife™. Continued overleaf.

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions)	Technique	PTV definition	Dose-volume objectives/ constraints	Dose, fractionation (BED (Gy); α/β=1.5) and prescription isodose if reported	Duration	Use of androgen deprivation	Outcome*
Fuller et al 2008 [57] Prospective phase II	10	Maximum follow-up 12 months	Low and intermediate	Cyberknife™ Fiducials Urinary catheter MRI fusion α-blockers Aimed to mimic HDR brachytherapy	Prostate + up to 2cm of SV + 2mm (except: i) posteriorly at the point where prostate abuts rectum where margin reduced to 0mm) ii) in intermediate risk + 5mm expansion posterolaterally	PTV: V38.4Gy≥95% Dmax: 76Gy Rectal wall: Dmax= 38Gy Rectal mucosa: Dmax= 28.5Gy Urethra: Dmax= 45.6Gy Bladder: Dmax= 45.6Gy	38Gy in 4 fractions (279) Prescribed to 56% isodose (median, range: 49%-67%, all relative to maximum value of 100%)	NR	NR	Fall in median PSA from 6.9ng/ml at baseline to 0.95ng/ml at 4 months (=86% reduction)
Friedland et al 2009 [68] Prospective	112	24 months	Low (majority), intermediate and high All T1-T2	Cyberknife™ 4 Fiducials MRI fusion	Prostate and proximal 1cm of SV + 5mm (3mm posteriorly)	PTV: V35Gy≥95% Rectum: V36Gy<1cc Bladder: V37Gy<10cc	35 to 36Gy in 5 fractions (198-209)	5 consecutive days	Yes- 19% (n=21)	Fall in mean PSA from 6.0ng/ml at baseline to 3.1ng/ml at one month. Mean PSA nadir of 0.6ng/ml at 18 months. 95% of patients with PSA nadir of ≤1.0ng/ml at 3 years. 3 PSA failures (based on persistently rising PSA)
Kang et al (2011) [70] and Choi et al (2007) [361] Retrospective	44	13 months (4-46)	T1c-T3b Low, intermediate and high (majority)	Cyberknife™ 6 fiducials in sacrum or prostate	Low risk: prostate only + 4mm (2mm posteriorly) Intermediate or high risk: prostate and SVs +4mm (2mm posteriorly)	PTV: 95% covered by 77-80% isodose Rectum: Dmax=100% V50%<50%	32-36Gy in 4 fractions (203-252) Prescribed to isocentre, 95% of PTV covered by 77-80% isodose	4 consecutive days	Yes-89% (n=39)	5-year biochemical free survival 93.6% (100% in low and intermediate patients, 91% in high risk patients, all failures in high risk group, Phoenix). Median PSA nadir 0.1ng/ml (range 0 to 1.13ng/ml) after median of 13 months

Table C1 cont. Clinical studies delivering prostate SABR using the Cyberknife™. Continued overleaf.

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions)	Technique	PTV definition	Dose-volume objectives/ constraints	Dose, fractionation (BED (Gy); α/β=1.5) and prescription isodose if reported	Duration	Use of androgen deprivation	Outcome*
Townsend et al 2011 [71] Retrospective	37	11.5 weeks	Low (majority), intermediate and high	Cyberknife™ 3-4 fiducials MRI fusion	Prostate + 5mm (3mm posteriorly)	PTV: V100%: ≥97% Dmax: 115% Rectum: D1cc<36Gy V50%<50Gy Bladder: D10cc<37Gy	35 -37.5Gy in 5 fractions (198-225) Prescription isodose: 85%	NR	Yes- 25% (n=12)	Fall in mean PSA from 9.34ng/ml at baseline to 2.41ng/ml at mean of 12 weeks (n=28 for this analysis, includes boost and non-boost patients- see 'boost' table)
Jabbari et al 2012 [72]	20	18.1 months (12.9-43.5)	Mainly low and favourable intermediate	Cyberknife™, 3 fiducials, MRI fusion	Prostate +/- Some or all SV on case by case basis 0-2mm margin, no overlap with rectum	Rectum: V75%<2cc Bladder: V75%<2cc Urethra: V120%<10% Plus other constraints similar to HDR brachytherapy	38Gy in 4 fractions (279) Prescription isodose 60-80%	Mostly 4 consecutive days	No	Median PSA nadir 0.47ng/ml, no evidence of progression
King et al 2012 [61] Prospective phase II	67	32.4 months	Low and favourable intermediate Previous TURP excluded	Cyberknife™ Fiducials	Prostate + 5mm (3mm posteriorly)	Rectum: V50%<50% V80%<20% V90%<10% V100%<5% Bladder: V50%<40% V100%<10% Femoral heads: V40%<5%	36.25Gy in 5 fractions (211)	5 consecutive days (n=22) or alternate days (n=45)	No	4-year biochemical relapse free survival 94% (95% CI 85-102%; Phoenix)

Table C1 cont. Clinical studies delivering prostate SABR using the Cyberknife™. Continued overleaf.

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions)	Technique	PTV definition	Dose-volume objectives/ constraints	Dose, fractionation (BED (Gy); α/β=1.5) and prescription isodose if reported	Duration	Use of androgen deprivation	Outcome*
Lee et al 2012 [74] Retrospective	29	41 months (12-69)	Low, intermediate (majority) and high	Cyberknife™, 3 or 4 fiducials, Vacuum bag	Prostate +5mm (2-3mm posteriorly)	PTV: V100%>95% Rectum: V50%<50% V100%<5%	35-37.5Gy in 5 fractions (198-225)	Consecutive days (48%) Alternate days (52%)	Yes - 21% (n=6)	Fall in median PSA from 7.96ng/ml at baseline to median nadir of 0.33ng/ml after 23 months 4-year biochemical relapse free survival 86% for all patients and 88% for those without androgen deprivation therapy 2 PSA failures (Phoenix) PSA bounce in 28% (increase >0.2ng/ml) at median of 9 months, median bounce 0.69ng/ml
McBride et al 2012 [73] Prospective phase I	45	44.5 months (0-62)	Low ≤80cc prostate IPSS≤15	Cyberknife™, 4 fiducials, urethra visualised with catheter if necessary MRI fusion for some Bowel prep	Prostate + 5mm (3mm posteriorly)	PTV: V100%≥95% Rectum: V36<1cc Bladder: V37.5<5cc Urethra: V49<10% Bulb: V29.5<50%	36.25-37.5Gy in 5 fractions (211-225; plus 1 patient, non-protocol dose) Prescription isodose 70% to 90%	Median time: 7 days (range 4-20) At least 12 hours between fractions	Not within 6 months of irradiation	3-year biochemical free survival 97.7% (Phoenix) Fall in median baseline PSA from 4.9ng/ml (range 1.4-9.4ng/ml) at baseline to 0.91ng/ml after 1 year PSA bounce in 20% (increase>0.4ng/ml) at median of 11.6months

Table C1 cont. Clinical studies delivering prostate SABR using the Cyberknife™. Continued overleaf.

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions)	Technique	PTV definition	Dose-volume objectives/ constraints	Dose, fractionation (BED (Gy); α/β=1.5) and prescription isodose if reported	Duration	Use of androgen deprivation	Outcome*
Aluwini et al 2013 [60] Prospective	50	23 months	Low (majority) and intermediate ≤90cc prostate and IPSS ≤15	Cyberknife™ 4 fiducials Low fibre diet, Bowel prep, Urinary catheter MRI fusion	Prostate +3mm	PTV: V38Gy≥100% Dmax<57Gy Rectal wall Dmax<38Gy, Rectal mucosa Dmax<28.5Gy, Whole rectum D1cc<32.5Gy, Bladder: Dmax=41.8Gy, D1cc<38Gy, Urethra: Dmax=45.6Gy D5%<45.5Gy, D10%<42Gy, D50%<40Gy Sigmoid/ intestine: 28.5Gy, Femoral head: 24Gy	38Gy in 4 fractions (279) (plus 44Gy in 4 fraction boost to dominant lesion in 14 patients)	4 consecutive days	No	2-year biochemical control: 100% (Phoenix) Median PSA nadir 0.6ng/ml in patients with ≥24 months follow-up PSA bounce in 14% (7; defined as any transient rise in PSA), mean time to bounce 12 months (range 4.0 to 22 months)

Table C1 cont. Clinical studies delivering prostate SABR using the Cyberknife™. Continued overleaf.

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions)	Technique	PTV definition	Dose-volume objectives/ constraints	Dose, fractionation (BED (Gy); α/β=1.5) and prescription isodose if reported	Duration	Use of androgen deprivation	Outcome*
Bolzicco et al 2013 [59] Prospective	100	36 months (6-76)	Low, intermediate and high (minority)	Cyberknife™ 4 fiducials Empty rectum Urinary catheter to identify urethra at planning MRI fusion Low gas diet	Prostate + one third of SV + 5mm (3mm posteriorly)	PTV: V35Gy≥95% Rectum: V38Gy<5%, Bladder: V40Gy<5% Urethra: V40Gy<5%, Penile bulb: V29Gy<25% Femoral head: V25Gy<25%	35Gy in 5 fractions (198) Prescription isodose 80%	5 consecutive days	Yes- 29% (n=29)	4 episodes of biochemical relapse (Phoenix) 3-year biochemical progression free survival 94.4% (95% CI: 85.3-97.9%) Fall in median pre-SABR PSA from 5.03ng/ml at baseline to 0.73ng/ml at 1 year and 0.67ng/ml at 2 years and 0.45ng/ml at 3 years. For patients receiving androgen deprivation: median pre-SABR PSA 1.90ng/ml falling to 0.26, 0.30 and 0.18ng/ml at 1, 2 and 3 years. For patients not receiving androgen deprivation, median pre-SABR PSA 6.31, falling to 0.93ng/ml, 0.87ng/ml and 0.62ng/ml at 1, 2 and 3 years PSA bounce in 12% of those not receiving androgen suppression (defined as transient rise in PSA), median bounce 1.08ng/ml after median of 23 months

Table C1 cont. Clinical studies delivering prostate SABR using the Cyberknife™. Continued overleaf.

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions)	Technique	PTV definition	Dose-volume objectives/ constraints	Dose, fractionation (BED (Gy); α/β=1.5) and prescription isodose if reported	Duration	Use of androgen deprivation	Outcome*
Oliai et al 2013 [78] Retrospective	70	31 months (13-51)	Low (majority), intermediate and high	Cyberknife™ 4 fiducials MRI fusion	Prostate +/- proximal 2cm of SV + 5mm (3mm posteriorly)	PTV: V100%: ≥95% Rectum: V36Gy: <1cc 50% isodose within rectum Bladder: V37Gy: <10cc	35Gy- 37.5Gy in 5 fractions (198-225) 35Gy: n=5 36.25Gy: n=36 37.5Gy: n=29 Prescription isodose: 75-85%	7-15 days	Yes- 33% (n=23)	3 year actuarial freedom from biochemical failure (Phoenix): for all patients: 94.5%, for low, intermediate and high risk patients: 100%, 95% and 77.1% respectively. For low dose patients (35Gy and 36.25Gy), median nadir to date: 0.3ng/ml. For high dose patients (37.5Gy), median nadir to date: 0.2ng/ml. PSA bounce in 9% of those not receiving androgen suppression (increase≥0.2ng/ml) at median of 19 months. Dose response for intermediate and high risk patients (p=0.0363) with 3 year freedom from biochemical failure of 72% and 100% in patients receiving low and high dose respectively. Trend only (p=0.0775) if low risk patients included

Table C1 cont. Clinical studies delivering prostate SABR using the Cyberknife™. Continued overleaf.

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions)	Technique	PTV definition	Dose-volume objectives/ constraints	Dose, fractionation (BED (Gy); α/β=1.5) and prescription isodose if reported	Duration	Use of androgen deprivation	Outcome*
Tree et al 2014 [77]	51	15 months	Low and intermediate	Cyberknife™	NR	NR	36.25Gy in 5 fractions (211)		Yes- 25% (n=13)	For hormone naïve patients: fall in median PSA from 7.5ng/ml at baseline to median of 1.9mg/ml at 12 months. No biochemical recurrences
Seattle group (some overlap between patient populations):										
Meier et al 2010 [69] Prospective phase II	211	NR	Low and intermediate	Cyberknife™ Fiducials MRI fusion	Prostate (+ SV if intermediate risk) Margins NR	NR	40Gy in 5 fractions 36.25Gy in 5 fractions to proximal SV if intermediate risk (253 to prostate, 211 to SV)	NR	No	Fall in median PSA from 5.2 at baseline to 0.9ng/ml at 12 months and 0.7ng/ml at 18 months. 1 PSA failure (Phoenix).
Meier et al 2012 [107] Prospective phase II (Intermediate risk patients only reported - some overlap with patients from Meier et al 2010)	129	30 months (range 10-42)	Intermediate	Cyberknife™ Fiducials MRI fusion	Prostate (+ SV if intermediate risk) Margins NR	NR	40Gy in 5 fractions 36.25Gy in 5 fractions to seminal vesicles Prescription isodose NR	NR	No	Fall in median PSA from 5.9 at baseline to 0.8ng/ml at 12 months, 0.38 at 24 months and 0.2ng/ml at 36 months. One biochemical failure at 3 months (Phoenix). 3-year biochemical progression free survival 99.2%

Table C1 cont. Clinical studies delivering prostate SABR using the Cyberknife™. Continued overleaf.

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions)	Technique	PTV definition	Dose-volume objectives/ constraints	Dose, fractionation (BED (Gy); α/β=1.5) and prescription isodose if reported	Duration	Use of androgen deprivation	Outcome*
Georgetown group (some overlap between patient populations):										
Chen et al 2013 [76] Data collection prospective, review retrospective including studies below	100	28 months (17-42)	Low, intermediate (majority) and high	Cyberknife™ Fiducials MRI fusion	Prostate + proximal SV up to split of left and right SV +5mm (3mm posteriorly)	PTV: V36.25≥95% Rectum: V50%<50% V75%<25% V80%<20% V90%<10% V100%<5% V36Gy<1cc Bladder: V50%<40% V100%<10% V37Gy<5cc Prostatic urethra: Dmax≤133% Membranous urethra: V37Gy<50% Penile bulb: V29.5Gy<50% Sigmoid colon: V30GY<1cc Testicles: D20%<2Gy	35 or 36.25Gy in 5 fractions (198 or 211) Prescription isodose ≥75%	Consecutive or alternate (range 5 to 16 days)	Yes- 11% (n=11)	Fall in median PSA from 6.2ng/ml to 0.49ng/ml at 2 years One biochemical failure (in high risk patient (Phoenix) 2-year biochemical RFS 99% PSA bounce (>0.2ng/ml) in 31% of 0.5ng/ml (median) after median of 15 months
Ju et al 2013 [89] (Intermediate risk patients only- some overlap with patients in Chen et al 2013)	41	21 months (13-27.5)	Intermediate	Cyberknife™, Fiducials MRI fusion	Prostate + proximal SV up to split of left and right SV +5mm (3mm posteriorly)		35 or 36.25Gy in 5 fractions (198 or 211) Median prescription isodose 77% (75%-80%)	Over 1-2 weeks- consecutive or alternate	No	Fall in mean baseline PSA from 7.67g/ml at baseline to mean of 1.35ng/ml at 12 months and 0.64ng/ml at 21 months. One biochemical failure (Phoenix) 2-year biochemical RFS 97.6%
Obayomi-Davis et al 2013 [127] (Hormone naïve patients only, some overlap with patients in Chen et al 2013)	97	32.4 months (minimum 24 months)	Low, intermediate (majority) and high	Cyberknife™ Fiducials MRI fusion	Prostate + proximal SV up to split of left and right SV +5mm (3mm posteriorly)		35 or 36.25Gy in 5 fractions (198 or 211)	Over 1-2 weeks- consecutive or alternate	No	Fall in median baseline PSA from 5.9ng/ml at baseline to median of 0.5ng/ml at 24 months. One biochemical failure (Phoenix) 2-year biochemical RFS 99%

Table C1 cont. Clinical studies delivering prostate SABR using the Cyberknife™. Continued overleaf.

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions)	Technique	PTV definition	Dose-volume objectives/ constraints	Dose, fractionation (BED (Gy); α/β=1.5) and prescription isodose if reported	Duration	Use of androgen deprivation	Outcome*
Georgetown group continued (some overlap between patient populations):										
Bhattasali et al 2014 [123] Data collection prospective, review retrospective (Hormone naïve patients only, some overlap with patients in Chen et al 2013)	228	45.6 months	Low, intermediate (majority) and high	Cyberknife™ Fiducials MRI fusion	Prostate + proximal SV up to split of left and right SV +5mm (3mm posteriorly)	PTV: V36.25≥95% Rectum: V50%<50% V75%<25% V80%<20% V90%<10% V100%<5% V36Gy<1cc Bladder: V50%<40% V100%<10% V37Gy<5cc Prostatic urethra: Dmax≤133% Membranous urethra: V37Gy<50% Penile bulb: V29.5Gy<50% Sigmoid colon: V30GY<1cc Testicles: D20%<2Gy	35 or 36.25Gy in 5 fractions (198 or 211) Prescription isodose≥75%	Treatment delivered over 1 to 2 weeks	No	6 biochemical failures (Phoenix) 2-year biochemical relapse free survival 97.2%

Table C1 cont. Clinical studies delivering prostate SABR using the Cyberknife™. Continued overleaf.

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions)	Technique	PTV definition	Dose-volume objectives/ constraints	Dose, fractionation (BED (Gy); α/β=1.5) and prescription isodose if reported	Duration	Use of androgen deprivation	Outcome*
Flushing Group (some overlap between studies):										
Katz et al 2013 [75] Retrospective	304 Group 1: n=50 Group 2: n=254	Group 1: 72 months (9-78) Group 2: 60 months (8-72)	Low (majority), intermediate and high	Cyberknife™ 4 fiducials MRI fusion Bowel prep Rectal amifostine	Low risk: Prostate + 5mm except 3mm posteriorly at rectum Intermediate risk: Prostate + proximal half SV + 5mm except 3mm posteriorly High risk: Prostate + proximal half SV + 5mm except 3mm posteriorly + 8mm on affected side.	PTV: Group 1: V35Gy≥96% Group 2: V36.25Gy≥96%	Group 1: 35Gy in5 fractions (198) Group 2: 36.25Gy in 5 fractions (211)	NR	Yes- 19% (n=57)	5-year biochemical recurrence free survival (Phoenix): 97% for low risk (no difference with dose), 90.7% for intermediate risk, 74.1% for high risk. Median PSA at 5years: 0.12ng/ml- dose had no impact on PSA No deaths due to prostate cancer PSA bounce in 17% (>0.2ng.ml), median time to bounce 30 months, median bounce 0.55ng/ml
Katz et al 2014 [90] Retrospective (low and intermediate risk patients only, differences in PTV and coverage- some overlap with patients in Katz et al above)	477 Group 1: n=154 Group 2: n=323	72 months (0-96)	Low (majority) and intermediate	Cyberknife™ 4 fiducials MRI fusion Bowel prep Rectal amifostine	Prostate + 5mm (3mm posteriorly)	Group 1: V35Gy≥95% Group 2: V36.25Gy≥95% Rectum: V50%<50% V80%<20% V90%<10% V100%<5% Bladder: V50%<40% V100%<10% Femoral heads: V40%<5%	Group 1: 35Gy in5 fractions (198; low and low-intermediate risk patients only)) Group 2: 36.25Gy in 5 fractions (211) Prescription isodose: 83-87%	NR	Yes-11% (n=51)	Fall in baseline mean PSA from 5.3ng/ml to median of 0.11 at 7 years 7-year freedom from biochemical failure 93.7% for all, 95.6% in low risk, 89.3% in intermediate risk No deaths due to prostate cancer No impact of dose on biochemical outcome for low and low-intermediate risk patients No impact of androgen deprivation on outcome PSA bounce in 16% (>0.2ng.ml), median time to bounce 36 months, median bounce 0.5ng/ml

Table C1 cont. Clinical studies delivering prostate SABR using the Cyberknife™

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions)	Technique	PTV definition	Dose-volume objectives/ constraints	Dose, fractionation (BED (Gy); α/β=1.5) and prescription isodose if reported	Duration	Use of androgen deprivation	Outcome*
Pooled data										
King et al 2013 [121] Prospective phase II POOLED DATA from 8 institutions Includes patients from institutions of: King et al 2012, Fuller et al 2008, Friedland et al 2009, Bolzicco et al 2010, Katz et al 2010, Meier et al 2010, Mcbride et al 2012, Chen et al 2013 (see above)	1100	36 months	Low (majority), intermediate and high	Cyberknife™ 3 or 4 fiducials Alpha cradle	Prostate +5mm (3mm posteriorly) for homogeneous planning, Prostate + 2mm (0mm posteriorly) for heterogeneous planning	For majority: Volume receiving prescription dose≥95% Rectum: V50%<50% V80%<20% V90%<10% V100%<5% Bladder: V50%<40% V100%<10% Femoral heads: V40%<5%	35- 40Gy in 5 fractions (homogeneous dose distributions in >90%, normalised to 90% isodose, heterogeneous (HDR-like) in remainder)	Consecutive in >95%, alternate day in remainder	Yes -14% (4 months in all) (n=147)	5-year biochemical relapse free survival 93% for all, 95%, 84% and 81% for low, intermediate and high risk patients (Phoenix) No difference in biochemical relapse free survival with dose No impact of androgen deprivation on outcome Median nadir 0.2ng/ml at 3 years PSA bounce in 16% (of >0.2ng/ml) in 16% after median of 18 months, median bounce 0.5ng/ml For patients with ≥5 years follow-up, 5-year biochemical relapse free survival: 99% for low risk and 93% for intermediate risk. No impact of dose of androgen deprivation on outcome

ASTRO: American Society for Radiation Oncology, BED: biologically equivalent dose, CI: confidence interval, Dmax: maximum dose, Dx: Dose received by x% or xcc of volume, HDR: high dose rate, IPSS: International Prostatic Symptom Score, MRI: magnetic resonance imaging, NR: not reported, PSA: prostate specific antigen, PTV: planning target volume, Vx: volume receiving at least x% of prescription dose or xGy * See Appendix A for Phoenix/ASTRO definitions of biochemical failure

Table C2 Clinical studies delivering prostate SABR using a linear accelerator. Continued overleaf.

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions)	Technique	PTV	Dose-volume objectives/ constraints	Dose, fractionation (BED (Gy); α/β=1.5) and prescription isodose if reported	Duration	Use of androgen deprivation	Outcome*
Pawlicki et al 2007 [362] (NB planning study only)	2	N/A-Planning study	NR	IMRT Fiducials kV imaging Vacuum bag	NR	Rectum: V19.5≤35% V31.5≤17% 1cc≤38.5Gy Bladder: V19.5≤50% V31.5≤25% Central PTV (urethra): Dose≤37Gy Femoral heads: V22≤1% Body: Dmax≤40.0Gy Peripheral dose: ≤15Gy for each beam angle	36.25Gy in 5 fractions (211)	NR	NR	More homogenous dose using IMRT compared to Cyberknife™. Improved urethral sparing and more rapid rectal dose fall-off with IMRT compared to Cyberknife™. 7 field IMRT plan resulted in 40% reduction in dose to periphery compared to 5-field plan
Pham 2010 [80] and Madsen 2007 [95] Prospective phase I/II	40	60 months (range 9-96)	Low	Linear accelerator Flex prone position 6 non-coplanar beams, quasi coronal beams tangential to the rectum, 3 fiducials, portal images Low gas diet with simethecone	NR	Prostate:5 D100%≥30.2Gy	33.5Gy in 5 fractions (183) Prescribed to isocentre	5 consecutive fractions for most patients	NR	5-year biochemical free survival 93% (Phoenix) and 71% (ASTRO) 5-year overall survival 75%- no known prostate cancer related deaths Median PSA nadir 0.65 ng/ml, median time to nadir 24 months PSA bounce (not defined) in 22.5%

Table C2 cont. Clinical studies delivering prostate SABR using a linear accelerator. Continued overleaf.

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions)	Technique	PTV	Dose-volume objectives/ constraints	Dose, fractionation (BED (Gy); α/β=1.5) and prescription isodose if reported	Duration	Use of androgen deprivation	Outcome*
Boike et al 2011 [83] Prospective phase I	45 Dose escalation trial- 15 patients in each of 3 dose levels	Group 1: 30months (3-36) Group 2: 18months (0-30) Group 3: 12 months (3-18)	Low to intermediate Prostate volume ≤60cc IPSS≤15 No previous TURP	TomoTherapy® or linear accelerator based- Trilogy system (including CBCT). Fiducials or Calypso® electromagnetic beacons. Bowel prep including enema. Rectal balloon Full bladder Catheter at simulation 4mg dexamethasone each fraction	Prostate +3mm	PTV: V100%≥95% Rectum: Anterior rectal wall Dmax 105%, Lateral rectal walls V90%<3cc Posterior rectal wall max: ≤45% Bladder wall Dmax 105% and D10cc<18.3Gy Prostatic urethra Dmax ≤105%	Group 1: 45Gy in 5 fraction (315;n=15) Group 2: 47.5Gy in 5 fractions (348;n=15) Group 3: 50Gy in 5 fractions (383; n=15)	One fraction at least every 36hours	Yes- 22% (n=10)	Biochemical failure free survival 100% (1 patient excluded from analysis as subsequently was found to have GS9 disease- this patient has relapsed; Phoenix)
Alongi et al 2013 [84] Prospective phase I/II	40	11 months (range 5-16 months)	Low (majority) and intermediate	Linear accelerator (VMAT 10MV FFF) MRI fusion Daily CBCT, intra-prostatic calcifications identified in all patients and used as surrogates for fiducials Rectal-prostate spacer in selected cases (n=8)	Prostate (+ some or all SV in higher risk) + 3-5mm	CTV: V95%>99% D99%>95% Dmax≤105% PTV: V95%>95% D99%>90% Dmax≤105% Rectum: V18Gy<35% V28Gy<10% V32Gy<5% Bladder: D1%<35Gy	35Gy in 5 fractions (198)	Alternate day	Yes	PSA reduction in all patients

Table C2 cont. Clinical studies delivering prostate SABR using a linear accelerator. Continued overleaf.

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions)	Technique	PTV	Dose-volume objectives/ constraints	Dose, fractionation (BED (Gy); α/β=1.5) and prescription isodose if reported	Duration	Use of androgen deprivation	Outcome*
Macias et al 2014 [85] Prospective	17	5 months (range 1-10)	Low, intermediate (majority) and high IPSS>20 and previous history urinary retention excluded	Helical TomoTherapy® Laxatives and catheter at planning Enema pre-treatment, drinking protocol, low gas diet, steroid enema each night CBCT	Low risk: Prostate + proximal 1cm of SV + 7-9mm anteriorly, 5-6mm laterally and 2-4mm posteriorly Intermediate and high risk: Prostate + whole SV + 7-9mm anteriorly, 5-6mm laterally and 2-4mm posteriorly	CTV: V100%≥95% PTV: V98%>95% D98%≥98% D2%≤103% Rectum: V43Gy≤10% V40Gy≤15% V37Gy≤20% V34Gy≤30% V28Gy≤40% Posterior rectum: V37Gy≤2% Bladder: V43Gy≤20% V40Gy≤30% V37Gy≤40% Femoral heads: V28Gy≤5% Penile bulb: V40Gy≤60% V28Gy≤90%	Low risk: 43.8Gy in 8 fractions (204) Intermediate and high risk: 45.2Gy in 8 fractions (215)	Alternate days	Yes- 82%	Only acute toxicity reported- see Table C5

Table C2 cont. Clinical studies delivering prostate SABR using a linear accelerator. Continued overleaf.

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions)	Technique	PTV	Dose-volume objectives/ constraints	Dose, fractionation (BED (Gy); α/β=1.5) and prescription isodose if reported	Duration	Use of androgen deprivation	Outcome*
Fort Myers Group (different studies):										
Mantz et al 2007 [79] Prospective phase II	22	NR (18 patients followed-up for a t least 1 month)	Low Prostate volume<60cc IPSS<18	Linear Accelerator CBCT	Prostate + 3mm	Rectum: Dmax:=85% Bladder: Dmax=100% Femoral heads: Dmax=50%	36.25Gy in 5 fractions (211) Prescription isodose chosen so OAR dose maxima not exceeded	Alternate days	NR	Only acute toxicity reported- see Table C5
Mantz et al 2010 [58] Prospective phase II	54	26 months, minimum follow-up 12 months	Low	Linear Accelerator CBCT Calypso®-electromagnetic fiducials tracking	NR	NR	40Gy in 5 fractions (253)	Alternate days	NR	Fall in median PSA from 6.9ng/ml at baseline to 1.0 and 0.3ng/ml at 12 and 24 months respectively

Table C2 cont. Clinical studies delivering prostate SABR using a linear accelerator

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions)	Technique	PTV	Dose-volume objectives/ constraints	Dose, fractionation (BED (Gy); α/β=1.5) and prescription isodose if reported	Duration	Use of androgen deprivation	Outcome*
Sunnybrook Group (different studies):										
Quon et al 2011 [81] Prospective phase I/II	30	3 months (range 1-6 months)	Low and intermediate	Linear accelerator IMRT Fiducials	Prostate + 5mm [128]	NR	40Gy in 5 fractions (253)	Once weekly, over 29 days	NR	NR
Loblaw et al 2013 [82] Prospective phase I/II	84	55 months (13-68)	Low Prostate volume <60cc IPSS≤19	Linear accelerator 6MV IMRT 3 fiducials, portal imaging Drinking protocol, Vacuum bag	Prostate + 4mm	Prostate: V35Gy>99% PTV V33.25Gy>99% Dmax≤105% Rectum: V28Gy≤40% V32Gy≤33% Bladder: V32Gy≤40% Penile bulb: V20Gy≤90%	35Gy in 5 fractions (198)	Once weekly fractions, over 29 days	Yes	5-year biochemical control 98% (95% CI: 96-100%; Phoenix). One episode of biochemical failure. 5-year biochemical control 97% (95%CI: 93-100%, ASTRO) Based on n=83 Median nadir 0.51ng/ml, median time to nadir 12months. PSA bounce (>0.2ng/ml) in 42%, median time to bounce 18 months Repeat biopsy at 36 months in 71, 4% (n-=3) positive biopsies

ASTRO: American Society for Radiation Oncology, BED: biologically equivalent dose, CBCT: cone beam computer tomography, CI: confidence interval, Dmax: maximum dose, Dx: Dose received by x% or xcc of volume, FFF: flattening filter free, IMRT: intensity modulated radiotherapy, MRI: magnetic resonance imaging, NR: not reported, PSA: prostate specific antigen, PTV: planning target volume, TURP: transurethral resection of the prostate, VMAT: volumetric modulated arc therapy, Vx: volume receiving at least x% of prescription dose or xGy * See Appendix A for Phoenix/ASTRO definitions of biochemical failure

Table C3 Clinical studies delivering prostate SABR as a boost following conventional fractionation. Continued overleaf.

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions for risk groups in each study)	Technique	PTV	Dose-volume objectives/ constraints	Dose, fractionation (BED (Gy); α/β=1.5) and prescription isodose if reported	Duration	Use of androgen deprivation	Outcome*
Katz et al 2010 [86]	73	33 months (22-43)	Intermediate and high	Cyberknife™ 4 fiducials Bowel prep Rectal amifostine	Boost: prostate + 5mm except 3mm posteriorly in region of the rectum	PTV: V100%=95%	45Gy in 25 fractions conformal + 18- 21Gy in 3 fractions (189-218), 83-87% isodose	3 consecutive days (2 weeks after conformal radiotherapy)	Yes- 48% (n=36)	3-year biochemical relapse free survival of 89.5% for intermediate risk and 77.7% for high risk. PSA nadir of 0.5ng/ml achieved in 72% after 24 months 10 PSA failures (Phoenix) at median of 15 months.
Miralbell et al 2010 [87]	50	63 months (18-88)	Low, intermediate and high	Linear accelerator IMRT Rectal balloon Infra-red detected surface markers Empty bladder, Catheter at planning	For boost: “dominant tumour region within prostate” (essentially horseshoe shape round urethra) +/- SV + 3mm margin	Initial constraints: Rectum and bladder: V50%< 50% V90%<30% Dmax=95% Urethra: NR but priority factor 100%	Conventional EBRT: 64-64.4Gy in 1.8 to 2Gy fractions Stereotactic boost: 10-16Gy in 2 fractions of 5 to 8Gy (193-268)	Boost:1 week between fractions	Yes- 66% (n=33)	5-year Biochemical relapse free survival 98% +/- 1.9% (Phoenix)

Table C3 cont. Studies delivering prostate SABR as a boost following conventional fractionation. Continued overleaf.

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions for risk groups in each study)	Technique	PTV	Dose-volume objectives/ constraints	Dose and fractionation (BED (Gy); α/β=1.5)	Duration	Use of androgen deprivation	Outcome*
Oermann et al 2010 [88]	24	9.3 months (6.6-16.9)	Intermediate and high	Cyberknife™ 4 fiducials Enemas Low gas/motility diet,	Prostate, regions of extracapsular spread, proximal SV plus 5mmm (3mm posteriorly)	PTV: V100%≥95% Rectum: V50%<50% V80%<20% V90%<10% V100%<5% D1cc ≤36Gy Bladder: D10cc<100% Penile bulb: V15Gy<50% Membranous urethra: V18Gy<50% Dmax:133% Bladder: D10cc< 19.5Gy Sigmoid colon and other bowel: D1cc<15Gy	19.5Gy in 3 fraction boost, prescription isodose ≥75% then 50.4Gy in 28 fractions IMRT (215)	Consecutive or alternate days	Yes- 42% (n=10)	Fall in median PSA from 10.6ng/ml at baseline to 1.5ng/ml at 6 months in patients not receiving androgen deprivation
Townsend et al 2011 [71] Retrospective	11	11.5 weeks (for boost and non-boost patients)	Low (majority), intermediate and high	Cyberknife™ 3-4 fiducials MRI fusion	Prostate + 5mm (3mm posteriorly)	PTV: V100%: ≥97% Dmax: 115% Rectum: D1cc<36Gy V50%<50Gy Bladder: D10cc<37Gy	Boost: 17.6-25Gy in 2-5 fractions (non-boost dose NR) Prescription isodose: 85%	NR	Yes- 25% (n=12)	Fall in mean PSA from 9.34ng/ml at baseline to 2.41ng/ml at mean of 12 weeks (n=28 for this analysis, includes boost and non-boost patients)

Table C3 cont. Studies delivering prostate SABR as a boost following conventional fractionation

Study and type of study (where available)	Patient no.	Follow-up (range)	Risk group (see Appendix B for definitions for risk groups in each study)	Technique	PTV	Dose-volume objectives/ constraints	Dose and fractionation (BED (Gy); α/β=1.5)	Duration	Use of androgen deprivation	Outcome*
Jabbari et al 2012 [72]	18	23.5 months (range12.6-34.5)	Intermediate and high	Cyberknife™, 3 fiducials MRI fusion	Prostate +/- Some or all SV on case by case basis, 0-2mm margin, no overlap with rectum	NR	Pelvic IMRT 45-50Gy (fraction size NR) 19Gy in 2 fraction boost (238 to 256 if 1.8-2Gy fractions for non-boost dose) Prescription isodose 60-80%	Mostly 2 consecutive days	Yes	Median PSA nadir 0.10ng/ml, no evidence of progression

ASTRO: American Society for Radiation Oncology, BED: biologically equivalent dose, Dmax: maximum dose, Dx: Dose received by x% or xcc of volume, IMRT: intensity modulated radiotherapy, MRI: magnetic resonance imaging, NR: not reported, PSA: prostate specific antigen, PTV: planning target volume, Vx: volume receiving at least x% of prescription dose or xGy * See Appendix A for Phoenix/ASTRO definitions of biochemical failure

Table C4 Toxicity from prostate SABR Cyberknife™ studies. Continued overleaf.

Study	Toxicity grading system	BED (Gy) to acute Tissues (αβ=10)	Acute genitourinary/ urinary toxicity grade (n) (within 3 months unless stated)				Acute gastrointestinal/ rectal toxicity grade (n) (within 3 months unless stated)				BED (Gy) to late tissues (αβ=3)	Late genitourinary/ urinary toxicity grade (n) (beyond 3 months unless stated)				Late gastrointestinal/ rectal toxicity grade (n) (beyond 3 months unless stated)			
			1	2	3	4	1	2	3	4		1	2	3	4	1	2	3	4
Fuller et al 2008 [57]	RTOG	74	NR			0	60% (6)		0		158	NR				NR			
Friedland et al 2009 [68]	NR	-	6%¤ (7)		1%¤ (1)	0	NR		0			NR		0		NR		1%§ (1)	0
Kang et al 2011 [70]	CTCAEv 3	58-68	30% (13)	14% (6)	0	0	16% (7)	9% (4)	0	0	117-144	9% (4)	7% (3)	0	0	2% (1)	11% (5)	0	0
Townsend et al 2011 [71]¥ (SABR alone patients)	CTCAEv 3	60-66	57% (21)	5% (2)	8% (3)	0	14% (5)	0	0	0	117-131	NR				NR			
Jabbari et al 2012 [72]†	CTCAEv 3	74	NR	45% (9)	0	0	NR	5% (1)	0	0	158	3%‡ (1)	8%‡ (3)	**5%‡ (2)**	0	5%‡ (2)	3%‡ (1)	0	0
King et al 2009 [363] (acute) and 2012 [61] (late)	RTOG	63	NR			0	NR			0	124	23% (13)	5% (3)	**4% (2)**	0	14% (8)	2% (1)	0	0
Lee et al 2012 [74]	CTCAEv 4	60-66	10% (3)	24% (7)	0	0	24% (7)	3% (1)	0	0	117-131	7% (2)	3% (1)	**3% (1)**	0	3% (1)	0	0	0

Table C4 cont. Toxicity from prostate SABR Cyberknife™ studies. Continued overleaf.

Study	Toxicity grading system	BED (Gy) to acute Tissues (αβ=10)	Acute genitourinary/ urinary toxicity grade (n) (within 3 months unless stated)				Acute gastrointestinal/ rectal toxicity grade (n) (within 3 months unless stated)				BED (Gy) to late tissues (αβ=3)	Late genitourinary/ urinary toxicity grade (n) (beyond 3 months unless stated)				Late gastrointestinal/ rectal toxicity grade (n) (beyond 3 months unless stated)			
			1	2	3	4	1	2	3	4		1	2	3	4	1	2	3	4
McBride et al 2012 [73]	CTCAEv 4	63-66	59% (25)	19% (8)	0	0	31% (13)	7% (3)	0	0	124-131	17% (7)	17% (7)	**2% (1)**	0	7% (3)	7% (3)	**5% (2)**	0
Aluwini 2013 et al [60]*	RTOG	74	NR	15%	8%	0	NR	12%	2%	0	158	NR	10%	**6%**	0	NR	3%	0	0
Bolzicco et al 2010 [59]†	RTOG	60	34%	12%	0	0	27%	18%	0	0	117	4%	3%	**1%**	0	2%	1%	0	0
Tree et al 2014 [77]	RTOG	63	NR				51% (26)	24% (12)	0	0	124	NR				NR	2% (1)	0	0
Seattle Group (some overlap between patient populations)																			
Meier et al 2010 [69]	CTCAEv 3	63-72	NR	20%	0	0	NR	9%	0	0	124-147	NR	6%	**0.4 % (1)**	0	NR	1%	0	0
Meier et al 2012 [107]	CTCAEv 3	63-72	NR	20%	0	0	NR	9%	0	0	124-147	NR	10%	**1% (1)**	0	NR	2%	0	0

Table C4 cont. Toxicity from prostate SABR Cyberknife™ studies. Continued overleaf.

Study	Toxicity grading system	BED (Gy) to acute Tissues (αβ=10)	Acute genitourinary/ urinary toxicity grade (n) (within 3 months unless stated)				Acute gastrointestinal/ rectal toxicity grade (n) (within 3 months unless stated)				BED (Gy) to late tissues (αβ=3)	Late genitourinary/ urinary toxicity grade (n) (beyond 3 months unless stated)				Late gastrointestinal/ rectal toxicity grade (n) (beyond 3 months unless stated)			
			1	2	3	4	1	2	3	4		1	2	3	4	1	2	3	4
Georgetown Group (some overlap between patient populations)																			
Chen et al 2013 [76]**	CTCAEv 3	60-63	36% (36)	35% (35)	0	0	35% (35)	5% (5)	0	0	117-124	23% (23)	17% (17)	**1% (1)**	0	12% (12)	1% (1)	0	0
Ju et al 2013 [89]†	CTCAEv 4	60-63	NR	NR	0	0	NR	NR	0	0	117-124	NR	44% (18)	0	0	NR	**7% (3)**	0	0
Arscott et al 2014 [116]† $	CTCAEv 3	60-63	NR	40%			NR				117-124	NR	41%			NR			
Katz et al (toxicity for each dose level shown separately for 2013 paper, some overlap between patients in 2013 and 2014 papers)																			
Katz et al 2013 [75] (35Gy group)	RTOG	60	72% (36)	4% (2)	0	0	76% (38)	4% (2)	0	0	117	6%	4%	0	0	4%	2%	0	0
Katz et al 2013 [75] (36.25Gy group)	RTOG	63	75% (190)	5% (12)	0	0	74% (189)	4% (9)	0	0	124	8%	9%	**2%**	0	5%	5%	0	0
Katz et al 2014 [90]	RTOG	60-63	NR	NR	0	0	NR	NR	0	0	117-124	NR	NR	**2% (9)**	0	NR	NR	0	0

Table C4 cont. Toxicity from prostate SABR Cyberknife™ studies

Study	Toxicity grading system	BED (Gy) to acute Tissues (αβ=10)	Acute genitourinary/ urinary toxicity grade (n) (within 3 months unless stated)				Acute gastrointestinal/ rectal toxicity grade (n) (within 3 months unless stated)				BED (Gy) to late tissues (αβ=3)	Late genitourinary/ urinary toxicity grade (n) (beyond 3 months unless stated)				Late gastrointestinal/ rectal toxicity grade (n) (beyond 3 months unless stated)			
			1	2	3	4	1	2	3	4		1	2	3	4	1	2	3	4
Oliai et al (toxicity for low dose and high dose groups shown separately)																			
Oliai et al 2013 [78] (35 and 36.25Gy group)	RTOG	60-63	54% (22)	22% (9)	5% (2)	0	20% (8)	7% (3)	0	0	117-124	41% (7)	32% (13)	0	0	10% (4)	10% (4)	0	0
Oliai et al 2013 [78] (37.5Gy group)	RTOG	66	59% (17)	14% (4)	3% (1)	0	14% (4)	0	0	0	131	48% (14)	24% (7)	7% (2)	0	10% (7)	7% (2)	0	0
Pooled data																			
Freeman and King 2011 [118] (pooled)	RTOG	60-63	NR				NR				117-124	25% (10)	7% (3)	**3% (1)**	0	13% (6)	3% (1)	0	0

CTCAEvX: Common Terminology Criteria of Adverse Events version X, NR: not reported, RTOG: Radiation Therapy Oncology Group, *Acute toxicity at two weeks post treatment and late toxicity at 6 months, ** highest toxicity reported at 1 month and 12 months post-treatment, † acute toxicity considered as within 6 months of SABR, and late toxicity thereafter, ¥ acute toxicity included up to 24 week assessment for some patients, median follow-up to 12 weeks, ‡ includes 18 additional patients treated with SABR as boost following pelvic external beam radiotherapy as well as SABR monotherapy patients; § timing of grade 3 rectal toxicity not reported- presumed to be late, $ 2-year cumulative incidence of acute and late urinary obstruction alone reported, ¤urinary retention reported in 7 patients, none of whom required catheterisation: judged as grade 1 or 2, one patient required trans-urethral resection of the prostate: judged to be grade 3

Table C5 Toxicity from prostate SABR linear accelerator studies. Continued overleaf.

Study	Toxicity grading system	BED (Gy) to acute Tissues (αβ=10)	Acute genitourinary/ urinary toxicity grade (n) (within 3 months unless stated)				Acute gastrointestinal/ rectal toxicity grade (n) (within 3 months unless stated)				BED (Gy) to late tissues (αβ=3)	Late genitourinary/ urinary toxicity grade (n) (beyond 3 months unless stated)				Late gastrointestinal/ rectal toxicity grade (n) (beyond 3 months unless stated)			
			1	2	3	4	1	2	3	4		1	2	3	4	1	2	3	4
Madsen et al 2007 [95] and Pham et al 2010 [80]§	RTOG/CTCAEv2	56	28% (11)	21% (8)	**3% (1)**	0	26% (10)	13% (5)	0	0	108	23% (NR)	13% (NR)	**3% (NR)**	0	23% (NR)	8% (NR)	0	0
Alongi et al 2013 [84]‡	CTCAEv4	60	20% (8)	40% (16)	0	0	15% (6)	10% (4)	0	0	117	12% (3)	4% (1)	0	0	0	0	0	0
Macias et al 2014 [85]		68-71	70%	6%	0	0	50%	0	0	0	124-130	NR				NR			
Fort Myers group (different studies)																			
Mantz et al 2007 [79]†	CTCAEv3	63	28% (5)	0	0	0	0	6% (1)	0	0	124	NR				NR			
Mantz et al 2010 [58]	CTCAEv3	72	NR				NR				147	NR	0			NR	0		
Sunnybrook group (different studies)																			
Quon et al 2011 [81]*	CTCAEv3	72	57%	13%	0	0	67%	3%	0	0	147	NR				NR			
Loblaw et al 2013 [82]	CTCAEv3	60	71%	19%	1%	0	67%	10%	0	0	117	2%	5% (4)	0	0	35%	7%	0	**1% (1)**

Table C5 cont. Toxicity from prostate SABR linear accelerator studies

Study	Toxicity grading system	BED (Gy) to acute Tissues (αβ=10)	Acute genitourinary/ urinary toxicity grade (n) (within 3 months unless stated)				Acute gastrointestinal/ rectal toxicity grade (n) (within 3 months unless stated)				BED (Gy) to late tissues (αβ=3)	Late genitourinary/ urinary toxicity grade (n) (beyond 3 months unless stated)				Late gastrointestinal/ rectal toxicity grade (n) (beyond 3 months unless stated)			
			1	2	3	4	1	2	3	4		1	2	3	4	1	2	3	4
Boike et al (toxicity for each dose level shown separately)																			
Boike et al 2011 [83] 45Gy arm	CTCAEv3	86	20% (3)	27% (4)	0	0	40% (6)	0	0	0	180	20% (3)	13% (2)	0	0	7% (1)	7% (1)	0	**0**
Boike et al 2011 [83] 47.5Gy arm	CTCAEv3	93	33% (5)	7% (1)	0	0	13 (2)	27% (4)	0	0	198	20% (3)	13% (2)	7% (1)	0	27% (4)	7% (1)	0	**0**
Boike et al 2011 [83] and Kim et al 2014 [117] [¥] 50Gy arm	CTCAEv3	100	33% (5)	33% (5)	0	0	47% (7)	7% (1)	0[¥]	0[¥]	217	0	0	7% (1)	0	33% (5)	0	**7%[¥] (4)**	**3%[¥] (2)**

CTCAEvX: Common Terminology Criteria of Adverse Events version X, NR: not reported, RTOG: Radiation Therapy Oncology Group,
§ late toxicity considered as toxicity beyond 1 month; *acute toxicity at 5 weeks (peak in symptoms reported at this time point), [†] acute toxicity reported at 1 month only, [‡] late toxicity from 6 months, [¥]Acute and late grade 3 and 4 rectal toxicity for 50Gy in 5 fraction arm from Kim et al [117] which included 15 patients from the original phase I trial and 46 additional patients treated within phase II component of the trial. Sufficient detail was provided to allow categorisation of the timing of grade 3 and 4 acute and late rectal toxicity to become the same as that reported in the phase I component of the trial (i.e. acute and late toxicity within and beyond 3 months of radiotherapy). All other data in this row is from original phase I trial with 15 patients.

Table C6 Toxicity from prostate studies which delivered conventionally fractionated radiotherapy and a prostate SABR boost

Study	Toxicity grading system	BED (Gy) to acute Tissues (αβ=10)	Acute genitourinary/ urinary toxicity grade (n if available)				Acute gastrointestinal/ rectal toxicity grade (n if available)				BED (Gy) to late tissues (αβ=3)	Late genitourinary/ urinary toxicity grade (n if available)				Late gastrointestinal/ rectal toxicity grade (n if available)			
			1	2	3	4	1	2	3	4		1	2	3	4	1	2	3	4
Katz et al 2010 [86]*	RTOG	82-89	72% (36)	4% (2)	0	0	75% (226)	5% (14)	0	0	126-142	5% (12)	5% (13)	**0.3% (1)**	0	5% (13)	2% (6)	0	0
Miralbell et al 2010 [87]**	RTOG	91-106	34% (17)	46% (23)	**4% (2)**	0	28% (14)	8% (4)	0	0	133-179	24% (12)	12% (6)	0	0	38% (19)	10% (5)	**10% (5)**	0
Oermann et al 2010 [88]†	CTCAEv 3	92	75% (18)	13% (3)	0	0	50% (12)	4% (1)	0	0	142	46% (11)	8% (2)	0	0	33% (8)	0	0	0
Townsend et al 2011 [71]¥ (Boost patients)	CTCAEv 3	38-43 + conventional	45% (5)	27% (3)	9% (1)	0	0	0	0	0	67-94 + conventional	NR				NR			
Jabbari et al 2012 [72]† (Boost patients)	CTCAEv 3	90-97	NR	39%	0	0	NR	17%	0	0	151-163	3%‡ (1)	8%‡ (3)	**5%‡ (2)**	0	5%‡ (2)	3%‡ (1)	0	0

CTCAEvX: Common Terminology Criteria of Adverse Events version X, NR: not reported, RTOG: Radiation Therapy Oncology Group,

* Acute toxicity considered as occurring and resolving within 5 months, ** Acute toxicity during radiotherapy, late toxicity at 6 months and beyond, † acute toxicity considered as within 6 months of SABR, and late toxicity thereafter, ¥ acute toxicity included up to 24 week assessment for some patients, median follow-up 12 weeks, ‡ includes 18 additional patients treated with SABR as boost following pelvic external beam radiotherapy as well as SABR monotherapy patients

Appendix D: Systematic review search strategy

1	exp Neoplasms, Radiation-Induced/
2	exp Neoplasms, Second Primary/
3	second cancer?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
4	second primary cancer?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5	secondary cancer?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
6	secondary carcinom*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
7	second tumo?r?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8	secondary tumo?r?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
9	second malignancy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
10	second malignancies.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
11	secondary malignanc*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
12	second neoplasm?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease

	supplementary concept, unique identifier]
13	secondary neoplasm?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
14	integral dose.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
15	radiation-induced neoplasm?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
16	radiation induced neoplasm?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
17	radiation-induced cancer?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
18	radiation induced cancer?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
19	radiation-induced tumo?r?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
20	radiation induced tumo?r?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
21	radiation-induced carcinom*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
22	radiation induced carcinom*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
23	radiotherapy-induced neoplasm?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

24	radiotherapy induced neoplasm?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
25	radiotherapy-induced cancer.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
26	radiotherapy induced cancer.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
27	radiotherapy-induced tumo?r?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
28	radiotherapy induced tumo?r?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
29	radiotherapy-induced carcinom*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
30	radiotherapy induced carcinom*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
31	radiotherapy-induced cancer?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
32	radiotherapy induced cancer?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
33	radiotherapy-induced second primary cancer?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
34	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 0r 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	exp Prostatic Neoplasms/
36	prostat* cancer?.mp. [mp=title, abstract, original title, name of substance word, subject heading

	word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
37	prostat* carcinom*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
38	prostat* neoplasm?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
39	prostat* tumo?r?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
40	prostat* adenocarcinom*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
41	35 or 36 or 37 or 38 or 39 or 40
42	exp Radiotherapy Planning, Computer-Assisted/ or exp Radiotherapy Dosage/ or exp Radiotherapy/ or exp Radiotherapy, Conformal/ or exp Radiotherapy, Intensity-Modulated/ or exp Radiotherapy, Computer-Assisted/ or exp Radiotherapy, High-Energy/
43	exp Brachytherapy/
44	(implant adj6 radiotherapy).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
45	(interstitial adj6 radiotherapy).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
46	(seed adj6 radiotherapy).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
47	(seed adj6 implant).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
48	(permanent adj6 implant).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

49	implant radiation.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
50	interstitial radiation.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
51	(implant adj6 radiation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
52	(interstitial adj6 radiation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
53	3D conformal radiotherapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
54	3D-conformal radiotherapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
55	(2D adj6 radiotherapy).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
56	intensity modulated radiotherapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
57	intensity-modulated radiotherapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
58	intensity modulated radiation.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
59	intensity-modulated radiation.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
60	IMRT.mp. [mp=title, abstract, original title, name of substance word, subject heading word,

	keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
61	exp Protons/
62	proton radiotherapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
63	proton radiation.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
64	proton therapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
65	external beam radiotherapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
66	external-beam radiotherapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
67	EBRT.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
68	external beam radiation.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
69	external-beam radiation.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
70	tomotherapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
71	volumetric modulated arc therapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
72	VMAT.mp. [mp=title, abstract, original title, name of substance word, subject heading word,

	keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
73	rapidarc.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
74	rapid arc.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
75	arc therap*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
76	42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75
77	34 and 41 and 76