Hypofractionated dose painting radiotherapy for prostate adenocarcinoma

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor of Medicine by Joachim Kwok-Chiu Chan

Feb 2020

Contents

Declaration

I declare as sole author of this thesis that the works presented represents my personal research conducted during my clinical research fellowship at the Clatterbridge Cancer Centre NHS Foundation Trust between September 2014 and September 2016. This centred upon retrospective analysis of a pilot study (with input by consultant radiologist Christopher Romaniuk, consultant nuclear medicine Sobhan Vinjamuri and physicist Anthony Carver) and prospective analysis of patients recruited into the BIOPROP20 study at the Clatterbridge Cancer Centre, one of two recruiting centres (with input by physicist Martin Green).

Dr Syndikus is the chief investigator for both studies, and designed the studies, applied for funding, and developed the radiotherapy guidelines together with the physics team (Alan Nahum, Julian Uzan and Eva Onjukka). I and Dr Syndikus jointly recruited, performed radiotherapy delineation, and reviewed the patients in clinic. Radiotherapy planning was performed by radiographers and physicists (Thelma Rowntree, Laura Howard, John Brunt and Helen Mayles). Administration for BIOPROP20 was undertaken by Liverpool Cancer Trials Unit.

Acknowledgements

Foremost, I would like to express my sincere gratitude to my supervisor Dr Syndikus for the tireless support and time committed to provide advice and review of my work. I would also like to thank Prof Vinjamuri, Dr Eswar, Dr Carver and Dr Brunt for their help and expertise. Finally, I would like to thank my family for their faith and encouragement.

List of abbreviations

ADC	Apparent diffusion coefficient
AR	Androgen receptor
AUC	Area under the curve
bDFS	Biochemical disease free survival
BPH	Benign prostatic hypertrophy
CBCT	Cone beam computed tomography
CI	Confidence interval
CRT	Conformal-radiotherapy
CT	Computed tomography
CTV	Clinical target volume
DCE	Dynamic contrast enhanced
DIL	Dominant intra-prostatic lesion
DRE	Digital rectal examination
DVH	Dose volume histogram
DWI	Diffusion weighted imaging
EBRT	External beam radiotherapy

EQD2	Equivalent dose in 2 Gy per fraction
FDG	Fluorodeoxyglucose
FLA	Focal laser ablation
GI	Gastro-intestinal
GTV	Gross tumour volume
GU	Genito-urinary
HIFU	High-intensity focused ultrasound
ICRU	International Commission on Radiation Units and Measurements
IGRT	Image guided radiotherapy
IMRT	Intensity modulated radiotherapy
IRE	Irreversible electroporation
MLC	Multi-leaf collimator
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NCCN	National Comprehensive Cancer Network
NPV	Negative predictive value
OAR	Organs at risk
OD	Once daily

OS	Overall survival
PDT	Photodynamic therapy
PFS	Progression free survival
PPV	Positive predictive value
PSA	Prostate specific antigen
PSMA	Prostate specific membrane antigen
PTV	Planning target volume
QOL	Quality of life
RT	Radiotherapy
SABR	Stereotactic ablative body radiation therapy
SIB	Simultaneous integrated boost
SUV	Standardised uptake value
SUV_{max}	Maximum standardised uptake value
SV	Seminal vesicle
TAC	Time activity curve
TRUS	Trans-rectal ultrasound
TT90%P	Time to 90% peak standardised uptake value
TURP	Transurethral resection of the prostate

List of Tables

List of Figures

Abstract

Hypofractionated dose painting radiotherapy for prostate adenocarcinoma (J. Chan)

For prostate adenocarcinoma, standard radiotherapy delivers a homogeneous dose to the whole organ; higher doses improve biochemical control but increases toxicities. Dose painting with simultaneous integrated boost (SIB) to the dominant intra-prostatic lesions (DILs) may improve outcomes without increased toxicities. There is only one published study (of 28 patients) on prostate dose painting using the moderately hypofractionated UK standard schedule 60 Gy/20 #/4 weeks (with boost to 68 Gy)(Onjukka et al. 2016), and dose painting with boosts to both prostate and pelvic lymph nodes using this dose fractionation schedule have not previously been described. To identify boost volumes, visible tumour lesions (DILs) are primarily delineated using multiparametric MRI. An alternative may be choline PET/CT; in this thesis, we used the tracer ^{18}F choline which was available during the time of patient recruitment.

This thesis will describe the dynamic tracer uptake profile of ^{18}F choline and the effect of bicalutamide on it; the difference in boost volume using either MRI or ^{18}F choline PET alone and compare this to the combination of MRI and ^{18}F choline PET/CT with and without bicalutamide; and the feasibility and tolerability of dose painting with a moderately hypofractionated schedule. This involves analysis of imaging, radiotherapy plans, and follow up of patients within the pilot study and the BIOPROP20 trial. Briefly, patients were offered to take part in the research if they had newly diagnosed intermediate or high risk histologically confirmed prostate adenocarcinoma staged as T2a-4, N0, M0, with pelvic nodal risk of 15% - 40% (Roach formula). In terms of planning aims, the radiation dose to the prostate was 60 Gy with a boost to the DIL of 68 Gy, and if treated, the pelvic nodes was 45 Gy with a boost to involved nodes of 50 Gy.

Dynamic imaging with ^{18}F choline PET/CT showed that tracer uptake was higher in tumour compared to benign tissue. Bicalutamide reduced whole prostate volume by 17%. If patients had PET/CT scans after 2-3 months of bicalutamide, there were no DILs on the 90 minutes static scan for around a third of patients, and the size of the detected DILs were significantly smaller when compared to corresponding MRI. Median DICE between MRI and PET/CT boost volumes were 0.51 and 0.61 when defined by SUV_{max} 60% threshold method and visual method respectively. If the final boost volume was defined by the combination of MRI and PET volume, the additional use of PET/CT significantly increased the overall boost volume when compared to using MRI alone.

It was possible to increase the dose to the prostatic boost volumes to 68 Gy for most patients; in some patients with boost volumes close to the OARs or large boost volume, the boost dose was lower to achieve the dose constraints for normal tissues (rectum, bowel,

bladder and urethra). The treatment was well tolerated with acute toxicity peaking at week 6 at the latest and with acceptable late toxicity.

In conclusion, the addition of ^{18}F choline PET/CT to MRI for prostate dose painting radiotherapy planning can significantly alter the boost volume, and PET/CT should be performed without bicalutamide. Planning and delivery of dose painting with a moderately hypofractionated schedule are both feasible and clinically acceptable regarding toxicity. The presented planning protocol has been used for a multicentre, randomised Phase III trial (PIVOTALboost); this should demonstrate any long term toxicity and clinical benefits of dose painting radiotherapy with this protocol when compared to conventional radiotherapy.

1 Introduction

1.1 Prostate Cancer

1.1.1 Epidemiology, staging and principals of treatment

Since the early 1990s, incidence of prostate cancer has increased by 44% in the UK, in part due to prostate specific antigen (PSA) screening(1). Currently, it is the commonest cancer in men in the UK, with 47,200 new cases in 2015. One in 8 men will be diagnosed with it in their lifetime, and most will be at an early stage with organ-confined disease(2). Approximately 70% of prostate cancers arise in the peripheral zone with 30% in the central gland(3), and disease may be unifocal or multifocal within the prostate(4). Recognised risk factors include increasing age, ethnicity (Afro-Caribbean heritage) and family history(5).

Disease assessment involves clinical staging (digital rectal examination (DRE) and multiparametric magnetic resonance imaging (mpMRI)), PSA levels, and histology (Gleason score and grade group)(2). Imaging of the prostate will be discussed in detail in subsequent sections of this introduction. PSA is a serine protease produced by both prostate epithelial cells and neoplastic prostatic cells. Therefore it can be raised for benign conditions such as benign prostatic hypertrophy (BPH) and prostatitis, or malignant conditions such as prostate adenocarcinoma. The Gleason score grades prostate adenocarcinoma based on degree of glandular differentiation and overall pattern of growth. The overall score is the summation of the primary and secondary patterns, ranging from 6 to 10, and gives a grade group of 1 to 5(6). These three factors are used to aid decision making by risk stratifying the disease to determine its overall clinical significance. A commonly used risk classification system is by NCCN as defined in Appendix 8.1(7). Although there are proposals for additional investigations that would further guide management decisions, such as by using novel biomarkers and risk calculators in the pre-biopsy setting to predict a positive prostate biopsy(8), and by molecular testing for men considered suitable for active surveillance with low risk and >10 years life expectancy (9), they are not currently in routine clinical use.

With localised disease, treatment aim is for cure whilst minimising toxicity. For intermediate and high risk disease, the two established modalities are surgery (radical prostatectomy +/-

lymph node dissection) and radiotherapy (external-beam radiotherapy (EBRT) +/- brachytherapy, with hormone therapy). As will be discussed in more detail later, many of these patients who have radical radiotherapy achieve disease control for several years (e.g. CHHiP showed that 91% of patients receiving 60Gy were biochemical or clinical failure free at 5 years(10)). Prostate cancer and its treatment are the leading cause of cancer years lived with disability. Therefore, consideration of survivorship issues including both acute and late toxicity is important.

Following radical treatment, patients are primarily assessed by clinical and biochemical monitoring. Biochemical endpoints involving PSA are used as surrogates for treatment efficacy, which can take several years to determine owing to the often slow natural history of the disease(6). Currently, biochemical failure after radiotherapy is defined by the Phoenix criteria: PSA rise of 2 ng/ml over the nadir(11).

1.2 Imaging in prostate cancer

1.2.1 MRI

MRI is currently recognised as the gold standard imaging modality for pre-treatment local staging of prostate cancer. It allows accurate identification and assessment of the local extent of disease, which aids selection of appropriate treatment strategies, without the use of ionising radiation or invasive procedures(12, 13). The technology has improved over time. Use of endorectal coils had allowed improved signal-to-noise ratio resulting in higher resolution images but with some image distortion(4). Modern MRI scanners do not require endorectal coils to provide highly detailed anatomy as they use higher field strength MRI imagers (e.g. 3Tesla (3T)) and multi-channel phased array surface coils(12, 13). An important advantage of using imaging is that TRUS guided biopsies mostly assess the peripheral zone only, which can lead to diagnostic errors with false negative results(4, 11).

MRI can perform multiple imaging sequences to assess different aspects of tumour biology(14). mpMRI uses a combination of high resolution anatomical (primarily T2w) and at least two functional (such as DWI, dynamic contrast enhanced (DCE) and magnetic resonance spectroscopy (MRS)) pulse sequences(6, 13). These individual sequences have

inherent strengths and weaknesses, which allows them to complement each other. Hence overall disease interpretation relies on combining these MRI sequences which improves accuracy of detection and localisation of tumours(4).

T2w MRI provides superior soft tissue contrast of the prostate(15-18). Normal tissues often exhibit high-signal intensity, whilst malignant tissues have low-signal intensity due to loss of glandular morphology. However low-signal intensity is not specific to cancer, and can indicate benign conditions such as post-biopsy haemorrhage, prostatitis, BPH, and post-treatment changes. Interpretation of the transitional zone is more difficult than the peripheral zone due to the presence of BPH, although BPH are generally well defined and round. T2w can determine whether tumour is confined to the prostate or whether there is extra-prostatic extension(19). In the latter, imaging can show the tumour directly extending outside the prostate and cause features such as asymmetry of the neurovascular bundle or prostate rotations. It can also determine seminal vesicle invasion, identified by low signal on a background of high signal normal tissue, although benign conditions of the seminal vesicles can again complicate interpretation such as calculi, clots or atrophy. Hence T2w sequencing is important to determine T-staging. Differing sensitivity and specificity values of T2w imaging have been reported due to differences in patient selection (affecting tumour characteristics) and the use of different standard comparators (e.g. biopsy, surgical specimens). For instance, T2w imaging alone by a 3T machine could identify large tumours (> 1 cm in diameter) with 80 – 90% accuracy, whilst smaller tumours had a lower accuracy(13).

DWI MRI relies on the random diffusion of water molecules within the extracellular space, and follows tissue planes and natural barriers(13, 20). This Brownian motion is restricted in regions of high cellular density and extracellular disorganisation, such as malignant tissues(14). By applying varying strengths of external magnetic gradients (b-values), moving water molecules acquire varying phase shifts according to the amount of motion, allowing a quantitative estimate of the overall water diffusion, which can create an apparent diffusion coefficient (ADC) map. In the peripheral zone, tumours are generally hyper-intense on DWI MRI and hypo-intense on ADC maps when compared to normal tissue. In the transitional zone, interpretation can again be more difficult due to BPH, which are also hypo-intense on ADC maps. The addition of DWI to T2w imaging improves sensitivity and allows better

detection of peripheral zone tumours(13). DWI is limited by poor spatial resolution and susceptibility to artefacts such as bowel gas(13).

DCE MRI assesses the perfusion and permeability of the microvasculature by using intravenous gadolinium-based contrast(14, 21). It involves rapid T1w imaging before, during and after IV contrast. Tumours have disorganised angiogenesis, which are highly permeable, generally resulting in more rapid and intense enhancement as well as faster washout. DCE is often interpreted by visual assessment and has a high sensitivity to detect malignant lesions and assess grade(13). As well as for preoperative staging including seminal vesicle invasion, DCE is particularly useful for identifying recurrence following primary treatments such as radiotherapy and focal ablation as they can cause anatomical and functional changes to which other sequences are susceptible. Limitations to DCE include poor spatial resolution and malignant tissue, especially if small and low grade, in the transitional zone have a similar enhancement to benign conditions such as BPH and prostatitis.

MRS is a functional imaging sequence, which identifies the relative concentrations of cellular metabolites such as choline and citrate(22). Choline is involved in membrane synthesis and the quantity is expected to be raised with cellular proliferation (14). Malignant tissues have high levels of choline, and low levels of citrate. MRS alone has been shown to predict cancer aggressiveness, and the addition of MRS to T2w MRI can increase specificity(13). However it also has poor spatial resolution and is technically challenging to perform. Interpretation of the imaging requires significant experience with variable results in multicentre studies when compared to other sequences. As a result, MRS is not often performed as part of prostate mpMRI.

In general, T2w allows optimal soft-tissue imaging and anatomically-defined tumour volumes to be identified(14), whilst the other functional sequences can confirm the detection of clinically significant higher grade intra-prostatic tumours. Overall, mpMRI has sensitivity and specificity values of 86% and 94% respectively for identifying lesions > 0.5 ml when compared to radical prostatectomy samples(13). In routine clinical practice, the Prostate Imaging – Reporting and Data System (PI-RADS) V2 framework is used to identify clinically significant prostate cancer on mpMRI, and this usually involves T2w and DWI sequences(23). PI-RADS V2 was able to correctly identify above 94% of cancer of ≥ 0.5 ml,

but was limited for Gleason ≥ 4+3 tumours of ≤ 0.5 ml size(24). An advantage of improved accuracy in detecting larger, higher grade tumours in the context of dose painting radiotherapy is that these lesions would likely benefit from dose escalation boosting, whilst smaller, lower grade tumours are likely to receive a sufficient dose without dose escalation boosting(11, 25).

For general radiotherapy planning, MRI can aid the delineating of structures that are more difficult to identify on the planning CT scan, such as prostatic apex which can reduce penile bulb dose and lead to reduced toxicity(26). It also allows more accurate delineation of the whole prostate, and has been found to reduce the total prostate clinical target volume (CTV) by 30% as well as inter-observer variation(27, 28). The mpMRI can be co-registered to the planning CT scan by using intra-prostatic fiducial markers as the reference landmark(29).

For identifying intra-prostatic lesions for dose escalation boosting, the evidence available are mostly from single institution studies and so are difficult to extrapolate to other institutions with different scanners. Also the studies primarily used pathology as the reference, and so limited the evaluation of this imaging modality to the specific patient population suitable for prostatectomy i.e. lower risk disease with lower disease burden when compared to the population suitable for radiotherapy. A recent study found mpMRI had sensitivity and specificity of 70% and 82% for detecting prostate cancer on histology(30). Another study showed that mpMRI based delineating achieved 44 – 89% tumour coverage (smallest lesion was 0.56 cc)(31). With estimated co-registration errors of 2 – 3 mm, a 5 mm margin improved this to 85-100%. Overall, mpMRI is able to guide tumour deleating for dose painting radiotherapy.

1.2.2 PET/CT

PET scanning is a functional and molecular imaging technique which uses a tracer (a positron-emitter bound to a targeted molecule) to assess the distribution of the targeted molecule (14). The tracer indirectly emits a pair of gamma rays. These are detected and a three dimensional reconstruction of the uptake can be created. Most modern machines have a CT scanner integrated with the PET scanner, allowing corresponding anatomical and functional information to be collected. Depending on the tracer characteristics, uptake can reflect

several biological processes including hypoxia, proliferation, metabolic activity, and perfusion(14). PET imaging is often more sensitive than MRI, but has a comparatively low spatial resolution(13).

Several tracers have been investigated for prostate cancer. However unlike MRI, there have not been large multicentre studies, which is partly due to scarcity of on-site cyclotrons at clinical trial research centres. Also comparing the accuracy of different tracers is difficult as institutions often use differing imaging protocols and image analysis methodologies(14).

The most commonly used compound in general oncology is ^{18}F fluorodeoxyglucose (FDG), a glucose analogue which is an indicator of glycolysis and metabolic activity, and is preferentially taken up more in malignant than benign tissue due to upregulation of GLUT-1 glucose transporters and increased glycolytic activity in cancers (Warburg effect)(13, 14). However in prostate cancer, it has been shown to perform poorly as lower grade disease do not rely on glycolysis and so have low levels of GLUT-1 expression related to inherently slower growth(6, 13, 32). Also ^{18}F FDG is not specific to malignancy but is also taken up in BPH and prostatitis(12, 13).

^{11}C acetate is taken up into the cell membrane of prostate cancer cells and is excreted primarily by the pancreas, making it suitable for prostate imaging. However ^{11}C has a short half-life of 20 minutes and so is only useful for centres with an on-site cyclotron. It has a higher sensitivity when compared to ^{18}F FDG, but it has a lower sensitivity and specificity compared to mpMRI (62% and 80%, vs. 82% and 95%)(13).

Choline is a cell membrane component, which is required by proliferating cells. It is transported into cells by choline kinase which is upregulated in prostate cancer (14). They are then phosphorylated and incorporated into the lipid cell membrane. ^{11}C choline and ^{18}F choline tracers have been used. The former has low urinary excretion, which is beneficial for prostate imaging, but a short half-life. The latter has a higher urinary excretion, but a longer half-life of 110 minutes(32). Studies of either tracer have often used different imaging protocols (such as tracer doses and tracer uptake time before scanning) and image analyses (such as using histopathology or MRI as the reference standard; correlation methods by laterality, sextants or octants; and determining imaging as positive for malignancy by visual

analysis or differing SUV thresholds), and have shown conflicting results (Tables 1-1, 1-2, 1-3). More studies have been performed for ^{11}C choline than ^{18}F choline. When comparing ^{11}C choline with histopathology, reported specificity ranges from 42.6% to 87.0%, and accuracy ranges from 59.6% to 84.0% (Table 1-1). When comparing ^{18}F choline with histopathology, reported specificity ranges from 76% to 90%, and accuracy ranges from 72% to 81% (Table 1-3). When correlating both choline and MRI with histopathology, ^{18}F choline has been shown in one study to perform better than MRI (accuracy 81% vs. 60% respectively; Table 1-4). This used a comparatively long tracer uptake time before PET scanning (static scanning at 48 minutes and 71 minutes after tracer injection)(33). Current evidence suggests that accuracy of ^{18}F choline PET is improved by increasing the tracer dose and by delayed scanning, but there is a lack of consensus on scanning protocols and the optimal techniques remain unclear(14).

Choline PET has been used to investigate intra-prostatic dose escalation radiotherapy planning. In a radiobiological modelling study, Chang et al. used ^{11}C choline with a tracer uptake time of over 60 minutes and SUV_{max} threshold of 60 and 70%. In planning and treatment studies, Pinkawa et al. used ^{18}F choline with a tracer uptake time of over 60 minutes and a threshold defined by a tumour-to-background SUV_{max} ratio of more than 2(33).

More recently, results from ^{68}Ga-labelled PSMA ligand PET imaging have been very encouraging and can now be used in routine clinical practice for patients with suspected recurrent following previous radical therapy in the UK. In the primary staging setting, PSMA-PET led to upstaging of disease and therefore treatment modification in 21% of patients(34, 35). PSMA-PET can detect intra-prostatic lesions in up to 95% of cases, and combining it with mpMRI can improve coverage of cancer on histology by providing complementary information(30, 36). Dose painting radiotherapy planning using PSMA PET/CT and mpMRI with dose fractionation of 2.0 to 2.2 Gy per fraction to the prostate is technically feasible(37).

Other radionuclide tracers have been used for prostate cancer but with fewer published studies. ^{18}F fluciclovine is a synthetic amino acid which undergoes increased uptake in malignant cells but also localises benign prostate hypertrophy nodules with similar avidity, and so its role in initial staging is not clear(38). ^{18}F MISO, CuATSM and FAZA have been used

to image hypoxic regions of the prostate which may be more radio-resistant, and FLT has been investigated for analysing tumour repopulation rates (14). However evidence for their use in dose painting radiotherapy planning is limited.

Limitations of PET imaging include spatial and temporal variability of the biological processes including perfusion, hypoxia and metabolic activity. With the former, these processes occur at a microscopic level and spatial resolution of individual voxels is generally poor, and so small lesions may not be detected due to partial voluming effects. With the latter, the reproducibility of imaging may be affected. Hence image analyses may be simplifying the various complex underlying processes(14). Currently, PET/CT for prostate cancer is primarily accepted for detecting recurrent disease as opposed to for primary staging, and in my thesis I will explore the value and additional benefits of adding choline PET to the staging and radiotherapy planning compared to mpMRI only.

Table 1-1 Studies correlating ^{11}C-choline PET and histopathology (All used PET/CT except Chang et al. who used PET and transmission scanning)

¤scan sequences were static except Chang et al. which was dynamic, * only pts who had radical prostatectomy in the study are included in this table (of these, 7 of 19 patients had preceding hormone therapy), † Unclear if contains patients from Farsad et al., ‡ All pts received chemotherapy before prostatectomy, n = number of patients, ND = not defined, PPV = positive predictive value, NPV = negative predictive value

Author	n	Correlation method	Uptake time	Tracer dose (MBq)	Scan sequence¤	Tumour size	Optimal method of tumour identification	Sensitivity	Specificity	PPV	NPV	Accuracy
Van den Bergh et al.(39)	49	octants	2 min	740 to 1000	over 5 min	> 5 mm diameter	Threshold of SUV_{max} 2.7	77.4%	44.9%	ND	ND	61.1%
Souvatzoglou et al.(40)	43	laterality	5 min	682 ± 75	over 3 min	ND	Not specified but highest uptake correlates with malignant segments in 79% of pts	ND	ND	ND	ND	ND
Bundschuh et al.(41)	20	manual delineation	5 min	544 to 773	over 3 - 5 min	mean 3.3 cm^3 (0.4 - 12.5 cm^3)	Fixed threshold SUV value of 4.9 ± 1.8 or variable threshold SUV_{max} of 75.6 ± 14%	ND	ND	ND	ND	ND
Giovacchini et al.(42)*	19	sextants	5min	370	over 4 min	ND	Threshold of SUV_{max} 2.5	71.6%	42.6%	64.0%	51.3%	59.6%

Farsad et al.(43)	36	sextants	5 min	370 to 555	over 5 min	ND	Visual analysis performed only	66%	81%	87%	55%	71%
Martorana et al.(44)†	43	individual nodules and sextants	5 min	370 to 555	over 5 min	ND	Visual analysis by sextants	65.6%	84.2%	87.7%	58.8%	72.5%
Testa et al.(45)	26	sextants	5 min	370 to 555	over 5 min	ND	Threshold of SUV_{max} 2.9	72%	65%	ND	ND	ND
Piert et al.(46)	14	using ex vivo MR and block face photography	5 min	700	over 7 min	0.03 - 12.6 cm^3	Not specified, but tumour to normal tissue ratio identified aggressive disease better than absolute value	ND	ND	ND	ND	ND
Reske et al.(47)	26	36 segments	5-10 min	1112 ± 131	over 3 min	> 5 mm diameter	Threshold of SUV_{max} 2.65	81%	87%	86%	83%	84%
Chang et al.(48)‡	8	at voxel level	Immediately	370	over 60 min	≥ 1 cm^3	Relative SUV thresholding of 60%	79 ± 13%	72 ± 17%	ND	ND	ND

Table 1-2 Sensitivity and specificity of ^{11}C choline PET for identifying malignancy with varying SUV_{max} threshold values

Author	n	Number of segments per prostate	Total number of segments analysed	SUV_{max} threshold	Sensitivity	Specificity
Giovacchini et al.(42)	19	6	114	2.5	71.6%	42.6%
Reske et al.(47)	26	36	936	2.65	81%	87%
Van den Bergh et al.(39)	49	24	1,176	2.7	77.4%	44.9%
Testa et al.(45)	26	6	156	2.9	72%	65%

Table 1-3 Studies correlating ^{18}F-choline PET and histopathology (all studies used ^{18}F-fluorocholine except Hartenbach et al. who used ^{18}F fluoroethylcholine)

¤ study included combination of newly confirmed diagnosis and recurrent prostate cancer pts, 2 of the pts had preceding hormone therapy

All studies used PET/CT except Kwee et al.*, Kwee e al.¤, and Hartenbach et al.†

Author	n	Correlation method	Uptake time (sequence and time per bed position)	Tracer dose	Tumour size	Optimal method of tumour identification	Sensitivity	Specificity	PPV	NPV	Accuracy
Schmid et al.(49)	10	subjective visual correlation	2 min (static over 3 min)	214 ± 14 MBq	ND	PET correlated with histopathology in 1 pt only	ND	ND	ND	ND	ND
Kwee et al.(50)*	15	sextants	10 min (static over 7 min)	3.3 to 4 MBq/kg	mean 4.9 ml	Threshold of SUV_{max} 5.6	64%	90%	ND	ND	72%
Kwee et al.(51)¤	26	sextants	7 min (static over 7 min) then 60min (static over 7 min)	3.3 to 4 MBq/kg	ND	Mean maligant-to-benign ratio increased from 1.4 to 1.8 on delayed scan	ND	ND	ND	ND	ND
Hartenbach et al.(52)†	38	direct analysis	Immediately (dynamic over 10 min), then 48 min (static over 3 min), then 71 min (static over 6 min)	3.3 MBq/kg	ND	Threshold of SUV_{mean} 3.4	63%	90%	83%	76%	81%
Pinaquy et al.(53)	47	sextants	Immediate (dynamic over 15 min), then 60 min (static over 2.5 min)	4 MBq/kg	ND	Threshold of SUV_{max} 4	60%	76%	ND	ND	ND
Beheshti et al.(54)	132	sextants	1 min (dynamic over 8 min) then 10 min (static over 4 min) then 90-120 min if abnormal at 10 min (static over 4 min)	4.1 MBq/kg	ND	Visual analysis performed only (highest SUV sextant had maximal tumoural infiltration)	ND	ND	ND	ND	ND

Table 1-4 Studies correlating both choline PET and MRI (Tesla of 1.5) with histopathology

Author	n	Correlation method	PET Tracer	PET tracer uptake time (sequence and duration)	PET tracer dose	MR techniques for prostate analysis	Tumour size	PET sensitivity	PET specificity	MRI sensitivity	MRI specificity	Conclusion
Van den Bergh et al.(39)	49	octants	^{11}C-choline	2 min (static over 5 min)	740 to 1000 MBq	T2w spin echo	> 5 mm diameter	77.4%	44.9%	33.5%	94.6%	PET (threshold SUV_{max} of 2.7) was more sensitive but less specific than MRI
Pinaquy et al.(53)	47	sextants	^{18}F-fluorocholine	Immediately (dynamic over 15 min), then 60 min (static over 2.5 min)	4 MBq/kg	T2w, DWI, DCE	ND	60%	76%	72%	69%	SUV_{max} threshold of 4 had higher specificity but lower sensitivity than DWI MRI

Testa et al.(45)	26	sextants	^{11}C-choline	5 min (static over 5 min)	370 to 555 MBq	T2w spin echo, MRS - endorectal coil used	ND	55%	86%	54%	75%	PET was more specific than either MRI or MRS, but not when both are combined (MRI/MRS specificity of 90%)
Yamaguchi et al.(55)	20	laterality	^{11}C-choline	5 min (static over 5 min)	370 MBq	T2w spin echo, MRS - endorectal coil used	ND	81%	ND	ND	ND	^{11}C-choline was superior to MRS
Hartenbach et al.(52)	38	direct correlation with histology	^{18}F-fluoroethycholine	Immediately (dynamic over 10 min), then 48 min (static over 2 min), then 71 min (static over 6 min)	3.3 MBq/kg	T2w spin echo - endorectal coil used	ND	90%	62%	73%	31%	PET visual analysis gave accuracy of 81%, whilst MRI gave accuracy of 60%

1.2.3 Pelvic lymph node staging

Prostate adenocarcinoma can spread to the regional pelvic lymph nodes. Conventional CT relies on morphological appearances and, considering up to 80% of metastatic lymph nodes have a short-axis diameter of < 7 mm, has a low sensitivity of around 25%(6, 32). MRI with diffusion weighted imaging (DWI) also performs poorly, with a prospective study showing lymph node region-based sensitivity of 19% and patient-based sensitivity of 43%(56). Overall, up to 25% of patients with presumed node negative disease on standard pre-operative staging scans are revealed to have metastasis on lymph node dissection(57). An alternative imaging modality which is not routinely used for lymph node staging is PET/CT(58, 59). The value of ^{18}F choline PET/CT in initial staging is unclear, with sensitivity ranging from 56% to 67%, and PPV ranging from 40% to 98%(60). A large prospective study involving 210 patients with intermediate and high risk disease showed that 41 patients (19.5%) had histologically involved nodes, and the sensitivity, specificity, PPV and NPV of ^{18}F choline PET were 56%, 94%, 40% and 97% (mean diameter of metastatic nodes was 10.3 mm)(61). This relatively low PPV contrasts with another study involving 47 patients with intermediate and high risk disease which showed that sensitivity and PPV of ^{18}F choline was 56% and 98% (median size of metastatic nodes was 9.2 mm)(53). Another study involving 48 patients with intermediate and high risk disease showed that sensitivity, specificity, PPV and NPV of ^{18}F choline PET were 67%, 93%, 86% and 82%(62).

In terms of pelvic lymph node regions that are at risk of metastasis, a mapping study of patients receiving extended pelvic lymph node dissection found that 81% of node positive patients had disease in the obturator and external iliac regions, 48% had disease in the internal iliac regions, and 37% had disease in the common iliac regions(63). Another surgical series show that internal iliac, external iliac, obturator, presacral, common iliac, and aortic bifurcation regions were involved in 35%, 26%, 25%, 9%, 3%, and 1% respectively of positive lymph nodes found in 34 patients(64).

For patients who are node negative on clinical staging, various tools have been developed to predict the risk of lymph node metastases. The Roach formula [10 x (Gleason score – 6) +

PSA x 2/3] is well established, although a study found that it overestimated risk as it was established prior to use of PSA screening which has led to stage migration(65, 66). More recent tools based on contemporary patients are available, such as updated Partin, MSKCC, and Briganti nomograms(67-69). These newer tools try to incorporate a measure of tumour bulk, and accuracy of these three tools are broadly similar(70). Despite the availability of them, the Roach formula remains in use due to its ease and convenience.

1.3 Hormone therapy in prostate cancer

Androgens bind to androgen receptors (AR), resulting in transcription of AR target genes that promote growth of normal and malignant prostatic tissue. Hormone therapy interferes with this process, causing accelerated apoptosis in normal, hyperplastic and dysplastic epithelial cells, leading to global glandular atrophy especially in the peripheral zone(6). The prostate gland volume is downsized by around 25 – 30%(27, 71). Furthermore, hormone therapy can improve outcomes by causing radio-sensitisation, improved oxygenation, and effects on micro metastases(72-74). There are two broad classes of non-surgical hormone therapy: LHRH agonists and anti-androgens(75).

LHRH agonists bind to LHRH receptors located in the anterior pituitary gland, resulting initially in a testosterone surge that can cause a tumour flare. However as the physiological levels of LHRH is pulsatile, the prolonged stimulation of LHRH receptors causes their downregulation and resultant downstream testosterone reduction to castrate levels(75). Anti-androgens (such as bicalutamide) are competitive inhibitors of the AR and do not cause reduction in testosterone levels, but renders the circulating androgens ineffective(73). For short course of hormone therapy (6 months of treatment), bicalutamide is most often used.

In the curative setting, hormone therapy is not used in isolation. This is supported by EORTC 30891 and Lu-Yao et al. studies: comparing observation and primary hormone therapy alone in non-metastatic patients, there was no difference in survival(76, 77)(Table 1-5).

When hormone therapy is used in combination with radical radiotherapy, no studies have directly compared the efficacy of LHRH agonist and antiandrogen, although studies 306 and 307 compared bicalutamide and castration (including medical castration with goserelin) and

found that there was no difference in overall survival or time to progression at 6.3 years follow up, and that bicalutamide was better tolerated than castration(78).

For early localised prostate cancer, there is little evidence to support the additional use of antiandrogens in addition to standard care. The SPCG-6 study showed that, when comparing standard care only and standard care with bicalutamide, there is no significant difference in progression free survival or overall survival in localised disease at 7.1 years follow up(79).

For locally advanced prostate cancer however, SPCG-6 did show significant benefit with the addition of bicalutamide on top of standard care(79). This is confirmed by RTOG 85-31, RTOG 86-10, EORTC 22863, and TROG 96.01(80-83).

In terms of duration of hormone therapy, EORTC 22961 showed that 6 months was inferior to 3 years in locally advanced disease(84). Also when specifically looking at high risk patients including those with Gleason 8 – 10, RTOG 92-02 showed that long term treatment did confer a significant survival advantage over short term treatment(85).

It should be noted that these studies used generally low radiation doses (< 70 Gy) compared to the modern era of dose escalation (> 70 Gy), where radiotherapy planning and delivery technologies have improved to allow conformal and IMRT planning resulting in higher doses delivered to the target volume whilst minimising doses to surrounding organs. Although there isn't a prospective randomised control trial to determine whether the benefit of hormone therapy in RT is maintained in the setting of dose escalation RT, evidence still suggests that long course hormone therapy significantly improves survival for intermediate and high risk disease compared to short course hormone therapy, such as the DART01/05 study where patients had 76 to 82 Gy delivered to the prostate and seminal vesicles(86-88).

As well as survival advantages, it is important to consider the toxicity of hormone therapy in the context of a disease where prognosis is generally good following radiotherapy. Toxicities include fatigue, hot flashes, gynaecomastia, metabolic (increased serum lipids, decreased insulin sensitivity, increased subcutaneous body fat and obesity), musculoskeletal (osteoporosis, muscle loss), neurocognitive (depression, mood swings), and sexual function(19, 77, 89). There is conflicting evidence regarding association between long-term

castration deprivation therapy and cardiovascular disease. EORTC 22863 found no difference in cardiovascular mortality between radiotherapy alone and radiotherapy + goserelin (3 years) group at 10 years follow-up. Furthermore, a meta-analysis combining 4,141 patients with unfavourable risk prostate cancer from eight prospective clinical trials found that the rate of cardiovascular death was not significantly different between patients given hormone therapy and those without (11.0% and 11.2%, p = 0.41)(90). However, analysis combining data from 1,372 patients from three prospective clinical trials found that 6 months of hormone therapy led to a shorter time to fatal myocardial infarction for those 65 years of age or older, but not in those below 65 years of age(91). This may therefore counteract the benefits of treatment in patients with cardiovascular morbidity (73, 75). Using anti-androgens instead of LHRH agonists can lead to improved quality of life such as sexual interest and physical capacity, and is generally more tolerable(78). It reduces the risk of osteoporosis, hot flashes and impotence, but has risk of gynaecomastia, breast pain, diarrhoea and hepatotoxicity(73, 92). Therefore a balance between the treatment benefits and the impact on quality of life should be weighed for each individual patient(75, 93).

In summary, there is evidence from multiple large randomised studies for the survival benefits of the addition of hormone therapy to conventional doses of radiotherapy in intermediate and high risk prostate cancer patients, and that longer duration of hormone therapy benefits patients with high risk features including locally advanced and Gleason ≥ 8 disease.

Table 1-5 Studies on the use of hormone therapy in radical treatment

Study name	Patient recruitment period	Study design	Number of patients	Patient characteristics	Radiotherapy dose fractionation	Radiotherapy technique	Hormone therapy used	Duration of hormone therapy	Outcome
EORTC 30891(76)	1990 to 1999	Prospectively randomised to hormone therapy alone or no treatment until symptomatic disease progression	985	Localised or locally advanced prostate cancer not suitable for or refused local curative treatment (T0-4, N0-2, M0)	-	-	Subcapsular orchidectomy or LHRH agonist (buserelin)	In the deferred arm, 2% started hormone therapy immediately, 54% started after a median of 2.8 years, 44% never started it	At 12.8 years, there was no difference in time to castration-resistant objective progressive disease or prostate cancer mortality
Lu-Yao et al.(77)	1992 to 2002	Retrospective data evaluating the association between primary hormone therapy and survival	19,271	Localised prostate cancer (≥ 66 years) without local therapy (T1 - 2)	-	-	Orchidectomy or LHRH agonists	≥ 180 days	At 10 years, prostate cancer specific survival was worse (80.1% vs. 82.6%) with no improvement in overall survival (30.2% vs. 30.3%) in primary hormone therapy group compared to conservative group
Studies 306 and 307(78)	1992 to 1993	Prospectively randomised to bicalutamide or castration (medical or surgical)	480	Locally advanced prostate cancer (T3 - 4)	-	-	Bicalutamide or castration (orchidectomy or goserelin)	Continuous	At 6.3 years, there was no difference in overall survival or time to progression between the bicalutamide and castration groups

Early Prostate Cancer Program (SPCG-6)(79)	1995 to 1998	Prospectively randomised to bicalutamide or placebo, starting after standard of care (radical prostatectomy, radiotherapy, or watchful waiting)	1,218 (of whom 65 had radiotherapy)	Localised (T1 - 2, N0/Nx) or locally advanced (T3 - 4, any N; or any T, N+)	Not specified	Not specified	Bicalutamide or placebo	Until disease progression	At 7.1 years, addition of bicalutamide to standard of care did not offer significant benefits in progression free survival or overall survival for localised disease, but did offer significant benefits for locally advanced disease
RTOG 85-31(80)	1987 to 1992	Prospectively randomised to RT only or RT+hormone therapy (LHRH agonist starting during last week of radiotherapy, continue indefinately or until progression)	977	Locally advanced disease -T3 or N1 (28% of patients)	64 Gy - 71 Gy to prostate, 44 Gy – 46 Gy to pelvis	Conventional planning (pelvic lymph node RT in 26% and 29% of patients in RT only and RT+hormones groups respectively)	LHRH agonist (goserelin) started during last week of RT or only at disease progression	Indefinitely or until progression	At 10 years, adjuvant hormones improved OS from 39% to 49% ($p < 0.01$) and disease-specific mortality from 78% to 84% ($p < 0.01$). Subset analysis showed no survival benefit for Gleason ≤ 6. Patients derived most benefit if treated with hormones for more than 5 years.
RTOG 86-10(81)	1987 to 1991	Prospectively randomised to RT alone or RT with 4 months of hormone therapy (prior to and during RT)	456	Bulky disease (T2 - 4) with palpable surface area of > 25 cm^2 on DRE	65 Gy – 70 Gy to prostate, 45 Gy to pelvic lymph node	Conventional planning (pelvic lymph node irradiation in 9% and 7% of patients in RT only and RT+hormone groups respectively)	Maximum androgen blockade (goserelin and flutamide)	2 months before and during radiotherapy	At 10 years, disease-specific mortality reduced from 36% to 23% with 4 months of hormones ($p = 0.01$), but improvement in overall survival was not statistically significant (34% vs. 43%, $p = 0.12$).

EORTC 22863(82)	1987 to 1995	Prospectively randomised to RT alone or RT with 3 years of concurrent and adjuvant hormone therapy	415	Localised with high risk features or locally advanced disease	70 Gy to prostate and SV, 50 Gy to pelvic lymph nodes	3D CRT (4 field technique for whole pelvis, 3 or 4 field technique for prostate and seminal vesicles)	Goserelin starting on first day of radiotherapy (with cyproterone acetate for first month only)	3 years	At 10 years, addition of hormones improved disease-free survival from 23% to 48% ($p < 0.01$), overall survival from 40% to 58% ($p < 0.01$), and prostate-cancer mortality from 30% to 10% ($p < 0.01$).
TROG 96.01(83)	1996 to 2000	All patients receiving RT were prospectively randomised to no hormones therapy, 3 months hormone therapy, and 6 months hormone therapy	818	Locally advanced disease, T2b - T4 N0 (stratified by PSA and Gleason)	66 Gy to prostate and SV	3D CRT with CT (multifield arrangements allowing shielding where reasonable)	3 months of goserelin with flutamide starting 2 months before radiotherapy, or 6 months of the same starting 5 months before radiotherapy	None, 3 months, or 6 months	At 10 years follow up, use of either 3 or 6 months hormone therapy improved outcomes (of note, 6 months compared to no hormones improved overall survival (from 57.5% to 70.8%, $p < 0.01$))
EORTC 22961(84)	1997 to 2001	Prospectively randomised to RT with either 6 months or 36 months of hormone therapy (non-inferiority study)	970	Locally advanced prostate cancer (73% had T3)	70 Gy to prostate and SV, 50 Gy to pelvic lymph nodes	3D CRT with 3 or 4 fields with two target volumes: whole pelvis and prostate+SV	LHRH agonist with either bicalutamide or flutamide	For both cohorts, first 6 months of maximal androgen blockade (anti-androgen started 1 week before RT, LHRH agonist started with RT); For 36 month hormones cohort, subsequent	At 5 years, overall survival with 6 months hormone therapy was inferior to 36 months hormone therapy (81% vs. 84.8%; HR p = 0.65 for non-inferiority).

								2.5 years was LHRH agonist alone	
RTOG 92-02(85)	1992 to 1995	Prospectively randomised to RT with either 4 months or 28 months hormone therapy	1,554	Locally advanced disease (T2c - T4)	65 - 70 Gy to prostate, 44 - 50 Gy to pelvic lymph nodes	Conventional planning (4 field technique for whole pelvis, followed by conedown to the prostate and seminal vesicles)	Goserelin and flutamide	All patients had 4 months of hormone therapy (2 months before and 2 months during RT); long term hormone therapy cohort received a further 24 months	At 10 years, 28 months of hormone therapy significantly improved disease free survival (22.5% vs. 13.2%; $p < 0.01$). Overall survival benefit at 10 years was noted only in Gleason 8 - 10 patients (45.1% vs. 31.9%; $p < 0.01$).
DART01/05 GICOR(86)	2005 to 2010	Prospectively randomised to RT with 4 months or 28 months of hormone therapy	355	T1c - 3b N0 M0 with intermediate-risk and high-risk features	76 Gy – 82 Gy to prostate and SV (pelvic lymph node RT was left to participating centre)	3D CRT with 6 fields	LHRH agonist (goserelin)with flutamide or bicalutamide	LHRH agonist started 2 months before RT (antiandrogen started at the same time, continued for 2 months only), continued for either 4 months or 28 months in total	At 5 years, 28 months hormone therapy improved biochemical disease-free survival (90% vs. 81%, $p = 0.01$), and overall survival (95% vs. 86%, $p < 0.01$) compared to 4 months hormone therapy. Subgroup analysis showed that benefits were more evident in high-risk than intermediate-risk patients.

1.4 Prostate Radiotherapy

1.4.1 External beam radiotherapy techniques (IMRT, IGRT)

External beam radiotherapy is a standard definitive treatment option for prostate cancer(94). It involves the use of a linear accelerator to produce megavoltage photons of between 4 and 20 MV energy(95). The primary objective of EBRT is to deliver a therapeutic dose to the target volume whilst minimising dose to benign neighbouring tissues, thereby achieving high tumour control probability and minimising normal tissue complication probability(20, 96).

Over the last decades, EBRT planning and delivery methods have evolved with improving technological advancements. Modern treatment protocols use rotational IMRT (VMAT) or tomotherapy in conjunction with IGRT. Rotational IMRT involves the continuous delivery of dose during gantry rotation and multi-leaf collimator (MLC) movements. IMRT is able to generate steep dose gradients, and allows doses to conform closely to the treatment target and so greater sparing of the surrounding normal tissues and correspondingly reduced toxicity(4, 94). During the radiotherapy planning process, dose volume histograms (DVHs) are used to assess the dose delivered to the treatment targets and organs at risk (OAR). For the latter, dose constraints are applied during inverse planning to control dose to these surrounding critical structures. OAR include the rectum, bladder, bowel, femoral heads, penile bulb and urethra. Modern dose constraints are derived from well-established clinical trials such as MRC RT01, RTOG studies and CHHiP(97-100). Genito-urinary (GU) and gastro-intestinal (GI) toxicities are the dose limiting toxicities in prostate radiotherapy, and complications can significantly reduce QOL(11, 96).

Interfraction movement of the prostate can be large (> 1 cm) especially in the anterior-posterior directions, and is due to variable filling of deformable organs surrounding the prostate, namely bladder and rectum(101, 102). Intrafraction movement of the prostate is variable and tends to be in the anterior-posterior and superior-inferior directions, and is due to physiological motions including peristalsis and pelvic floor muscle changes(103-105). IGRT

uses kV x-rays or cone beam CT imaging to localise the treatment target. Fiducial markers inserted within the prostate can act as a surrogate of prostate positioning(106, 107). On-board imaging can be performed daily prior to each fraction to help track internal organ motion. By being able to determine the positioning of the intended target volume before each fraction, it allows precise RT delivery and reduction of the treatment volume margins used(4, 87, 94, 96). This is crucial as geographical miss is a significant risk factor for future relapse(108). Both IMRT and IGRT are now considered standard in prostate radiotherapy.

Several studies have shown the overall survival benefit of hormone therapy + radiotherapy over hormone therapy alone (Table 1-6). SPCG-7 showed that if radiotherapy is given in addition to hormone therapy for locally advanced disease, 10 years prostate cancer specific mortality and overall mortality reduced significantly (23.9% vs. 11.9%, and 39.4% vs. 29.6% respectively)(73). PR07 included comparatively higher risk patients and confirmed that the addition of radiotherapy to hormone therapy significantly improved 10 year overall survival (55% vs. 49%) and 10 year biochemical progression-free rate (63% vs. 27%). The radiotherapy toxicities were modest, and G3 toxicities were uncommon(109, 110). These studies provide strong evidence for the use of radiotherapy with hormone therapy for men with locally advanced prostate cancer, even with modest radiation doses when compared to the modern standard used in the current era of at least 75.6 Gy(75). In addition, Mottet et al. showed that the addition of RT to 3 years of hormone therapy in locally advanced disease improved 5 year progression free survival (64.7% vs. 15.4%), but overall survival and disease-specific survival may require longer follow-up to be assessed(111). Even for patients with pelvic node positive disease, the addition of radiotherapy to hormone therapy led to improved failure free survival (81% vs. 53%), although longer follow up is required to determine any improvement in overall survival(112).

Local disease control in high-risk prostate cancer patients is associated with reduced risk of distant metastasis and cancer-specific mortality, and hence it is important to optimise local disease control(19, 92). Relapse following radical radiotherapy can be local due to geographic miss or intrinsic radioresistance(12, 20). Regional or metastatic relapse may occur due to micrometastatic disease or inaccurate staging at presentation.

Table 1-6 Studies on the use of radiotherapy in radical treatment

Study name	Patient recruitment period	Study design	Number of patients	Patient characteristics	Radiotherapy dose fractionation	Radiotherapy technique	Hormone therapy used	Duration of hormone therapy	Outcome
SPCG-7(73)	1996 to 2002	Prospectively randomised to hormone therapy alone or hormone therapy+RT	875	Locally advanced (78% were T3), node negative	70 Gy to prostate, 50Gy to seminal vesicles	Started radiotherapy after 6 months of hormone therapy. 3D CRT with at least 70 Gy to prostate. No pelvic LN irradiation planned.	Total androgen blockade with LHRH agonist (leuprorelin) and flutamide for 3 months, then continuous flutamide alone	Continuous	10 years cumulative incidence for overall mortality was 39.4% and 29.6% in hormones alone and hormone+RT groups respectively ($p < 0.01$). 10 years cumulative incidence for PSA recurrence was 74.7% and 25.9% respectively ($p < 0.01$)
PR07 (also referred to as Intergroup T94-0110)(109, 110)	1995 to 2005	Prospectively randomised to hormone therapy alone or hormone therapy+RT	1,205	High risk (88% were T3 or T4)	65 - 69 Gy to prostate and seminal vesicles +/- 45 Gy to pelvic LN	Started RT 8 weeks after starting hormone therapy at the earliest, 4-field box technique, whole pelvis +	Either bilateral orchidectomy or LHRH agonist (given with 2 weeks of antiandrogens)	Continuous	10 years overall survival was 49% with hormones alone and 55% with hormones+RT ($p = 0.03$). 10 years biochemical

						prostate + seminal vesicles + external + internal iliac LN, with subsequent boost to prostate			progression-free rate was 27% and 63% respectively
Mottet et al.(111)	2000 to 2003	Prospectively randomised to hormone therapy alone or hormone therapy+RT	264	Locally advanced (T3 or T4), N0, M0	66 Gy – 74 Gy to prostate and SV, 44 Gy – 48 Gy to pelvic lymph nodes	Started within 3 months of randomisation, 3D CRT, 4-field technique for pelvic volume, 4 or 6 field technique for prostate	LHRH (leuprorelin) with flutamide for one month	3 years	5 year biochemical progression free survival was 15.4% with hormones alone and 64.7% with hormones+RT ($p < 0.01$), overall survival was 71.5% and 71.4% respectively
STAMPEDE standard of care arm(112)	2005 to 2014	Prospectively recruited, non-randomised to hormone therapy alone or hormone therapy+RT	721	High risk +/- node positive disease	According to local protocol (recommended 74 Gy to prostate and SV, +/- 55 Gy to pelvic lymph nodes)	Started RT approx. 6 to 9 months after randomisation (technique according to local protocol – IMRT recommended)	Orchidectomy, or LHRH agonist/antagonist +/- oral anti-androgens	At least 2 years	RT improved 2 year failure free survival in both node negative and node positive patients, but not overall survival

1.4.2 Whole prostate dose escalation RT

Large prospective trials have consistently shown that higher doses given in standard 1.8 Gy to 2 Gy fractions favour improved biochemical control and disease specific survival which is maintained for up to 10 years follow-up, with around a 12% improvement in control for a 10 Gy increase in dose(4)(Table 1-7). This was found whether radiotherapy was given with hormone therapy (MD Anderson study, Dutch trial, RT01) or without hormone therapy (PROG/ACR95-09, GETUG 06, RTOG 0126). Zelefsky et al. retrospectively reviewed 2,047 patients treated by 3DCRT with doses between 66 Gy and 86.4 Gy, and found no differences in biochemical relapse free survival or distant metastasis free survival for low risk patients, but significant improvement with higher doses for intermediate and high risk patients(113). The evidence for whole prostate escalation radiotherapy is strongest for intermediate and high risk, with MD Anderson finding most benefit for those with PSA > 10 ng/ml, and GETUG 06 for those with PSA > 15 ng/ml. Another large retrospective non-randomised study found that intermediate and high risk patients did derive an overall survival benefit when treated with 75.6 Gy to 90 Gy total doses when compared with 68.4 Gy to <75.6 Gy(114). Finally, the RT01 trial (which compared 64 Gy with 74 Gy) used hormone therapy in all patients, and confirmed benefit in biochemical control with the higher dose although overall survival was not significantly improved(115).

With this improvement in biochemical control from dose escalation, toxicity also increases in tandem(87). These studies had used various different toxicity grading tools, but had all used versions of RTOG scoring which allows some comparison between them (Table 1-7).

Acute toxicity was similar between lower and higher doses but PROG/ACR 95-09 did show higher acute GI toxicity with higher doses, and RT01 showed more patients had G≥2 GU and GI toxicity between 8 to 10 weeks, although they settled and were similar at around week 12 and 18.

In comparison, late toxicity was higher with higher doses, especially for GI (MD Anderson, Dutch study, GUTUG 06, RT01, and RTOG 0126) although two trials also showed this for urinary toxicity (GETUG 06 and RTOG 0126). A meta-analysis showed that dose escalation using 3DCRT increased significantly the risk of late G2 GU and GI toxicity(116).

It should be noted that many studies did not use IMRT and IGRT, which can reduce and limit radiation doses to organs at risk and improve conformity and homogeneity in the CTV. However, for organs at risk inside or close to the prostate CTV, for example urethra, anterior rectal wall or base of bladder, these risks cannot be reduced unless the dose is reduced.

In summary, increasing radiation doses can improve biochemical control but the dose is ultimately limited by toxicity from dose to surrounding organs at risk(20). Current accepted clinical practice for intermediate and high risk patients usually involves a total dose of > 76 Gy delivered by conformal techniques if conventional fraction sizes of 1.8 to 2 Gy are used(75).

Table 1-7 Studies on whole prostate dose escalation radiotherapy

All studies are prospectively randomised to standard dose or escalated dose of RT

Study name	Patient recruitment period	Number of patients	Patient characteristics	Radiotherapy dose fractionation	Radiotherapy technique	Hormone therapy used	Disease outcome	GU toxicity		GI toxicity		Toxicity score used
								Acute	Late	Acute	Late	
MD Anderson(117-119)	1993 to 1998	301	T1b - T3, N0, M0	70 Gy or 78 Gy (2 Gy per fraction)	4 field box technique up to 46 Gy. For 70 Gy arm, rest of dose delivered with smaller field sizes. For 78 Gy arm, rest of dose delivered by 3DCRT with 6 fields.	No neoadjuvant, concurrent, or adjuvant hormone therapy	At 8.7 years, 78 Gy had better biochemical control than 70 Gy (78% vs. 59%; p < 0.01)	For 70 Gy and 78 Gy, G≤2 was 90% and 97% (p > 0.4), G3 for 1 patient per group, G4 for 2 and 0 patients respectively	For 70 Gy and 78 Gy, 10 year incidence of G≥2 was 8% and 13% (not sig different), G3 was 5% and 4% respectively	For 70 Gy and 78 Gy, G≤2 was 97% and 100% (p > 0.4), G3 for no patients, G4 for 0 and 1 patien respectively	For 70 Gy and 78 Gy, 10 year incidence of G≥2 was 13% and 26% (p = 0.013); G3 was 1% and 7% respectively (p = 0.018)	Acute toxicity: RTOG Late toxicity: modified RTOG-LENT
Dutch trial(120-123)	1997 to 2003	664	T1b - T4, N0, M0	68 Gy or 78 Gy (2 Gy per fraction)	Mainly 3DCRT	(Neo)adjuvant hormone therapy was used in 30% of patients (6 months or 3 years)	At 9 years, 78 Gy had better bioochemical control than 68 Gy (54% vs. 47%; p = 0.03), but not overall survival (69% vs. 69%; p = 0.9).	For 68 Gy and 78 Gy, G≤2 was 40% and 42% respectively, and G3 was 13% and 13% respectively (p = 0.5)	For 68 Gy and 78 Gy, 7 year incidence of G≥2 was 41% and 40% respectively (p = 0.6), G≥3 was 12% and 13% respectively (p = 0.6), G4 was 1% in both arms	For 68 Gy and 78 Gy, G≤2 was 41% and 47% respectively, and G3 was 6% and 4% respectively (p = 0.5)	For 68 Gy and 78 Gy, 7 year incidence of G≥2 was 25% and 35% respectively (p = 0.04), G≥3 was 4% and 6% respectively (p = 0.3), G4 was 0 and 1% respectively	Acute toxicity: RTOG Late toxicity: modified RTOG and EORTC

PROG/ACR 95-09(124)	1996 to 1999	393	T1b - T2b, PSA ≤ 15 ng/ml (58% were low risk)	70.2 Gy or 79.2 Gy (50.4 Gy in 1.8 Gy fractions)	3D CRT (photons) to prostate and seminal vesicles of 50.4 Gy, followed by 3D conformal proton boost to prostate to 70.2 Gy or 79.2 Gy in total	No neoadjuvant, concurrent, or adjuvant hormone therapy	At 10 years, 79.2 Gy had better biochemical control than 70.2 Gy (83% vs. 68%; p < 0.01), but not overall survival (78% vs. 83%; p = 0.41)	For 70.2 Gy and 79.2 Gy, G≥2 was 54% and 63% respectively, G≥3 was 3% in both arms (p = 0.07)	For 70.2 Gy and 79.2 Gy, 8.9 year incidence of G≥2 was 24% and 29% respectively, G≥3 was 2% in both arms (p = 0.79)	For 70.2 Gy and 79.2 Gy, G≥2 was 45% and 64% respectively, G≥3 was 1% in both arms (p < 0.01)	For 70.2 Gy and 79.2 Gy, 8.9 year incidence of G≥2 was 13% and 25% respectively, G≥3 was 0% and 1% respectively (p = 0.09)	Acute toxicity: RTOG Late toxicity: RTOG
GETUG 06(125)	1999 to 2002	306	Localised prostate cancer with T1b - T3a, N0, M0	70 Gy or 80 Gy (2 Gy per fraction)	3DCRT	No neoadjuvant, concurrent, or adjuvant hormone therapy	At 5 years,80 Gy was not better than 70 Gy in biochemical control (76% vs. 68%; p = 0.09), although patients with initial PSA > 15 ng/ml benefited	-	For 70 Gy and 80 Gy, 5 year incidence of G≥2 was 10% and 17.5% respectively (p < 0.05)	-	For 70 Gy and 80 Gy, 5 year incidence of G≥2 was 14% and 19.5% respectively (p = 0.22)	Late toxicity: RTOG
RT01(115, 126, 127)	1998 to 2001	843	T1b - T3a N0 M0 (43% high risk)	64 Gy or 74 Gy (2 Gy per fraction)	3DCRT	Neoadjuvant LHRH agonist with antiandrogen to cover flare (3 to 6 months before RT until end of RT)	At 10 years, 74 Gy was better than 64 Gy in biochemical control (55% vs. 43%, p < 0.01) but not overall survival (71% vs. 71%)	For 64 Gy and 74 Gy, incidence of G≥2 was 38% and 39% respectively	For 64 Gy and 74 Gy, 5 year incidence of G≥2 was 8% and 11% respectively (p = 0.14)	For 64 Gy and 74 Gy, incidence of G≥2 was 30% and 33% respectively	For 64 Gy and 74 Gy, 5 year incidence of G≥2 was 24% and 33% respectively (p < 0.01)	Acute toxicity: RTOG Late toxicity: RTOG

RTOG 0126(128)	2002 to 2008	1,532	Intermediate risk (cT1b - T2b with Gleason 2 - 6 and PSA ≥ 10 and < 20, or Gleason 7 and PSA < 15)	70.2 Gy or 79.2 Gy (1.8 Gy per fraction)	3DCRT	No neoadjuvant, concurrent, or adjuvant hormone therapy	At 10 years,79.2 Gy was better than 70.2 Gy in biochemical control (74% vs. 57%, p < 0.01) but not overall survival (67% vs. 66%)	-	For 70.2 Gy and 79.2 Gy, 10 year incidence of G≥2 was 10% and 15% (p < 0.01)	-	For 70.2 Gy and 79.2 Gy, 10 year incidence of G≥2 was 16% and 22% (p < 0.01)	Late toxicity: RTOG/EORTC

1.4.3 Hypofractionated RT

Conventional fractionation schedules require 7 to 8 weeks of daily treatments, which can be logistically and financially challenging for patients, and it limits patient throughput for the finite health resources in the NHS, with its limited number of available linear accelerators(92).

Radiobiological studies have shown that prostate cancer has a low alpha/beta ratio of around 1.8 Gy(129). A low alpha/beta ratio allows greater sensitivity to increasing fraction size(130). The alpha/beta ratio of surrounding late reacting OAR such as rectum and bladder are higher at around 3 to 4 Gy. Therefore hypofractionation can improve the therapeutic ratio(131). Currently, two broad categories of hypofractionated radiotherapy are recognised: moderate hypofractionation (around 2.5 Gy/# to 3.5 Gy/#) and extreme hypofractionation (> 5 Gy/#).

For disease control, several randomised trials of moderately hypofractionated schedules have demonstrated non-inferior biochemical control compared to conventional fractionation of around 1.8 Gy/# to 2.0 Gy/# with a trend in favouring hypofractionation, including a large UK based study called CHHiP which showed that 60 Gy/20 # is non-inferior to 74 Gy/37 # in disease control (Table 1-8). However one trial, the MD Anderson study, did demonstrate a significant improvement in treatment outcome with 2.4 Gy/# (72 Gy total dose) over 1.8 Gy/# (75.6 Gy total dose) over 8.4 years despite being a small study with an increase of 0.6 Gy/# only(132, 133).

For toxicity, there are differences between acute and late toxicity (Table 1-8). For acute toxicity, Pollack and NRG0415 did not find differences in urinary or bowel toxicity (although the former found that patients with pre-existing impaired urinary function had significantly worse function after hypofractionated radiotherapy), but PROFIT and HYPRO did show more acute GI toxicity but not more acute GU toxicity(134-137). This may have been due to the lack of image guidance, including the seminal vesicle in the high dose planning volume, and bladder dose constraints used in radiotherapy planning and delivery for HYPRO. CHHiP found that acute toxicity in the hypofractionated arms had faster onsets and higher peaks, and also returned to baseline faster. For late toxicity, MD Anderson and Arcangeli found no difference

in late GU toxicity (although urinary toxicity continued to increase after 4 years in the latter), whilst NRG 0415 and PROFIT showed more late GI toxicity with hypofractionation. It should be noted that Lieng found that 66 Gy in 3.3 Gy/# was associated with significantly worse GI toxicity that 60 Gy in 3.0 Gy/#. This shows a steep normal dose response curve, with 66 Gy/22 # meeting their early stopping rules even though both arms had the same dose constraints.

Although most of these studies are large multi-centre randomised controlled trials, the data are not yet mature enough to indicate very late effects. One single institution study, comparing 80 Gy/40 # and 62 Gy/20 #, found an actuarial estimate of haematuria of 9.7% and 24.3% respectively at 8 years ($p < 0.01$)(138). Therefore continued monitoring of patients beyond 10 years is required.

Overall, the studies have demonstrated that contemporary radiotherapy techniques with IMRT and IGRT allow the safe implementation of moderate hypofractionation schedules which have been accepted as non-inferior to conventional fractionation at 5 years follow up, with increased but well-tolerated and acceptable GI toxicity profiles(92, 108). Since last year, 60 Gy/20 # has been adopted as the standard of care for prostate radiotherapy in the UK as a result of the CHHiP study(87, 139, 140).

Table 1-8 Studies on moderately hypofractionated radiotherapy

Study name	Patient recruitment period	Study design (no. of pts)	Patient characteristics	Radiotherapy dose fractionation	Radiotherapy technique	Hormone therapy used and duration	Disease outcome	GU toxicity		GI toxicity		Toxicity score used
								Acute	Late	Acute	Late	
MD Anderson(132, 133, 141)	2001 to 2010	Randomised Phase III trial (206 pts)	Mostly intermediate (71%) and low risk (28%)	75.6 Gy/42 # (1.8 Gy/#) vs. 72 Gy/30 # (2.4 Gy/#)	IMRT	Yes (in 24% of patients), ≤ 4 months	At 8.4 years, 2.4 Gy/# was better than 1.8 Gy/# in relapse (10.7% vs. 15.4%, p = 0.04), but not overall survival (p = 0.39)	Not reported	For 1.8 Gy/# and 2.4 Gy/#, 8.4 year toxicity G2/3 was 16.4% and 15.1% respectively (p = 0.84)	Not reported	For 1.8 Gy/# and 2.4 Gy/#, 8.4 year toxicity G2/3 was 5.0% and 12.6% respectively (p = 0.08)	Late toxicity: modified RTOG
Arcangeli(142, 143)	2003 to 2007	Randomised Phase III trial (168 pts)	High risk prostate cancer	80 Gy/40 # (2.0 Gy/#) vs. 62 Gy/20 # (3.1 Gy/#)	3DCRT	Yes (maximum androgen blockade), 9 months	At 5.8 years, 3.1 Gy/# was not different to 2.0 Gy/# in biochemical control (85% vs. 74%, p = 0.07)	For 2.0 Gy/# and 3.1 Gy/#, G≥2 was 40% and 47% respectively (p = 0.45). Only 1 patient in each group had G3 toxicity.	For 2.0 Gy/# and 3.1 Gy/#, 3 year toxicity G≥2 was 11% and 16% respectively (p > 0.05)	For 2.0 Gy/# and 3.1 Gy/#, G2 was 21% and 35% respectively (p = 0.07). No patients in either group had G3/4 toxicity.	For 2.0 Gy/# and 3.1 Gy/#, 3 year toxicity G≥2 was 14% and 17% respectively (p > 0.05)	Acute toxicity: extended RTOG/EORTC Late toxicity: LENT-SOMA

Pollack(134)	2002 to 2006	Randomised Phase III study (303 pts)	Intermediate (66%) and high (34%) risk	76 Gy/38 # (2.0 Gy/#) vs. 70.2 Gy/26 # (2.7 Gy/#) (if LN treatment, 56 Gy/38 # and 50-52 Gy/26 # respectively)	IMRT; pelvic LN treatment given in 35% of patients	Yes (in 46% of patients), 75% had 24 months	At 5 year, 2.7 Gy/# was not better than 2.0 Gy/# in biochemical control (77% vs. 79%, p = 0.75)	No difference in toxicity (p = 0.58)	For 2.0 Gy/# and 2.7 Gy/#, 5 year toxicity G≥2 was 13.4% and 21.5% respectively (p = 0.16)	No difference in toxicity (p = 0.57)	For 2.0 Gy/# and 2.7 Gy/#, 5 year toxicity G≥2 was 22.5% and 18.1% respectively (p = 0.39)	Acute toxicity: modified LENT/RTOG Late toxicity: modified LENT/RTOG
Lieng (precursor study to PROFIT)(144)	2001 to 2005	Phase II study (123 pts)	Mostly intermediate (67%) and low risk (26%)	60 Gy/20 # (3.0 Gy/#) vs. 66 Gy/22 # (3.3 Gy/#)	IMRT and IGRT	Yes (in 10% of pts), 3 to 36 months duration	At 8 years, 3.3 Gy/# was not better than 3.0 Gy/# in biochemical control (73% vs. 67%, p = 0.22)	Not reported	For 3.0 Gy/# and 3.3 Gy/#, 8 year toxicity G≥2 was 13% and 8%, and G≥3 was 2% and 4% respectively	Not reported	For 3.0 Gy/# and 3.3 Gy/#, 8 year toxicity G≥2 was 4% and 18%, and G≥3 was 1% and 11% respectively	Late toxicity: RTOG
RTOG NRG 0415(135)	2006 to 2009	Randomised non-inferiority phase III (1092 pts)	Low risk prostate cancer	73.8 Gy/41 # (1.8 Gy/#) vs. 70 Gy/28 # (2.5 Gy/#)	3DCRT (21%) and IMRT (79%)	None	At 5 years, 2.5 Gy/# was non inferior to 1.8 Gy/# for disease free survival (86.3% vs. 85.3%)	For 1.8 Gy/# and 2.5 Gy/#, G≥2 was 27.1% and 27.0% respectively (p = 0.83)	For 1.8 Gy/# and 2.5 Gy/#, 5 year toxicity G≥2 was 22.8% and 29.7% respectively, and ≥ G3 was 2.3% and 0% respectively (p = 0.06)	For 1.8 Gy/# and 2.5 Gy/#, G≥2 was 10.3% and 10.7% respectively (p = 0.54)	For 1.8 Gy/# and 2.5 Gy/#, 5 year toxicity G≥2 was 14% and 22.4% respectively, and ≥ G3 was 2.6% and 4.1% respectively (p = 0.002)	Acute toxicity: CTCAE Late toxicity: CTCAE

PROFIT(136)	2005 to 2012	Randomised non-inferiority phase III (1206 pts)	Intermediate risk prostate cancer	78 Gy/39 # (2.0 Gy/#) vs. 60 Gy/20 # (3.0 Gy/#)	3DCRT or IMRT, IGRT	Hormone therapy allowed up to 90 days pre-randomisation	At 6 years, 3.0 Gy/# was non inferior to 2.0 Gy/# for biochemical control (72.7% vs. 71.6%, p < 0.01), and for overall survival (87.5% vs. 87.0%)	For 2.0 Gy/# and 3.0 Gy/#, G≥2 was 31% and 30% respectively (p = 0.93) , and G≥3 was 4.0% in both arms (p = 0.97)	For 2.0 Gy/# and 3.0 Gy/#, G≥2 was 22% in both groups (p = 0.98), and G≥3 was 3.0% and 2.1% respectively (p = 0.33)	For 2.0 Gy/# and 3.0 Gy/#, G≥2 was 10% and 16% respectively (p < 0.01), and G≥3 was 0.5% and 0.7% respectively (p = 0.74)	For 2.0 Gy/# and 3.0 Gy/#, G≥2 was 14% and 9% respectively (p < 0.01), and G≥3 was 2.8% and 1.5% respectively (p = 0.10)	Acute toxicity: RTOG Late toxicity: RTOG
CHHiP(10, 87)	2002 to 2011	Randomised non-inferiority phase III (3216 pts)	All risk groups, mostly intermediate risk (73%)	74 Gy/37 # (2.0 Gy/#) vs. 60 Gy/20 # (3.0 Gy/#) vs. 57 Gy/19 # (3.0 Gy/#)	Forward or inverse planned IMRT	Yes (median 5.6 months)	At 5 years: biochemical control rates were 88.3% (control), 90.5% (60 Gy), and 85.8% (57 Gy); OS were 91.4% (control), 93.2% (60 Gy), and 91.9% (57 Gy)	G≥2 were 46.4%, 49.5% and 45.9% in 74 Gy, 60 Gy and 57 Gy arms respectively, and G≥3 were 8.2%, 9.2% and 9.3% respectively (not sig difference)	At 5 years, G≥2 was 13.5%, 13.2% and 11.2% in 74 Gy, 60 Gy and 57 Gy arms respectively	G≥2 were 24.6%, 38.5% and 37.8% in 74 Gy, 60 Gy and 57 Gy arms respectively, and G≥3 were 0.8%, 2.4% and 2.2% respectively (significantly higher in hypofractionation arms)	At 5 years, G≥2 was 1.3%, 2.3% and 2.0% in 74 Gy, 60 Gy and 57 Gy arms respectively	Acute toxicity: RTOG Late toxicity: RTOG for GI, LENT-SOMA for GU
HYPRO(137, 145, 146)	2007 to 2010	Randomised phase III (820 pts)	High (73%) and intermediate (27%) risk	78 Gy/39 # (2.0 Gy/#) vs. 64.6 Gy/ 19# (3.4 Gy/#)	IMRT and IGRT	Yes (in 67% of patients), median 1.7 months before RT	At 5 years, 3.4 Gy/# was similar to 2.0 Gy/# for relapse free survival (81% vs. 77%, p = 0.36)	For 2.0 Gy/# and 3.4 Gy/#, G≥2 was 58% and 61% respectively (p = 0.43)	For 2.0 Gy/# and 3.4 Gy/#, 5 year toxicity G≥3 was 12.9% and 19% respectively (p = 0.02)	For 2.0 Gy/# and 3.4 Gy/#, G≥2 was 31% and 42% respectively (p < 0.01)	For 2.0 Gy/# and 3.4 Gy/#, 5 year toxicity G≥3 was 2.6% and 3.3% respectively (p = 0.55)	Acute toxicity: RTOG-EORTC Late toxicity: RTOG-EORTC

1.4.4 Dose painting RT

The standard treatment approach to prostate radiotherapy involves the delivery of a homogeneous treatment dose distribution to the whole organ, in part due to the inability of identifying tumours on planning CT scans(20, 147). However, improved imaging modalities have now allowed the visualisation of intra-prostatic lesions as discussed above.

Studies have investigated treating only the intra-prostatic lesions instead of the whole organ, but found that this leads in worse biochemical outcomes(4). This may be due to multiple factors, including geographic miss of intended targets and that the disease may be multifocal with microscopic disease not identified on imaging and therefore not included in treatment volumes. Therefore it remains crucial to maintain an adequate dose to the whole organ(92).

Instead of dose escalating to the whole prostate which comes at the cost of increased toxicity, it would be rational to perform focal dose escalation to regions with high risk of potential recurrence whilst treating the whole prostate to an adequate dose (dose painting radiotherapy), thereby optimising both disease control and preserving erectile, urinary and rectal function. As discussed previously, prospective randomised clinical trials have shown that the addition of hormone therapy to RT improves overall survival, whilst whole organ dose escalation has not with the follow up durations so far. As the trials on combining hormone therapy and RT were performed with low radiotherapy doses, the survival benefit of hormone therapy (short and/or long course) may be reduced or lost if dose escalation is performed with modern techniques(75). Therefore it may be possible to reduce the duration hormone therapy if these new techniques are used.

Determining a clinically relevant, high risk region within the prostate that would benefit from dose intensification is a prerequisite for dose painting radiotherapy(20). Macroscopic disease is more treatment resistant than microscopic disease, and disease recurrence has been shown to usually occur at the site of the dominant lesions at staging(4, 87, 148). Therefore these lesions often drive the natural progression of the cancer, and it would be reasonable to use macroscopic disease (referred to as dominant intra-prostatic lesions (DILs)) with a margin to create boost volumes(20).

Both functional MRI and PET can provide complimentary information(4, 14). Combined boost volumes from different imaging modalities will be larger with a higher toxicity risk, but may include more of the primary tumour volumes and hence may be more effective than using a single imaging modality alone. These imaging modalities are fused to the planning CT scan. Multi-modality image registration involves a geometric transformation to align landmarks between the corresponding scans. Implanted fiducial markers within the prostate can be used as points of reference given that the in vivo configuration of prostate in relation to surrounding tissues will be altered by differing bladder and rectal filling(20). Registration can be performed manually with the clinician using their visual judgement, or automatically by rigid (allowing only linear transformations e.g. translation and rotation) or deformable (allowing warping to potentially achieve better matching) registration(11). Both manual and automatic registrations of the prostate between CT and MRI are comparable(149). Deformable registration may not be available with some planning softwares and the expertise for it may not be present at some treatment centres, and so rigid registration is often used(20).

Avoiding geometric miss is especially important for prostate dose painting radiotherapy as the target boost volumes are relatively small, and increased toxicity may occur if organs at risk migrate into the dose escalation region. For example, if boost volumes are located at the peripheral zone of the prostate, the rectum may move within the boost region(20). Both delineating and radiotherapy planning are based on a scan performed at a specific time point, with which a course of treatment is delivered over several weeks. Hence the actual treatment received by a patient may not reflect the dose distribution planned, and accounting for target movement is crucial(150). Therefore image guidance is a prerequisite to safely achieve dose painting(151).

Boost volumes can be defined using either the DILs or by the region of the prostate. The former involves identifying the clinically significant lesions. This can be based on size, features on imaging such as intensity of tracer uptake on PET, and any other information such as Gleason score on template biopsies. This delineating is a subjective process based on clinician judgement. For instance, some would argue that lesions of < 0.5 mls will not require dose escalation as they would be treated adequately by the standard dose, and that larger lesions are more likely to determine future clinical progression(11). The other strategy

of boosting a whole region of the prostate (e.g. the middle third of the right side of the prostate) has the benefit of treating multiple tumour foci, but would result in dose escalating more extensive volumes of the prostate (11).

The higher biologically effective radiation dose for dose painting can be produced by delivering a higher total dose or higher dose per fraction(20). The former can be achieved by sequential boosting, whereby standard radiation is delivered to the whole organ in the initial phase, followed by additional focused treatment to the boost volume. This is suitable for tumour sites where treatment should ideally be instigated without delay, and it allows the use of different radiotherapy methods including electrons to be combined to produce the desired dose distributions(20). However, tissue response to the initial phase complicates subsequent registration for the following boost phase which often uses pre-treatment data for planning. Also, the sequential boost strategy often increases doses to the PTV outside the boost volume as there is spill over from the phase II into the phase I volume and can increase normal tissue doses. In comparison, dose painting by using higher doses per fraction can be delivered by simultaneous integrated boost (SIB), whereby IMRT (static or rotational) can be used to plan a heterogeneous dose distribution with a concomitant boost, all in a single phase. In comparison with sequential boosting, this allows the need for one radiotherapy plan only and should therefore improve conformality(20).

Dose painting have already been used for prostate radiotherapy and other sites(20, 152). For the former, previous dosimetric studies have shown that it is feasible to deliver a boost dose to MRI defined intra-prostatic lesions without compromising the dose to the whole prostate or the dose constraints to surrounding organs at risk(153-156). For treatment delivery, different techniques have been combined including EBRT, brachytherapy and stereotactic radiosurgery.

Studies which have only used EBRT for prostate dose painting radiotherapy are shown in the Table 1-9. Intra-prostatic lesions have been identified by various methods: MRI, SPECT and PET. In the non-randomised studies where dose painting was performed if intra-prostatic lesions were identified, the proportion of patients who received dose painting varied from 51% to 69%. Of note, Wong et al. (which was a single cohort study) reported that 28% of patients did not have uptake on ProstaScint, and Schild found that 21% of patients did not

have an intra-prostatic lesion on MRI, whilst Pinkawa found that ≥ 3 lesions were found in 13% of patients(157-159). As expected, IMRT was used to deliver the boost doses for all the studies, and daily IGRT methods used included ultrasound, CBCT, and fiducial markers (ultrasound based studies predated the use of fiducial markers). The margin added to the intra-prostatic lesions varied from no margin (e.g. Sundahl) to 15 mm (Ippolito)(158, 160). All the studies used SIB except Miralbell which used sequential phase II boost of up to 16 Gy in 2# (this study was the only one that delivered pelvic radiotherapy (50.4 Gy/28 #) also, to 56% of patients)(101). The EQD2 to prostate varied from 64 Gy to 81 Gy, and EQD2 to boost varied from 80 Gy to 114 Gy.

Despite these boost levels, the toxicity levels reported were clinically safe and FLAME reported no significant difference in toxicity up to 2 years follow up between patients receiving standard treatment and those receiving dose painting. For late urinary toxicity, patients with prior TURP were more likely to develop late urinary incontinence (Sundahl) and toxicity was related with prostatic urethral dose (Ippolito). Late rectal toxicity was related to higher rectal D_{mean} and V30 mean values (Ippolito).

Most of these dose painting prostate radiotherapy studies have used conventional dose fractionations. Only one study has investigated this technique using the current UK standard moderately hypofractionated dose fractionation of 60 Gy/20 #/4 weeks(161). This small pilot study of 28 patients with intermediate and high risk prostate cancer was performed at the Clatterbridge Cancer Centre NHS Foundation Trust, and used mpMRI to identify DILs to which a boost dose of up to 68 Gy were delivered. Most of the patients achieved 68 Gy boost (25 out of 28 patients), and the rest achieved 67 Gy only due to proximity of DIL to urethra and rectum. With follow up of at least 32 months, no patients had grade 3 urinary or bowel toxicity, and only 3 patients had disease relapse. As a result of the low toxicity levels in this pilot study, the phase II single arm BIOPROP20 clinical trial was established.

Other treatment modalities specifically targeting the DILs without the sole use of conventional external beam ionising radiation are also being investigated. Brachytherapy involves either the permanent implantation (low dose rate, LDR) or temporary placement (high dose rate, HDR) of radiation sources directly into the target, and can be performed alone or in combination with external beam radiotherapy for focal dose escalation.

Stereotactic ablative body radiation (SABR) therapy involves the delivery of a high ablative dose to the target in a few fractions (often < 5) whilst avoiding surrounding OARs via steep dose gradients by using precise targeting, effective immobilisation, and tumour motion management. For brachytherapy, the mean EQD2 boost dose (if α/β ratio for prostate is 1.5 Gy) that has been delivered in clinical trials is 178 Gy (range 150 to 217 Gy, with average differential dose when compared to the non-boosted prostate of 62 Gy) by LDR, and 106 Gy (range 90 to 151 Gy, with average differential dose of 32Gy) by HDR(162). For SABR, the mean EQD2 boost dose has been 136 Gy (range 90 to 164 Gy, with average differential dose of 45 Gy). Available biochemical disease-free survival (bDFS) for LDR was 85% to 98% at 5 years, for HDR was 71% to 100% at 5 years, and for SABR was 96% to 100% at 2 years. In terms of side effects, the median G≥3 acute and late GU toxicity were 0% and 2% for LDR, 3% and 5% for HDR, and 6% and 6% for SABR respectively. The median G≥3 acute and late GI toxicity were 0% and 6% for LDR, 0% and 4% for HDR, and 2% and 10% for SABR respectively. Overall, these techniques allowed increased differential doses between the boosted and non-boosted prostate when compared to using EBRT alone (differential dose of 18Gy in BIOPROP20).

Techniques specifically targeting the DILs without the use of ionising radiation include cryotherapy and high-intensity focused ultrasound (HIFU). Case series have been reported for both technologies. These treat the tumour volume with a 6-8 mm margin, but not the whole prostate. Cryotherapy is an invasive procedure often with the patient under general anaesthetic where consecutive freezing and thawing of the target leads to cytolysis. A UK-based series of 122 patients with intermediate (71%) and high (29%) risk disease had a 3 years failure free survival of 91%, with 0% patients having urinary incontinence and 16% having erectile dysfunction(163). HIFU involves delivering focused ultrasound waves to create irreversible coagulation necrosis and tumour lysis in a target by thermal effect. A UK-based series of 625 patients (84% had either intermediate or high risk disease) had a 5 years failure free survival of 88%, with 2% having urinary incontinence(164). The maximal length of HIFU systems currently available is up to 67 mm, and so this technique is limited in large prostates and anterior DILs.

Other techniques investigated include focal laser ablation (FLA), photodynamic therapy (PDT), and irreversible electroporation (IRE)(165). FLA uses high energy laser light delivered

by fibres inserted transperineally for thermal ablation. Post treatment positive biopsies ranged from 4 to 64% with up to 12 months follow up(166). PDT uses the interaction between light from intraprostatic laser fibers and either an oral or intravenous photosensitive agent, which results in production of reactive oxygen species causing thrombosis within the target. Post treatment positive biopsies ranged from 26 to 51% with up to 24 months follow up(166). IRE involves generating an electric field to increase cell membrane permeability and resultant apoptosis. Post treatment positive biopsies ranged from 3 to 33% with up to 12 months follow up(166). FLA and IRE were associated with <1% urinary incontinence, whilst PDT was associated with <5% urinary incontinence. Overall, these techniques have been used in small studies and require specialist equipment which are not widely available currently.

In summary, the objective of dose painting radiotherapy is to improve therapeutic ratio by achieving optimal local control with minimal effect on toxicity(87). Focal dose escalation, biologically or in conventional fractionation, requires accurate treatment delivery. It is suggested that BED of up to 200 Gy (at α/β of 1.5, corresponding to around 86Gy in 2 Gy/#) will improve disease control, with limited further benefit beyond that dose(167).

Table 1-9 Studies on dose painting radiotherapy to prostate using EBRT

All studies used IMRT techniques

Study name	Patient recruitment period	Study design	Boost dose identification technique	Number of patients	Patient characteristics	Radiotherapy dose fractionation	EQD2 to prostate	EQD2 to boost volume	Hormone therapy used	Outcome	GU toxicity		GI toxicity	
											Acute	Late	Acute	Late
Fonteyne(168)	2002 to 2007	Non randomised comparison	MRI +/- MRS	230 (118 with dose painting, 112 without)	T1-4 N0 M0 (43% intermediate risk, 50% high risk)	78 Gy/ 38 # to prostate +/- 81 Gy by SIB	79	82	Used in 93%	No difference in G2-3 acute GI or GU toxicity after dose painting	At 3 months, cumulative incidence of G2 in 41%, G3 in 7%	-	At 3 months, cumulative incidence of G2 in 11%, no G3/4	-
Miralbell(101)	2001 to 2004	Single cohort study	MRI	50	Non-metastatic prostate cancer (74% with T3 disease, 66% were high risk)	64.4 Gy/ 32# to prostate + 10 to 16 Gy boost in 2# by sequential boost	64	82 to 104	Used in 66%	5 year disease free survival was 100%	At 3 months, G≥2 in 50%, G3 in 4% (all of whom had 16 Gy in 2# boost)	≥ 6 months, G≥2 in 12% (no G3)	At 3 months, G≥2 in 8% (no G3)	≥ 6 months, G≥2 in 20%, G3 in 10% (of whom 80% had 16 Gy in 2#)
FLAME(169)	2009 to 2016	Phase III single blinded randomised controlled trial	MRI	571 (284 with dose painting, 287 without)	Intermediate to high risk (90% high risk)	77 Gy/35 # to prostate +/- 95 Gy by SIB	81	114	Used in 66%	Awaited	During radiotherapy, G≥2 in 42.3% with boost and 46.0% without boost	Up to 2 years after radiotherapy, G≥2 in 27.1% with boost and 22.6% without boost	During radiotherapy, G≥2 in 14.8% with boost and 10.1% without boost	Up to 2 years after radiotherapy, G≥2 in 10.2% with boost and 11.1% without boost
Wong(157)	2002 to 2005	Single cohort study	SPECT (ProstaScint)	71	T1-4 N0 M0 (44% low risk, 42% intermediate risk)	75.6 Gy/42 # to prostate + 82 Gy by SIB	71	81	Used in 24%	At 5 years, overall survival was 93%, biochemical control was 94%	At 3 months, G2 in 54%, G3 in 1%	≥ 3 months, G2 in 39%, G3 in 4%, G4 in 1%	At 3 months, G2 in 45% (no G3)	≥ 3 months, G2 in 21% (no G3)

Sundahl(170)	2002 to 2014	Non randomised comparison	MRI +/- MRS	410 (225 with dose painting, 185 without)	T1-4 N0 M0 (46% intermediate risk, 48% high risk)	78 Gy/38 # to prostate +/- 82 Gy by SIB	79	86	Used in 94%	At 6 years, biochemical relapse free survival was 84% with boost vs. 85% without boost (not sig), but was 81% and 62% respectively for high risk (p = 0.03)	With and without boost, G2 was 38% and 46% respectively; G3 was 7% and 5% respectively	> 3 months, with and without boost, G2 was 24% and 25% respectively; G3 was 5% and 8% respectively	With and without boost, G2 was 10% and G3 was 0% in both groups	> 3 months with and without boost, G2 was 8% and 10% respectively; G3 was 0% and 2% respectively
Ippolito(160)	Not specified (published 2012)	Single cohort study	MRI	40	T2-3 N0 M0 (42.5% intermediate risk, 47.5% high risk)	72 Gy/ 40 # to prostate + 80 Gy by SIB	68	80	Used in 100%	Biochemical outcomes not reported	At 3 months, G2 was 30%, G3 was 2.5%, no G4	At 2 years, G≥2 was 13.3%	At 3 months, G2 was 15%, G3 was 5%, no G4	At 2 years, G≥2 was 9.5%
Pinkawa(171)	2008 to 2009	Non randomised comparison	^{18}F choline PET	67 (46 with dose painting, 21 without)	T1-3 N0 M0 (majority are low/intermediate risk)	76 Gy in 38 # to prostate +/- 80 Gy by SIB	76	82.7	Used in 18%	Biochemical outcomes not reported	No difference between patients with vs. without SBI	No difference between patients with vs. without SBI	No difference between patients with vs. without SBI	No difference between patients with vs. without SBI
Schild(158)	2009 to 2013	Single cohort	MRI	78	T1-3 N0 M0 (23% low risk, 55% intermediate risk, 22% high risk)	77.4Gy in 43# to prostate + 83 Gy by SIB	73	88	Used in 41%	At 3 years, biochemical control was 92%	At 3 months, G2 was 53%, none with G3 or G4	At 3 years, G2 was 26%, G3 was 3%	At 3 months, G2 was 19%, none with G3 or G4	At 3 years, G2 was 4%, none with G3 or G4
Garibaldi(172)	2012 to 2014	Single cohort	MRI	15	Stage II to III, intermediate/high risk	75.2Gy in 32# to prostate + 83.2 Gy by SIB	80.5	93.2	Not specified	At 16 months, biochemical control was 100%	G2 was 13.3%, no G3 or G4 toxicity	No G>2	G2 was 6.6%, no G3 or G4 toxicity	No G>2

Onjukka(161)	Not specified (published 2017)	Single cohort pilot study	MRI	28	High risk localised with at least 2 of 3 risk factors (PSA ≥ 20, dominant Gleason 4 or 5, T3a or T4), or 1 risk factor and DIL > 5 mm	60Gy in 20# to prostate + 68Gy SIB	72	86	Used in 100%	At median 38 months, biochemical control was 89%	Max prevalence of G2 was 35%	No G≥2	No G≥2	No G≥2

1.4.5 Pelvic lymph node radiotherapy

For clinically node negative disease, patients with high risk features may have micro-metastases in pelvic lymph nodes, and therefore the addition of pelvic nodal radiotherapy may lead to survival advantages compared to prostate radiotherapy alone(75). However, no prospective randomised trial have so far demonstrated overall survival benefit from prophylactic pelvic lymph node irradiation with conventional dose fractionations (46 to 50 Gy)(173). RTOG 94-13 and GETUG-01 did not show a difference in progression free survival between all patients receiving whole pelvis radiotherapy and all those receiving prostate only radiotherapy (Table 1-10)(174). However these studies were performed before the modern era of IMRT and dose escalation radiotherapy, and hence the nodal dose of 46 Gy in 23 # used at the time may have been suboptimal. Also, GETUG-01 used a lower superior border of the pelvic field and most patients had <15% risk of lymph node involvement (Roach formula). More recently, PIVOTAL showed that the addition of high dose pelvic radiotherapy (60 Gy in 37 #) to prostate radiotherapy using modern IMRT +/- IGRT is well tolerated, but its effect on disease control is not yet established(175). Mature data from PIVOTAL and the ongoing RTOG 09-24 trials will determine the benefits of whole pelvic radiotherapy with conventional dose fractionations using modern technology. Another notable trial (RTOG 0924) is a large randomised phase III trial with a recruitment aim of 2580 patients with high risk disease and aimed to treat pelvic nodes to 45 Gy/ 25 #, but there are no published results as yet(176). Current guidelines generally suggest that high risk clinically node negative patients should be considered on an individual basis for prostate and pelvic lymph node radiotherapy(75).

For clinically node positive disease, there is a lack of prospective randomised control trials to determine the optimal treatment regime. A large retrospective study using the National Cancer Database (2003 – 2011) found that local treatment (radical prostatectomy or radiotherapy) may be associated with overall mortality-free survival when compared to hormone therapy alone(177). Another large retrospective study using the SEER Database (1995 – 2005) found that local treatment (radiotherapy +/- prostatectomy) improved overall survival and prostate cancer specific survival compared to no local treatment(178). Overall, definitive local radiotherapy with conventional dose fractionation for clinically node positive disease is associated with 5 year overall survival of around 70%(179). In terms of pelvic

radiotherapy with conventional dose fractionation for clinically node positive disease, patients who were randomised into the control arm of the STAMPEDE trial were offered optional radiotherapy including to the pelvis. These 71 patients (82% received radiotherapy to both prostate and pelvis; 89% received conventional dose fractionation) had 5 year overall survival of 71%(112).

Hypofractionated dose fractionations have been used in several studies for pelvic nodal radiotherapy (Table 1-11). One randomised trial for node negative patients, which compared 76Gy/38# to prostate and 46Gy/23# to LN, with 63Gy/20# to prostate and 44Gy/20# to LN, found that GI and GU toxicity both occurred and settled faster with the hypofractionated arm(180). Single cohort studies for node positive patients have shown that hypofractionated IMRT is feasible with temporarily increased toxicity but is generally well tolerated(181, 182).

A concern with simultaneous prostate and pelvic radiotherapy with a hypofractionated schedule is accurate delivery to both the prostate and the pelvic lymph nodes when both may not move in tandem, providing a technical challenge. Current clinical practice for concurrent prostate and pelvic radiotherapy with standard fractionation usually involves matching bony anatomy between planning CT and on board cone beam CT without fiducial markers and using wider margins to PTV to account for set up errors.

Overall there are no randomised trials in either the node negative or node positive settings which have shown overall survival benefit with the addition of pelvic nodal radiotherapy to prostate radiotherapy. As a result, although it is technically feasible, the selection criteria remain undefined. If offered to the patient, long term hormone therapy is preferable due to poor outcomes(84, 183).

Table 1-10 Randomised studies on prostate and pelvic radiotherapy with conventional dose fractionation

Study name	Patient recruitment period	Study design	Number of patients	Patient characteristics	Radiotherapy dose fractionation	Radiotherapy technique	Outcome
RTOG 9413(184)	1995 to 1999	Randomised 2 x 2 factorial design (neoadjuvant + concurrent hormones (NCHT) with adjuvant; and prostate only RT with prostate + LN RT)	1323	Localised disease, PSA ≤ 100 ng/ml, risk of LN involvement ≥ 15% (Roach formula)	70.2 Gy to prostate +/- 50.4 Gy to pelvic lymph nodes (all with 1.8 Gy/# to prostate)	Conventional 4 field technique	At 10 years, prostate + LN RT with NHT improves PFS compared to prostate only RT with NHT
GETUG-01(185)	1998 to 2004	Randomised phase III study (prostate only RT vs. prostate + LN RT) – high risk patients had 6 months hormone therapy	444	T1b – T3, N0 pNx, M0	66-77 Gy to prostate +/- 46 Gy to pelvic lymph nodes (all with 2 Gy/# to prostate)	Conventional 4 field techniques or conformal 3D approach	5 year OS and PFS were similar
PIVOTAL(175)	2011 to 2013	Randomised phase II study (prostate only RT vs. prostate + LN RT) – All patients except one had LHRH +/- bicalutamide	124	T3b – T4, N0, risk of LN involvement ≥ 30% (Roach formula)	74 Gy to prostate +/- 60 Gy to pelvic lymph nodes (all with 2 Gy/# to prostate)	IMRT	Pelvic treatment led to more acute G2 bowel but not bladder toxicity, and no sig difference in late toxicity at 2 years; effect on disease control is not yet established

Table 1-11 Studies on prostate and pelvic radiotherapy with hypofractionation

Study name	Patient recruitment period	Study design	Number of patients	Patient characteristics	Radiotherapy dose fractionation	Radiotherapy technique	Hormone therapy used	Duration of Hormone therapy	Disease outcome	GU toxicity		GI toxicity	
										Acute	Late	Acute	Late
Norkus(180)	2010 to 2012	Randomised Phase III study	124	High risk, N0	Arm 1: 76Gy/38# (prostate) and 46Gy/23# (pelvis), Arm 2: 63Gy/20# (prostate) and 44Gy/20# (pelvis)	IMRT with 5 to 7 fields, daily kv CBRT	Used for all patients	All had ≥ 6 months	No disease outcome data	At week 12, G≥2 in arm 1 and arm 2 were 28% and 23% respectively (G3 was 7% in both arms, no G4)	Awaiting	At week 12, G≥2 in arm 1 and arm 2 were 40% and 39% respectively (no G3 or G4 in both arms)	Awaiting
Fonteyne(181)	2005 to 2008	Single cohort study	31	N1	68.1Gy/25# to prostate and involved nodes (EQD2 of 78Gy) and at least 48.6Gy/25# to pelvis (EQD2 45Gy)	Rotational IMRT	Used for all patients	2- 3 years	No disease outcome data	G1, G2 and G3 experienced by 39%, 42%,and 6% respectively (at 3 months, 67% had either resolved or improved	Awaiting	G1 and G2 experienced by 45%, none had G3 (at 3 months, 61% had either resolved or improved)	Awaiting

Fonteyne(182)	2005 to 2012	Single cohort study	80	N1	69.3Gy/25# to prostate and involved nodes (EQD2 of 80Gy) and at least 45Gy/25# to pelvis (EQD2 45Gy) – with boost of up to 72Gy (EQD2 of 84Gy) and 65Gy (EQD2 of 72.8Gy) to intra-prostatic lesion and pathological nodes respectively	Rotational IMRT	Used for all patients	2 – 3 years	3 year bRFS was 81%, 3 year OS was 88%, 3 year cancer specific survival was 95%	Not reported	At 3 years, G2 was 29%, G3 was 5%, G4 was 1%	Not reported	At 3 years, G2 was 17%, G3 was 6%

1.5 Toxicity and Quality of Life scores

As well as efficacy, important endpoints when considering novel radiotherapy techniques are both acute and late toxicity, especially as prognosis is generally good after radical prostate radiotherapy and so survivorship issues are paramount(186). Commonly used clinician assessed toxicity scores include Common Terminology Criteria for Adverse Events (CTCAE) and Radiation Therapy Oncology Group (RTOG – which uses different scoring systems for acute and late toxicity), and commonly used patient reported outcome scores include Expanded Prostate Cancer Index Composite (EPIC) and International Prostate Symptom Score (IPSS) (75, 96, 187). Both clinician assessed scores and patient reported outcomes are complementary and allow a holistic assessment of the treatment.

Clinician assessed scores consist of standardised definitions that describe the severity of toxicities and a grade is assigned by the clinician according to symptoms reported by the patient. RTOG has been the histological gold standard for acute toxicity, but it tends to combine several symptoms into one overall score and so may lead to loss of information. Many of the late toxicity items are very rare or not seen any more at all with the current radiotherapy technology. A number of different modifications have been devised over the years to improve the capture of different side effects. It is however simple to use and most prostate radiotherapy trials still report the RTOG toxicity score for comparison with other studies. In comparison, CTCAE is generally more descriptive and comprehensive. The proportion of radiation studies utilising CTCAE has been increasing and it is becoming the commonly used standard(188). CTCAE and RTOG are similar but not equivalent. For instance, in terms of the actual scores themselves, rectal bleeding requiring transfusion is grade 3 by CTCAE v4.0 but grade 4 by RTOG, and in terms of clinical use of the scores in prostate cancer patients treated with HDR brachytherapy alone, CTCAE v3.0 identified more G1-2 GU adverse reactions than RTOG(189). EPIC is an expansion of the University of California – Los Angeles Prostate Cancer Index (UCLA-PCI) validated health-related quality of life questionnaire and is a patient reported outcome measure that categorises by urinary function, bowel habits, sexual function, and hormone function. IPSS is a short efficient questionnaire to screen and track urinary symptoms, although a weakness of it is the lack of

haematuria scoring(190). Overall, clinician assessed scores can predict significant clinical events, whilst patient reported outcomes can better reflect the daily health status of the patient(191).

It is recognised that clinician assessed scoring frequently reports symptoms as less severe than from the patient's perspective and so underestimate the effects on the patient's quality of life, thereby limiting their sensitivity in detecting subtle changes(192). For instance, EPIC was more sensitive to changes in acute bowel toxicity during a course of prostate 3DCRT treatment than RTOG(193). With technological advances in radiotherapy delivery, it is important that these toxicity assessment tools are able to detect subtle but clinically meaningful changes in toxicity when assessing their clinical impact. Furthermore, it should be noted that a statistically significant change in toxicity on a clinician score may not be clinically relevant from the patient's perspective, and vice versa(75).

Assessing pre-treatment baseline symptoms as well as acute toxicities is critical as they can both influence late sequaelae(171). For example, spontaneous erections prior to treatment can predict subsequent maintenance of erectile function after treatment, a lack of acute RTOG GI adverse reaction could predict lack of late adverse reaction such as radiation proctitis, and those that developed acute G≥2 CTCAE GI and GU symptoms from 3DCRT and IMRT had a 7 and 3.5 fold increased risk of late GI and GU toxicities respectively(96, 189, 194, 195). Therefore, collecting pre-treatment symptomatic data as well as acute toxicity data is of importance.

Uneven reporting standards between studies, due to use of different toxicity scores at different time points in relation to radiotherapy, can make comparing therapy effects difficult(96, 160). Therefore, to assess the toxicity of hypofractionated dose painting radiotherapy, it would be prudent to use well established toxicity scoring tools that have already been used by preceding studies to facilitate consistency and comparison.

2 Dynamic ^{18}F choline tracer uptake on PET/CT in prostate cancer and the effects of bicalutamide on it

2.1 Introduction

For prostate dose painting radiotherapy, an imaging modality that can be used to identify boost volumes is PET/CT. This can be performed at staging (before any treatment has commenced) or at planning (during hormone therapy). The former ensures that imaging is not affected by hormone therapy, whilst the latter would minimise changes to anatomy that may result in the 2 - 3 months period between imaging and planning, such as prostate shrinkage due to hormone therapy. The latter would have the added advantage of potentially using the PET/CT as the planning CT, so as to minimise patient radiation exposure and improve convenience. Therefore the effect of hormone therapy on PET tracer uptake is of interest to determine the optimal timing of PET imaging. This would also be informative for other tracers such as PSMA which is now increasingly used to identify sites of disease recurrence following PSA relapse, and may be performed before or after initiation of hormone therapy.

PET imaging can provide static imaging (where activity at a certain time point is analysed and represented in a fixed image) or dynamic imaging (where sinogram data is collected continuously which can be binned into specific static time intervals, capturing the change in activity for individual voxels over time in the form of time activity curves (TAC)).

For dynamic imaging in prostate adenocarcinoma with choline PET, only a few studies have been performed. ^{11}C choline was used in only one study of 14 patients of whom only 3 patients were on hormone therapy at the time of imaging, and visual evaluation found that hormone therapy resulted in low prostatic tracer accumulation(196). ^{18}F choline was used in four studies, but none of the patients were on hormone therapy at the time of imaging(197-200). Therefore the effects of hormone therapy on ^{18}F choline dynamic uptake is not known.

For static imaging, DIL delineation with choline PET can be performed manually (i.e. visually) or automatically (i.e. using an SUV threshold). With the latter, the optimal threshold for ^{11}C choline PET/CT was been shown to be 60% of prostate SUV_{max}, but there has been no studies

to determine the optimal threshold for ^{18}F choline PET/CT although various thresholds have been used(201). Pinkawa et al. defined the DIL by a tumour-to-background uptake value ratio of > 2(171). However the disadvantage of this is their definition of background (an area of around 1 cm^2 within the prostate with the lowest activity on visual assessment, and the SUV_{max} in this area was used as the background uptake value) is subjective and so is not reliably reproducible.

At the Clatterbridge Cancer Centre, an institutionally approved pilot study on prostate dose painting radiotherapy was conducted before the BIOPROP20 study (phase II single cohort study on moderately hypofractionated prostate dose painting radiotherapy) was initiated. For this, consented patients received ^{18}F choline PET/CT imaging during which a dynamic imaging sequence was performed. Initially, patients had imaging whilst on bicalutamide. However as the tracer uptake was felt to be low on visual assessment, subsequent patients had imaging before starting bicalutamide. For this chapter, I have retrospectively analysed the dynamic scans available from the pilot study and those that were available from the ongoing BIOPROP20 trial at the time of writing this chapter.

2.2 Aims

To describe the effect of bicalutamide on the differences in the TAC between tumour and benign prostatic tissue for ^{18}F choline PET/CT.

2.3 Method

2.3.1 Patients selection (inclusion and exclusion criteria)

Newly diagnosed patients were considered if eligibility criteria were fulfilled:

2.3.1.1 Inclusion criteria

- Histologically confirmed prostate adenocarcinoma
- NCCN intermediate/high risk disease/locally advanced (2010 guidelines – Appendix 8.1) and estimated risk of pelvic lymph node involvement of 15 – 40% (Roach formula: ((Gleason score – 6) x 10) + 2/3 PSA)

- MRI staging T2a – T4, N0, M0
- 18 – 80 years of age at registration
- WHO PS 0 or 1
- Fully informed written consent

2.3.1.2 Exclusion criteria

- Previous prostate or pelvic radiotherapy
- Previous hormone therapy or radical prostatectomy
- Total hip replacement
- Clinically significant inflammatory bowel disease
- Contraindications to MRI imaging

2.3.2 PET/CT

Patients had three fiducial markers inserted into the prostate at least 2 weeks before PET/CT imaging. Initially, patients had already commenced bicalutamide 150mg OD before imaging. However subsequent patients were not commenced on bicalutamide until after imaging.

Patients were fasted for at least four hours prior to imaging and asked to drink 500 ml of water before an intravenous injection of 370 MBq of ^{18}F choline (fluoroethylcholine). Starting simultaneously with tracer injection, a GE Discovery 690 PET/CT scanner (GE Medical Systems, Milwaukee, Wisconsin) was used to acquire continuous list-mode time of flight PET data using a single bed position over the pelvis. List-mode collection involved recording each photon pair detection event with a time stamp so that subsequent time-binning of the image data can be performed. This was performed for 30 minutes. The CT based attenuation correction for the PET component is 3.75 mm and the standard CT reconstruction is 2.5 mm. Retrospective reconstruction was performed with data binned into 40 individual time frames, consisting of 12 x 10 second frames, and 28 x 1 minute frames. SUV was normalised to body weight.

A static PET/CT scan was also performed at 90 minutes after injection, consisting of a 10 minute acquisition in a single bed position over the pelvis.

2.3.3 Delineation

The prostatic volume (whole prostate and any extraprostatic extension) was manually delineated by a board-certified nuclear medicine consultant of over 20 years experience (Professor S. Vinjamuri (SV) of The Royal Liverpool University Hospital). The tumour volume was defined on the 90 minutes static imaging by two methods: threshold and visual methods. The threshold method ($SUV_{60\%}$) was performed by identifying the SUV_{max} of the prostatic volume, and the Hermes Hybrid3D software (Hermes Medical Solutions, Stockholm, Sweden) was used to automatically delineate a region within this prostatic volume which was ≥60% of the SUV_{max}. The visual method was performed by a nuclear medicine consultant (SV) who manually delineated on the PET/CT without access to any other information including histology or MRI.

In order to transfer the tumour volumes generated from the 90 minutes static imaging to the dynamic imaging, the CT sequences of both scans were rigidly co-registered by using the three fiducial markers and these coordinates were used.

2.3.4 Analysis

For the tumour and benign prostatic tissues, the median SUV value within each time bin was calculated, and data were collected to evaluate the effect of bicalutamide on:

1) Time to peak 90% (TT90%P) SUV (from time of tracer injection to the time where 90% of maximal SUV uptake is reached) of tumour and of benign prostatic tissue;
2) The SUV_{max} of tumour and of benign prostatic tissue;
3) Difference in AUC between tumour and benign prostatic tissue.

The data for tumour and for benign prostatic tissue are presented with median and range values. The 95% confidence interval (CI) for the median values are also presented (as the data is non-parametric, the bootstrapping method with 1000 samples was used).

2.4 Results

Dynamic PET/CT imaging was available for 40 patients who had imaging without bicalutamide, and 10 patients who had imaging with bicalutamide (Table 2-1). With the threshold method, all 50 patients had identifiable tumour volumes. With the visual method, all 40 patients who had imaging without bicalutamide had identifiable tumour volumes, but only 7 out of the 10 patients who had imaging during bicalutamide had identifiable tumour volumes. As a proportion of the whole prostatic volume, the tumour volume ranged from 1.6 % to 41.7 % (Table 2-2).

On visual evaluation, the initial tracer uptake in the tumour and benign prostatic tissues were rapid within the first 5 minutes (Figure 2-1). Thereafter the TACs either plateaued or showed gradual increase in activity with no apparent differences in pattern between tumour and benign prostatic tissue (Figure 2-2 and 2-3). However the range of SUV values appear larger for tumour than for benign prostatic tissue.

Table 2-1 Patient demographics

*Median and range

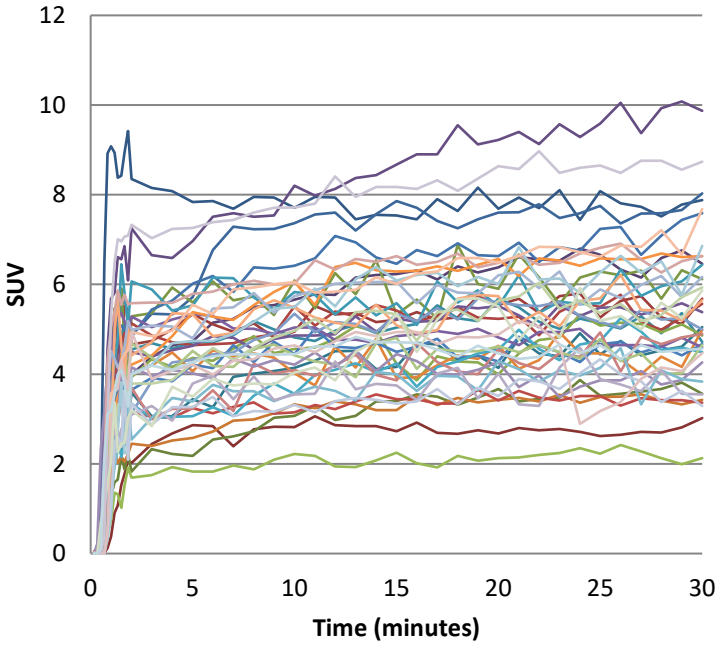
		With bicalutamide	Without bicalutamide
No. of patients		**10**	**40**
Age (years)*		**62 (56 – 76)**	**68 (56 – 78)**
PSA (ng/ml)*		**17.3 (10.9 – 59.1)**	**10.0 (4.4 – 39.4)**
Bicalutamide duration before PET/CT (days)*		**82 (42 – 193)**	**-**
High risk		**9**	**28**
Gleason score	**6**	**0**	**1**
	7	**5**	**29**
	8, 9	**5**	**10**
TNM staging	**T2**	**3**	**15**
	T3	**7**	**25**

Table 2-2 Tumour volume as a percentage of the whole prostatic volume

		With bicalutamide		Without bicalutamide	
		Median	**Range**	**Median**	**Range**
Threshold method	**DIL volume (ml)**	**6.5**	**1.7 – 11.1**	**3.7**	**0.9 – 16.8**
	Prostate volume (ml)	**30.4**	**20.2 – 55.0**	**33.7**	**14.7 – 95.0**
	DIL/ prostate (%)	**14.2**	**6.6 – 32.7**	**9.9**	**2.3 – 41.7**
Visual method	**DIL volume (ml)**	**2.5**	**1.0 – 14.3**	**2.2**	**0.6 – 10.6**
	Prostate volume (ml)	**38.7**	**25.1 – 61.1**	**37.9**	**19.2 – 87.6**
	DIL/prostate (%)	**6.1**	**2.0 – 26.9**	**5.8**	**1.6 – 17.5**

Figure 2-1 TACs of tumour (A) and benign prostatic tissue (B) for all patients without bicalutamide as defined by visual method

A



B

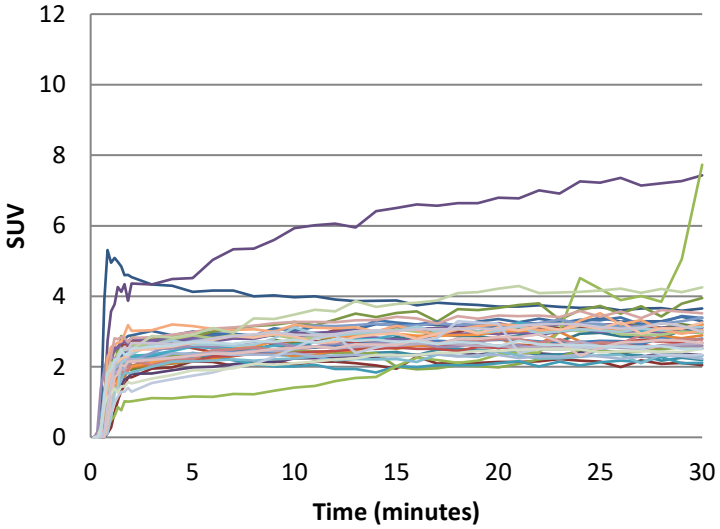
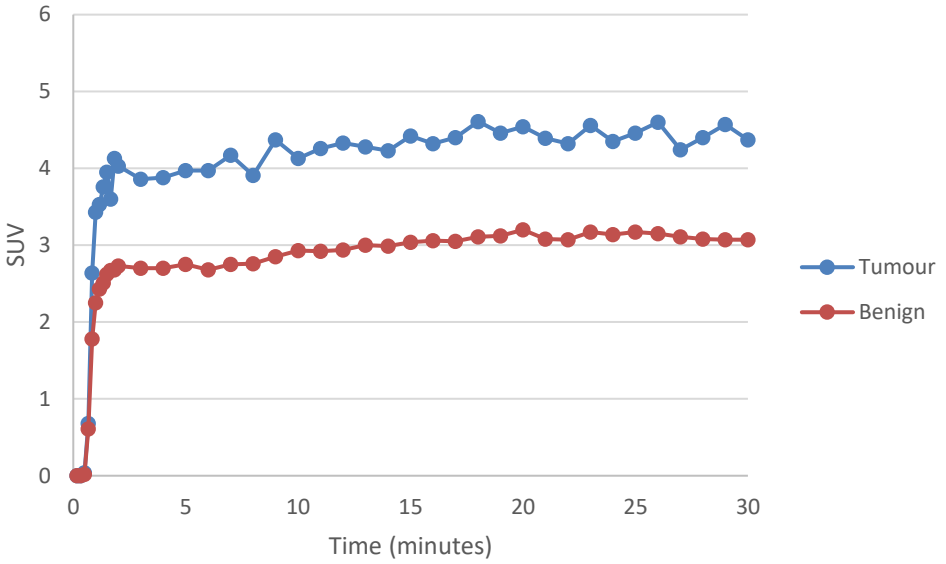


Figure 2-2 Example of TACs for a patient who had imaging without bicalutamide, with tumour identified by the threshold method (A) and by the visual method (B)

A



B

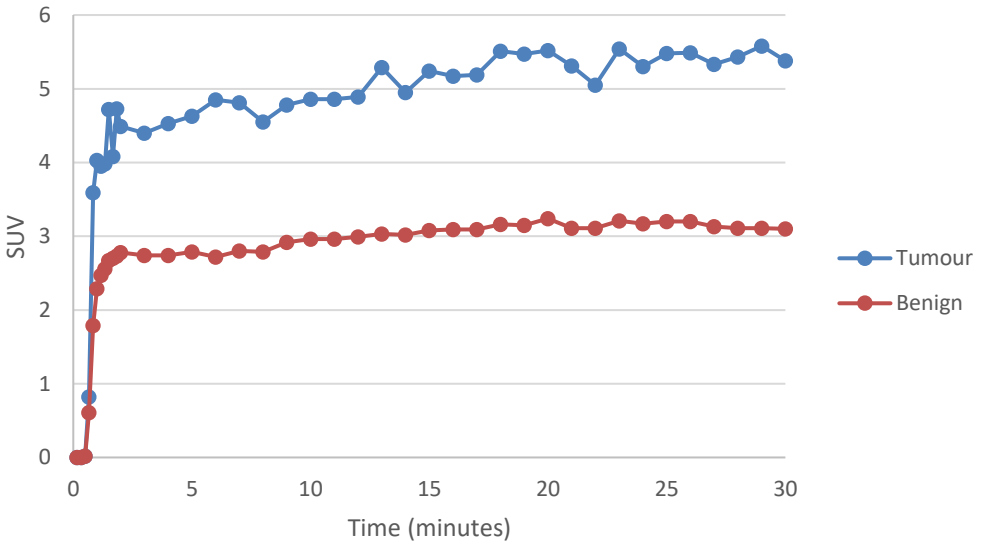
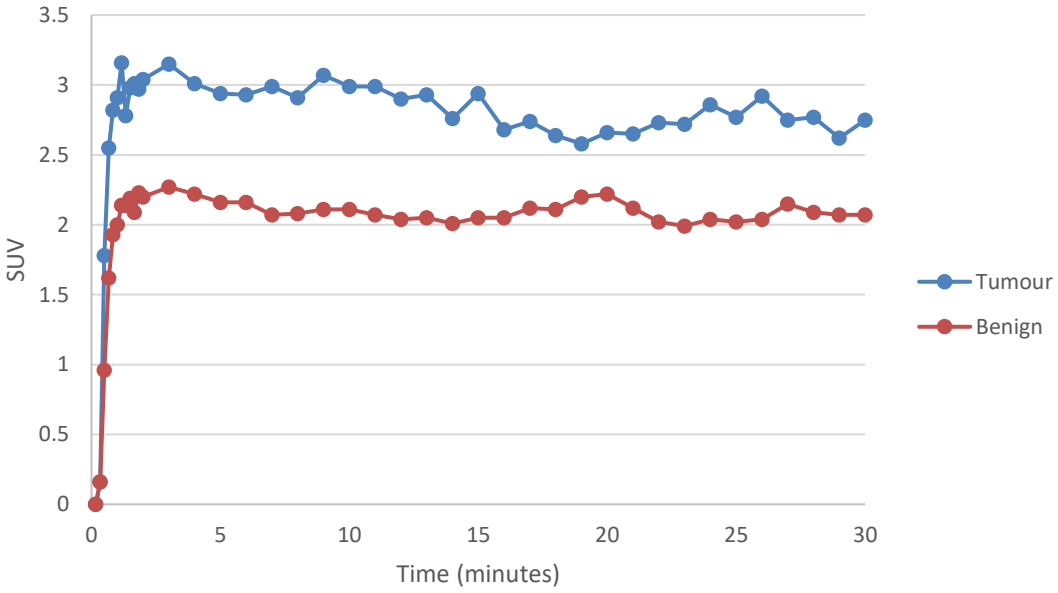
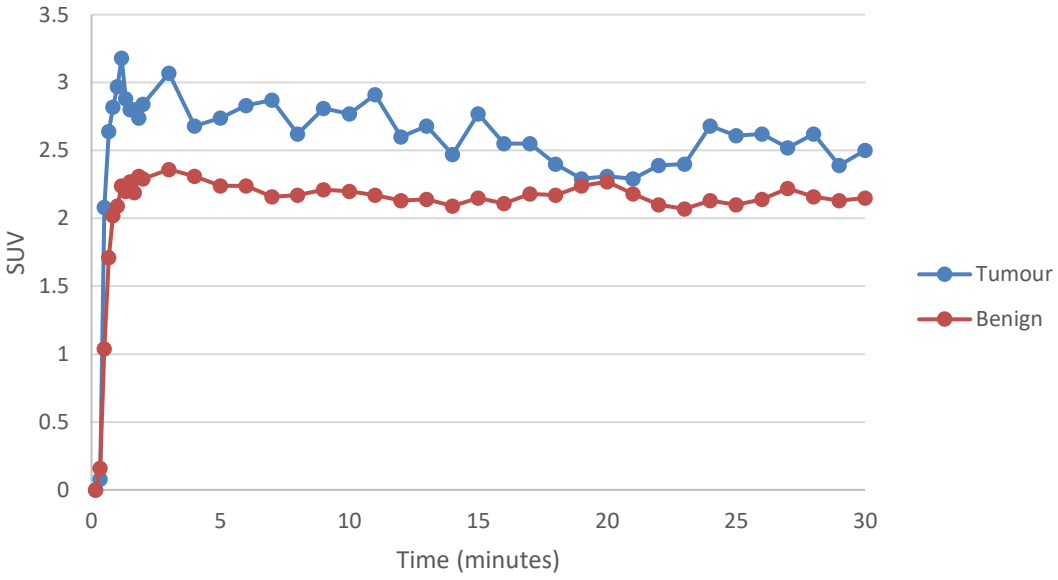


Figure 2-3 Example of TACs for a patient who had imaging with bicalutamide, with tumour identified by the threshold method (A) and by the visual method (B)

A



B



2.4.1 TT90%P

For the group of patients who had imaging without bicalutamide, the median TT90%P SUV within the tumour as identified by the threshold method was 8.0 minutes, whilst that of the benign tissue was 9.0 minutes (Table 2-3). However there is generally a significant variation of TT90%P from patient to patient (for instance, TT90%P within the tumour ranged from 0.7 minutes to 27.0 minutes). The TT90%P within the tumour occurred before that of the benign tissue in 18 patients, at the same time in 4 patients, and after in 18 patients. On an individual patient by patient basis, there was no significant difference in TT90%P between tumour and benign prostatic tissue (although this ranged from -23.0 to 13.0 minutes).

For the group of patients who had imaging with bicalutamide, the median TT90%P SUV within the tumour as identified by the threshold method was 2.9 minutes, whilst that of the benign tissue was 1.9 minutes (Table 2-3). Again, there is generally a significant variation of TTP from patient to patient (for instance, TT90%P within the tumour ranged from 0.8 minutes to 23.0 minutes). The TT90%P within the tumour occurred before that of the benign tissue in 3 patients, at the same time in 4 patients, and after in 3 patients. On an individual patient by patient basis, there was again no significant difference in TT90%P between tumour and benign prostatic tissue.

Therefore, whether tumour is identified by the threshold or visual method, the difference in TT90%P of tumour and of benign tissue was not significant, whether PET/CT was performed with or without bicalutamide (Table 2-3).

Also there is a trend for TT90%P without bicalutamide to be longer than with bicalutamide, although was no statistical significance (using independent samples Mann Whitney U test: with the threshold method, p value for tumour and benign were 0.22 and 0.51 respectively; with the visual method, p value for tumour and benign were 0.35 and 0.17 respectively).

Table 2-3 Time to 90% peak (TT90%P) in minutes

*statistical comparison between tumour and benign using Wilcoxon signed rank test

		Tumour		Benign		Difference in TT90%P between tumour and benign on a patient by patient basis		Statistical comparison*
		Median	95% CI	Median	95% CI	Median	95% CI	p value
Threshold method	With bicalutamide	2.9	1.6 to 11.0	1.9	1.5 to 18.0	0.0	-2.5 to 1.6	0.75
	Without bicalutamide	8.0	4.5 to 11.0	9.0	6.5 to 10.0	0.0	-2.0 to 1.7	0.89
Visual method	With bicalutamide	1.8	1.2 to 18.0	1.3	1.2 to 18.0	0.0	-0.2 to 0.5	0.69
	Without bicalutamide	9.0	6.5 to 11.0	9.0	6.5 to 12.0	1.0	-0.2 to 3.0	0.27

2.4.2 SUV_{max}

For the group of patients who had imaging without bicalutamide, the SUV_{max} within the tumour as identified by the threshold method was 5.3, whilst that of the benign tissue was 2.9 (Table 2-4). On an individual patient by patient basis, the difference in SUV_{max} between tumour and benign tissue was statistically significant ($p < 0.01$). For the group of patients who had imaging with bicalutamide, the SUV_{max} within the tumour as identified by the threshold method was 3.4, whilst that of the benign tissue was 2.4. Again, for the individual patients, the difference in SUV_{max} between tumour and benign tissue was statistically significant ($p = 0.01$). This was also found if the tumour is identified by the visual method.

Therefore, whether tumour is identified by the threshold or visual method, the SUV_{max} of tumour is significantly higher than that of the benign tissue, whether PET/CT was performed with or without bicalutamide (Table 2-4).

Table 2-4 SUV_{max}
*statistical comparison between tumour and benign using Wilcoxon signed rank test

		Tumour		Benign		Statistical comparison*
		Median	95% CI	Median	95% CI	p value
Threshold method	With bicalutamide	3.4	3.2 to 6.2	2.4	1.9 to 3.5	0.01
	Without bicalutamide	5.3	4.6 to 5.6	2.9	2.8 to 3.2	<0.01
Visual method	With bicalutamide	3.9	3.2 to 8.5	2.6	2.0 to 3.3	0.03
	Without bicalutamide	5.6	5.0 to 6.1	3.1	2.8 to 3.2	<0.01

2.4.3 Difference in AUC of the TAC between tumour and benign tissue

When imaging was performed without bicalutamide, the AUC of the tumour as identified by the threshold method was larger than that of the benign tissue by a median of 1.7 times (range of 0.8 to 3.3) (Table 2-5). When imaging was performed with bicalutamide, the AUC of the tumour was larger than that of the benign tissue by a median of 1.4 times (range 1.1 to 2.8). However this difference in AUC between tumour and benign tissue was not significantly different whether imaging was performed without or with bicalutamide ($p = 0.10$). This was also found if the tumour was identified by the visual method.

Therefore, whether tumour is identified by the threshold or visual method, bicalutamide does not significantly affect the difference in AUC between tumour and benign tissue.

Table 2-5 Relative difference in AUC between tumour and benign tissue
*statistical comparison between without bicalutamide and with bicalutamide using independent samples non parametric Mann Whitney U test

		Relative difference between tumour and benign tissue		Statistical comparison*
		Median	95% CI	p value
Threshold method	With bicalutamide	1.4	1.3 to 1.9	0.10
	Without bicalutamide	1.7	1.6 to 1.9	
Visual method	With bicalutamide	1.4	1.2 to 2.4	0.32
	Without bicalutamide	1.7	1.6 to 1.9	

2.5 Discussion

Semi-quantitative analyses of our results show that whether using the $SUV_{60\%}$ threshold method or the visual method to differentiate between malignant and benign prostatic tissue, there is a trend (although not statistically significant) for SUV in both malignant and benign prostatic tissue to peak slower when scanned without bicalutamide than when scanned with bicalutamide. Also the SUV_{max} and bicalutamide are significantly higher in tumour than in benign tissue, and this is not affected by bicalutamide. For these analyses of 30 minutes dynamic imaging, static imaging performed at 90 minutes were used as the standard with which to define the tumour, and around a third of patients who were imaged with bicalutamide had no visually identifiable tumour and therefore analysis using the visual method was not possible for these patients.

The TACs generated in our study support the observations within the published literature. Our malignant lesions had generally rapid ^{18}F choline uptake within the first 5 minutes then subsequently plateaued or continued to rise slowly. This has been described for both ^{11}C choline(196) and ^{18}F choline(197, 199). Of note, one of these studies which performed kinetic

studies using compartmental modelling for ^{18}F choline had used a dynamic scan over 60 minutes, and it found that reliable estimates of all parameters could be achieved with a 30 minutes dynamic scan instead, thereby suggesting that our dynamic imaging protocol is sufficient to obtain data from(197).

In the published literature, the only study that I am aware of which assessed dynamic choline PET imaging in patients during hormone therapy was by Sutinen et al., which used ^{11}C choline and showed that the two patients on hormonal treatment with goserelin had the lowest tracer accumulation of all the studied patients, with SUV of 1.8 and 2.8(196). There was another patient who had orchiectomy 7 years prior to PET imaging, but his tracer uptake profile was not specifically described. Although our study had used ^{18}F choline instead, it also showed that tumour SUV without hormone therapy is generally higher than tumour SUV with hormone therapy, but that the difference in SUV between tumour and benign prostatic tissue is statistically significant whether without or with hormone therapy. Also of note, our study showed that PET scanning without hormone therapy can result in a more prolonged and increased tracer uptake over time, whereas hormone therapy can result in a shortened and lower tracer uptake. Overall, this suggests that dynamic PET scanning without hormone therapy will allow tumour to be more easily identifiable by visual assessment than if performed with hormone therapy, but that hormone therapy should not affect the ability to differentiate between tumour and benign prostate tissue. Therefore if dynamic PET imaging is to be used for the purposes of identifying DILs for dose painting radiotherapy delineation, they should be performed without hormone therapy.

The effect of bicalutamide on ^{18}F choline tracer uptake may be due to modulation of signalling pathways. Prostate cancer cells have been shown to have an increased uptake of choline due to increased cell proliferation and upregulation of choline kinase. Bicalutamide is a pure anti-androgen which blocks androgen receptors, downregulating the expression of several genes including those involved in lipid metabolism and regulating the Ras signalling pathway, leading to reduced choline transporter and choline kinase activity as well as inhibiting of angiogenesis and proliferation of cancer cells(202). Bicalutamide has previously been found to inhibit prostate ^{11}C choline uptake, and it is likely to have a similar effect on ^{18}F choline(203, 204).

There are limitations to our methodology. The reference standard comparator was not histology, but instead was the static PET imaging at 90 minutes after tracer injection. Therefore this requires an assumption that the 90 minutes scan can accurately identify malignant DILs without histological confirmation. Furthermore, the $SUV_{60\%}$ threshold method used for the 90 minutes scan was derived from studies using ^{11}C choline, and so there are inherent uncertainties about whether this threshold method is as accurate for ^{18}F choline. Our methodology involved rigid co-registration of the CT component of the PET/CT scans by using three fiducial markers, in order to delineate the region of the prostate on the dynamic scan which was identified as malignant on the 90 minutes scan. The rigid co-registration process between the CT components was straight forward, but there are inherent uncertainties between the registration of the PET and CT components. It has been shown that, despite a patient lying still on the imaging bed, prostate positioning can increase with elapsed time from physiological motions (i.e. rectal activity and bladder filling) and from pelvic muscular contractions, especially as the dynamic PET and static PET data were acquired over 30 minutes and 10 minutes respectively, whilst the associated CT imaging for both were taken in a significantly shorter period of time(205). This may explain the anomalies in Figure 2-1B, where one patient has a comparatively higher SUV than the other patients, and another patient has a rise in SUV after around 28 minutes. The former patient may have had a shift between the PET and CT components of either dynamic or static scans, resulting in mis-registration of the PET despite good registration between the CT scans. This may have led to part of the tumour migrating into the region which has been designated benign tissue, thereby resulting in a TAC that actually represents tumour. The latter patient may have also had a similar shift, resulting in the bladder or urethra migrating into the region which has been designated benign tissue, and so explain the delayed uptake on the TAC. Another limitation is that our TT90%P methodology has not been used in other studies, and hence it is difficult to compare our results. Also we had not performed kinetic modelling nor quantitative analysis. However we had performed semi-quantitative analysis with SUV, and studies support the use of SUV methods to assess tracer uptake in the clinical setting(196).

2.6 Conclusion

Dynamic PET scanning without bicalutamide will allow tumour to be more easily identifiable by visual assessment than if performed with bicalutamide, but bicalutamide should not affect the ability to differentiate between tumour and benign prostate tissue. Therefore if dynamic PET imaging is to be used for the purposes of identifying DILs for dose painting radiotherapy delineation, they should be performed without bicalutamide.

3 Effect of bicalutamide on prostate dose painting radiotherapy boost volumes identified on ^{18}F choline PET/CT

3.1 Introduction

Prostate dose painting radiotherapy requires the delineation of DILs within the target volumes to which an escalated dose can be delivered. mpMRI is the standard method used for identifying intra-prostatic lesions due to the superior soft tissue definition it affords. An alternative imaging modality which can be used is PET/CT with various tracers including radiolabelled choline.

Standard treatment for intermediate and high risk patients involves several months of neo-adjuvant hormone therapy. As discussed in the previous chapter, PET/CT scan can be performed before hormone therapy (i.e. at staging) which allows delineating of the original DIL, or during hormone therapy which allows the CT component to be used for planning. There is no published data to suggest if these two schedules produce significantly different boost volumes although reduced tracer uptake has been observed in patients who were imaged with hormone therapy(206).

For this chapter, I have retrospectively analysed the PET/CT imaging from the pilot study and those that were available from the ongoing BIOPROP20 trial at the time of writing this chapter. As will be discussed later in the methods section, this chapter required input from consultants and physicists at the Clatterbridge Cancer Centre for DIL delineating and use of Aria to obtain DSC data.

3.2 Aims

a) To determine whether sizes of DILs identified on ^{18}F choline PET/CT are significantly affected by bicalutamide;

b) To determine the optimal delineating method for ^{18}F choline PET/CT between visual method and threshold method (using 60% of prostate SUV_{max}).

3.3 Methods

3.3.1 Study design

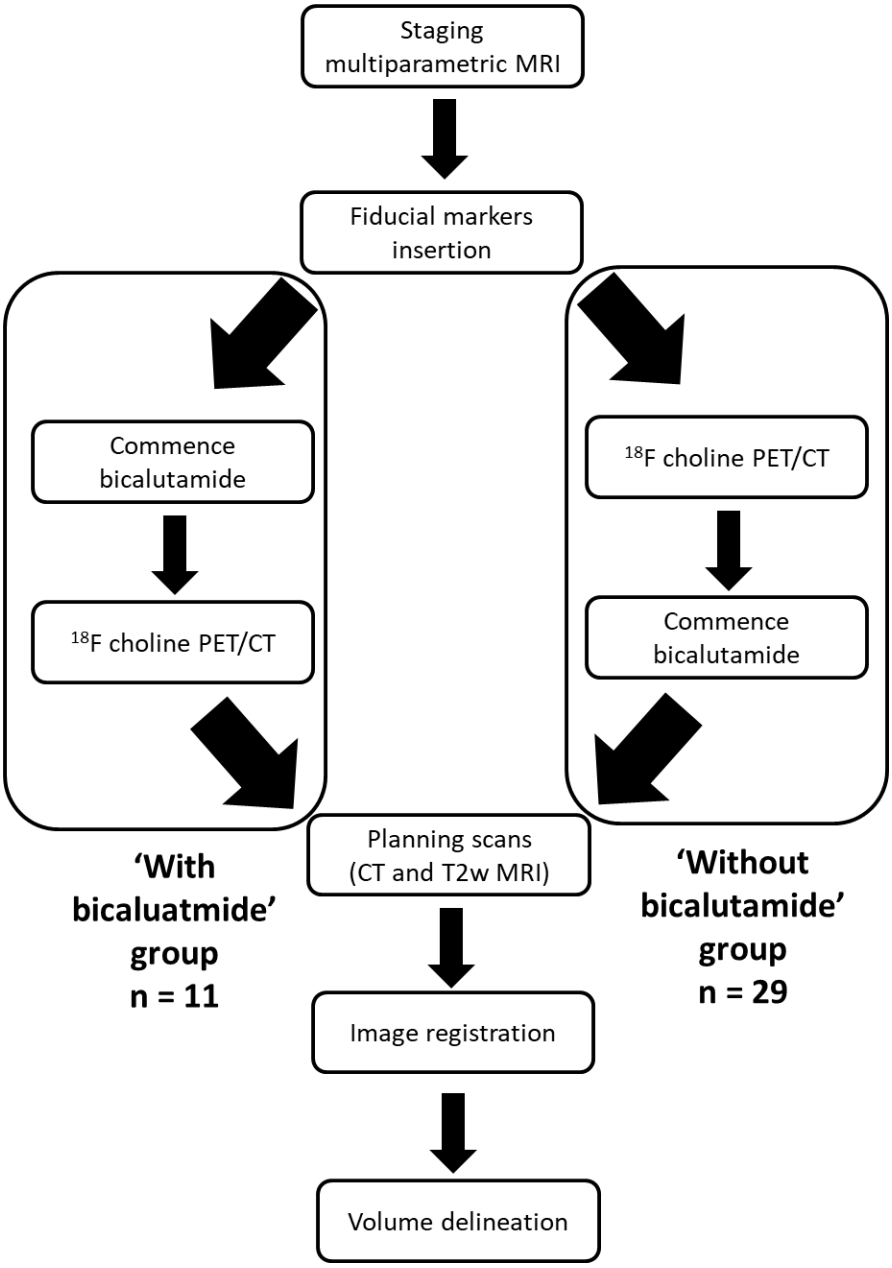
This was a retrospective study using imaging for a cohort of patients who have had both MRI (staging mpMRI and planning T2w MRI) and ^{18}F choline PET/CT for prostate dose painting radiotherapy planning. Initially patients had PET/CT imaging at planning, whilst on bicalutamide ('with bicalutamide' group). As visual tracer uptake was noted to be low, subsequent patients had PET/CT imaging at staging, before bicalutamide ('without bicalutamide' group).

3.3.2 Patient selection (inclusion and exclusion criteria)

Patients had the same eligibility criteria as chapter 2. Of note, the work for the previous chapter was performed at a later time point than that of this chapter, thereby accounting for the differences in patient numbers.

Patients who had received ^{18}F choline PET/CT were identified and separated into either the 'with bicalutamide' group or the 'without bicalutamide' group. The only difference in the planning pathways between the two groups was whether bicalutamide was started before or after the PET/CT. In all patients, gold fiducial markers were inserted in the prostate prior to PET/CT, planning MRI and planning CT (Figure 3-1).

Figure 3-1 Diagram of the sequences of imaging for the 'With bicalutamide' and the 'Without bicalutamide' groups



3.3.3 Imaging protocol

All patients were scanned with the same PET/CT imaging protocol. Patients were fasted for at least four hours prior to imaging and asked to drink 500 ml of water before an intravenous

injection of 370 MBq of ^{18}F choline (fluoroethylcholine). A static pelvic scan performed at 90 minutes post injection in a single bed position over 10 minutes with a GE Discovery 690 PET/CT scanner (GE Medical Systems, Milwaukee, Wisconsin) was used. Images were reconstructed using the iterative line of response (LOR) algorithm. SUV was normalised to body weight.

Prior to the planning T2w MRI and planning CT, patients emptied their bowels with a micro enema (Relaxit 5 ml per rectum) and drank 300 ml of water. These scans were acquired with an indwelling 12 gauge soft Foley urethral catheter. The planning MRI was performed with Turbo Spin Echo thin slice acquisition using a Philips Intera 1.5T MRI scanner with phased array coils. The planning CT was performed by a Philips Brilliance wide bore scanner, giving a 3 mm slice width.

3.3.4 DIL delineation protocol

On ProSoma (OSL Oncology Systems Limited, UK), the PET/CT and planning T2w MRI images were rigidly co-registered to the planning CT using the fiducial markers and catheter. The whole prostate was delineated on both PET/CT and planning CT. The identification of DILs on MRI was performed by two radiation oncologists together by delineating on the planning T2w MRI whilst using the staging MRI (anatomical T2w and functional diffusion weighted imaging) for reference. The identification of DILs on PET was performed visually ('visual PET') by the two radiation oncologists on ProSoma, and automatically using a threshold defined as 60% of prostate SUV_{max} ('threshold PET') on Mirada (Mirada Medical Limited, UK) where SUV_{max} uptake data was also collected. For standardisation of visual assessments between patients, the PET windowing was altered until bone marrow uptake was visually detectable. All information was available at time of delineation (including pathology and other imaging).

3.3.5 Boost volume analysis

To unite the structures from both ProSoma and Mirada systems, the delineations were imported into ARIA version 11 (Varian Medical Systems, USA) which displayed the registered images along with all structures. Size data on DIL volumes were collected from ARIA. In order to account for registration errors between the primary data set (planning CT) and the

secondary data sets (MRI or PET), a 5 mm isotropic expansion margin was performed around the DIL delineations (to create the boost volumes) and the prostate delineations within ARIA. Correlation analyses were used with these expanded volumes, with four different metrics used. Dice similarity coefficient (DSC) was defined according to the following formula (where A and B are the volumes of the MRI-defined and PET-defined boosts, and A∩B is the volume of the overlapping boosts): DSC = 2 x A∩B / (A+B). Sensitivity, specificity and Youden index were calculated according to the following formulas (TP (true positive) – overlapping volume between MRI and PET boosts; FP (false positive) – PET boost volume excluding the MRI boost volume; FN (false negative) – MRI boost volume excluding the PET boost volume; TN (true negative) – planning CT prostate delineation excluding both MRI and PET boost volumes): Sensitivity = TP / (TP+FN); Specificity = TN / (TN+FP); Youden index = Sensitivity + Specificity – 1.

3.3.6 Statistical analysis

SPSS V22.0 (International Business Machines Corporation, US) was used for statistical analysis. Due to the skewed distribution of the delineation volumes and SUV uptake values, they were reported by median and range, with 2-tailed significance testing using Wilcoxon signed rank test. As the distribution of the correlation analyses tended to the normal distribution (kurtosis were all well below 3 except for DSC between MRI and threshold $SUV_{60\%}$ PET during bicalutamide which was 3.3), they were reported by mean ± standard deviation (SD) with 2-tailed significance testing using independent T test.

3.4 Results

There were 11 patients in the ‘with bicalutamide’ group (150 mg once a day orally), and 29 patients in the ‘without bicalutamide’ group (Table 3-1).

Table 3-1 Patient demographics
*Median and range

		With bicalutamide	Without bicalutamide
No. of patients		**11**	**29**
Age (years)*		**63 (49 – 76)**	**68 (50 – 77)**
PSA (ng/ml)*		**16.6 (10.9 – 28.6)**	**9.0 (3.6 – 39.4)**
Bicalutamide duration before PET/CT (days)*		**85 (42 – 193)**	**-**
High risk †		**11**	**25**
Gleason score	**6**	**0**	**1**
	7	**7**	**21**
	8, 9	**4**	**7**
TNM staging	**T2a**	**0**	**5**
	T2b, c	**4**	**6**
	T3a, b	**7**	**18**

There was no significant change in prostate volume between PET/CT and planning CT scans for the 'with bicalutamide' group (median 0.34%, $p = 0.48$), but there was a significant reduction in the 'without bicalutamide' group (median -16.9%, $p < 0.01$, Table 3-2).

Table 3-2 Prostate and boost volumes

		With bicalutamide		Without bicalutamide	
		Median	**95% CI**	**Median**	**95% CI**
Prostate volumes [ml]	**PET/CT**	**38.02**	**30.16 – 44.07**	**47.02**	**44.18 – 56.95**
	Planning CT	**36.92**	**29.62 – 45.05**	**39.07**	**35.68 – 48.94**
	%Change	**0.03 %**	**-3.08 to 3.32**	**-16.94 %**	**-22.43 to -12.15**
Boost volumes [ml]	**MRI**	**1.98**	**0.67 – 7.20**	**2.17**	**2.07 – 3.77**
	visual PET	**1.34**	**0.15 – 3.41**	**2.62**	**2.15 – 3.65**
	threshold PET	**4.81**	**2.87 – 7.49**	**3.71**	**2.81 – 6.31**

There was a trend for prostate SUV_{max} to be lower in the 'with bicalutamide' group (median 4.2, range 2.7 to 12.0) compared to the 'without bicalutamide' group (median 6.6, range 4.1 to 18.6) although it did not reach statistical significance (Mann-Whitney U test; p = 0.06).

In the 'with bicalutamide' group, all patients had one MRI DIL, but 3 patients had no visually identifiable PET DIL. In the 'without bicalutamide' group, 28 patients had at least one MRI DIL, one patient had no MRI DIL that could be confidently delineated, and all patients had at least one visually identifiable PET DIL(Table 3-3).

In both groups, the median DILs on MRI were small (1.98 and 2.17 ml), but there was a large variation between patients (0.53 – 17.83 ml, Table 3-2). Per individual patient, the visual PET DILs were significantly smaller than the MRI DILs in the 'with bicalutamide' group (median reduction of 63%, p = 0.03) but not in the 'without bicalutamide' group (median reduction of 5%, p = 0.84)(Table 3-4). The threshold PET DILs were generally larger than the MRI DILs in both groups, but this varied between patients and was not statistically significant (median increase of 60%, p = 0.33; median increase of 20%, p = 0.19 respectively).

The correlation analyses showed that both visual and threshold PET have a moderate sensitivity (0.50 to 0.68) and a high specificity (0.85 to 0.98) for identifying MRI-defined disease (Table 3-4). There was a trend for the PET boost volumes (especially visually defined) to correlate better with the MRI boost volumes in the 'without bicalutamide' group.

Table 3-3 Number of DILs identified

	n	With bicalutamide	Without bicalutamide
No. of patients with *n* MRI DILs	0	0	1
	1	11	25
	2	0	3
No. of patients with *n* visual PET DILs	0	3	0
	1	7	20
	2	1	9
No. of patients with *n* threshold PET DILs	0	0	0
	1	10	21
	2	1	6
	3	0	1
	4	0	1

Table 3-4 Comparison of size and correlation between prostate volumes and boost volumes (with 5 mm margin)

*Mean ± SD

		With bicalutamide*	Without bicalutamide*	Independent T test (2-tailed) p value
PET/CT vs Planning CT prostate (+ 5 mm)	**DSC**	**0.86 ± 0.05**	**0.86 ± 0.06**	**-**
MRI vs visual PET DIL (+ 5 mm)	**Size comparison Paired T test (2-tailed)**	**0.03**	**0.84**	
	DSC	**0.56 ± 0.11**	**0.61 ± 0.15**	**0.41**
	Sensitivity	**0.50 ± 0.11**	**0.68 ± 0.18**	**0.12**
	Specificity	**0.98 ± 0.03**	**0.92 ± 0.08**	**<0.05**
	Youden	**0.48 ± 0.10**	**0.60 ± 0.20**	**0.11**
MRI vs threshold PET DIL (+ 5 mm)	**Size comparison Paired T test (2-tailed)**	**0.33**	**0.19**	
	DSC	**0.49 ± 0.15**	**0.51 ± 0.15**	**0.72**
	Sensitivity	**0.64 ± 0.22**	**0.63 ± 0.25**	**0.99**
	Specificity	**0.85 ± 0.14**	**0.87 ± 0.11**	**0.63**
	Youden	**0.48 ± 0.20**	**0.50 ± 0.21**	**0.80**

3.5 Discussion

Although the observation of reduced tracer uptake in patients on hormone therapy has previously been described, these results have quantified this effect(206). If the PET/CT was performed with bicalutamide, the prostate SUV_{max} was lower although it did not reach statistical significance, and over a quarter of patients had no visually identifiable PET DILs (Figure 3-2). If the PET/CT was performed without bicalutamide, all patients had at least one visually identifiable PET DIL, and two patients had three to four threshold-identified PET DILs. These additional volumes tended to be small (0.1 to 0.3 ml) and in practice, would be omitted from the total boost volume.

For the patients who had PET/CT imaging with bicalutamide, visually identified PET DILs were similar in size to those seen on MRI, whilst those identified in patients who were imaged with bicalutamide were significantly smaller (Figure 3-3 and 3-4). This suggests that choline tracer uptake in malignant lesions is reduced by bicalutamide on PET imaging, and therefore bicalutamide should ideally be commenced after imaging has been performed. This effect might also be found for PET imaging with other tracers such as PSMA, which is increasingly used for identifying sites of recurrence following radical treatment.

Figure 3-2 Example of a patient who had PET/CT with bicalutamide (left). No DIL could be identified visually. T2 MRI (right) for comparison.

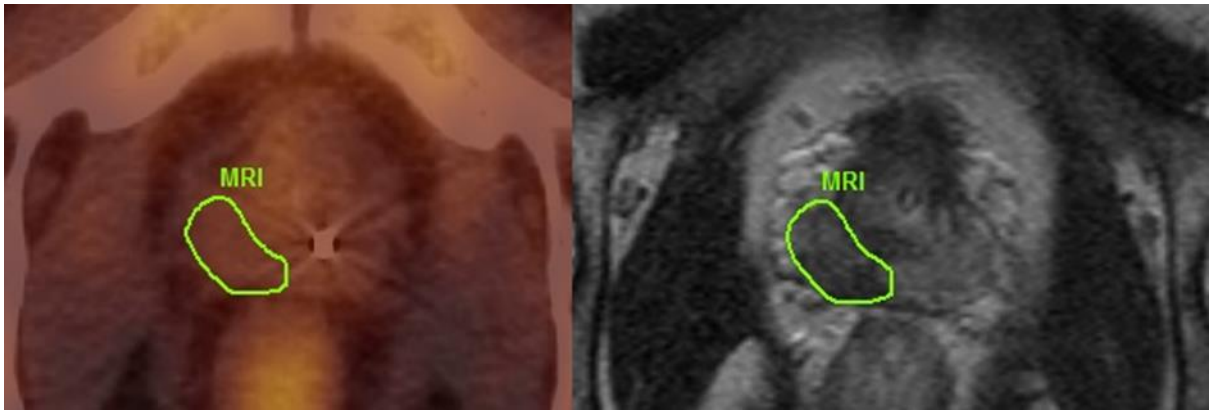


Figure 3-3 Example of a patient who had PET/CT (left) with bicalutamide. The DIL identified visually by PET is smaller than the corresponding DIL identified by MRI (right).

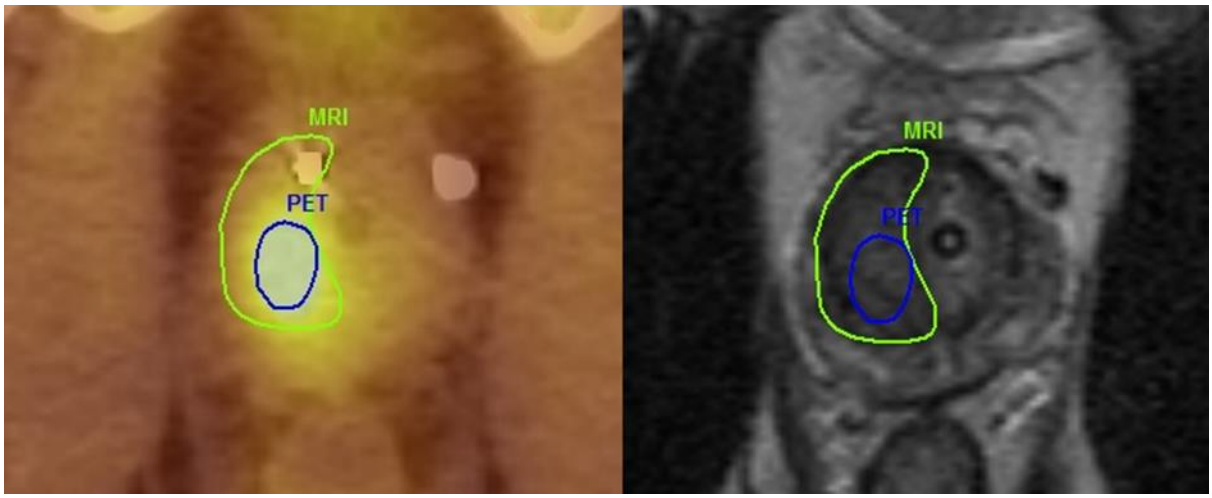
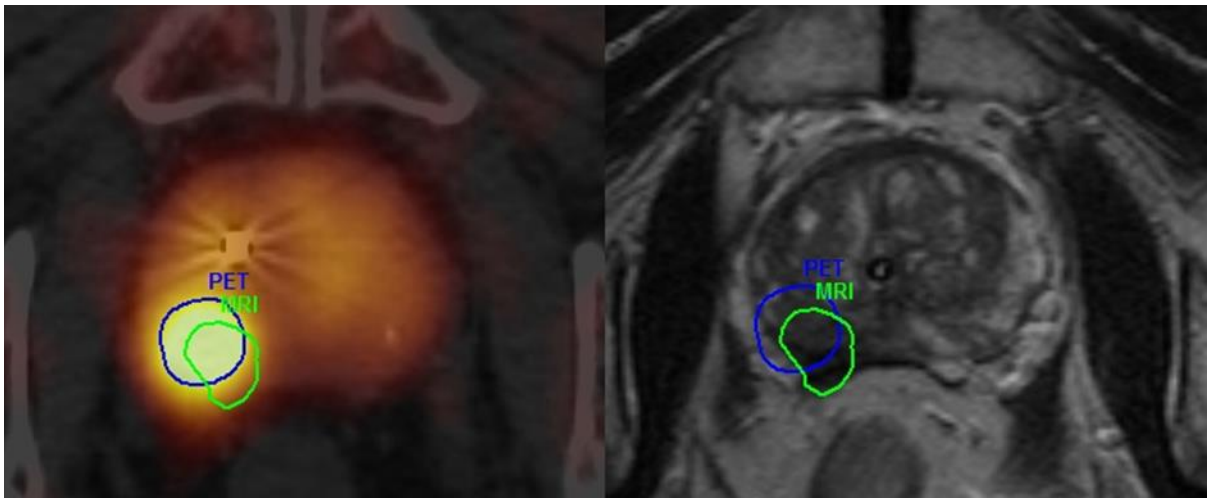


Figure 3-4 Example of a patient who had PET/CT (left) without bicalutamide. The DIL identified visually on PET overlaps the corresponding DIL identified on MRI (right).



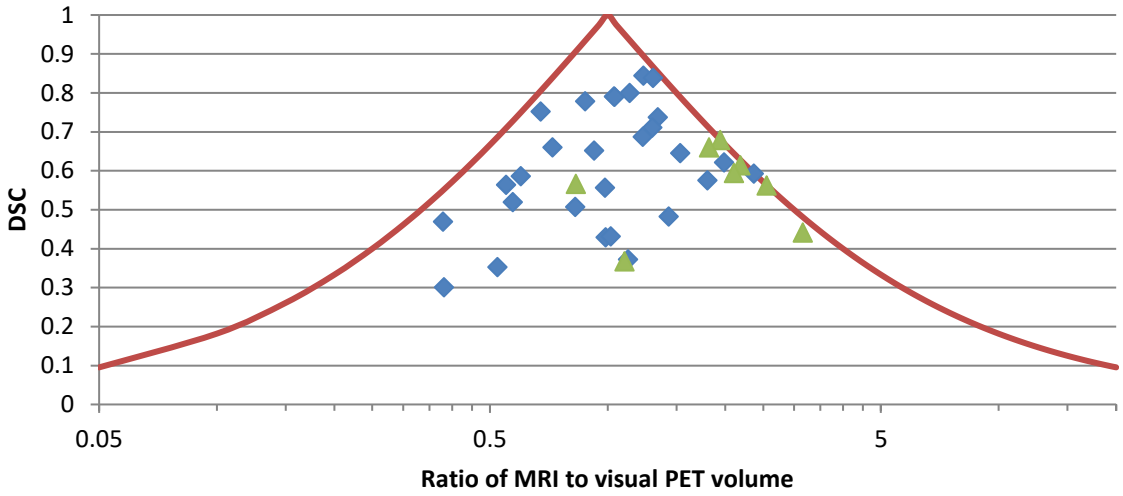
Although it would be expected that a similar effect should be found for DILs delineated by the threshold PET method, these results have not shown this. This may be because the threshold level of SUV_{max} 60% is too low for our PET imaging protocol, resulting in generally larger DILs which may have obscured any effect from bicalutamide.

Although it did not reach statistical significance, the correlation between threshold PET boost volumes and MRI boost volumes were generally poorer than with the visual PET method. This is likely to be because clinicians had access to all relevant clinic details at time of visual delineation, as per real life clinical practice. The overall DSC values were highest for the visual PET in the 'without bicalutamide' group (Figure 3-5).

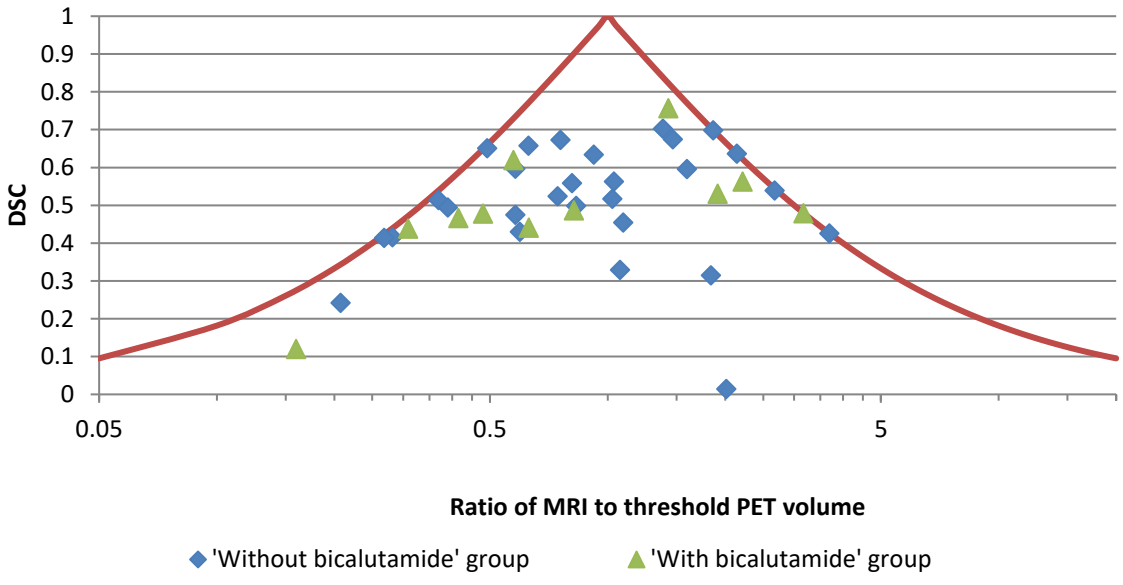
Our data have also shown that around two and a half months of bicalutamide can reduce the overall prostate volume by 17%, albeit with significant inter-patient variation. When both PET/CT and planning CT were performed with bicalutamide, the prostate volumes were similar although there were differences of up to 7.7% which reflects the difficulty delineating pelvic soft tissue on CT. Despite the reduction in prostate size from bicalutamide, the DSC between the prostate volumes were the same between the two groups (0.86) which may suggest that the variation due to the change in size is on the same scale as the variation due to difficulty delineating on CT. Rigid co-registration of the PET/CT and planning CT using the fiducial markers and catheter was generally uncomplicated.

Figure 3-5 Distribution of DSC values between (A) MRI and visual PET, (B) MRI and threshold PET (the red line depicts the maximum DSC achievable with the given size differences between the MRI and PET boost volumes)

A



B



The duration of bicalutamide before PET/CT was performed varied from 42 to 193 days, in part due to the busy clinical schedule of the nuclear medicine department. Although it is not clear in the literature the duration of bicalutamide at which the effect on prostate volume size is maximal, this variability may have influenced volume reduction. The hormone therapy used in this study was bicalutamide, an antiandrogen. Other hormone therapies commonly used in clinical practice include LHRH agonists which may be expected to have a larger effect on SUV_{max} and boost volume reduction.

For this study, a standard injected activity of 370 MBq of ^{18}F choline was used, as opposed to a dose calibrated to the patient's weight. This was because when ^{18}F choline PET/CT imaging was first introduced in our department, the optimum time of imaging was unclear i.e. whether delayed imaging at 90 minutes would be appropriate. Hence, the maximum activity possible under the regulations were used. Since this study was conducted, there is more evidence for weight based reduction of injected activity which has now been adopted within the department. For visual assessment of the static imaging, the windowing could be altered to adjust the perceived uptake, and so for consistency the windowing was increased until bone marrow uptake was visually detectable. There is no available evidence for the optimal window setting for identifying intra-prostatic lesions, although a published paper suggested adjusting with the liver as the reference(207). However the liver is not included in the pelvic scan, and therefore for consistency, a pragmatic approach was taken to adjust the windowing until uptake was seen in the bone marrow. MRI and Nuclear Medicine specialists were not directly involved in delineating for this study as radiotherapy delineation is principally performed by radiation oncologists in the UK. Therefore these results are directly relevant to potential clinical practice.

There are differing views about the benefit of the addition of ^{11}C choline PET/CT with MRI to detect intra-prostatic tumours(39, 208). However Hartenbach et al. showed the increased accuracy of using ^{18}F choline PET/MRI (a scanning protocol with a comparatively prolonged tracer uptake time) for identifying intra-prostatic tumour compared to MRI alone(52). It may be the prolonged uptake time possible with using ^{18}F choline which allows better differentiation between malignant and benign prostate tissue.

Due to the lack of available literature identifying the optimal threshold level for ^{18}F choline PET/CT, the threshold level of SUV_{max} 60% which was identified by Chang et al. to provide the best correlation between ^{11}C choline PET and pathology was used(201). However there are key differences between their methodology and that of this study including radioisotope used, registration method, and the defined standard (histology vs. MRI) for comparison.

It is acknowledged that there is a substantial difference in the number of patients between the two groups in this retrospective study, and that each group individually constitutes a small sample size. However the boost volume correlation methodology deployed here followed that in the published work (involving a smaller number of subjects than in either of our groups) of Chang et al.(201).

A limitation of this retrospective study is that the patients were not randomised into the two groups, but instead the groups were recruited in sequence from one cohort of patients. This should not have resulted in differing group characteristics as the inclusion criteria were constant throughout. However, subjective visual identification of DILs may have changed over time with increasing experience in analysing choline PET/CT imaging. Furthermore, there was a lack of the gold standard comparison with cross-sectional histology. It should be noted that surgical series may often include lower risk patients and histology samples distort significantly after preparation and mounting. An alternative to cross sectional histology is template biopsies, which would have offered an accurate assessment of the location and size of significant high grade tumour. Overall, any visual method is by definition subjective, and so the conclusions from this study will ideally be confirmed by future studies using different PET/CT imaging protocols. Further studies are required to determine whether the addition of PET for the planning process will ultimately improve clinical treatment outcomes.

3.6 Conclusions

For visual delineation of DILs in prostate dose painting radiotherapy, ^{18}F choline PET/CT should be performed before bicalutamide. For threshold delineation of DILs using this specific PET/CT scanning protocol, threshold levels of >60% of prostate SUV_{max} may be more suitable. The location and size of PET DILs can vary to that of the MRI boost volumes, and so the additional use of PET with MRI for radiotherapy planning can significantly change the

overall boost volumes compared to using MRI alone. However, further studies are required to determine whether the addition of PET for the planning process will ultimately improve clinical treatment outcomes. Similar effects of bicalutamide on PET/CT using other tracers, such as PSMA, may exist.

4 Planning of moderately hypofractionated dose painting radiotherapy for prostate adenocarcinoma

4.1 Introduction

Whole prostate dose escalation radiotherapy is an effective treatment modality for prostate adenocarcinoma but the dose is limited by toxicities. Advanced technology allows delivery of highly sculpted inhomogeneous dose distributions with simultaneous dose escalation to a boost volume within the clinical target volume (CTV) where there is a higher risk of recurrence, whilst still delivering a tumouricidal dose to the rest of the CTV. This simultaneous integrated boost (SIB) technique is already standard practice for treating prostate and seminal vesicles to different doses. However, studies have shown that it is feasible to devise radiotherapy plans with an additional third higher dose level, identified by mpMRI, choline PET/CT, or ProstaScint SPECT, although mature biochemical and overall survival outcome data are not yet currently available (Table 1-9). Of these studies, only one had used the current standard UK prostate dose fractionation schedule of 60 Gy/ 20 #/ 4 weeks(161). This pilot study of 28 patients was performed at the Clatterbridge Cancer Centre, and it showed that delivering a SIB of 68 Gy to the prostatic lesions by rotational IMRT with IGRT was feasible within the organs at risk (OAR) constraints and had an acceptable safety profile. Therefore a phase II single arm trial (BIOPROP20) was initiated by Dr Syndikus (Clinical Oncology Consultant), with recruitment at two UK centres: Clatterbridge Cancer Centre and Velindre Cancer Centre.

For the BIOPROP20 trial, I (together with Dr Syndikus) performed radiotherapy delineating for the patients recruited at Clatterbridge Cancer Centre and reviewed the plans created by the radiographers. For this chapter, I have collated and analysed the data from these radiotherapy plans.

4.2 Aim

To determine whether prostate dose painting radiotherapy with planning aims of 60 Gy in 20 # over 4 weeks to the prostate and a SIB of up to 68Gy is likely to meet a level of acceptable toxicity before proceeding with a large randomised controlled phase III trial.

4.3 Methods

4.3.1 Study design

This phase II single cohort study (BIOPROP20) aimed to recruit 50 patients which would allow an upper limit of 25% of ≥G2 toxicity to be ruled out with a power of 87.8% using the Fleming A'Hern design(209).

4.3.2 Patients selection (inclusion and exclusion criteria)

Patients had the same eligibility criteria as chapter 2.

4.3.3 Trial protocol

All patients who fulfilled the inclusion and exclusion criteria were seen in clinic where the options of standard treatment and study treatment were discussed. Patients have already had staging pelvic mpMRI at their referring hospitals, with the scanner and sequence used depending on local availability and local protocols. Patients were provided with the patient information sheets and given at least 24 hours to consider the treatment options. Patients subsequently returned to clinic where any outstanding questions were addressed by the clinicians, and informed written consent was obtained and patients were registered.

For IGRT, patients received insertion of three gold fiducial markers which was performed trans-rectally, assisted by TRUS and under local anaesthetic. Voluntary choline PET/CT was offered to patients, and was performed at least 2 weeks after fiducial marker insertions but within 4 weeks of patient registration although it could be deferred for logistic reasons. The PET/CT imaging protocol has already been described in chapter 3.

For those patients who received a choline PET/CT, bicalutamide was commenced after the PET/CT (overall duration and choice was at the clinician's discretion). In general, all intermediate risk patients and those with high risk disease localised within the prostate received 6 months of oral bicalutamide (150 mg daily). The rest of the high risk patients had 2 to 3 years treatment with either oral bicalutamide or subcutaneous goserelin (10.8 mg every 3 months, or 3.6 mg every month).

Following 2 to 3 months of bicalutamide, patients received planning T2w MRI and planning CT scans. The planning scan protocol has already been described in chapter 3.

In terms of set-up, patients were scanned and treated in the supine position with arms positioned outside the radiotherapy field, and immobilisation techniques (knee and ankle supports) indexed to the treatment couch were used. Planning scan limits were from bottom of the sacro-iliac joints to below the anal margin. If the anterior-posterior diameter of the rectum was > 4 cm at any level adjacent to the prostate, the patient was given another micro enema and rescanned.

The choline PET/CT and both planning scans were uploaded into ProSoma (OSL Oncology Systems Limited, UK). The planning CT was the primary dataset to which the choline PET/CT and planning MRI were rigidly co-registered manually using the fiducial markers and urethral catheter. To register planning CT and PET component of the PET/CT, the registration parameters between the planning CT and the CT component of the PET/CT (fiducial markers were easily defined on CT) were used. To register planning CT and planning T2w MRI, the registration parameters between the planning CT and the gradient echo MRI sequence were used because the fiducial markers were more difficult to identify in the T2w MRI sequence.

Delineation was performed by two radiation oncologists; clinical information including prior imaging (namely staging mpMRI) and histology reports were available. The prostate and seminal vesicles were delineated primarily using the planning MRI whilst referring to the planning CT to ensure agreement. The overall DIL volume (GTV3) were defined by combining the individual DILs manually delineated by using the MRI and the PET images. A 3 mm margin was applied to create the CTV3 within the prostatic tissue, and a further 2 mm margin was applied to create the Boost volume (PTV3).

Table 4-1 CTV and PTV definition and radiotherapy planning aim objectives

Clinical Target Volume	ICRU Planning Target Volume	Dose objectives to ICRU Planning Target Volume
CTV1 **Prostate and seminal vesicles (including disease extending outside the prostate)**	**PTV1** **Margin: CTV1 + 10 mm**	**$D_{50\%}$ ≥ 53 Gy (median)** **$D_{98\%}$ ≥ 50.35 Gy (near minimum)** **50.35 Gy isodose should encompass PTV1**
CTV2 **Prostate and any involved seminal vesicle (including disease extending outside the prostate)**	**PTV2** **Margin: CTV2 + 5 mm**	**$D_{50\%}$ ≥ 60 Gy (median)** **$D_{98\%}$ ≥ 57 Gy (near minimum)** **57 Gy isodose should encompass PTV2** **CTV2 $D_{50\%}$ ≤ 64 Gy**
CTV3 **GTV3 + 3 mm, but CTV3 remains within CTV2**	**PTV3** **Margin: CTV3 + 2 mm**	**$D_{50\%}$ 60 Gy – 68 Gy** **$D_{2\%}$ ≤ 71 Gy**

Radiotherapy planning software used was Pinnacle^3 SmartArc v9.1 (Philips) for a VMAT (volumetric modulated arc therapy) plan with two full 6 MV arcs. The median dose to PTV3 was escalated as much as possible to 68 Gy, allowing for dose constraints to OAR (Table 4-1). OAR were bladder, rectum, small and large bowel (as a single structure), bilateral femoral heads (as a single structure), urethra, and urethral bulb (Table 4-2). Each optimisation was recommended to run for 25 iterations.

For quality assurance, the dosimetry of dose painting radiotherapy plans have previously been verified using Delta4 phantom (Scandidos, Sweden) within the pilot study, which had used the same dose fractionation, planning and treatment equipment, including 3D simulators, software and linear accelerators(161).

Whilst the inclusion criteria was for clinically node negative patients on staging pelvic MRI imaging, some of the recruited patients were subsequently found to have involved pelvic lymph nodes on choline PET/CT. As they remained suitable for radical treatment, they were planned for simultaneous prostate and lymph node dose painting radiotherapy: prostate was planned as above, with lymph nodes PTV (delineated using a vascular expansion technique with a bowel expansion volume as per PIVOTAL study guidelines, and a CTV to PTV margin of 5 mm) treated to median dose of 45 Gy and lymph node boost PTV (defined as involved nodes with 3 mm margin) treated to median dose of 50 Gy(150).

Table 4-2 OAR dose constraints

Organ	Dose for 20# (Gy)	Maximum volume	
		Optimal	Mandatory
Rectum (between recto-sigmoid junction and bottom of ischial tuberosities)	24.6	70%	-
	32.4	60%	-
	40.8	50%	60%
	48.6	35%	50%
	52.8	30%	30%
	57.0	15%	15%
	60.0	3%	5%
	64.0	0%	1%
	68.0	0%	0%
Bowel (including small bowel, large bowel, and sigmoid colon; between recto-sigmoid junction and 2 cm beyond the superior extent of CTV1)	45	78 cc	158 cc
	50	17 cc	110 cc
	55	14 cc	28 cc
	60	0.5 cc	6 cc
	65	0 cc	0 cc
Urethra (between inferior and superior ends of PTV1)	$D_{2\%}$	61 Gy	61 Gy
Bladder (entire bladder volume including contents)	40.8	50%	-
	48.6	25%	50%
	60	5%	35%
Femoral heads (not including femoral necks)	40.8	5%	50%

4.4 Results

In total, 57 patients were registered between 14th March 2014 and 15th April 2016 at Clatterbridge Cancer Centre. Fifty-five patients had choline PET/CT. Five patients had pelvic lymph node positive disease on choline PET/CT, whilst 1 patient had bone metastasis on choline PET/CT. Therefore, overall 56 patients had dose painting radiotherapy planning, of whom 51 patients had prostate only dose painting and 5 patients had prostate and lymph node dose painting radiotherapy planning (Figure 4-1)(Table 4-3).

Of the 5 patients with pelvic nodal boost volumes, 3 patients had a single node (2 were external iliac, 1 was internal iliac) and 2 patients had multiple nodes (one patient had ipsilateral nodes involving common iliac and external iliac nodes, and one patient had bilateral nodes involving inguinal, internal and external iliac nodes regions).

Figure 4-1 Flow diagram of study participants at the Clatterbridge Cancer Centre

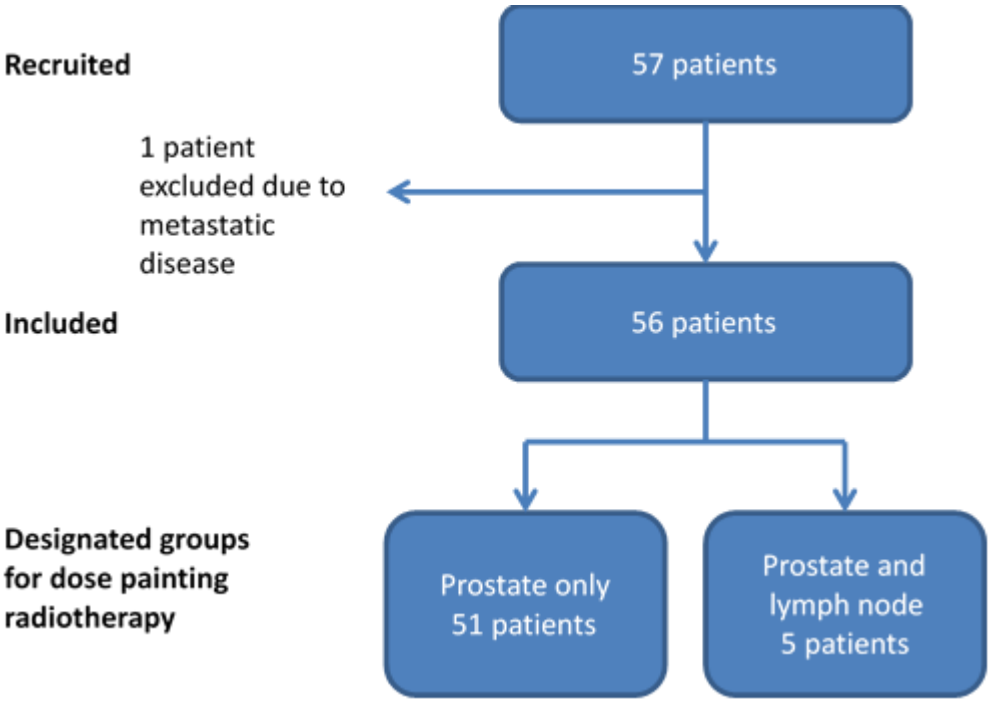


Table 4-3 Patient demographics
* Roach formula for LN risk

		All patients who received dose painting radiotherapy planning (n = 56)		Patients with prostate only dose painting (n = 51)		Patients with prostate and lymph node dose painting (n = 5)	
		Median	Range	Median	Range	Median	Range
Age		68	50 - 77	69	56 - 77	66	50 - 77
Gleason	6	1		0		1	
	7	42		38		4	
	8	5		5		0	
	9	8		8		0	
PSA (µg/ml)		10.0	3.9 - 39.4	9.1	3.9 – 39.4	12.2	7.2 - 32.0
Staging	T2	18		17		1	
	T3a	34		31		3	
	T3b	4		3		1	
	T4	0		0		0	
Risk category	Intermediate	13		12		1	
	High	43		39		4	
Risk of LN disease* (%)		18	15 - 40	18	15 - 40	19	15 - 28
PS	0	51		46		5	
	1	5		5		0	

4.4.1 Identifying DILs for dose painting radiotherapy

4.4.1.1 MRI

The use of both fiducial markers and indwelling catheter for rigid registration between the planning CT and planning MRI was uncomplicated. Although the prostate and seminal vesicles were predominantly delineated using the planning CT as the primary dataset, the

planning T2w MRI was useful in determining the inferior border of the prostate which can be difficult to distinguish from the urogenital diaphragm. The DILs were generally identifiable on planning MRI with visual reference to the staging MRI.

4.4.1.2 Choline PET/CT

Visual assessment of the registration within the choline PET/CT, and between PET and planning CT, did not show any significant registration issues for the patients in this study.

4.4.2 Planning

The overall GTV3 were formed by combining the DILs from both imaging modalities. In order to account for delineation uncertainties, expansion margins were used to define the PTV3. The median size (and range) of the GTV3 volumes were 3.5 ml (1.2 ml to 14.9 ml) and 4.2 ml (6.8 ml to 20.1 ml) for patients receiving 'prostate only' and 'prostate and lymph node' dose painting respectively. The median size (and range) of PTV3 volumes were 13.5 ml (8.2 ml to 33.1 ml) and 16.3 ml (8.1 ml to 32.0 ml) respectively.

Planning within the dose constraints was possible for all patients (Tables 4-4 and 4-5). 'PTV3' is the prostate boost volume; 'PTV2_PTV3' is the prostate and involved seminal vesicles without the PTV3 boost volume; 'PTV1_PTV2' is the prostate and whole seminal vesicles without PTV2; 'PTV LN50' is the lymph node boost volume; and 'PTV LN45_LN50' is the lymph node volume without the boost volume.

For the 'prostate only' dose painting group, the median D50% dose achieved to the PTV3 was 68.1 Gy, and the lowest D50% dose for an individual patient was 66.2 Gy. Of the 51 patients, 32 (63%) patients had PTV3 D50% of ≥ 68 Gy.

For the 'prostate and lymph node' dose painting group, the median D50% dose achieved to the PTV3 was 67.2 Gy, and the lowest D50% dose for an individual patient was 66.8 Gy. Of the 5 patients, 1 patient (20%) had PTV3 D50% of ≥ 68 Gy, and all patients had PTV LN50 D50% of ≥ 50 Gy.

Table 4-4 PTV reported doses

		Planning target	Prostate only dose painting group (n = 51)		Prostate and lymph node dose painting group (n = 5)	
			Median	Range	Median	Range
PTV1_PTV2 (prostate and seminal vesicles)	D2%		59.24	58.60 - 62.02	59.39	59.00 - 59.99
	D50%	≥ 53.00	56.01	54.98 - 56.96	55.66	55.10 - 55.84
	D90%		53.25	51.99 - 54.03	52.94	52.64 - 53.04
	D98%	≥ 50.35	51.40	50.52 - 52.49	51.51	51.11 - 51.66
	Mean dose		55.83	55.12 - 56.95	55.61	55.17 - 55.74
	Volume (ml)		44.34	35.04 – 85.90	67.00	48.05 - 99.96
PTV2_PTV3 (prostate and any involved seminal vesicles)	D2%		66.37	64.09 - 68.95	66.19	64.68 - 67.62
	D50%	≥ 60.00; ≤ 64.00	61.02	60.39 - 61.67	60.98	60.85 - 61.17
	D90%		59.21	58.37 - 59.76	59.15	58.79 - 59.41
	D98%	≥ 57.00	58.07	57.19 - 59.01	58.03	57.07 - 58.31
	Mean dose		61.37	60.74 - 62.06	61.34	60.98 - 61.45
	Volume (ml)		62.05	36.42 - 135.14	92.79	65.04 - 114.46
	D2%	≤ 71.00	70.09	69.04 - 71.01	70.32	69.18 - 70.95

PTV3 (prostate boost volume)	D50%	60.00 - 68.00	68.10	66.21 - 68.86	67.23	66.79 - 68.46
	D90%		63.81	61.69 - 67.01	63.92	61.38 - 66.42
	D98%		60.93	59.19 - 64.81	62.02	59.52 - 64.57
	Mean dose		67.38	65.96 - 68.45	66.99	66.46 - 67.99
	Volume		13.53	8.22 - 33.10	16.26	8.12 - 32.03
PTV LN45_LN50 (LN without boost)	D2%		NA	NA	53.16	52.25 - 56.69
	D50%		NA	NA	45.22	45.12 - 45.68
	D98%		NA	NA	35.69	35.52 - 40.03
	Mean dose		NA	NA	45.25	45.15 - 45.77
	Volume		NA	NA	700.85	437.67 - 919.73
PTV LN50 (LN boost volume)	D2%		NA	NA	53.29	51.51 - 54.67
	D50%		NA	NA	51.04	50.13 - 51.39
	D98%		NA	NA	48.61	46.36 - 49.04
	Mean dose		NA	NA	51.04	50.04 - 51.33
	Volume		NA	NA	12.6	8.01 - 30.14

Table 4-5 OAR reported doses

		Optimal planning constraints	Prostate only dose painting group (n = 51)		Prostate and lymph node dose painting group (n = 5)	
			Median	Range	Median	Range
Rectum (%)	V40.8	50%	21.39	13.83 - 42.85	26.34	12.02 - 35.65
	V48.6	35%	15.07	9.09 - 33.32	17.78	6.00 - 18.27
	V52.8	30%	11.29	5.90 - 25.56	10.26	3.08 - 12.40
	V57	15%	4.66	0.29 - 10.43	4.62	0.49 - 5.33
	V60	3%	0.55	0 - 4.66	0.17	0.04 - 1.11
	V64	0%	0	0 - 0.25	0	0 - 0.0
	V68	0%	0	0 - 0	0	0 - 0
	Maximum dose		62.36	58.17 - 66.43	62.84	61.64 - 64.62
	Mean dose		21.48	14.99 - 34.32	28.99	23.08 - 33.87
	Volume		51.35	28.93 - 86.43	56.49	43.31 - 88.12
Bladder (%)	V40.8	50%	15.52	4.49 - 43.53	42.21	24.55 - 46.56
	V48.6	25%	19.15	3.05 - 31.87	19.77	9.25 - 26.92
	V60	5%	2.47	0.08 - 6.87	2.39	1.37 - 3.19
	Maximum dose		63.59	60.65 - 70.90	64.14	62.52 - 65.38

	Mean dose		**17.48**	**7.10 – 35.89**	**39.56**	**32.47 - 42.18**
	Volume		**181.07**	**48.15 - 678.91**	**167.75**	**97.01 - 318.58**
Urethral (%)	**D2%**	**61**	**60.44**	**59.95 - 61.19**	**60.73**	**60.17 - 60.79**
	Volume		**1.77**	**0.30 - 4.16**	**2**	**1.25 - 2.26**
Bowel (cc)	**V45**	**78 cc**	**0**	**0 – 2.69**	**2.71**	**0.1 - 25.1**
	V50	**17 cc**	**0**	**0 – 1.68**	**0.02**	**0 - 0.61**
	V55	**14 cc**	**0**	**0 - 0.74**	**0**	**0 - 0**
	V60	**0.5 cc**	**0**	**0 - 0**	**0**	**0 - 0**
	V65	**0 cc**	**0**	**0 - 0**	**0**	**0 - 0**
	Maximum dose		**22.82**	**1.97 - 58.49**	**50.9**	**45.60 - 52.78**
	Mean dose		**6.56**	**0.57 – 12.03**	**20.04**	**13.02 - 26.38**
	Volume		**21.81**	**0.58 - 314.22**	**447.55**	**383.84 - 1066.1**
Femoral heads (%)	**V40.8**	**5%**	**0**	**0 - 1.26**	**0**	**0 - 7.02**
	Maximum dose		**35.55**	**27.32 - 43.99**	**40.2**	**39.84 - 46.70**
	Mean dose		**21.91**	**10.26 - 30.74**	**27.56**	**22.37 - 32.13**
	Volume		**120.36**	**78.9 - 207.07**	**123.32**	**118.53 - 158.19**

4.5 Discussion

Whilst planning within the dose constraints was possible for all patients, the position of the boost volumes within the prostate was the main factor that limited the deliverable boost dose. During the optimisation, the planning software sometimes struggled as a result of the proximity of the OARs (mainly urethra and rectum) and their dose constraints. Extra optimisation structures were often required to achieve dose drop off, and superior and inferior shells were occasionally required to force superior-inferior dose conformity.

Overall, more than half of 'prostate only' radiotherapy patients achieved a prostatic boost dose of ≥ 68 Gy, but only 20% of 'prostate and lymph node' radiotherapy patients achieved a prostatic boost dose of ≥ 68 Gy whilst all achieved a lymph node boost dose of ≥ 50 Gy.

Despite the addition of lymph node dose painting radiotherapy, the D50% doses to the prostate boost volumes for 'prostate only' group (median 68.1 Gy; range 66.2 Gy to 68.9 Gy) and for 'prostate and lymph node' group (median 67.2 Gy; range 66.8 Gy to 68.5 Gy) were not significantly different (Mann Whitney U test, $p = 0.09$). The BIOPROP20 study also recruited at Velindre Cancer Centre, and the D50% doses to the prostate boost volumes of the patients recruited there, all of whom were for prostate only dose painting radiotherapy (median 65.4 Gy; range 64.0 Gy to 67.6 Gy) were significantly lower to that at Clatterbridge Cancer Centre (Mann Whitney U test, $p < 0.01$). This may be due to differences in experience of the radiographers. Velindre Cancer Centre had only planned 5 patients in total, whilst Clatterbridge Cancer Centre had planned 56 patients within BIOPROP20 and also had prior experience in prostate dose painting from the pilot study.

For the CHHiP study, one of the treatment arms aimed to deliver 60 Gy for localised prostate cancer with three dose levels also(10). These were 60 Gy/ 57.6 Gy/ 48 Gy, compared with 68 Gy/ 60 Gy/ 53 Gy in the BIOPROP20 study, whilst the high dose volume for CHHiP was the whole prostate (60 Gy) compared to DILs (68Gy). There was no posterior margin (CTV3 to PTV3) for the high dose volume in CHHiP whilst the maximal extension of the high dose volume beyond the boundaries of the prostate in BIOPROP20 was 2 mm, which could lead to higher maximum doses in the rectum for BIOPROP20 than for CHHiP. On the other hand, margins used for the lower dose levels in CHHiP were 5/10 mm compared to 3/6 mm for

BIOPROP20, which could lead to lower median doses in the rectum for BIOPROP20 than for CHHiP. From the data presented in this chapter, the median volume of rectum irradiated to 60 Gy was 0.6%, whilst in CHHiP (for those who had inverse planning) it was 16.0%(210). This comparison has to be treated with caution however as the CHHiP data, although published in 2019, was for the early cohort of patients treated between 2002 and 2006 using various different treatment planning systems and at a time when IMRT was a relatively new technique.

The preceding pilot study for 'prostate only' patients, using the same planning aims, was reported to have achieved a mean of the PTV68 D50% of 67 Gy (63 to 71 Gy)(161). In the current group of 'prostate only' patients at Clatterbridge Cancer Centre in the BIOPROP20, the median of the PTV68 D50% was 68 Gy. A notable difference between these two studies was that the pilot study had used only MRI for DIL delineation, whilst this study had used both MRI and PET. However the median DIL volumes were similar (4.3 cm^3 and 3.5 cm^3 for the pilot and this study respectively).

International Commission on Radiation Units and Measurements (ICRU) Report 83 was published to standardise the nomenclature of prescribing, recording, and reporting photon-beam IMRT, where GTV is defined as "the gross demonstrable extent and location of the tumour" and CTV is defined as "a volume of tissue that contains a demonstrable GTV and/or subclinical malignant disease with a certain probability of occurrence considered relevant for therapy"(211). Whilst it may be argued that the whole prostate outside of the boost volume is already being treated with a radical dose which should eliminate subclinical microscopic malignant disease and therefore a margin around the DIL to create an intra-prostatic CTV for the boost volume is not required, we felt it was still reasonable to have a margin given that the primary aim of dose painting radiotherapy is to deliver dose escalation to the macroscopic DIL for which there is some uncertainty in the accuracy of delineation on imaging.

When MRI has been used to define the prostatic boost volume in previous studies, the margins used from the DIL have ranged from 0 mm to 15 mm (Table 4-5). Compared to the other studies, Miralbell defined a "tumour-bearing zone" not only on MRI but also used information from rectal examination and biopsy specimens(101). This resulted in a

sequential boost volume which typically "included the peripheral and central zone tumour-bearing regions, together with the seminal vesicles if involved" although the sizes of the boost volumes were not specified and so it is not known if these volumes would have been larger than those of other studies which used imaging alone. When PET has been used to define the prostatic boost volume (Wong and Pinkawa), the margins used have ranged from 0 mm to 4 mm(157, 159). Unlike these other studies, the BIOPROP20 utilised both MRI and PET, and so an overall boost margin of 5 mm was used to take into account the additional imaging uncertainty that results from subjective visual delineation, image registration and effect of bicalutamide on DIL on planning MRI. By referring to the staging mpMRI on another monitor at the radiotherapy planning terminal, the malignant nature and size of the abnormalities on planning T2w MR imaging were confirmed and the delineations were adapted accordingly. This method of visual transfer is subjective but was felt to be acceptable given that DILs are given a margin and that the whole prostate is planned to receive a radical, albeit lower, dose.

Table 4-6 Margins used in previous prostate +/- pelvic dose painting studies

Study name	**Prostate boost margin**	**Prostate +/- SV margin (CTV to PTV)**	**Pelvic boost margin**	**Pelvic margin**
Fonteyne(168)	8 mm from DIL to boost volume	4 mm	-	-
Miralbell(101)	3 mm from tumour-bearing zone to boost volume	Not specified	-	Not specified
FLAME(169)	No DIL margin	5 to 8 mm	-	-
Wong(157)	No DIL margin	6 mm	-	-
Sundahl(170)	No DIL margin	7 mm	-	-
Ippolito(160)	5 mm from DIL to boost CTV 10 mm margin from boost CTV to boost PTV (except 8 mm posteriorly)	10 mm margin from prostate + SV to PTV (except 8 mm posteriorly)	-	-

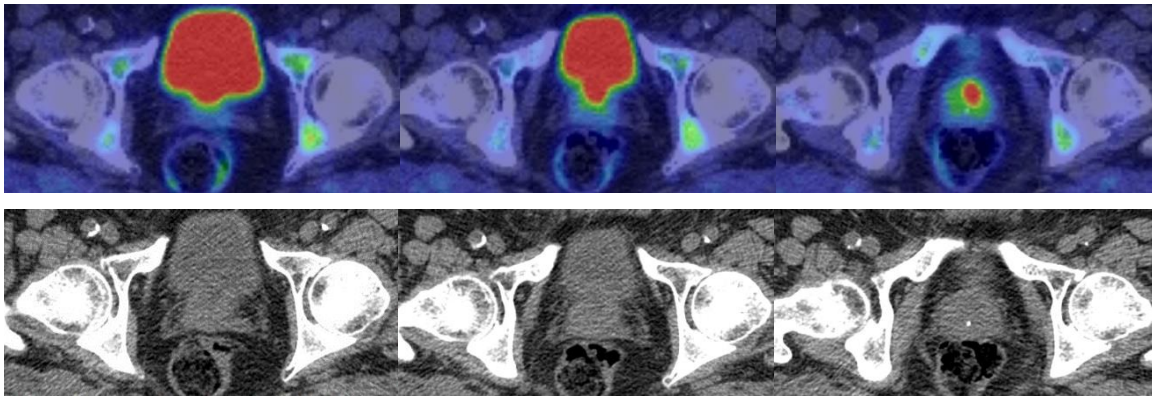
Pinkawa(171)	4 mm margin to boost (except 3 mm posteriorly)	8 mm margin laterally/anteriorly 5 mm margin superiorly/inferiorly 4 mm margin posteriorly	-	-
Schild(158)	No DIL margin	3 mm margin	-	-
Garibaldi(172)	Not specified	Not specified	-	-
Onjukka(161)	3 mm margin to boost CTV 2 mm margin from boost CTV to boost PTV	5 mm margin from prostate 9 mm margin from prostate + SV	-	-
Fonteyne(181)	No DIL margin	7 mm margin from prostate + SV	2 mm margin to elective CTV 5 mm margin to elective PTV	7 mm margin from involved node to involved nodal PTV
Fonteyne(182)	No DIL margin	7 mm margin from prostate + SV	2 mm margin to elective CTV 5 mm margin to elective PTV	7 mm margin from involved node to involved nodal PTV

When PET has been used to define the pelvic nodal boost volume in previous studies (Fonteyne), the margin used from the involved nodes to boost PTV was 7 mm(181, 182). For PET node positive patients in the BIOPROP20, the margin used from the involved nodes to the boost PTV was 3 mm, in addition to the 5 mm PTV margin for the lower dose elective nodal CTV. Therefore a tighter nodal boost margin has been used in BIOPROP20 when compared to Fonteyne. Of note, the only other study which treated elective pelvic nodes (Miralbell) used a four-field box technique and the specific borders were not described(101).

Within the registration process between the planning CT and the PET, there are several potential stages where inaccuracies can occur. During PET/CT acquisition, patient movement between the PET and CT portions of the scan may result in an intrinsically suboptimal registration, and this inaccuracy will then be transferred downstream and incorporated into the registration between the PET and planning CT, as the initial step for this registration is to match the planning CT with the CT from the PET/CT, where errors can also occur in itself. Furthermore, the reduction in prostate volume due to bicalutamide between the PET/CT and planning CT may cause registration difficulties, although this reduction is expected to be mostly concentric and seem not to result in marked change in fiducial marker position in the two dimensional plane. Another factor that may contribute is any difference in bladder filling between the scans which can displace the prostate inferiorly, but registration using the three fiducial markers embedded within the treatment volume should be able to account for this. Despite all these movement uncertainties, the PET/CT and planning CT registration was uncomplicated because of the fiducial markers. Of note, a patient with a history of transurethral resection of the prostate (TURP) had a dilated bladder neck which led to urinary uptake being visualised in the prostate (Figure 4-2). This was confirmed on the MRI.

Figure 4-2 Figure of PET/CT with TURP

In this patient with a history of TURP, there is a region of localised tracer uptake within the prostate (right image), but on reviewing the imaging superiorly (left and middle images), it is clear that this is due to urine within the dilated bladder neck.



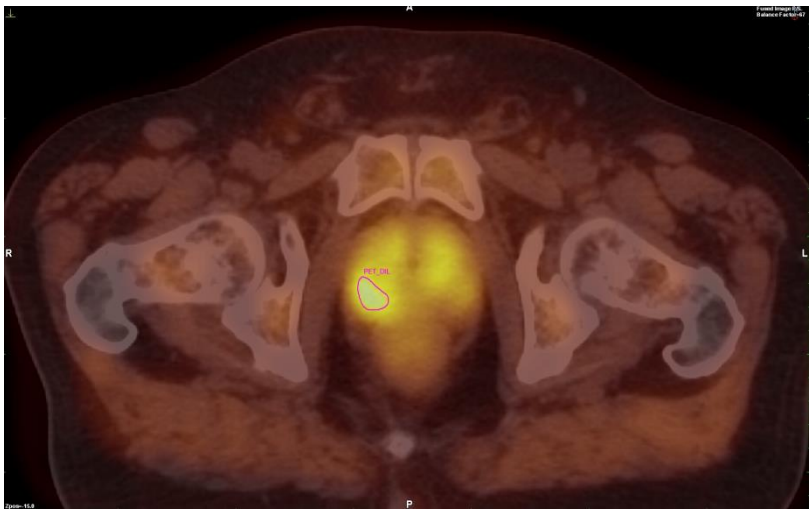
As discussed in chapter 1, there is no consensus in the current published literature as to a universally agreed optimum imaging protocol for identifying intra-prostatic lesions on ^{18}F choline PET/CT. As experience at Clatterbridge Cancer Centre had shown that uptake

appeared visually to be more focal on late imaging, a pragmatic approach was taken to use imaging performed 90 minutes following tracer injection. However there were some cases with generally diffuse uptake throughout the prostate, and a clinical decision was made for the DIL to be delineated at a region of highest visual uptake (Figure 4-3). This was obvious in a patient who developed an infection and prostatitis after the fiducial marker insertion.

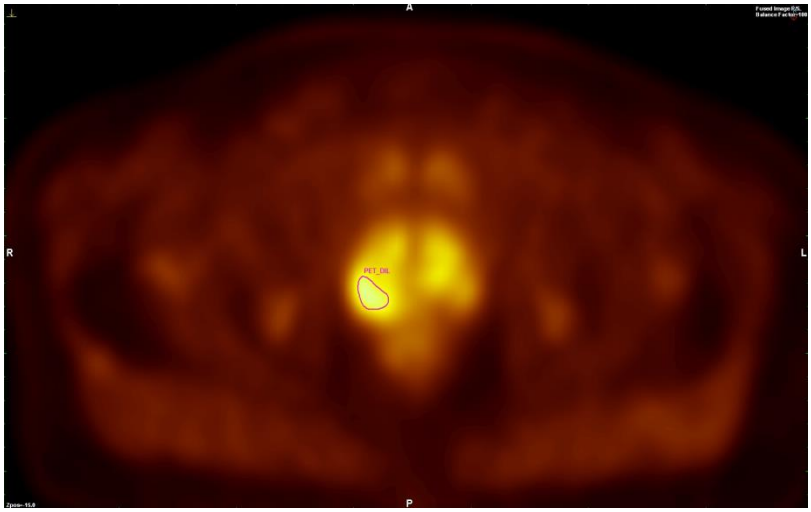
Figure 4-3 Example of generally diffuse choline tracer uptake

Example of generally diffuse choline tracer uptake throughout the prostate on PET/CT (A) and the PET sequence alone (B), and the DIL was delineated at a region of highest visual uptake

A



B



The previous chapter has shown that automatic delineation by using a threshold of SUV_{max} 60% produces larger DILs with lower sensitivity and specificity than manually delineation when compared with MRI DILs. This suggests that our methodology of using manual delineation on the choline PET is more acceptable than using automatic threshold delineation. Manual delineation allows the operator more flexibility in defining DILs, but can

increase variability depending on the windowing chosen (Figure 4-4). A pragmatic decision was made to adjust the windowing until uptake was seen in the bone marrow before delineating.

According to a large contemporary series, the risk of pathological pelvic lymph node involvement in intermediate and high risk prostate cancer patients are 7.2% and 25.5% respectively(65). For this group of BIOPROP20 patients with intermediate and high risk disease (23.2% and 76.8% respectively), 5 of the 55 staging ^{18}F choline PET/CT scans (9.1%) showed radiologically positive pelvic lymph node uptake (Figure 4-5). It is expected that the proportion of radiologically detected lymph node involvement is lower than that from surgically detected studies because PET/CT imaging has a comparatively lower sensitivity than histopathology(212). Another study of intermediate and high risk prostate cancer patients found that 19 out of 130 patients (14.6%) had lymph node or bone metastasis on ^{18}F choline PET/CT(54). Although none of the patients in this group of BIOPROP20 patients had bone metastasis detected on ^{18}F choline PET/CT, one patient did have unexpected thyroid uptake which led to investigations that confirmed early stage papillary thyroid carcinoma for which he subsequently received a thyroidectomy.

Figure 4-4 Example of varying choline PET windowing

Before delineation, the windowing is adjusted until uptake is seen in the bone marrow (middle image). The windowing either side of that level would produce a smaller or larger DIL.

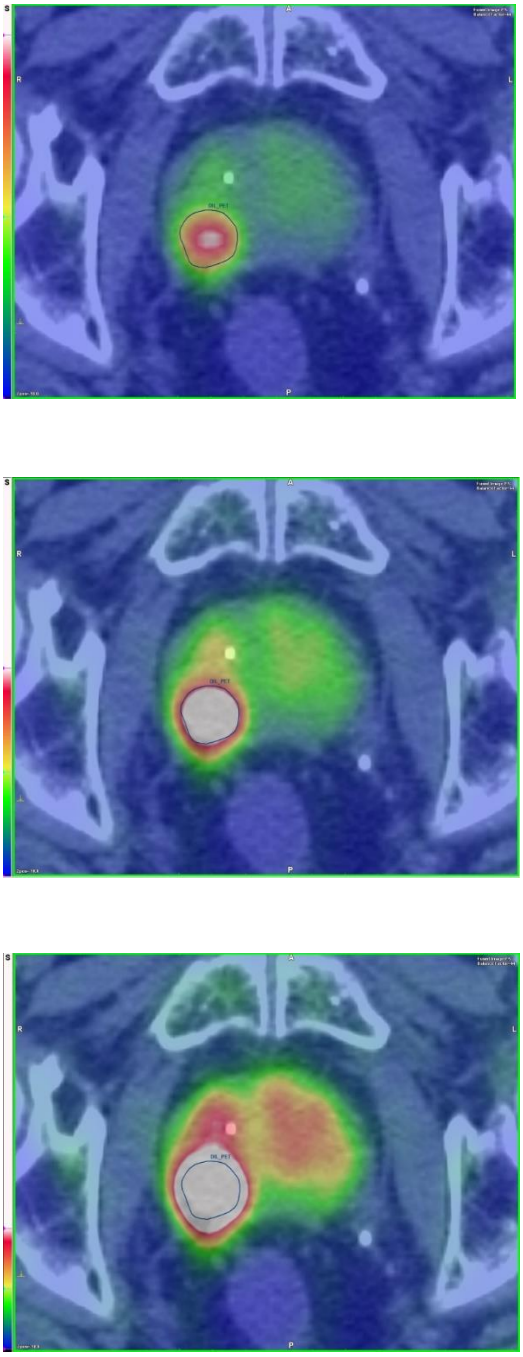
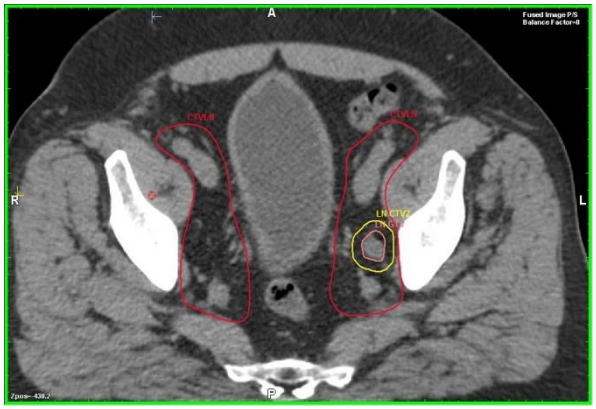
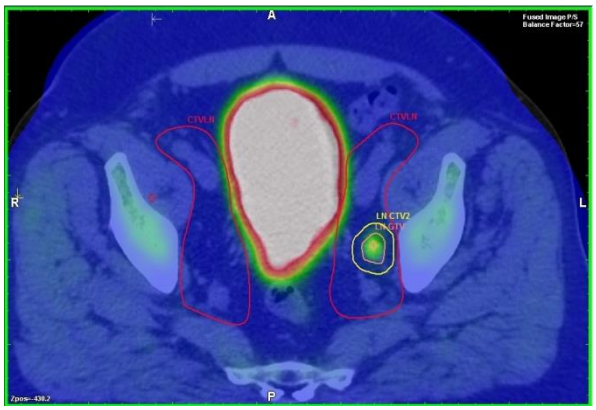


Figure 4-5 Example of choline uptake in pelvic lymph node





4.6 Conclusion

For intermediate and high risk prostate cancer patients, rotational dose painting IMRT planning using a moderately hypofractionated schedule of 60 Gy in 20 fractions with an intra-prostatic boost dose that reached 68 Gy, using a combination of MRI and PET, was achievable for more than half of patients. Additional planning with pelvic radiotherapy for involved nodal boost dose that reached 50 Gy was achievable for all patients, but led to a reduction of prostatic boost dose to less than 68 Gy in most patients.

5 Acute toxicity of moderately hypofractionated dose painting radiotherapy for prostate adenocarcinoma

5.1 Introduction

For standard radiotherapy, the urethra and base of bladder are included in the prostate PTV, and the anterior rectal wall is often close to or included in the prostate PTV. In addition, the prostate is a relatively mobile target volume, with the rectum and bladder subject to variable filling, movement and deformity (213). Therefore, both acute and late toxicities are experienced by a proportion of patients receiving prostate radiotherapy who are generally expected to have good long-term survival. With dose painting prostate radiotherapy, the addition of a boost volume for dose escalation risks increasing toxicity further. The previous chapter demonstrated that it is theoretically feasible to deliver moderately hypofractionated dose painting radiotherapy whilst adhering to dose constraints. This chapter will assess the acute toxicity of this treatment.

For prostate cancer, various patient reported outcomes (IPSS, EPIC) and clinician reported outcomes (CTCAE, RTOG) have been used in seminal trials(190, 214-216). These validated questionnaires can prospectively evaluate symptoms prior to, during, and following treatment. Performance status (PS) assesses the ability of the patient to undertake activities of daily living, and is used to predict their ability to tolerate treatment and their prognosis(217).

For the BIOPROP20 trial, I (together with Dr Syndikus) recruited and reviewed patients at the Clatterbridge Cancer Centre. For this chapter, I have collated and analysed the acute toxicity data.

5.2 Aims

-To determine the acute toxicities of moderately hypofractionated dose painting radiotherapy for prostate adenocarcinoma with 60 Gy in 20 # over 4 weeks and a SIB of up to 68 Gy.

5.3 Methods

5.3.1 Schedule

For quality assurance, the dosimetry of dose painting radiotherapy plans have previously been verified using Delta4 phantom (Scandidos, Sweden) within the pilot study, which had used the same dose fractionation, planning and treatment equipment, including 3D simulators, software and linear accelerators(161).

IGRT was delivered using Varian and Elekta linear accelerators with on-board imaging. The record and verify system used was Aria (version 11, Varian Medical Systems, USA). Set-up verification involved daily online planar orthogonal pair kV imaging (5 cm x 5 cm size) of the fiducial markers. All shifts of more than 2 mm were corrected. If shifts of over 1 cm were observed, wide field of view CBCT was to be performed. If CTV60 or CTV68 lay outside of their PTVs, re-planning was required.

When patients were registered to the study, baseline assessments were made on CTCAE v4.0, RTOG, IPSS, EPIC and PS (Appendix 8.2). Patients were initially assessed with LENT/SOMA at the beginning of study recruitment, but EPIC subsequently became standard with trial protocol amendment.

When patients attended for radiotherapy planning (i.e. whilst patients were on bicalutamide and before radiotherapy delivery), CTCAE and RTOG were completed again (Figure 5-1).

During each week of radiotherapy (Week 1, Week 2, Week 3, and Week 4), CTCAE, RTOG, and EPIC were completed.

Six, eight and twelve weeks following commencement of radiotherapy (Week 6, Week 8, and Week 12 respectively), CTCAE, RTOG, and EPIC were completed.

Eighteen weeks following commencement of radiotherapy (Week 18), CTCAE, RTOG, IPSS, EPIC, and PS were completed.

Toxicities up to and including Week 18 were regarded as acute toxicities. Assessments were performed within review outpatient clinics, and patients were reassured that the patient

reported outcomes data would not affect their clinician's approach to them or their treatments, and so they should answer as honestly as possible.

Figure 5-1 Assessments schedule (Weeks 1 to 4 were during radiotherapy)

Assessment	Registration	Planning	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 12	Week 18
CTCAE	*	*	*	*	*	*	*	*	*	*
RTOG	*	*	*	*	*	*	*	*	*	*
IPSS	*									*
IPSS QoL	*									*
EPIC	*		*	*	*	*	*	*	*	*
EPIC patient satisfaction	*		*	*	*	*	*	*	*	*
PS	*									*

5.3.2 Analysis of assessments for acute toxicity

For CTCAE (in each classification: bladder, lower GI, and toxicities other than urinary and lower GI), the number of patients with a G1, G2, G3 and G4 were obtained for each time point. This allowed a graph showing the distribution of CTCAE toxicity grade by time point. From this, it was possible to show the prevalence of patients with at least a certain toxicity value (e.g. G1+ bladder toxicity referred to the proportion of patients with G1 or worse bladder toxicity, G2+ lower GI referred to the proportion of patients with G2 or worse lower GI toxicity). Furthermore, the prevalence of specific toxicities within each classification were shown on a graph at each time point (e.g. G2+ urinary frequency referred to the proportion of patients with G2 or worse urinary frequency).

For RTOG (in each classification: bladder and lower GI), the same analysis was performed. In addition, cumulative incidence graphs were created to show the proportion of patients who were experiencing or had experienced a certain level of toxicity up to the specific time point (for acute toxicity, this was from week 1 to week 18).

For IPSS, the differences in scores from the time of registration to the time of Week 18 assessment were calculated, and a waterfall plot was created. A high IPSS score reflected a

large amount of urinary symptoms. Therefore when calculating a change in IPSS score between these two time points, a negative value reflected improved urinary symptoms, whereas a positive value reflected worsened urinary symptoms. As part of the IPSS questionnaire, the final question (Question 8: Quality of Life (QoL)) does not contribute to the IPSS score itself. Therefore the same analysis was performed specifically for this IPSS QoL. The statistical significance of the difference in IPSS scores between registration and Week 18 was calculated using related samples Wilcoxon signed rank test.

For EPIC, domain summary scores were calculated for each of the four categories: Urinary, Bowel, Sexual, and Hormonal. Domain-specific subscales were calculated within each of these four categories: urinary subscales (function, bother; incontinence, irritative/obstructive), bowel subscales (function, bother), sexual subscales (function, bother), and hormonal subscales (function, bother). The lower quartile, median, and upper quartile values were calculated. If 20% or more of items that comprise the domain summary score or subscale score were missing, the corresponding domain summary score or subscale score were not calculated(190).

For PS, the scores were collected at the time of registration and the time of Week 18 assessment. The prevalence of the scores were calculated for these two time points, and the proportion of patients with changes in scores between these two time points were calculated.

5.4 Results

Fifty-one patients received dose painting radiotherapy to the prostate alone (Figures 5-2 to 5-12), and five patients received dose painting radiotherapy to the prostate and pelvic lymph nodes (Figure 5-13 to 5-23) at the Clatterbridge Cancer Centre. All patients had their first fraction between June 2014 and March 2016. Where data was available, non-parametric paired analysis was performed between registration and Week 18, and between Week 1 and Week 18 (Table 5-1).

Figure 5-2 Acute urinary and lower GI CTCAE toxicity by time point for prostate only radiotherapy

Prevalence (A) and distribution (B) of urinary toxicity grades. Prevalence (C) and distribution (D) of lower GI toxicity grades

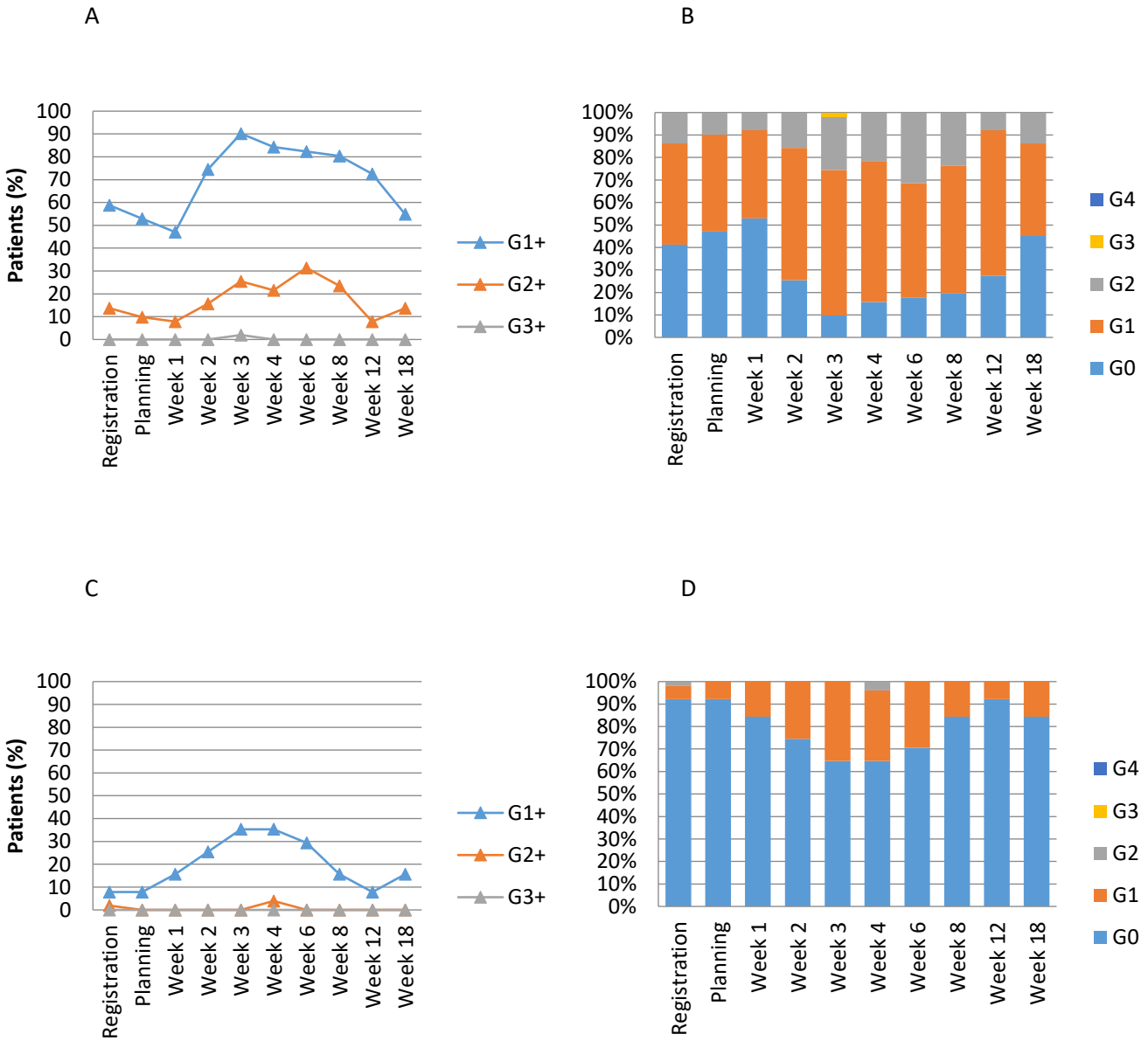


Figure 5-3 Prevalence of specific acute CTCAE toxicities by time point for prostate only radiotherapy
Prevalence of acute CTCAE urinary toxicities (A) and lower GI toxicities (B)

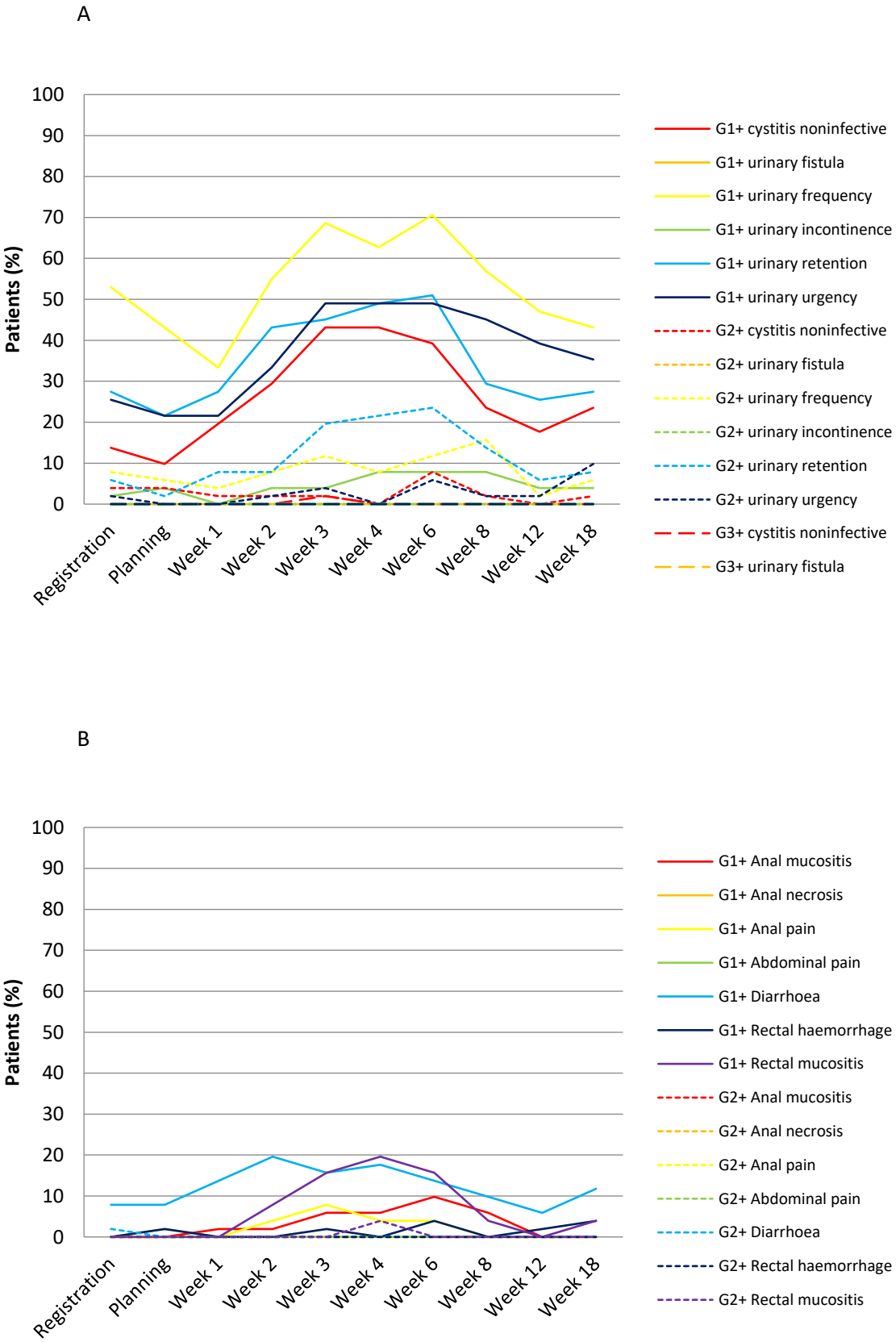


Figure 5-4 Other acute CTCAE toxicities (not urinary or lower GI) by time point for prostate only radiotherapy
Prevalence of acute CTCAE toxicities (A), distribution of maximal grades (B), and prevalence of specific CTCAE (C)

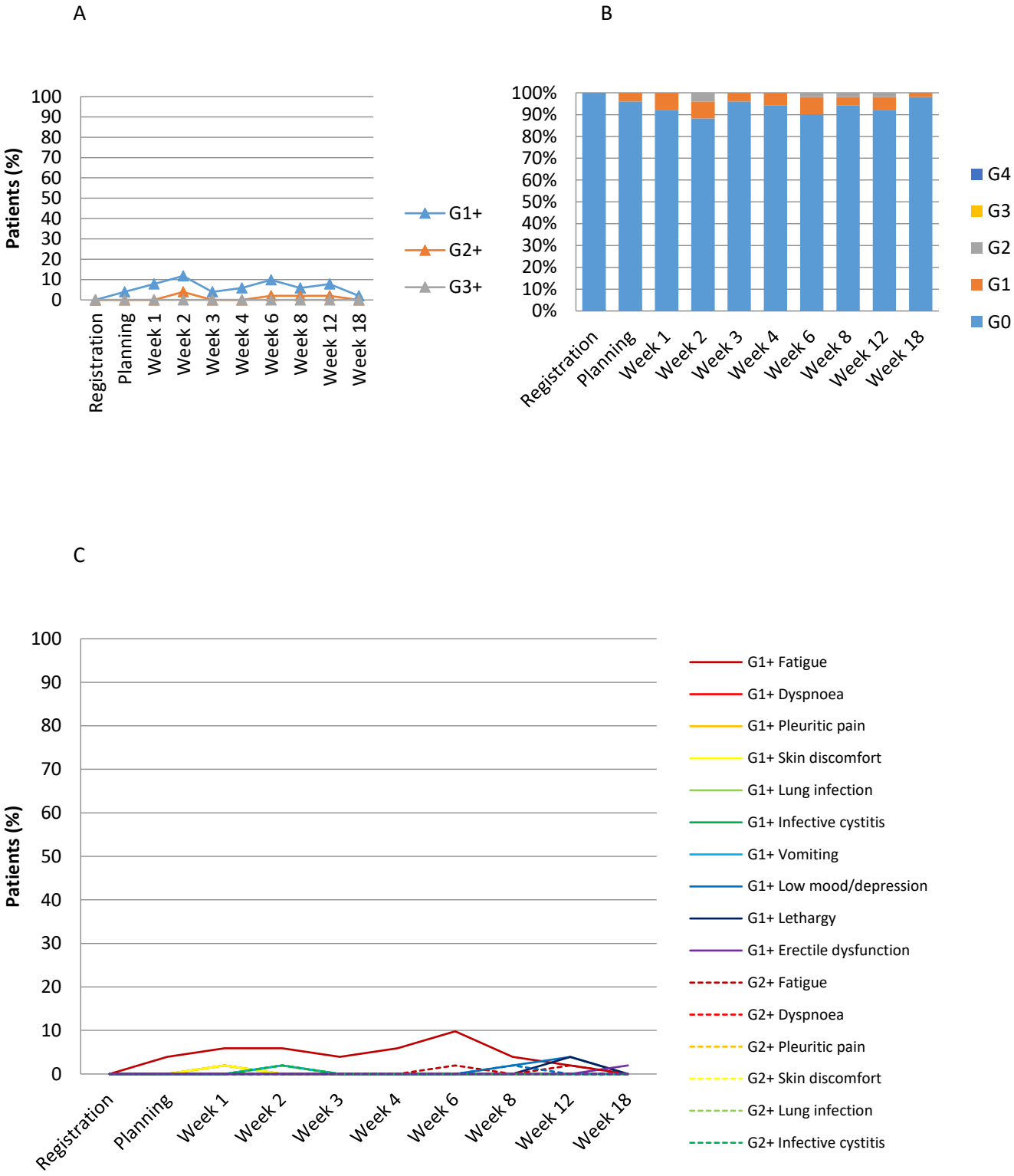


Figure 5-5 Prevalence of acute RTOG toxicity by time point for prostate only radiotherapy

Prevalence (A) and distribution (B) of urinary toxicity grades. Prevalence (C) and distribution (D) of lower GI toxicity grades

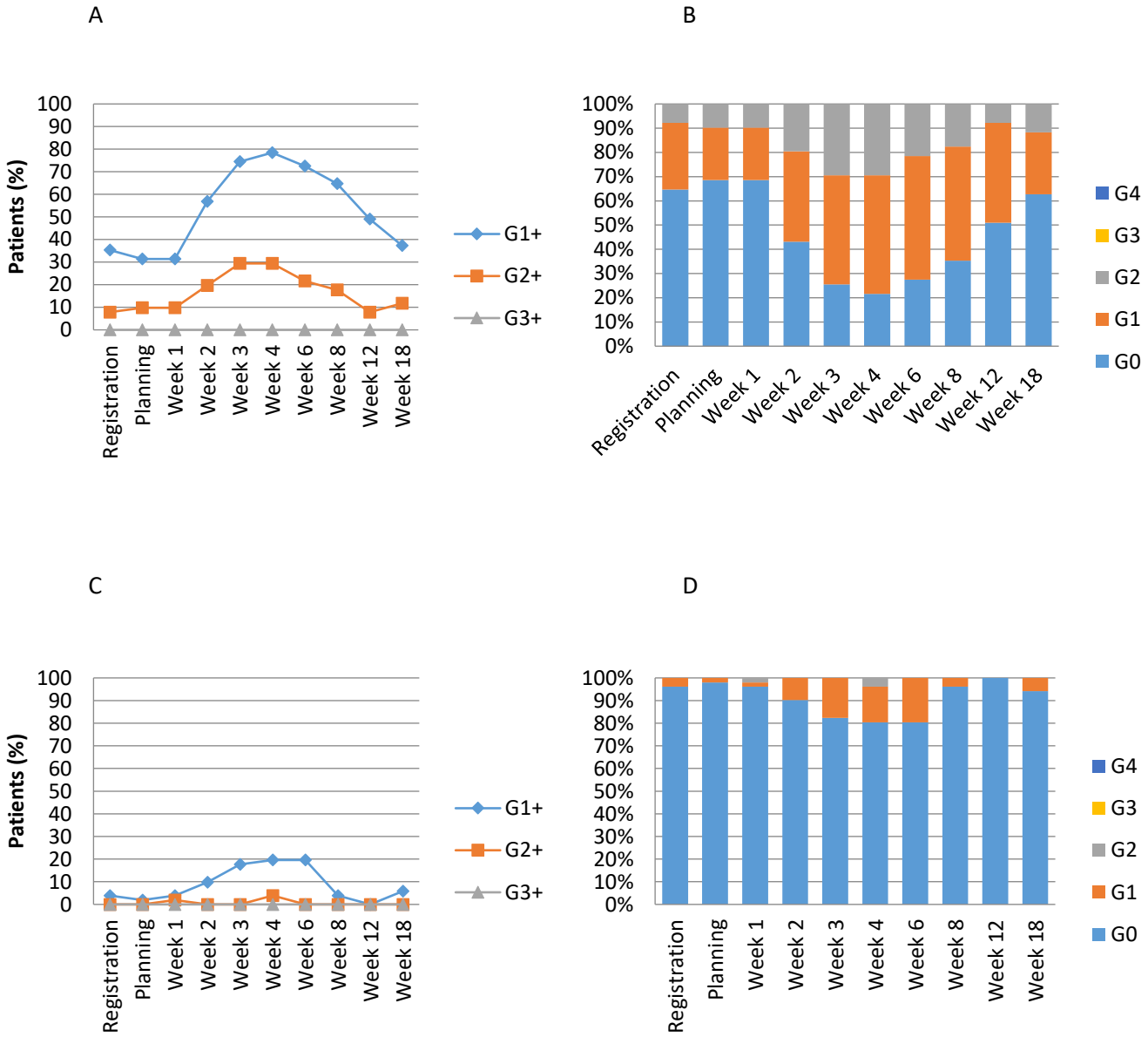
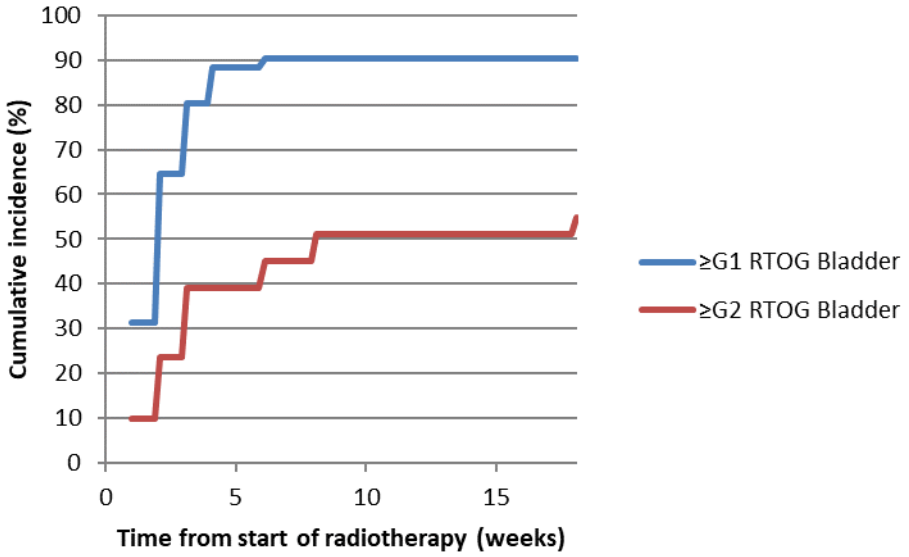


Figure 5-6 Cumulative incidence of acute RTOG toxicity by time point for prostate only radiotherapy
Cumulative incidence of urinary toxicity (A) and lower GI toxicity (B)

A



B

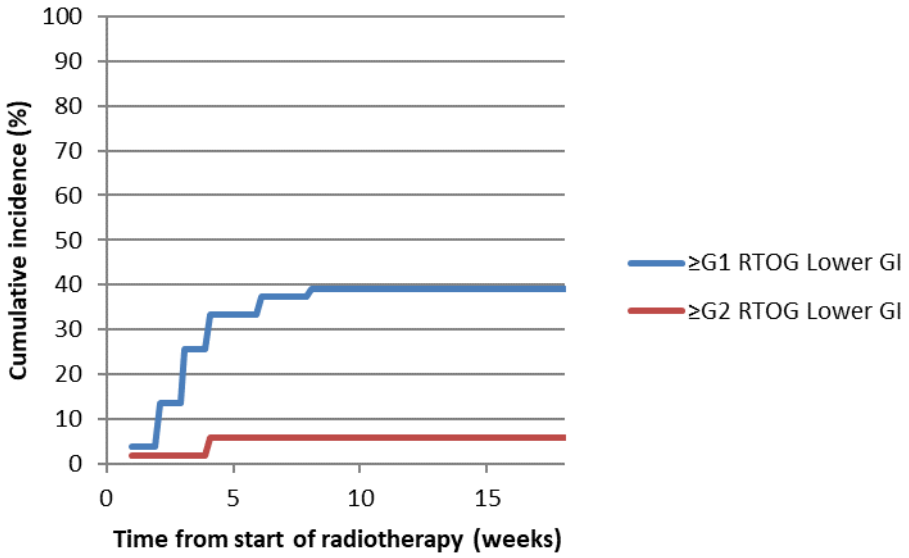


Figure 5-7 Change in IPSS for prostate only radiotherapy between Registration and Week 18
Waterfall plot of change in IPSS score (A) and IPSS Quality of Life score (B)

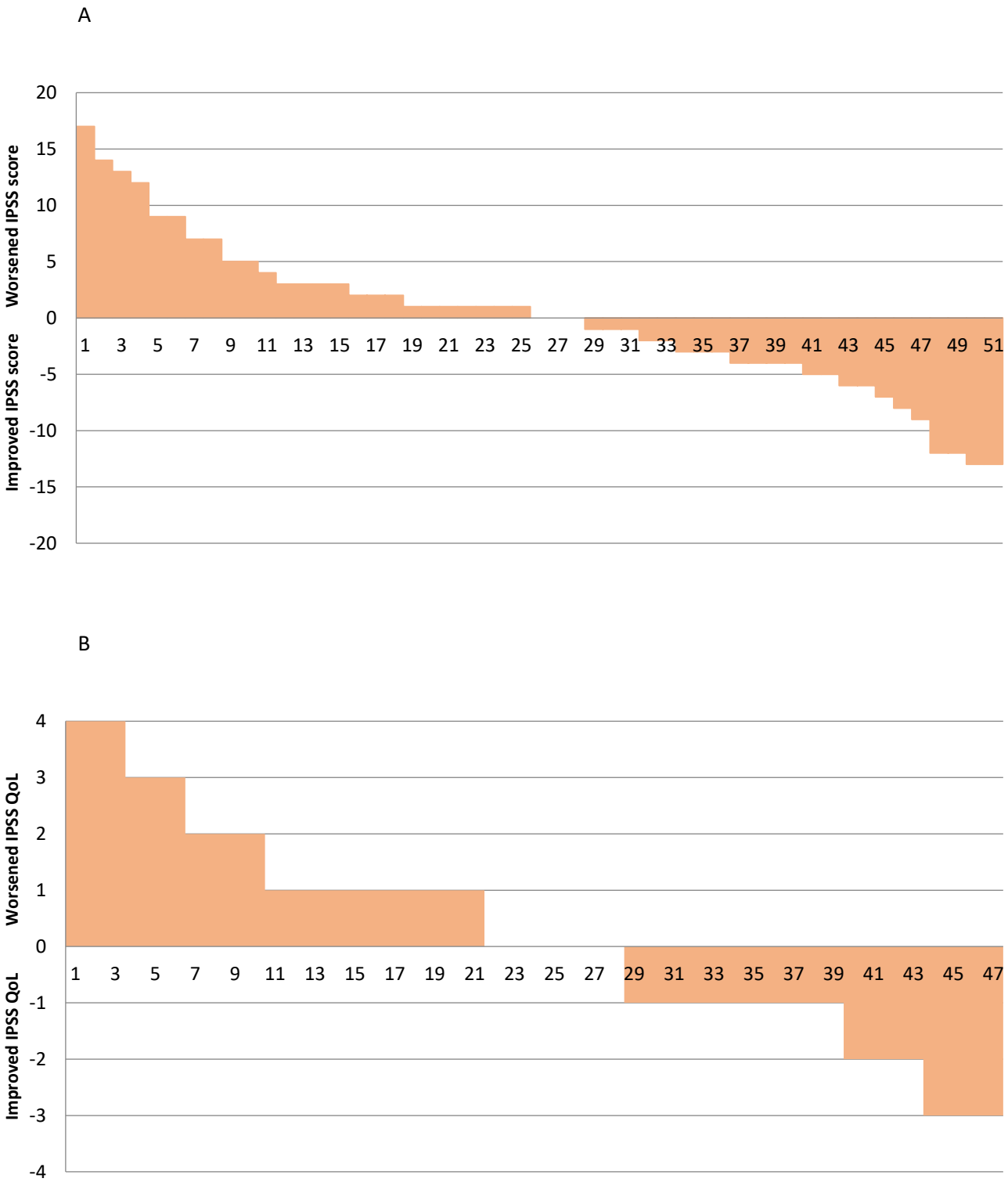


Figure 5-8 Summary EPIC scores by time point for prostate only radiotherapy

Urinary summary (A), bowel summary (B), sexual summary (C) and hormonal summary (D). Upper quartile, median, and lower quartile are plotted

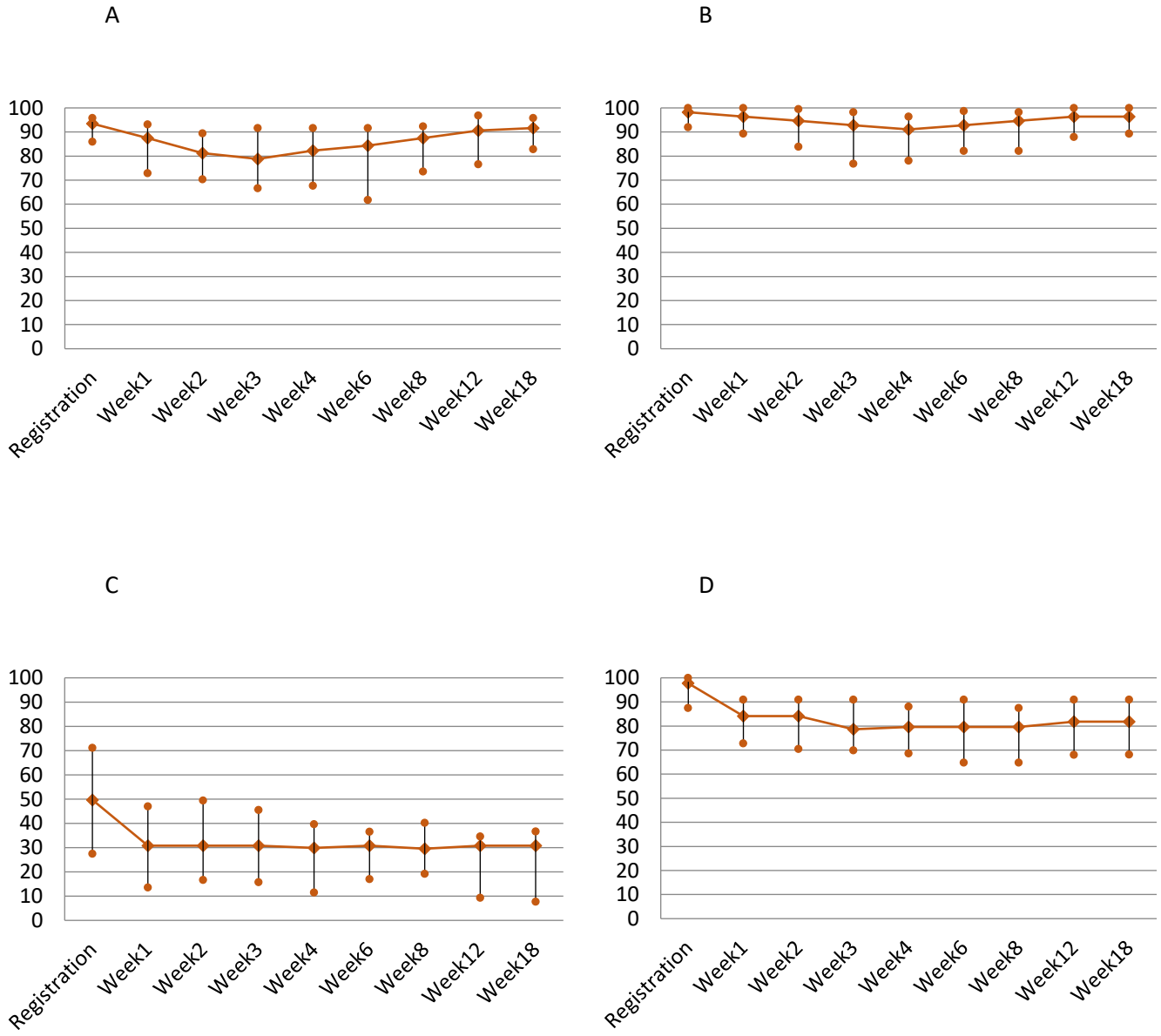


Figure 5-9 EPIC Urinary subcategories by time point for prostate only radiotherapy

Urinary function (A), urinary bother (B), urinary incontinence (C), and urinary irritative/obstructive symptoms (D). Upper quartile, median, and lower quartile are plotted

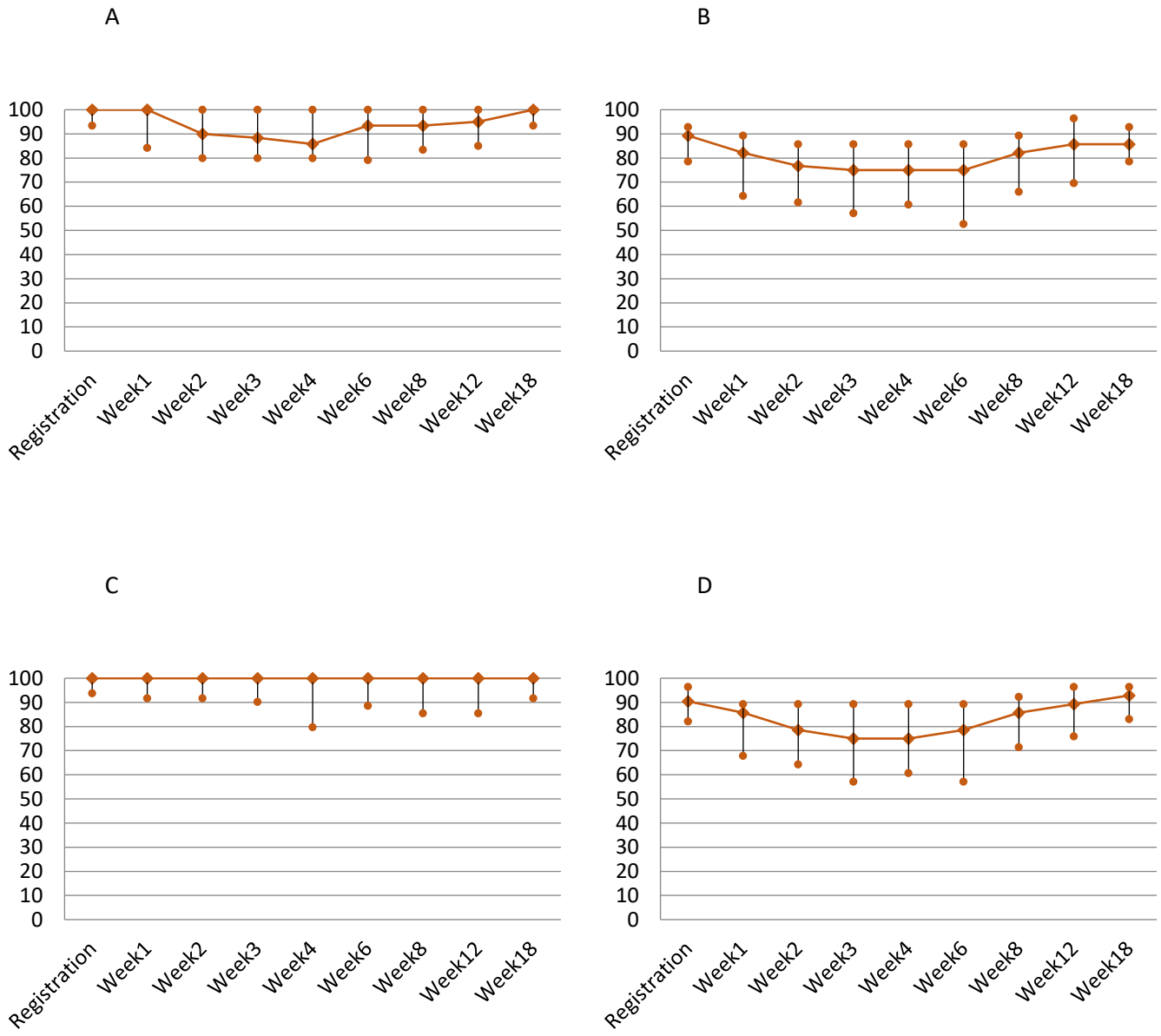


Figure 5-10 EPIC bowel subcategories by time point for prostate only radiotherapy
Bowel function (A), and bowel bother (B). Upper quartile, median, and lower quartile are plotted

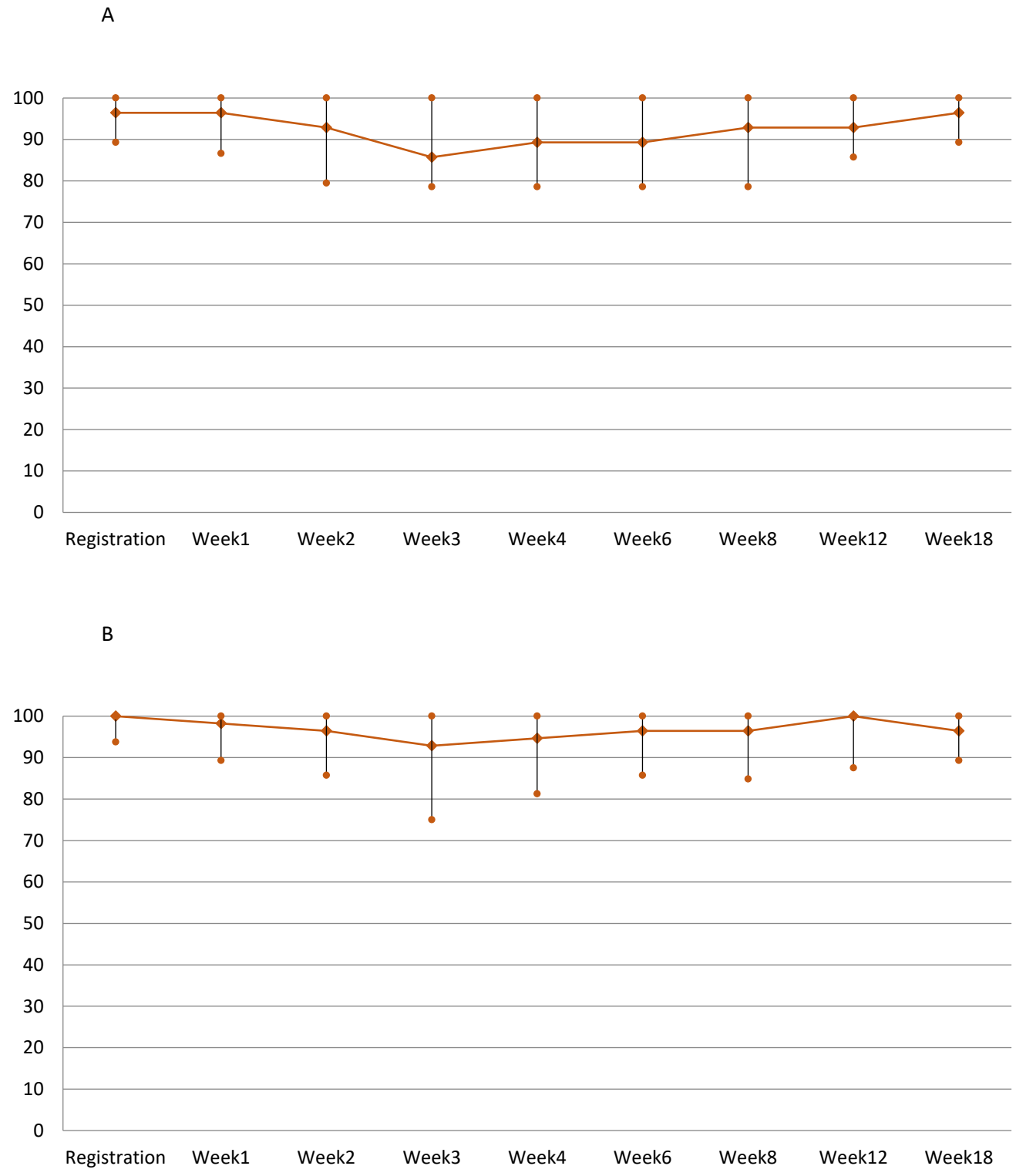
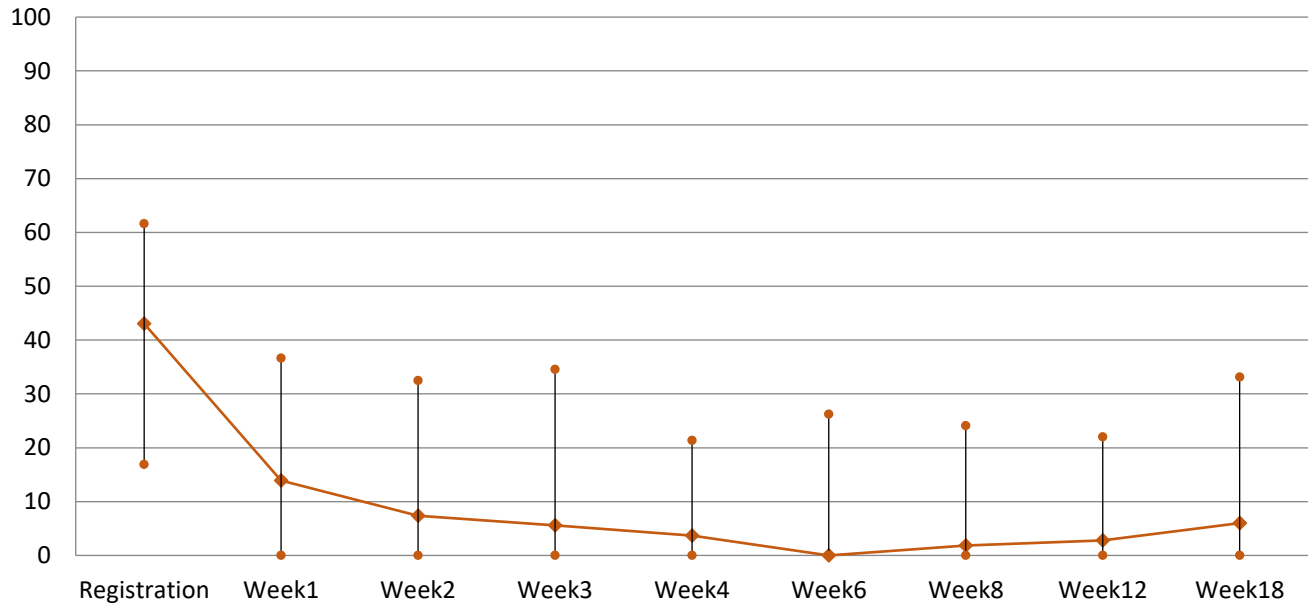


Figure 5-11 EPIC sexual subcategories by time point for prostate only radiotherapy
Sexual function (A), and sexual bother (B). Upper quartile, median, and lower quartile are plotted

A



B

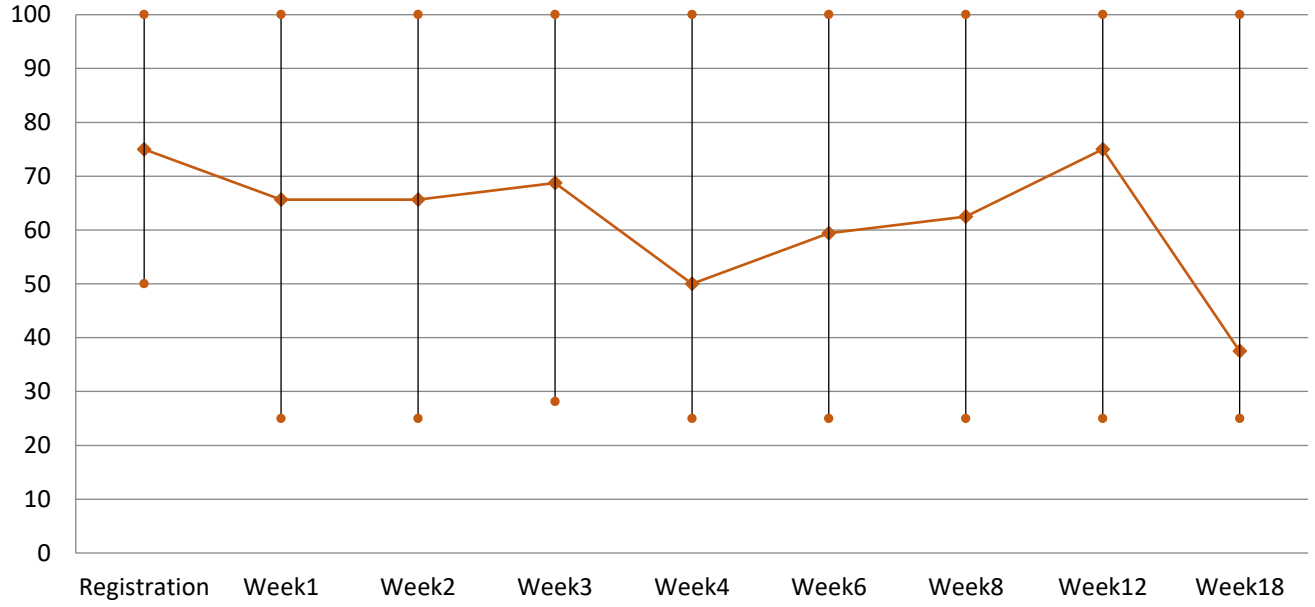
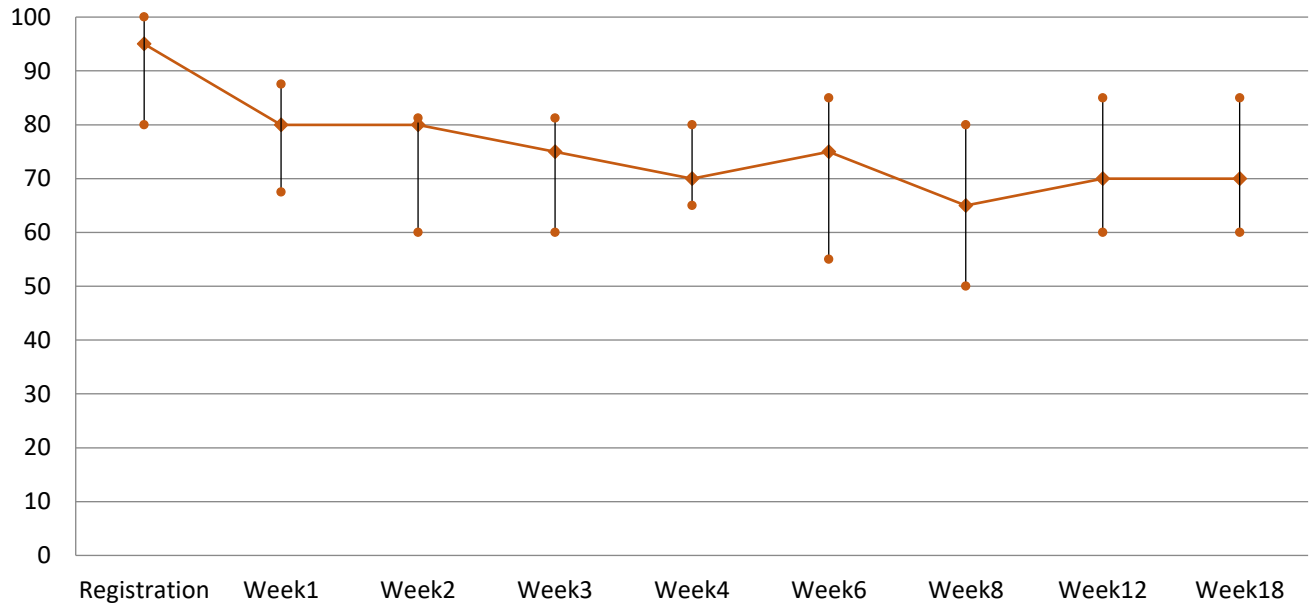


Figure 5-12 EPIC hormonal subcategories by time point for prostate only radiotherapy
Hormonal function (A), and hormonal bother (B). Upper quartile, median, and lower quartile are plotted

A



B

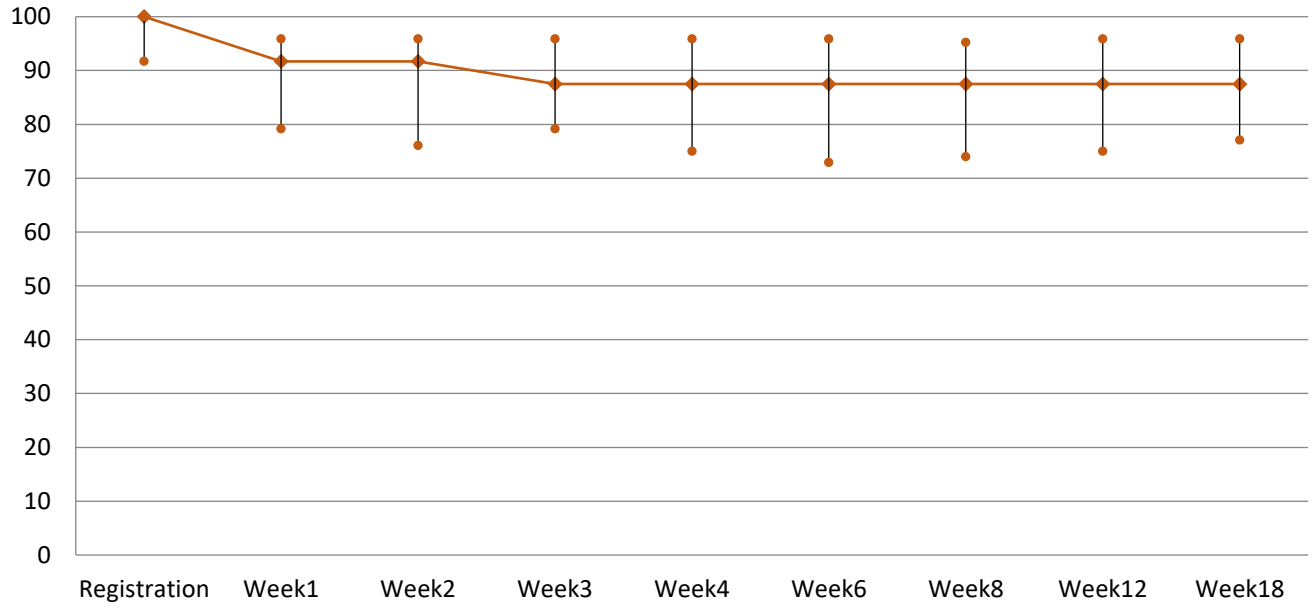


Figure 5-13 Acute urinary and lower GI CTCAE toxicity by time point for prostate and lymph node radiotherapy
Prevalence (A) and distribution (B) of urinary toxicity grades. Prevalence (C) and distribution (D) of maximal lower GI toxicity grades

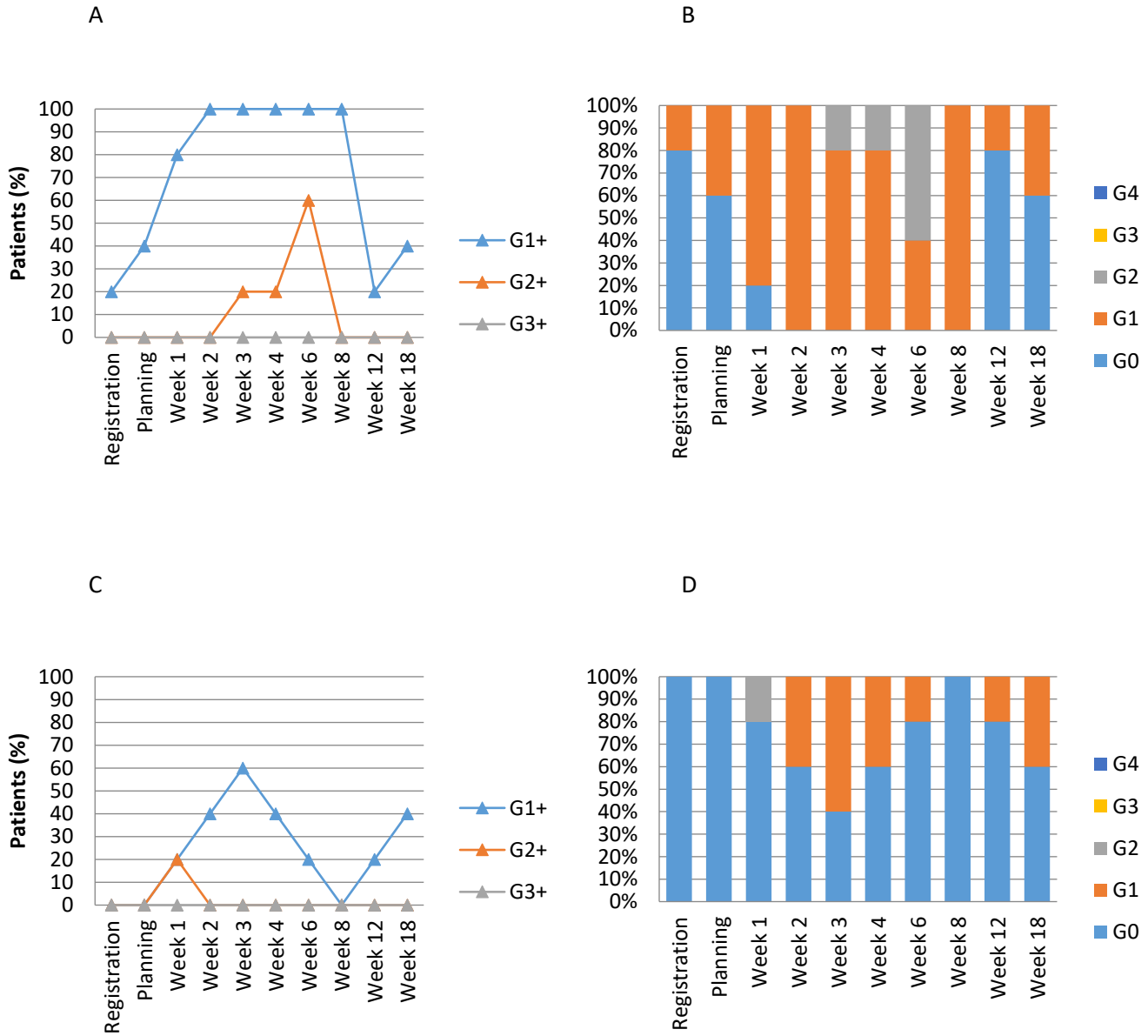


Figure 5-14 Prevalence of specific acute CTCAE toxicities by time point for prostate and lymph node radiotherapy
Prevalence of acute CTCAE urinary toxicities (A) and lower GI toxicities (B)

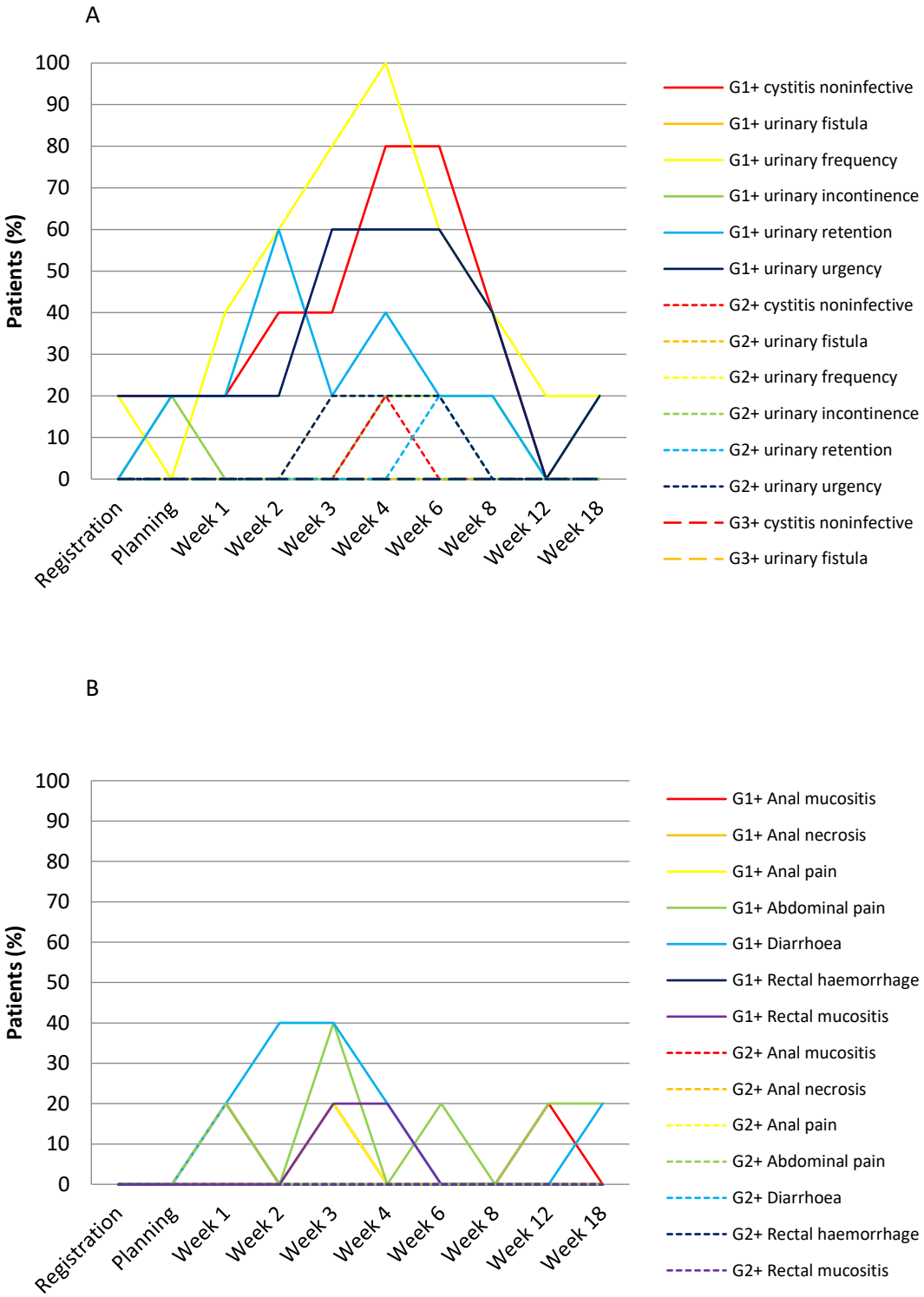


Figure 5-15 Other acute CTCAE toxicities (not urinary or lower GI) by time point for prostate and lymph node radiotherapy

Prevalence of acute CTCAE toxicities (A), distribution of maximal grades (B), and prevalence of specific CTCAE (C)

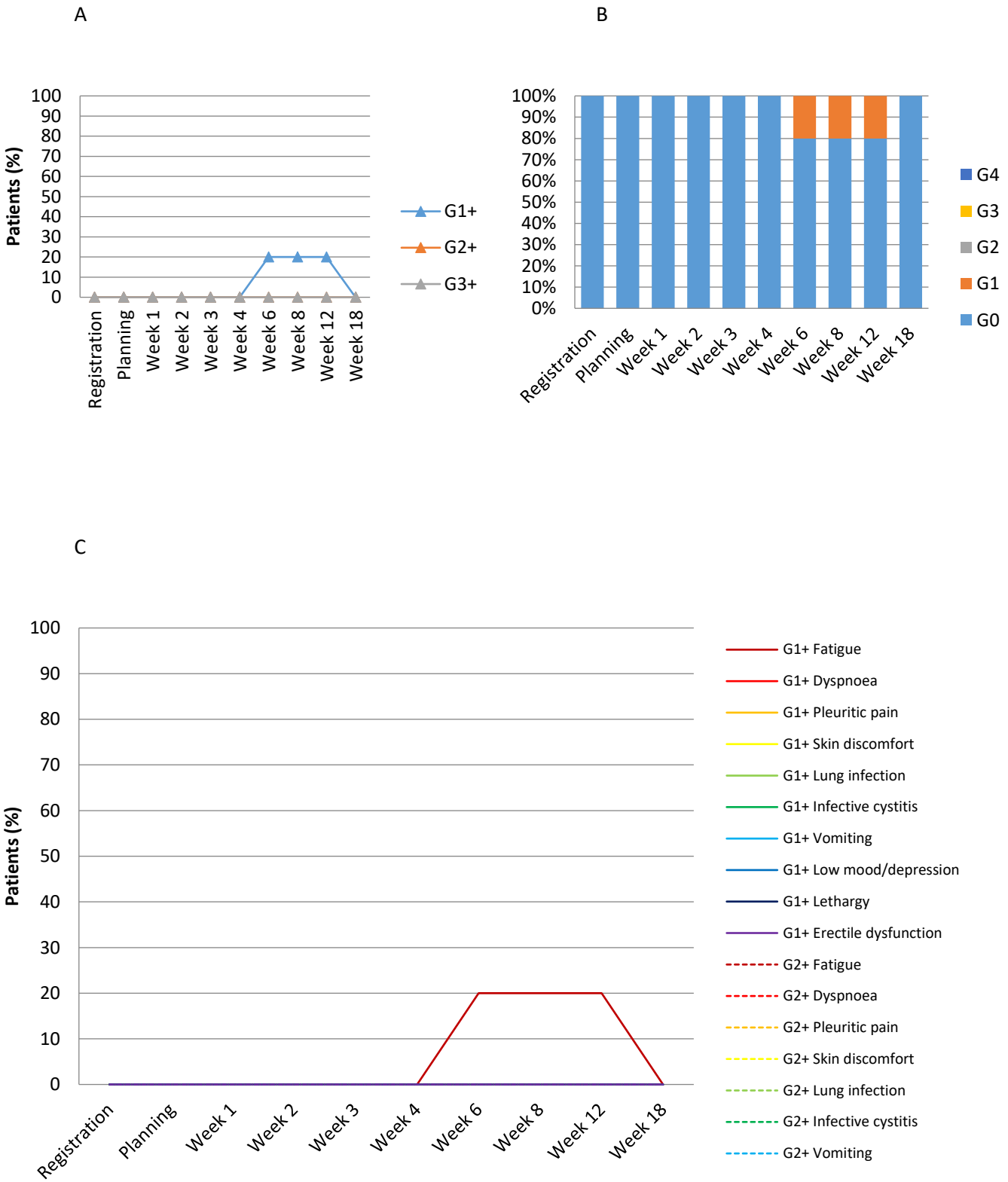


Figure 5-16 Acute RTOG toxicity by time point for prostate and lymph node radiotherapy

Prevalence (A) and distribution (B) of urinary toxicity grades. Prevalence (C) and distribution (D) of lower GI toxicity grades

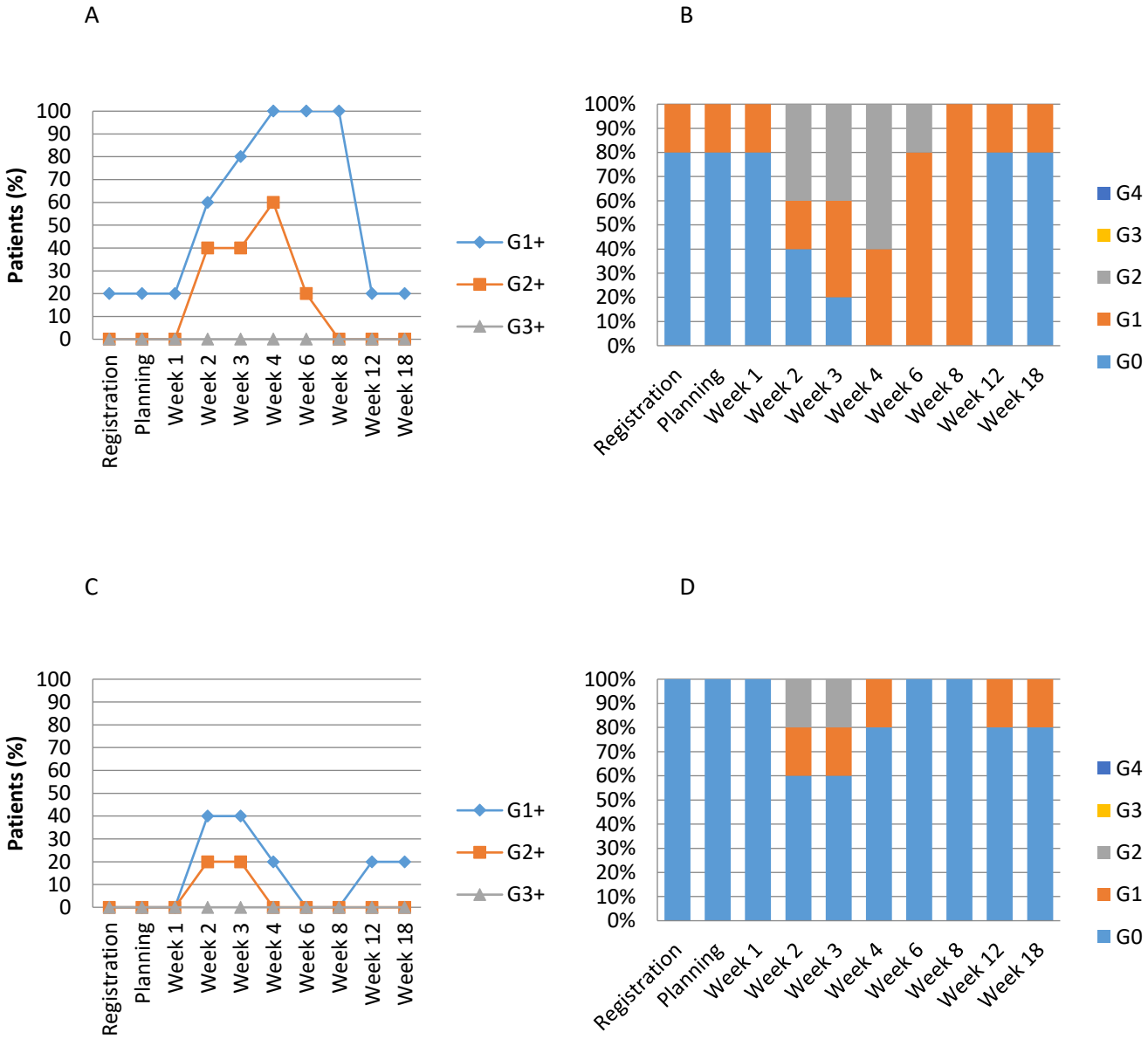
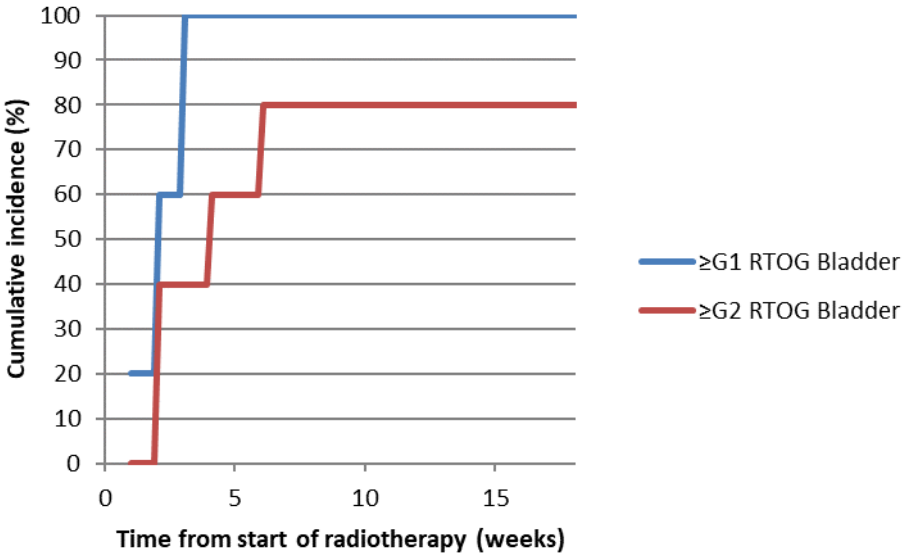


Figure 5-17 Cumulative incidence of acute RTOG toxicity by time point for prostate and lymph node radiotherapy

Cumulative incidence of urinary toxicity (A) and lower GI toxicity (B)

A



B

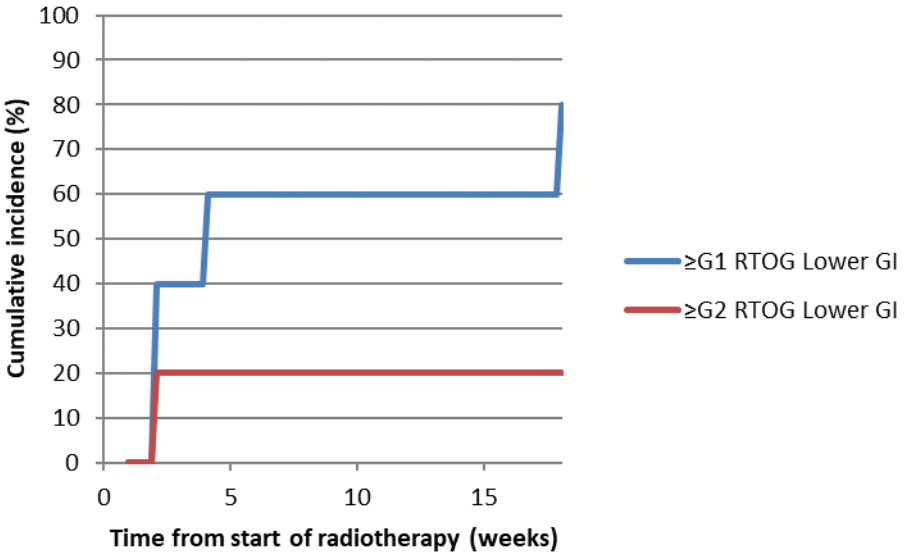


Figure 5-18 Change in IPSS for prostate and lymph node radiotherapy between Registration and Week 18
Waterfall plot of change in IPSS score (A) and IPSS Quality of Life score (B)

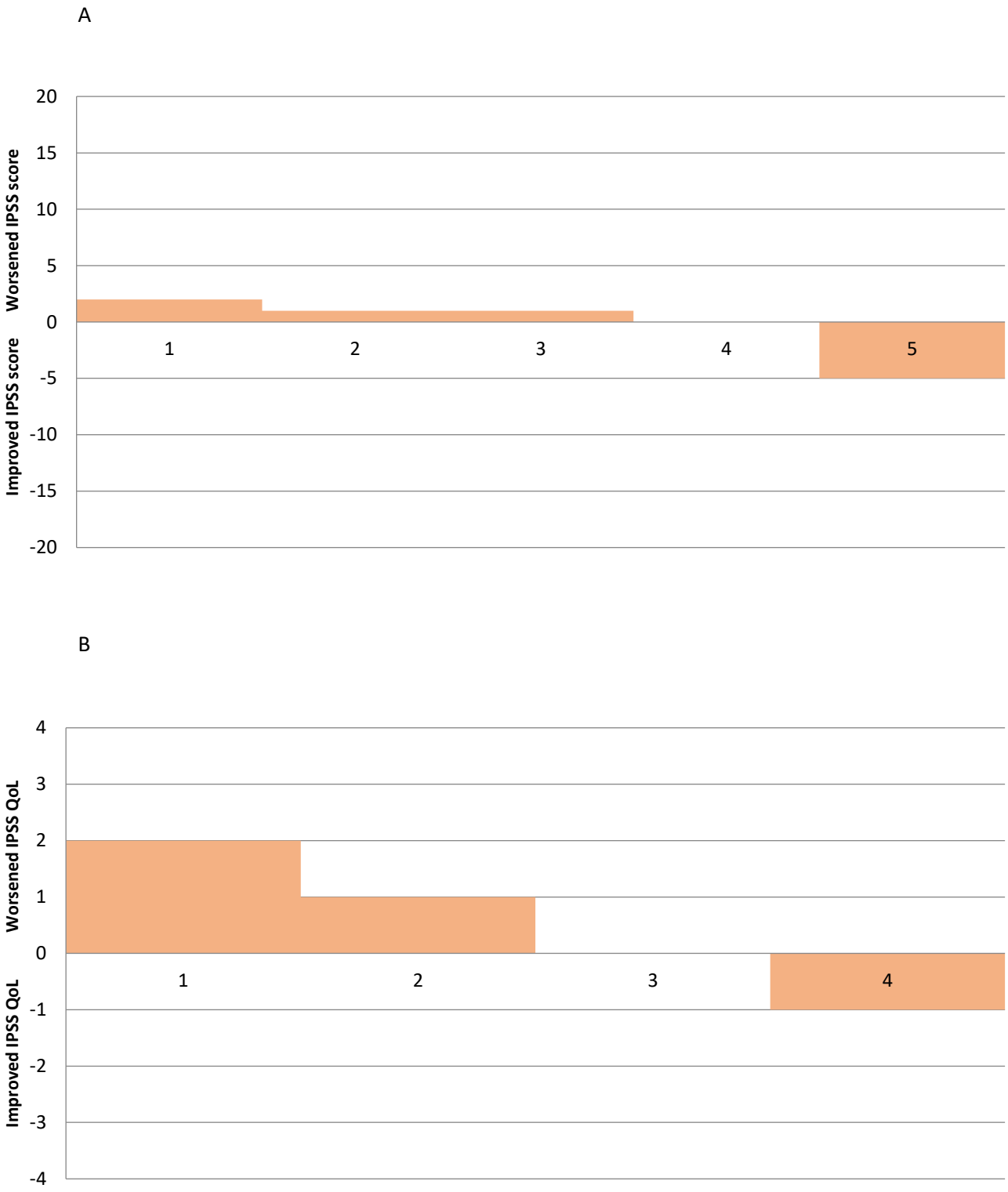


Figure 5-19 Summary EPIC scores by time point for prostate and lymph node radiotherapy
Urinary summary (A), bowel summary (B), sexual summary (C) and hormonal summary (D). Upper quartile, median, and lower quartile are plotted

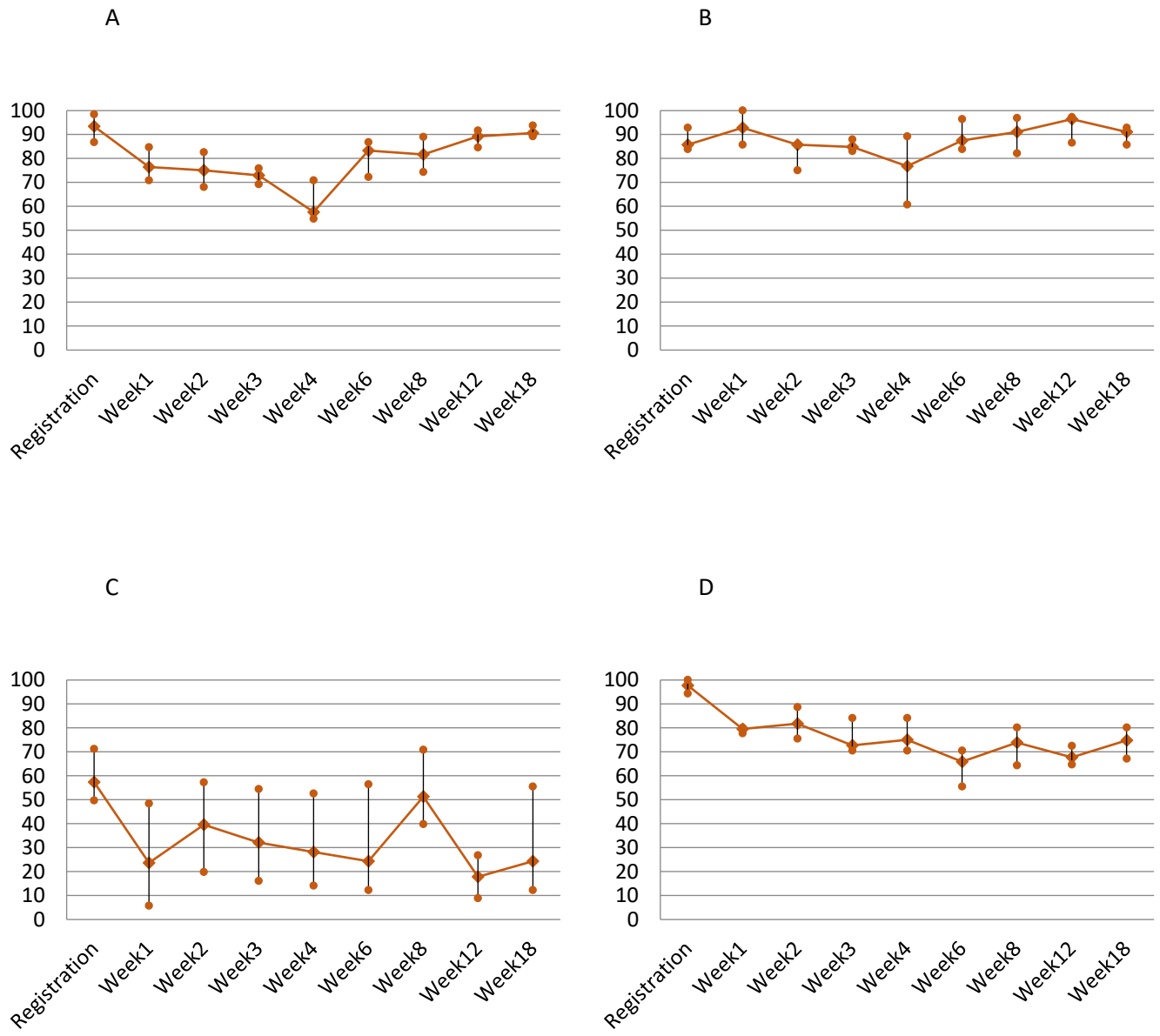


Figure 5-20 EPIC Urinary subcategories by time point for prostate and lymph node radiotherapy

Urinary function (A), urinary bother (B), urinary incontinence (C), and urinary irritative/obstructive symptoms (D). Upper quartile, median, and lower quartile are plotted

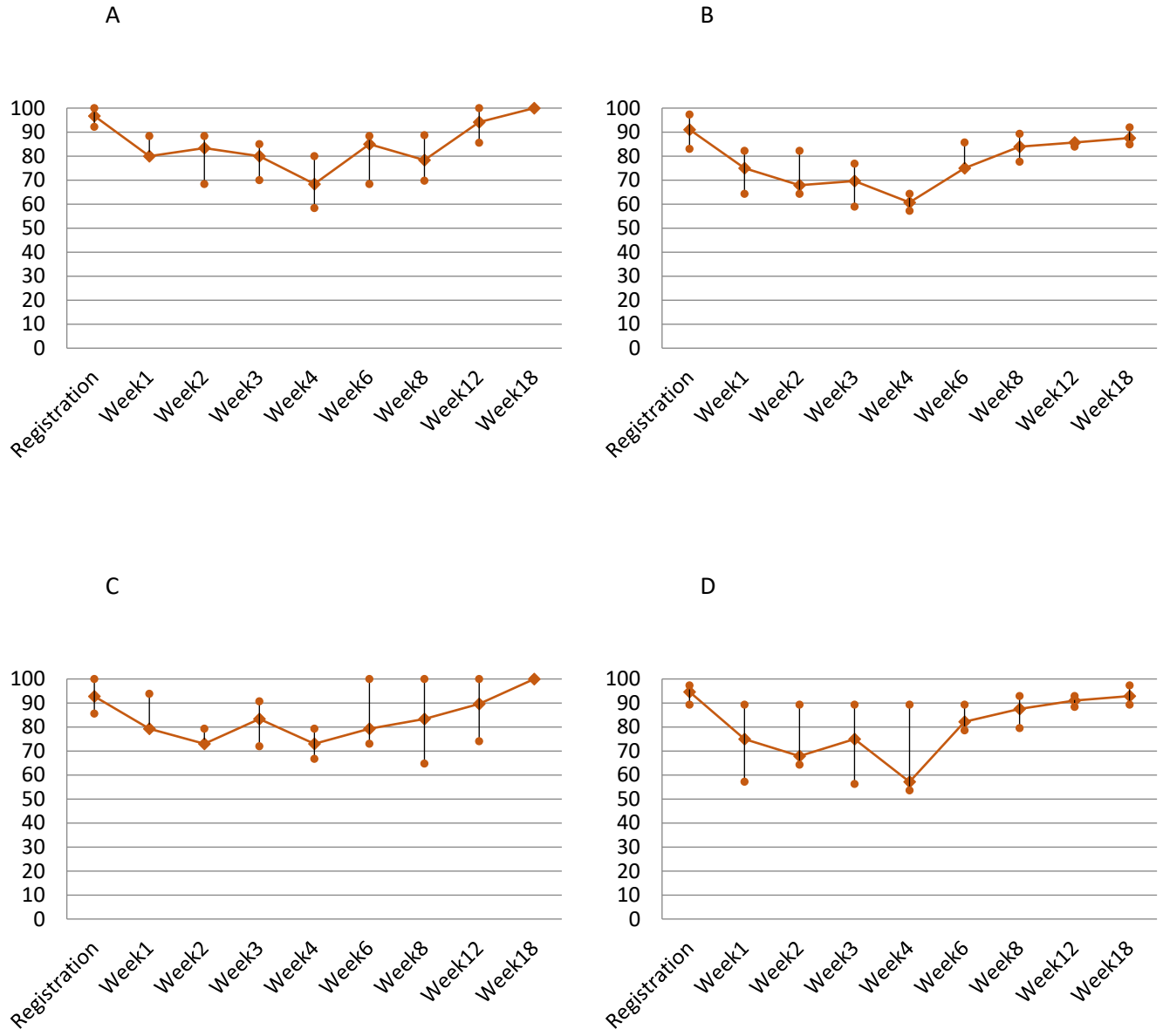


Figure 5-21 EPIC bowel subcategories by time point for prostate and lymph node radiotherapy
Bowel function (A), and bowel bother (B). Upper quartile, median, and lower quartile are plotted

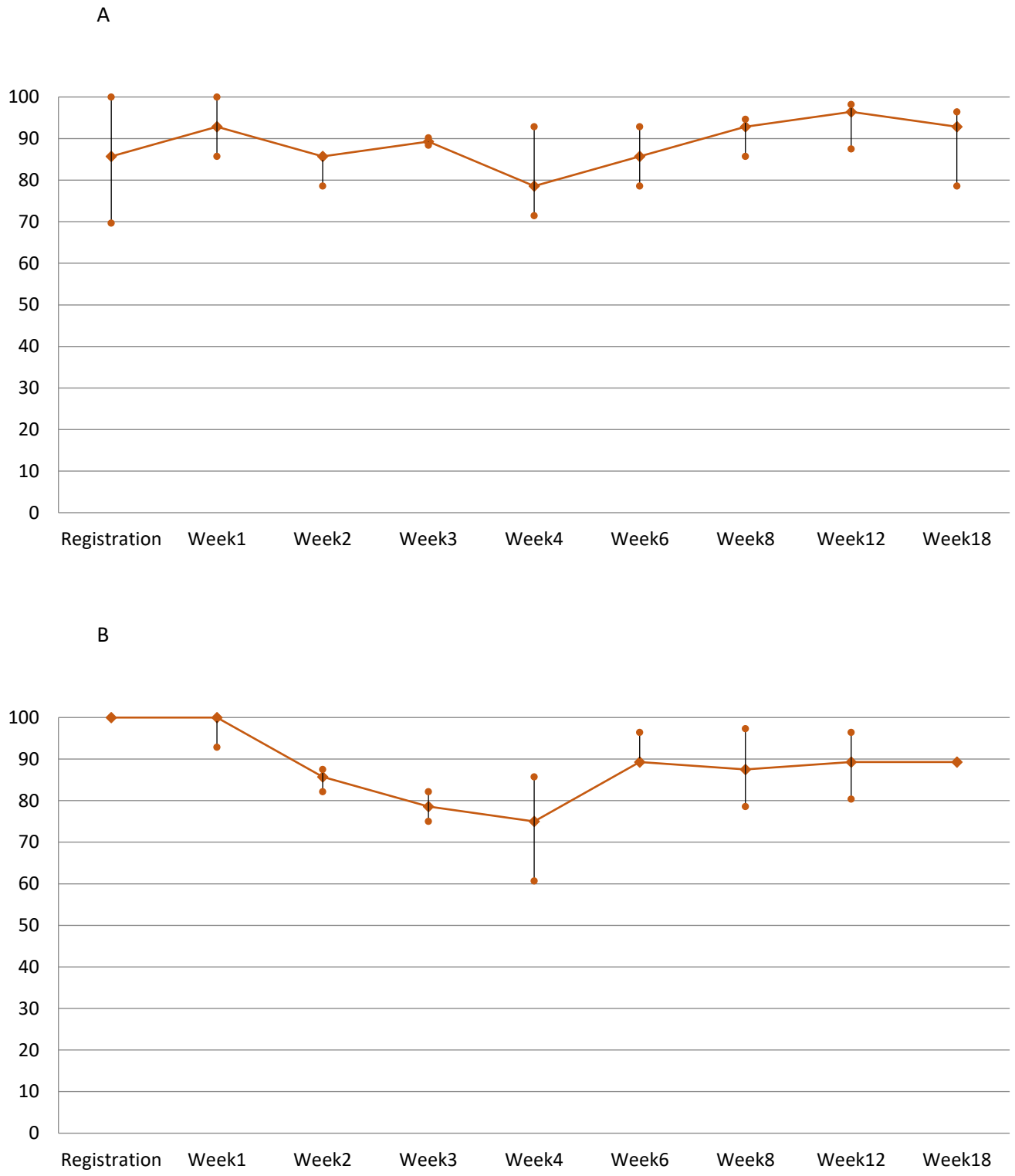
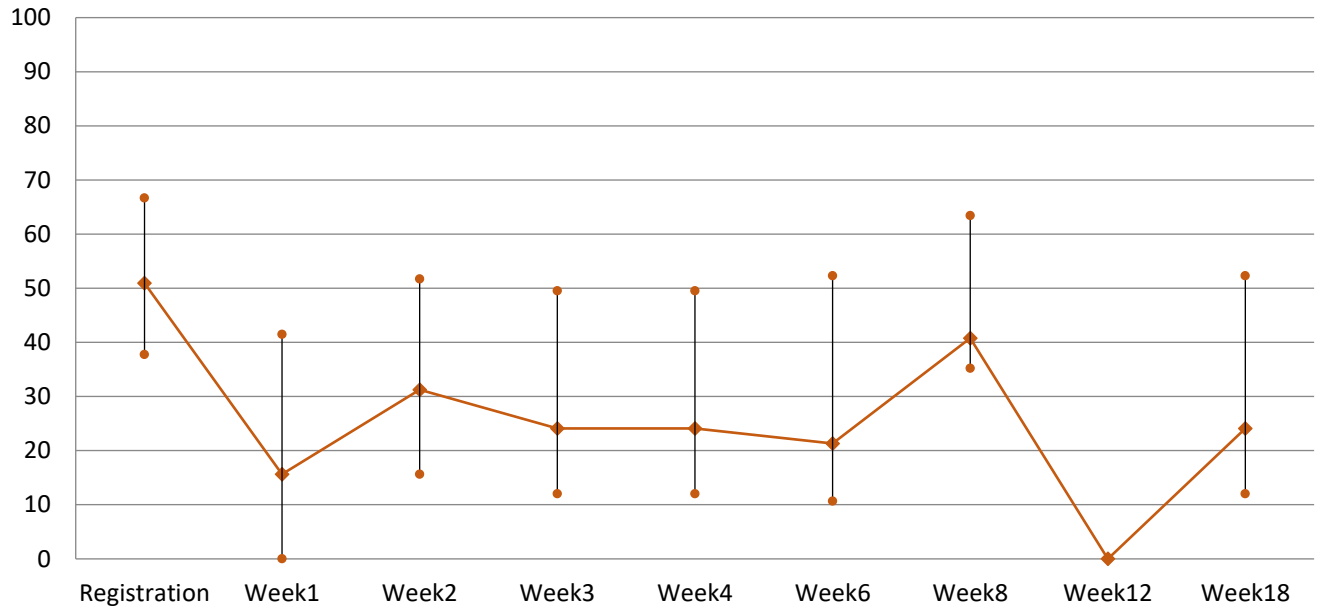


Figure 5-22 EPIC sexual subcategories by time point for prostate and lymph node radiotherapy
Sexual function (A), and sexual bother (B). Upper quartile, median, and lower quartile are plotted

A



B

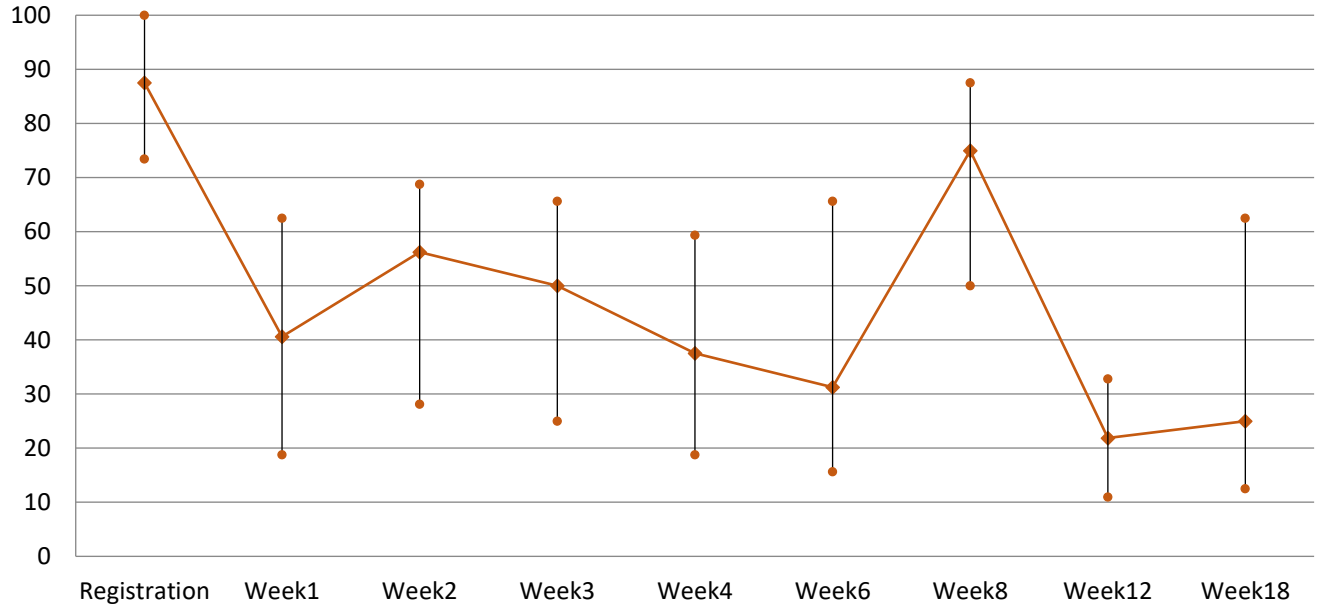


Figure 5-23 EPIC hormonal subcategories by time point for prostate and lymph node radiotherapy
Hormonal function (A), and hormonal bother (B). Upper quartile, median, and lower quartile are plotted

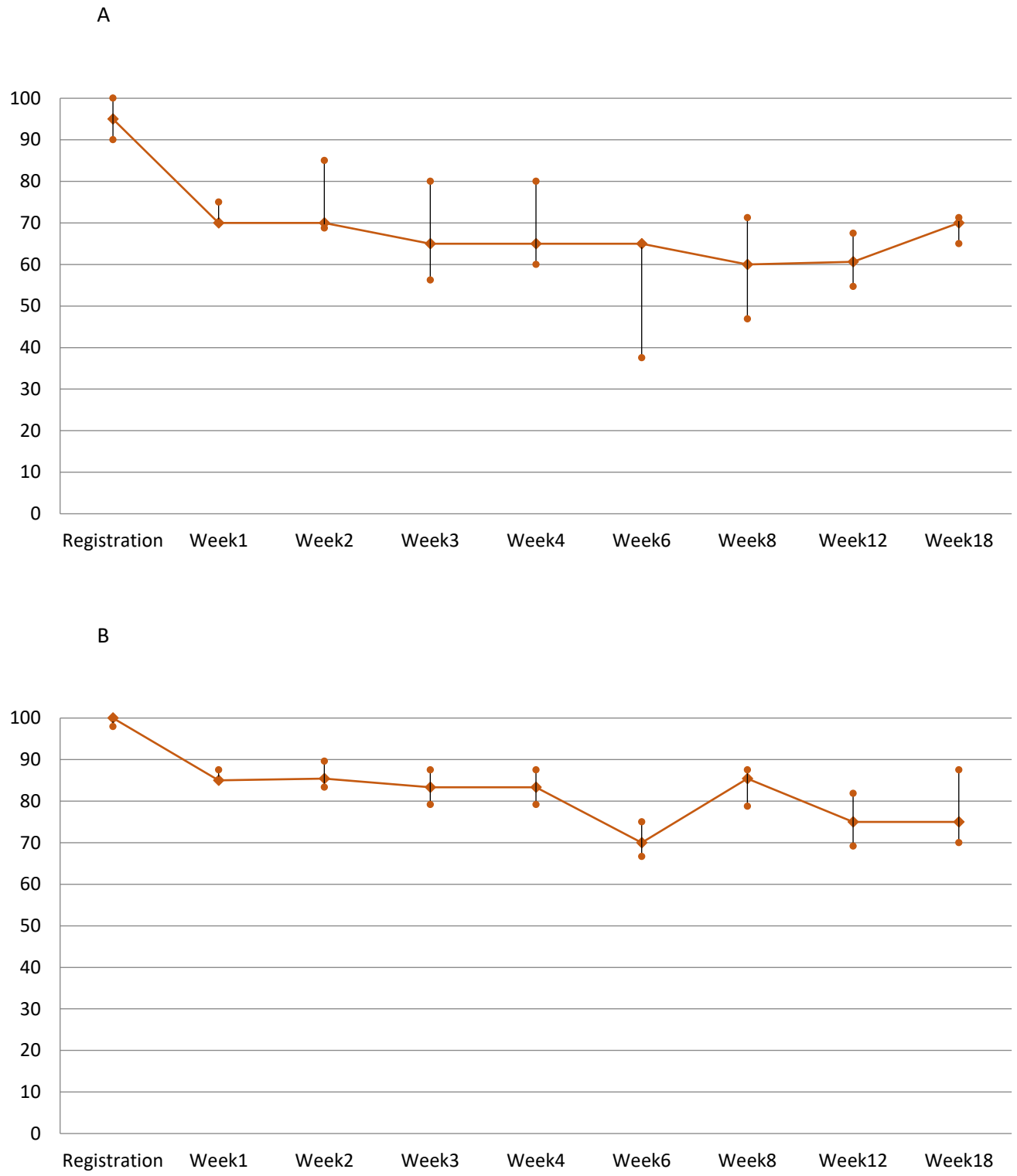


Table 5-1 Statistical comparisons of symptom scores between registration and week 18, and between week 1 and week 18

Comparison for prostate only group using Wilcoxon signed rank test (p values)

		Registration vs. Week 18	Week 1 vs. Week 18
PS		0.10	-
IPSS	Score	0.83	-
	QoL	0.57	-
EPIC	Patient satisfaction	0.61	0.31
EPIC summary	Urinary	0.82	0.02
	Bowel	0.14	0.88
	Sexual	<0.01	0.17
	Hormonal	<0.01	0.22
EPIC urinary	Function	0.58	0.09
	Bother	0.98	<0.01
	Incontinence	0.76	0.48
	Irritative obstructive	0.86	<0.01
EPIC bowel	Function	0.39	0.85
	Bother	0.10	0.66
EPIC sexual	Function	<0.01	0.62
	Bother	0.10	0.09
EPIC hormonal	Function	<0.01	0.05
	Bother	<0.01	0.60

For the 5 patients who had prostate and lymph node radiotherapy, similar comparisons showed no significant differences for registration vs. week 18 and for week1 vs. week18.

Table 5-2 Performance status (PS) within the prostate only radiotherapy group (to week 18)
Prevalence at registration and week 18 (A), and change in PS between the time points (B)

A

	Registration		Week 18	
	PS 0	PS 1	PS 0	PS 1
No. of pts	46	5	41	10

B

Change in PS from registration to Week 18	No. of patients
PS 0 to 0	39
PS 0 to 1	7
PS 1 to 0	2
PS 1 to 1	3

Table 5-3 Performance status (PS) within the prostate and lymph node radiotherapy group (to week 18)
Prevalence at registration and week 18 (A), and change in PS between the time points (B)

A

	Registration		Week 18	
	PS 0	PS 1	PS 0	PS 1
No. of pts	5	0	4	1

B

Change in PS from registration to Week 18	No. of patients
PS 0 to 0	4
PS 0 to 1	1
PS 1 to 0	0
PS 1 to 1	0

5.4.1 CTCAE v4.0

All patients had CTCAE assessments at each of the 10 time points (510 assessments in total for the 'prostate only' group, and 50 assessments in total for the 'prostate and pelvic lymph node' group).

For the 'prostate only' group (Figures 5-2 to 5-4):

- **acute urinary toxicity** generally peaked at Week 3, although G2 toxicity continued until Week 6. Only one patient experienced G3 toxicity.
- **acute bowel toxicity** was generally low, peaking at Weeks 3 and 4. No patients had G3 toxicity.
- **other than urinary or bowel categories**, the main toxicity was fatigue, with 10% of patients with G≥1 fatigue. At Week 18, no patients had fatigue.

For the 'prostate and pelvic lymph node' group (Figures 5-13 to 5-15):

- **acute urinary toxicity** peaked at Week 6 where 60% had G2 urinary toxicity. However no patients had G2 toxicity thereafter. No patients had G3 toxicity.
- **acute bowel toxicity** was generally low, peaking at Week 3. Only one patient experienced G2 toxicity. No patients had G3 toxicity.
- **other than urinary or bowel categories**, the only toxicity was fatigue, with 20% of patients with G1 fatigue. No patients had G2 toxicities.

5.4.2 RTOG

All patients had RTOG assessments at each of the 10 time points (510 assessments in total for the 'prostate only' group, and 50 assessments in total for the 'prostate and pelvic lymph node' group).

For the 'prostate only' group (Figures 5-5 to 5-6):

- **acute urinary toxicity** peaked at Week 4. G2 toxicity was experienced by 29%. No patients had G3 toxicity.

- **acute bowel toxicity** was generally low, and peaked at Week 4 to Week 6. G2 toxicity was only noted in 4%.

For the 'prostate and pelvic lymph node' group (Figures 5-16 to 5-17):

- **acute urinary toxicity** also peaked at Week 4. G2 toxicity was experienced by 60%. No patients had G3 toxicity.
- **acute bowel toxicity** peaked at Week 2 to Week 3. Only 1 patient experienced G2 toxicity.

5.4.3 IPSS

All patients completed the IPSS score at the two time points (102 assessments in total for the 'prostate only' group, and 10 assessments in total for the 'prostate and pelvic lymph node' group).

For the IPSS QoL question, 4 patients in the 'prostate only' group did not provide an answer at registration but all patients provided an answer at Week 18 (therefore 47 patients had QoL values at both time points), whilst 1 patient in the 'prostate and pelvic lymph node' group did not provide an answer at registration but all provided an answer at Week 18 (therefore 4 patients had QoL values at both time points).

For the 'prostate only' group (Figure 5-7):

- There was generally an even distribution between patients who experienced an improved IPSS score and patients who experienced a worsened IPSS score, with no significant difference between the IPSS scores at registration and at Week 18 (p=0.83; Wilcoxon signed rank test). Similarly there was a broadly even distribution between patients who experienced an improved IPSS QoL and patients who experienced a worsened IPSS QoL (p=0.57; Wilcoxon signed rank test).

For the 'prostate and pelvic lymph node' group (Figure 5-18):

- There was no significant difference at registration and at Week 18 in both IPSS score and IPSS QoL (p=0.71 and p=0.41 respectively; Wilcoxon signed rank test).

5.4.4 EPIC

For the 'prostate only' group, EPIC questionnaires were collected from 44 patients at registration (for those without EPIC: missing for one patient, and the rest had LENT/SOMA as they were registered prior to trial protocol amendment which specified the use of EPIC instead). Response rates for the EPIC questionnaires were: all 51 patients at Week 1, 50 patients at Week 2, 49 patients at Week 3, 48 patients at Week 4, 48 patients at Week 6, 48 patients at Week 8, 47 patients at Week 12, and all 51 patients at Week 18. Overall, 436 EPIC questionnaires were collected out of 459 overall time points (this is excluding the one patient who was recruited but subsequently found to be ineligible due to metastatic disease and therefore did not receive radiotherapy).

For the 'prostate and pelvic lymph node' group, response rates for the EPIC questionnaires were: 4 patients at registration, 5 patients at Week 1, 5 patients at Week 2, 5 patients at Week 3, 5 patients at Week 4, 5 patients at Week 6, 4 patients at Week 8, 4 patients at Week 12, and 5 patients at Week 18. Overall, 42 EPIC questionnaires were collected out of an expected 45 questionnaires.

For the 'prostate only' group (Figures 5-8 to 5-12):

- Urinary summary toxicity and bowel summary toxicity peaked at Week 3 and Week 4 respectively (urinary function, urinary bother, urinary irritative/obstructive symptoms, bowel function, and bowel bother). However there was generally no change in urinary continence. Sexual summary and hormonal summary toxicity declined between registration and Week 1 as expected from bicalutamide, but generally did not change during or up to Week 18. When comparing the EPIC scores for registration/Week 1 and EPIC scores for Week 18, there is generally a significant worsening of sexual and hormonal toxicity between registration and Week 18, but not between Week 1 and Week 18 (Table 5-1). Furthermore, there is generally a significant improvement in urinary toxicity between Week 1 and Week 18, but not between registration and Week 18 (Table 5-1). However, there is no difference in patient satisfaction between the different time points.

For the 'prostate and pelvic lymph node' group (Figures 5-19 to 5-23):

- Both urinary summary toxicity and bowel summary toxicity peaked at Week 4. However urinary continence was also affected. Sexual summary and hormonal summary toxicity declined between registration and Week 1 as expected from bicalutamide, and generally did not change during or up to Week 18. Overall, there is generally no significant difference in the various EPIC scores and patient satisfaction between the different time points (Table 5-1).

5.4.5 Performance status

All patients had a PS assessment at the two time points (102 assessments in total for the 'prostate only' group, and 10 assessments in total for the 'prostate and pelvic lymph node' group).

In the 'prostate only' group, most patients had no change in PS, with 14% had worsening PS (Table 5-2). In the 'prostate and pelvic lymph node' group, most patients had no change, with 1 patient having worsening PS (Table 5-3).

5.5 Discussion

Treatment of clinically node-negative prostate cancer with moderately hypofractionated dose painting radiotherapy to the prostate alone was well tolerated in terms of acute urinary and bowel toxicities according to clinician reported outcomes. Most patients experienced at least G1 urinary toxicity, whereas most patients did not experience G1 bowel toxicity. However, these toxicities were temporary. As the symptom profile was similar between those at registration/planning and those at Week 18, patients recovered from their acute toxicities to their pre-radiotherapy state.

Treatment of clinically node-positive prostate cancer with dose painting radiotherapy to both the prostate and pelvic lymph nodes was also generally well tolerated although it was more toxic than dose painting radiotherapy to the prostate alone according to clinician reported outcomes. Although the cohort size of five patients is small, three patients (60%) with dose painting radiotherapy to both prostate and lymph nodes experienced G2 urinary toxicity (compared to 30% with dose painting radiotherapy to prostate alone) and this peaked at the same time point (2 weeks following completion of radiotherapy). However, this was also transient, and no patients experienced G3 toxicity. Prevalence of bowel toxicity

was higher for dose painting radiotherapy to both prostate and lymph nodes, with G2 toxicity of around 20% (compared to 5% with dose painting radiotherapy to prostate alone). This would be expected due to increased mean and maximal doses to the bowel and bladder as shown in radiotherapy planning dosimetry data in the previous chapter. No patients had G2 bowel toxicity at Week 18 in either group.

From the patient reported outcomes, the IPSS scores also suggest that urinary symptoms do not worsen for the patients as a group between registration and Week 18 (i.e. from treatments with both bicalutamide and dose painting radiotherapy). However the EPIC scores show a small, but statistically significant, improvement in the urinary categories between Week 1 and Week 18 in the prostate only group. This should be interpreted with caution, as the patients may have already started to experience toxicity at Week 1, although unlikely, and hence cannot be regarded as patients experiencing improved urinary toxicity due to dose painting radiotherapy. In retrospect, it would have been informative to have EPIC data collected at planning, together with the CTCAE and RTOG data. With the EPIC data available to compare symptoms at registration and Week 18, patients did not experience residual urinary or bowel toxicity following the acute phase from both bicalutamide and dose painting radiotherapy. In comparison, patients did experience significant sexual and hormonal toxicity, primarily from bicalutamide (rapid reduction in EPIC scores between registration and Week 1), and this did not generally deteriorate from the subsequent dose painting radiotherapy.

One of the CHHiP treatment arms involved delivering 60 Gy/20 #/4 weeks for localised prostate cancer(10, 98). It aimed to deliver three dose levels also ([60 Gy/ 57.6 Gy/ 48 Gy] vs. [68 Gy/ 60 Gy/ 53 Gy]), but the high dose volume was the whole prostate (60 Gy) as opposed to the DILs (68 Gy). In addition, no posterior margin for the high dose volume (from CTV3 to PTV3) was used within CHHiP, whilst the maximal extension of the high dose volume beyond the boundaries of the prostate within the BIOPROP20 protocol was 2 mm. Additional margins for the lower dose levels used in CHHiP were 5/10 mm, compared to 3/6 mm for BIOPROP20. The inclusion criteria for CHHiP allowed for lower risk disease when compared to BIOPROP20 (T1b-T3a compared to T2a-T4; PSA ≤ 30 ng/ml compared to no upper limit; estimated risk of lymph node involvement of < 30% compared to <40%), with only 8% of their patients having T3 disease compared to 67% in this study. In terms of treatment delivery for CHHiP, static-field IMRT was used and IGRT techniques with 3 mm tolerance were permitted although not required (was used in 30% of patients). In comparison for

BIOPROP20, rotational IMRT was used and IGRT technique with fiducial markers and 2 mm tolerance were standard for all patients.

Despite these notable differences in trial protocol between the CHHiP and BIOPROP20 studies and hence a direct comparison cannot be drawn, the acute RTOG toxicity profiles for prostate only dose painting patients who received a SIB to 68 Gy did not seem to be significantly higher than those who received homogenous prostate radiotherapy of 60 Gy/20 #(10). Bowel and bladder toxicity peaked at weeks 4 to 5 in CHHiP, whilst it peaked at weeks 4 to 6 in this study. Cumulative incidence of patients who reported RTOG G2 or worse bowel toxicity in CHHiP was 38%, compared to 6% in this study. Cumulative incidence of patients who reported RTOG G2 or worse bladder toxicity in CHHiP was 49%, compared to 55% in this study. Prevalence of RTOG G2 or worse bowel toxicity at week 18 in CHHiP was 3%, compared to 0% in this study. Prevalence of RTOG G2 or worse bladder toxicity at week 18 in CHHiP was 5%, compared to 12% in this study. Therefore, the main difference is actually reduced bowel toxicity in this study compared to CHHiP, which may be explained by the routine use of IGRT with fiducial markers and tighter set-up tolerance in the BIOPROP20 protocol than in the CHHiP protocol.

There are limitations to this study and the analysis made. Patients were encouraged to complete the EPIC forms fully, but some patients did not answer enough questions in the sexual categories to allow a score to be calculated (for instance, 23 out of 56 of all included patients did not have an EPIC sexual summary score at the Week 18 time point). This may be due to significantly reduced sexual activity as a result of the treatment, although the answer options available still allowed patients to provide an answer for this. Also, not all the symptoms/toxicity scores were performed at every time point (Figure 5-1). This was with the purpose of improving patient compliance and response rates for questionnaire completions, especially as the EPIC questionnaire is 9 pages in total. But as discussed above, it would have been of interest to have obtained EPIC data at planning, to allow differentiation between bicalutamide and radiotherapy as the cause of patient reported urinary toxicity. Also performing multiple statistical comparisons, in this case between different time points for the various EPIC subcategories, can result in erroneous inferences (Table 5-1). However, the result of these comparisons are expected e.g. sexual toxicity would primarily be from bicalutamide.

Generally, it is preferable to obtain both patient reported and clinician reported outcomes, given that patient reported outcomes may detect toxicities more reliably that clinician reported outcomes(218, 219). But there are some considerations to be made. For patient reported questionnaires, patients may feel obliged to report less severe toxicities. For clinician reported questionnaires, reporting of symptomatic adverse events can be unreliable and clinicians often under-report the incidence and severity of symptoms/toxicities compared to patients(220). However, although not directly comparable, the peak toxicities of the CTCAE/RTOG and the EPIC scores are in general agreement in this study.

Overall, the phase II BIOPROP20 study aimed to recruit 50 patients at both Clatterbridge Cancer Centre and Velindre Cancer Centre in order to rule out an upper limit of G≥2 toxicity of 25% (with power of 87.8%). According to the Fleming-A'Hern design, if 8 or more patients developed G≥2 toxicity at week 18, the null hypothesis will not be rejected (i.e. the 25% upper limit is not ruled out). Although the analysis of this chapter consisted of the 51 patients treated with prostate only dose painting radiotherapy at Clatterbridge Cancer Centre alone, 7 patients had G≥2 urinary toxicity at week 18 (CTCAE) and no patients had G≥2 bowel toxicity. The final statistical analysis for the whole of the BIOPROP20 study is currently pending.

5.6 Conclusion

Acute toxicity of moderately hypofractionated dose painting radiotherapy for prostate adenocarcinoma appears to be well tolerated and clinically acceptable.

6 Late toxicity of moderately hypofractionated dose painting radiotherapy for prostate adenocarcinoma

6.1 Introduction

Although the previous chapters show that dose painting radiotherapy is feasible and appears well tolerated in the acute setting, longer term follow up is required to assess late toxicity. This is important given that prognosis is generally good for locally advanced prostate cancer, with patients often surviving for years even with metastatic disease as a result of the increasing number of effective palliative treatment options available. For instance in a recent STAMPEDE paper which reported outcomes from the up-front addition of abiraterone and docetaxel for patients with either high risk non-metastatic disease or metastatic disease, median survival had not been reached despite a median follow up of 4 years(221).

Total follow up of patients within the BIOPROP20 study was for 2 years. For the Clatterbridge Cancer Centre patients, I (together with Dr Syndikus) reviewed patients up to their 2 year follow up time point. I have collated and analysed the late toxicity data.

6.2 Aims

- To determine the late toxicities of moderately hypofractionated dose painting radiotherapy for prostate adenocarcinoma with 60 Gy in 20 # over 4 weeks and a SIB of up to 68 Gy.

6.3 Methods

Patients were reviewed at 6 months, 12 months, 18 months and 24 months following commencement of radiotherapy. At all of these time points, PSA levels, CTCAE toxicity score, RTOG toxicity score, and IPSS scores were collected. At the 24 months follow up, additional

data were collected for physical examination and performance status. Acceptable time intervals for assessments to be performed were within 3 months of the expected date of completion (as per the CHHiP protocol).

The toxicity scores were analysed and presented as per Chapter 5. For RTOG cumulative incidence graphs, the late toxicity time frame was from month 6 to month 24. After the last patient had reached 24 months follow up, data on survival and PSA relapse at the latest follow up were collected for all patients.

6.4 Results

Of the 51 patients who received dose painting radiotherapy to the prostate alone, one had died of myocardial infarction before 2 year follow up was reached (his last PSA was 0.1 at month 18, and he was still on hormone therapy with no evidence of disease recurrence). At 2 year follow up, 6 of the 50 surviving patients were on adjuvant hormone therapy (12%) and 1 had biochemical relapse (2%) with PSMA scan showing local as well as distant metastatic disease.

Of the 5 patients who received dose painting radiotherapy to the prostate and pelvic lymph nodes, all were alive at 2 year follow up, at which point 3 patients were on adjuvant hormone therapy (60%) and none had biochemical relapse (0%).

6.4.1 CTCAE v4.0

All patients had CTCAE assessments at each of the four time points except the patient who had assessments at three time points and died before 2 year follow up (203 assessments in total for the 'prostate only' group, and 20 assessments in total for the 'prostate and pelvic lymph node' group).

For the 'prostate only' group (Figures 6-1 to 6-3):

- **Late urinary toxicity** was generally static without significant change from month 6 to month 24 follow up. G2 toxicity was reported for 6% of patients at month 24. No patients had G3 urinary toxicity.
- **Late bowel toxicity** was generally low. G2 toxicity was reported for 2% at month 24. No patients had G3 bowel toxicity.
- **Other than urinary or bowel categories,** toxicities were rare and those reported were gynaecomastia and groin pain**.**

For the 'prostate and pelvic lymph node' group (Figures 6-8 to 6-10):

- **Late urinary toxicity** of G1 was experienced by 60% but no patients had G2 at month 24.
- **Late bowel toxicity** of G1 was experienced by 40% but no patients had G2 at month 24.
- **Other than urinary or bowel toxicity,** the only toxicity noted was G2 mood changes in one patient.

6.4.2 RTOG

All patients had RTOG assessments at each of the four time points except the patient who died before 2 year follow up (203 assessments in total for 'prostate only' group, and 20 assessments in total for the 'prostate and pelvic lymph node' group).

For the 'prostate only' group (Figures 6-4 to 6-5):

- **Late urinary toxicity** was generally static. G2 toxicity was reported for 6% of patients at month 24. No patients had G3 toxicity.
- **Late bowel toxicity** was rare with G2 toxicity reported for only 2%. No patients had G3 bowel toxicity.

For the 'prostate and pelvic lymph node' group (Figure 6-11 to 6-12):

- **Late urinary toxicity** of G1 was experienced by 40%, but no patients had G2 at month 24.

- **Late bowel toxicity** of G1 was experienced by 20%, but no patients had G2 at month 24.

6.4.3 IPSS

All patients completed the IPSS score except one 'prostate only' patient at month 6, one 'prostate only' patient at month 18, and the patient who had died before 2 year follow up (201 assessments in total for the 'prostate only' group, and 20 assessment in total for the 'prostate and pelvic lymph node' group).

For the IPSS QoL question, one patient did not submit a score at month 6, two patients at month 18, and two patients (including the patient that had died) at month 24. These were all patients in the 'prostate only' group. There was no missing data in the 'prostate and pelvic lymph node' group (therefore 199 assessments in total for the 'prostate only' group and 20 assessments in total for the 'prostate and pelvic lymph node' group).

For the 'prostate only' group (Figures 6-6 to 6-7):

- IPSS scores were generally stable between month 6 and month 24 for the group as a whole, and there was no significant difference between the IPSS scores at registration and at month 24 ($p = 0.26$; Wilcoxon signed rank test). This was similar for the IPSS QOL scores also ($p = 0.26$; Wilcoxon signed rank test).

For the 'prostate and pelvic lymph node' group (Figures 6-13 to 6-14):

- There appears to be a trend for a consistent rise in IPSS score for the whole group between month 6 and month 24 but there was no significant difference between the IPSS score at registration and at month 24 ($p = 0.07$; Wilcoxon signed rank test). IPSS QOL scores appeared stable between month 6 and month 24, and there was no difference at all between the IPSS QOL scores at registration and at month 24 ($p = 1.00$; Wilcoxon signed rank test).

6.4.4 Performance status

All patients had a PS assessment at registration and at month 24 except for the patient who died before 2 year follow up (101 assessments in total for the 'prostate only' group, and 10 assessments in total for the 'prostate and pelvic lymph node' group).

In the 'prostate only' group, most patient remained at PS 0 (38 out of 50), 8 patients (16%) had a deterioration in PS, but there was no significant change in PS between registration and month 24 ($p = 0.05$; Wilcoxon signed rank test)(Table 6-1). In the 'prostate and pelvic lymph node' group, all patients remained at PS 0 ($p = 1.00$; Wilcoxon signed rank test)(Table 6-2).

6.4.5 Treatment outcome

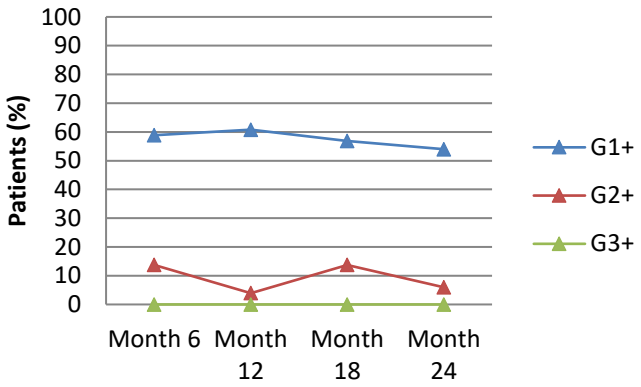
After the last living patient had reached 2 year follow up, survival and PSA data at the last follow up for each patient was collected on 30th November 2018. Median follow up was 36 months (range 20 to 49 months, including the patient who died before 2 year follow up).

Of the 56 patients, 3 (all had prostate only dose painting radiotherapy) had died of causes unrelated to the prostate adenocarcinoma (myocardial infarction and oesophageal adenocarcinoma); they did not have PSA relapse at their last follow up (Figure 6-15). Two patients had PSA relapse (by Phoenix criteria), both of which were following completion of adjuvant hormone therapy (Figure 6-16). One of these patients (he had received prostate and lymph node treatment) was found to have bone metastasis for which he was recommenced on hormone therapy together with zolendronic acid. The other patient (he had received prostate only treatment) was found to have bone and nodal metastasis, and was initially recommenced on hormone therapy alone but subsequently progressed and so received docetaxel, palliative radiotherapy, and now starting enzalutamide. Of those patients without PSA relapse as of November 2018, median PSA was 0.21 (range 0.05 to 1.6).

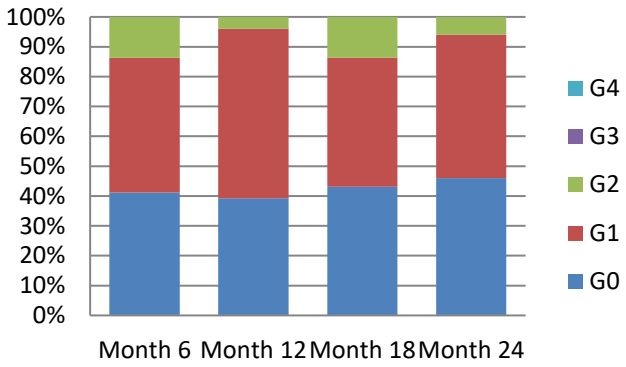
Figure 6-1 Late urinary and lower GI CTCAE toxicity by time point for prostate only radiotherapy

Prevalence (A) and distribution (B) of urinary toxicity grades. Prevalence (C) and distribution (D) of lower GI toxicity grades

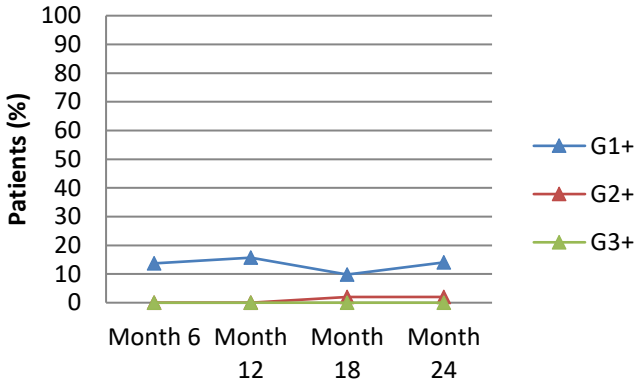
A



B



C



D

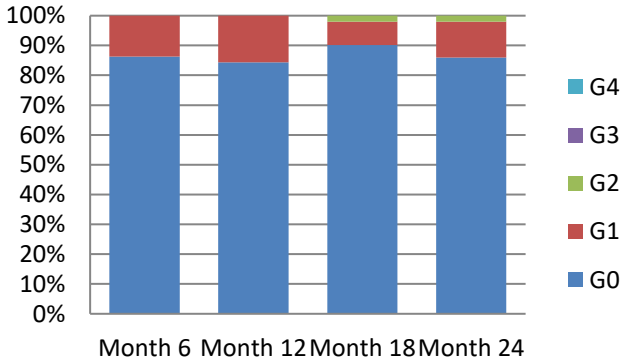
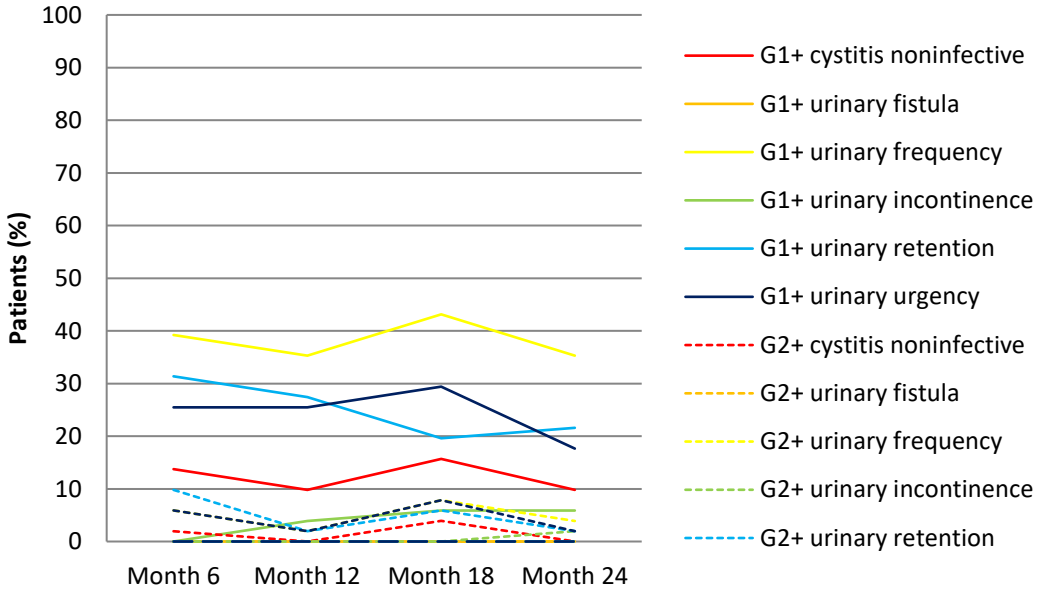


Figure 6-2 Prevalence of specific late CTCAE toxicities by time point for prostate only radiotherapy
Prevalence of late CTCAE urinary toxicities (A) and lower GI toxicities (B)

A



B

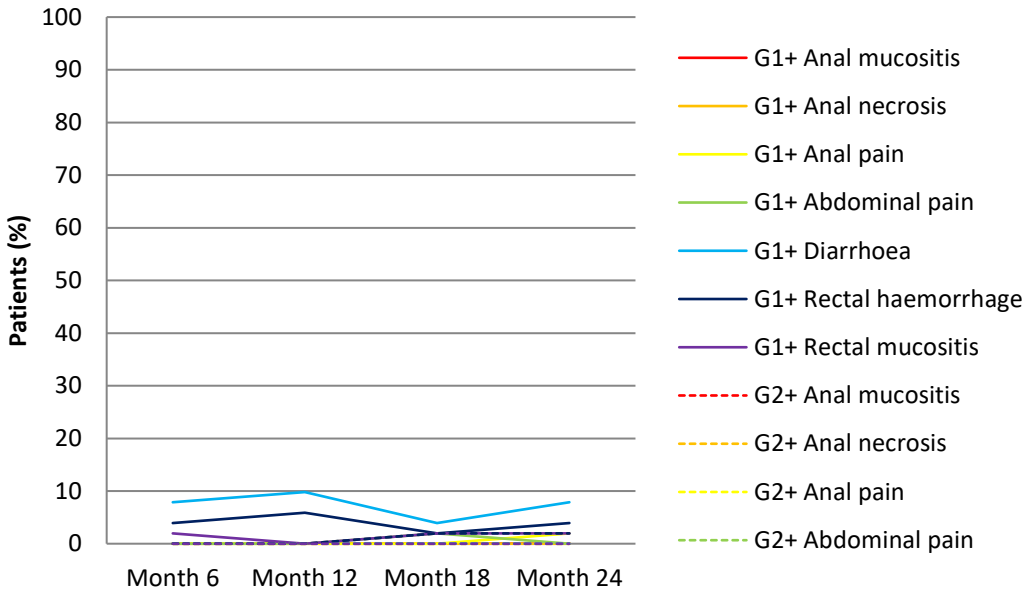
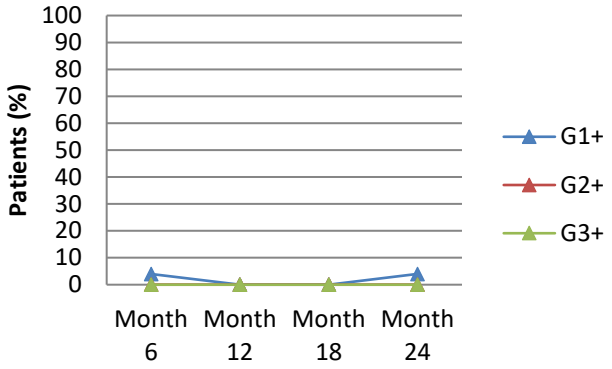


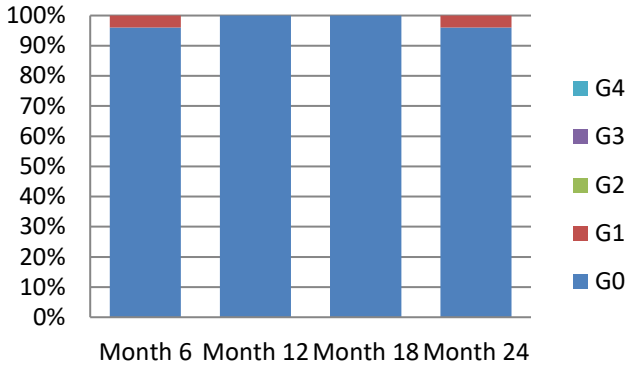
Figure 6-3 Other late CTCAE toxicities (not urinary or lower GI) by time point for prostate only radiotherapy

Prevalence of late CTCAE toxicities (A), distribution of grades (B), and prevalence of specific CTCAE (C)

A



B



C

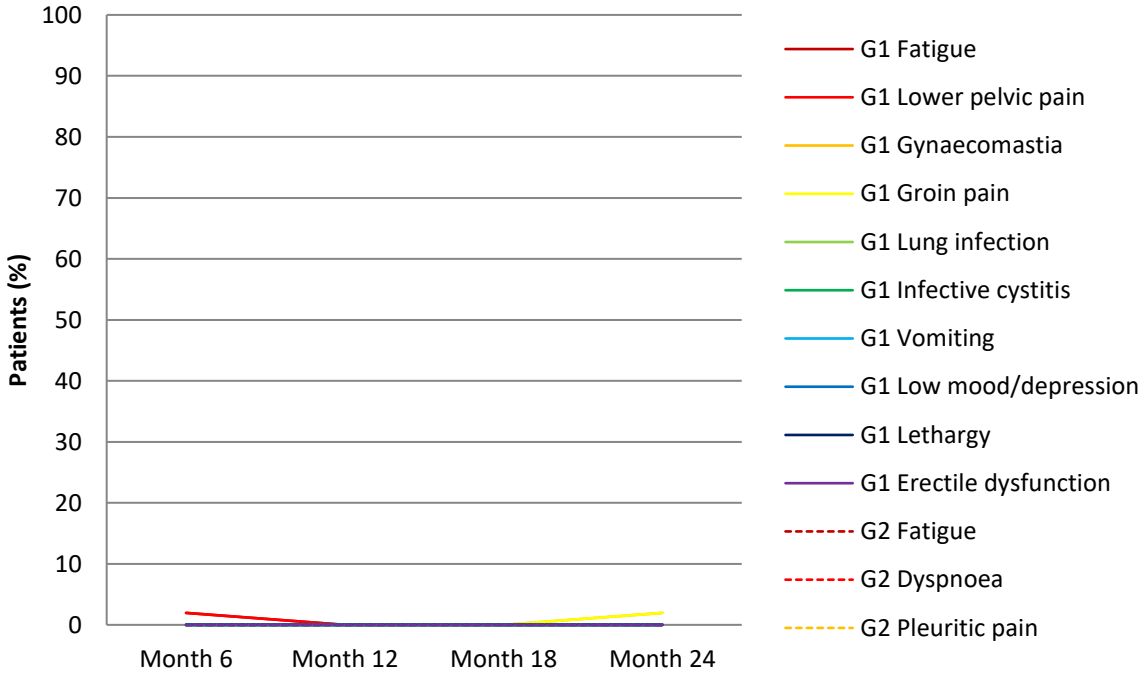
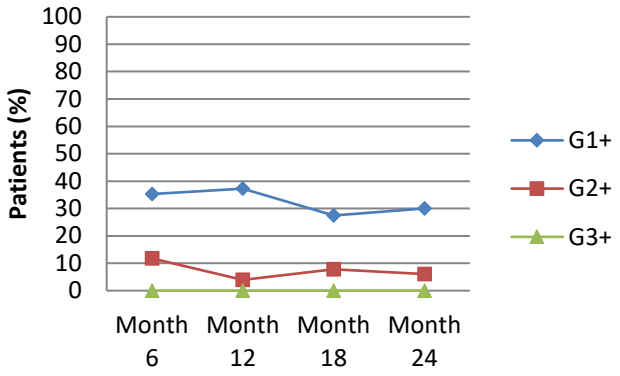


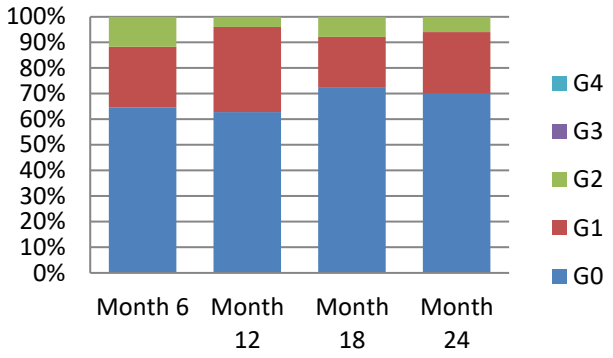
Figure 6-4 Late RTOG toxicity by time point for prostate only radiotherapy

Prevalence (A) and distribution (B) of urinary toxicity grades. Prevalence (C) and distribution (D) of lower GI toxicity grades

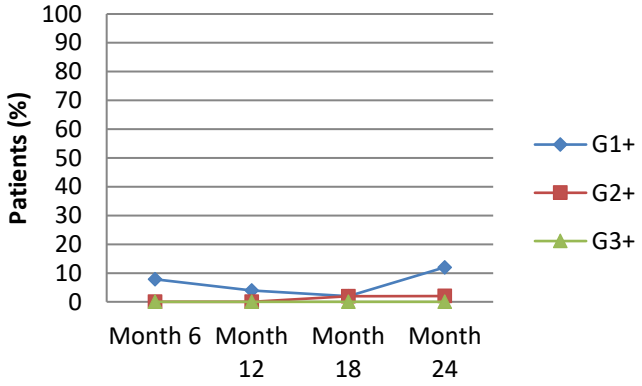
A



B



C



D

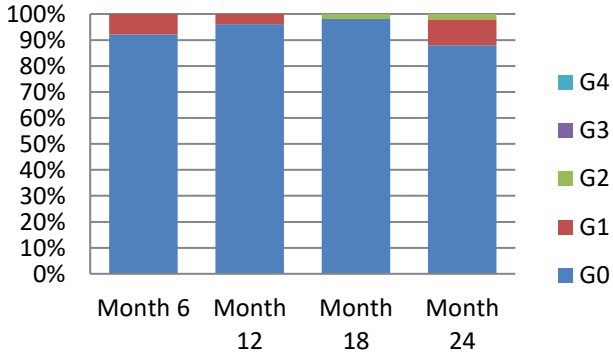
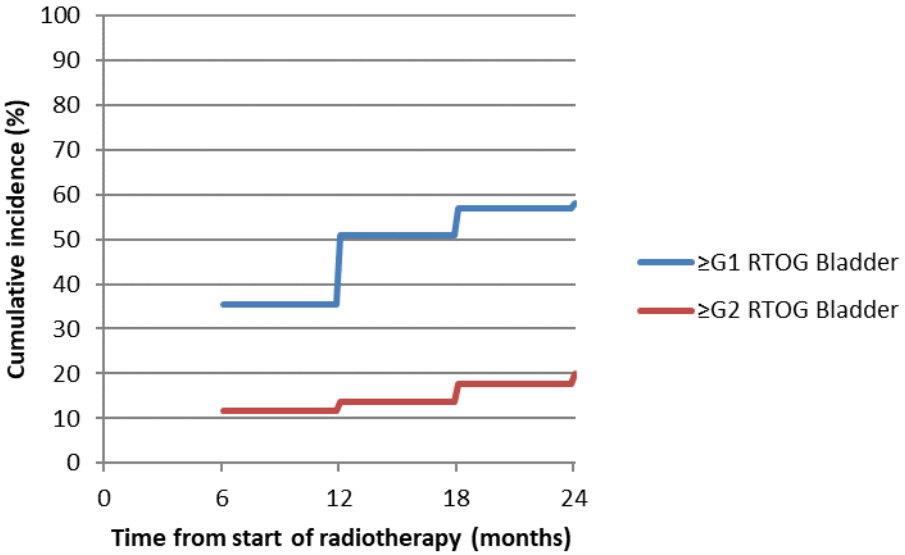


Figure 6-5 Cumulative incidence of late RTOG toxicity by time point for prostate only radiotherapy
Cumulative incidence of urinary toxicity (A) and lower GI toxicity (B)

A



B

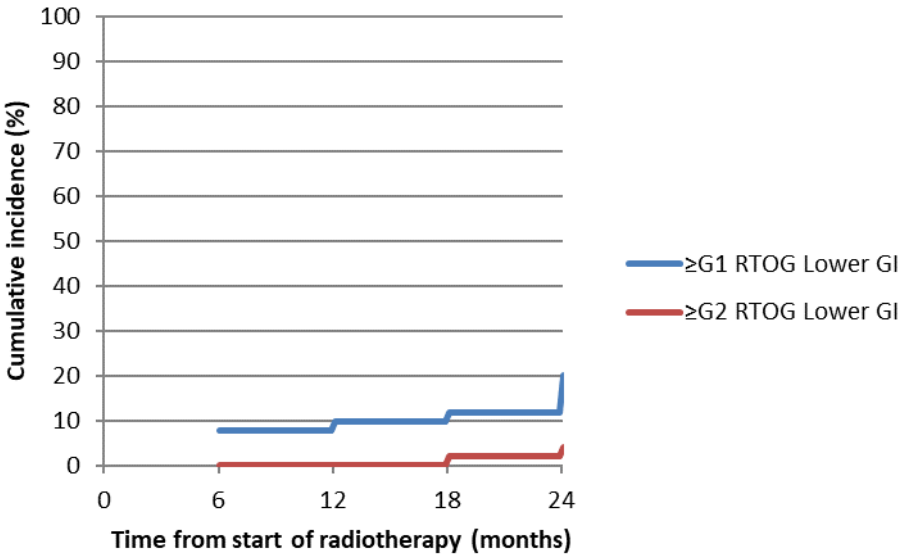
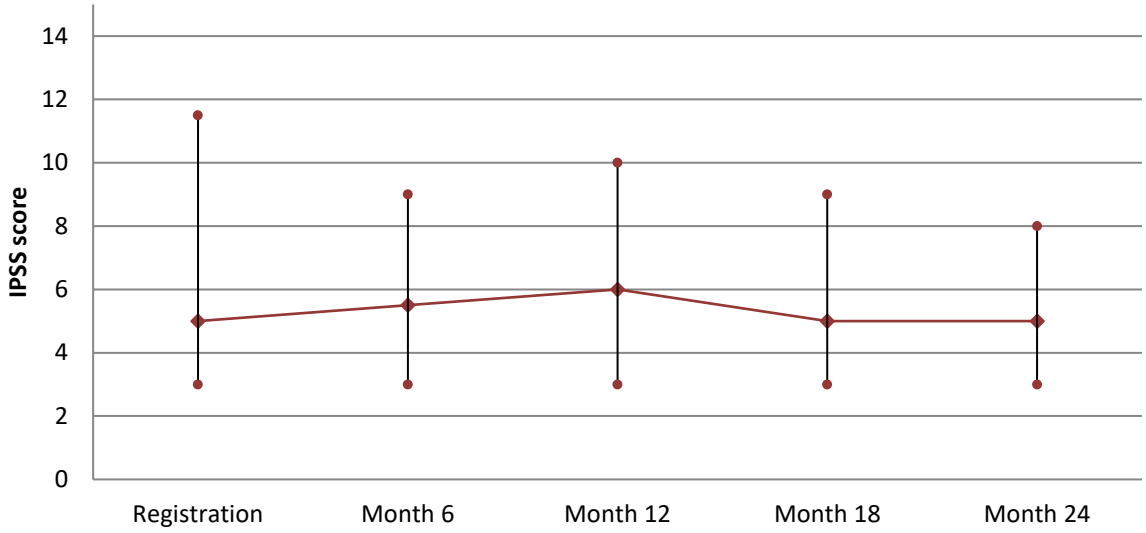


Figure 6-6 IPSS score (A) and IPSS Quality of Life score (B) between registration and month 24 for prostate only radiotherapy

Upper quartile, median, and lower quartile are plotted

A



B

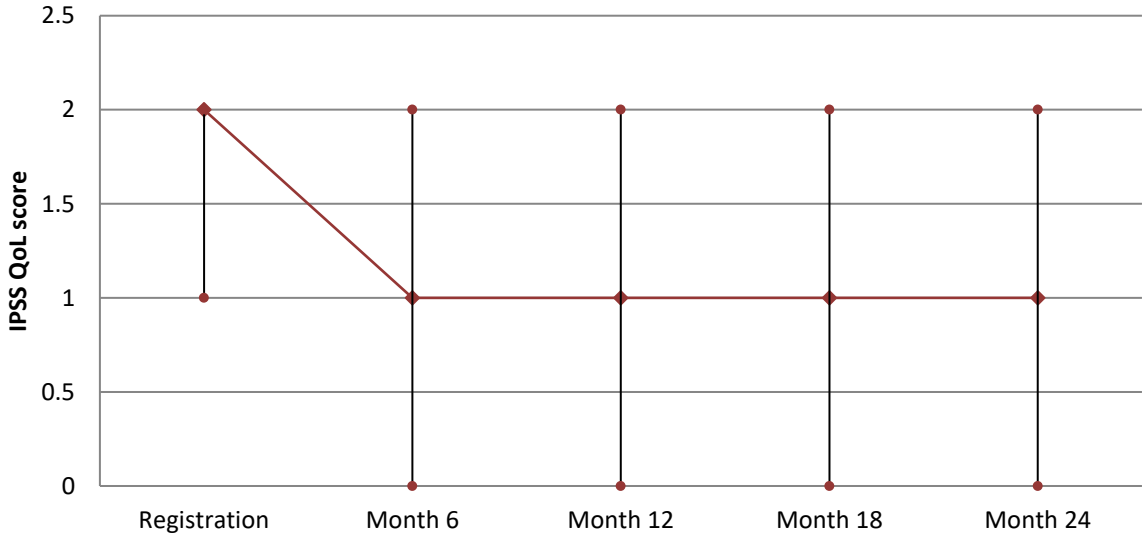
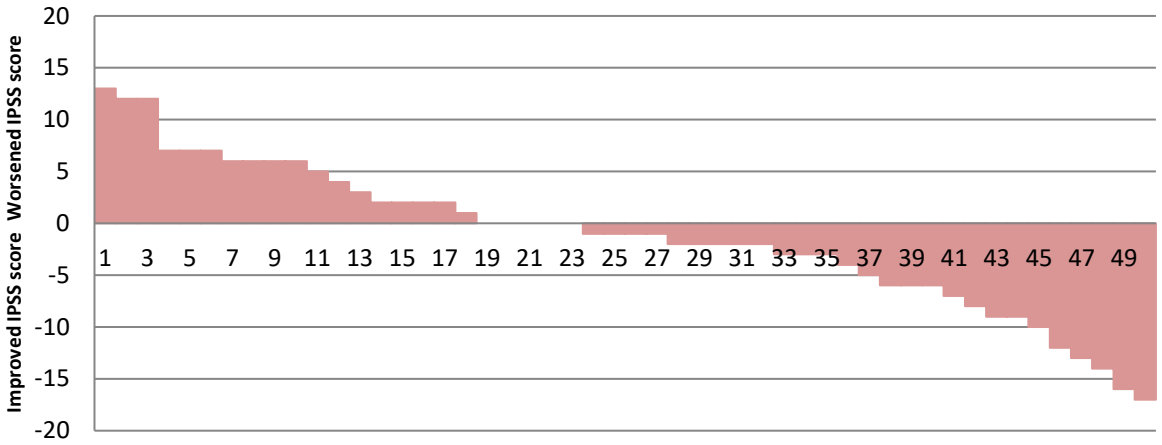


Figure 6-7 Change in IPSS for prostate only radiotherapy between registration and month 24

Waterfall plot of change in IPSS score (A) and IPSS Quality of Life score (B)

A



B

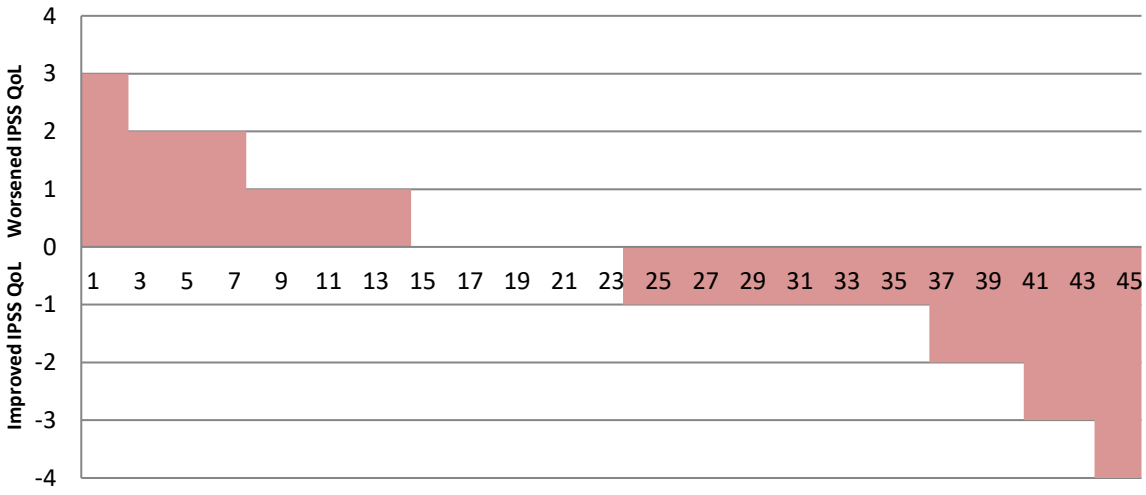
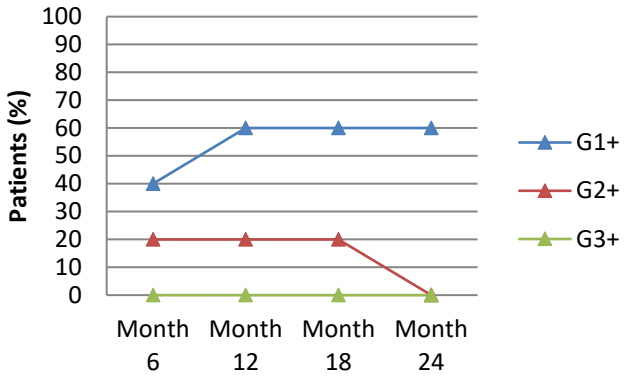


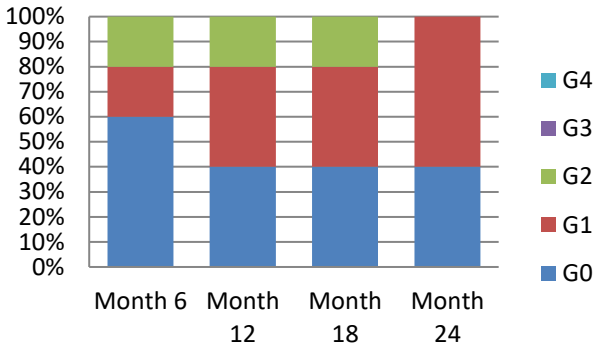
Figure 6-8 Late urinary and lower GI CTCAE toxicity by time point for prostate and lymph node radiotherapy

Prevalence (A) and distribution (B) of urinary toxicity grades. Prevalence (C) and distribution (D) of lower GI toxicity grades

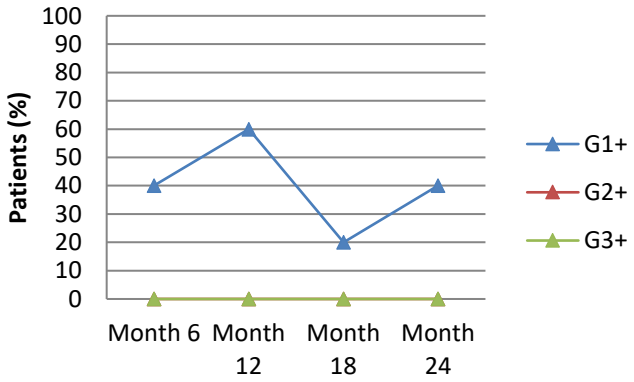
A



B



C



D

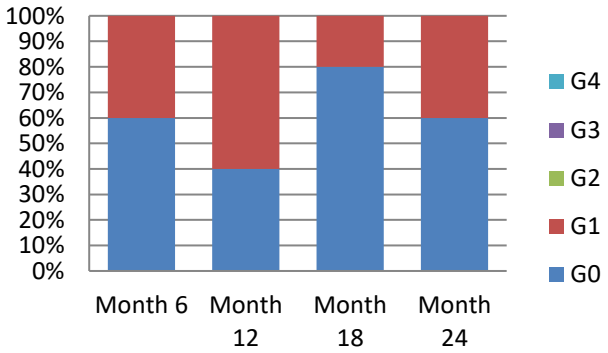
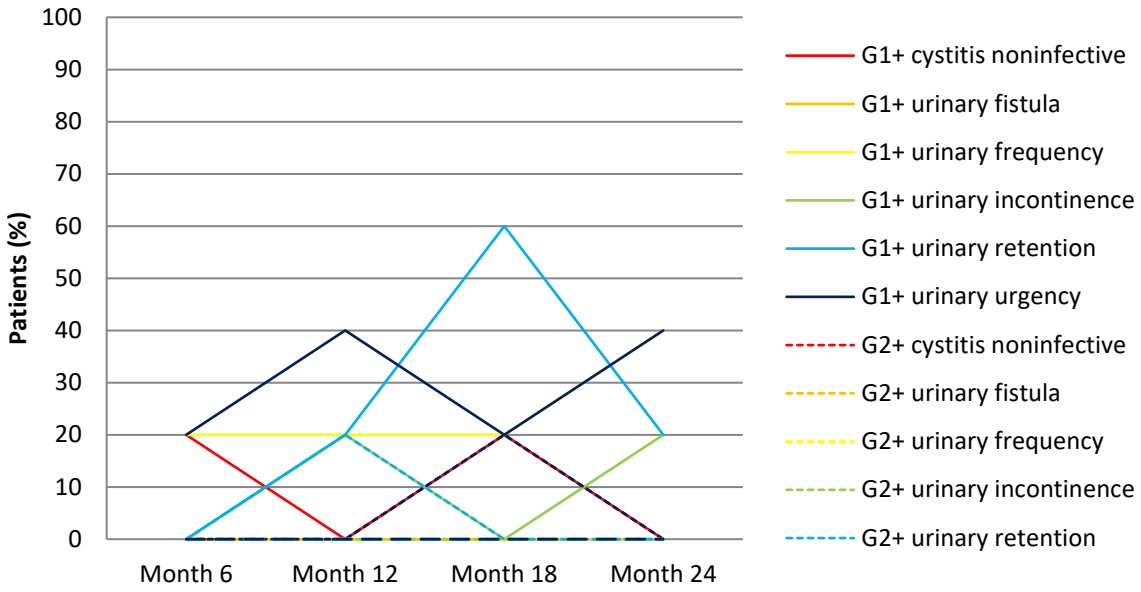


Figure 6-9 Prevalence of specific late CTCAE toxicities by time point for prostate and lymph node radiotherapy

Prevalence of late CTCAE urinary toxicities (A) and lower GI toxicities (B)

A



B

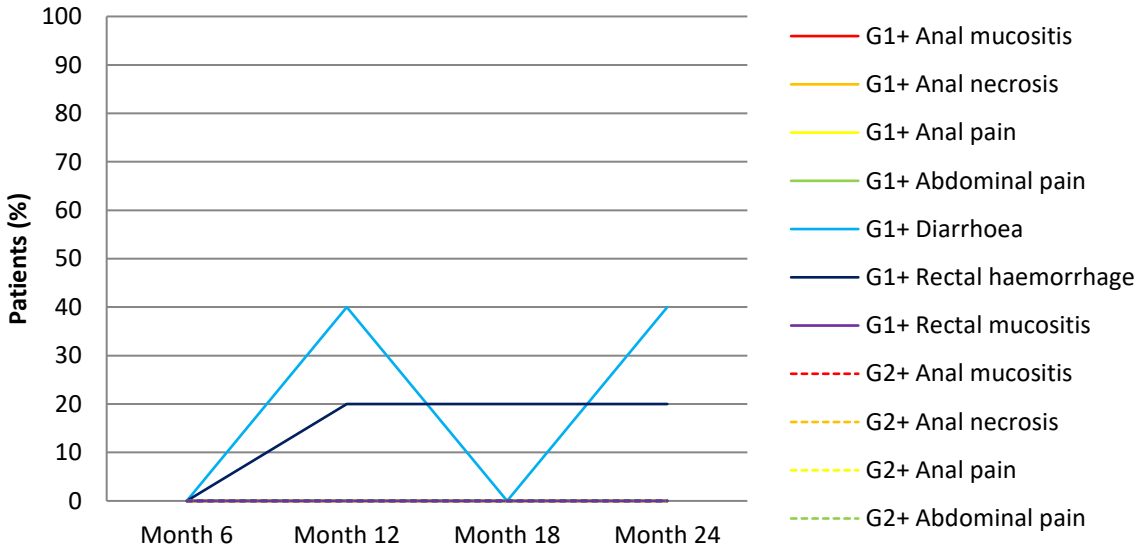
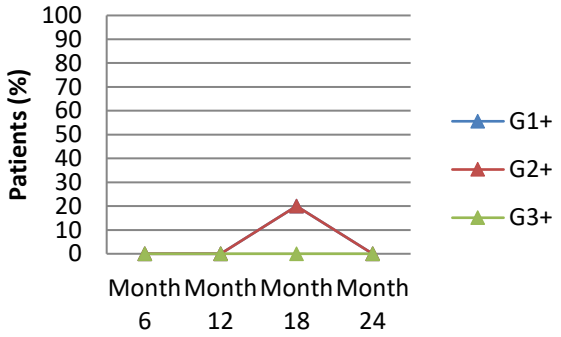


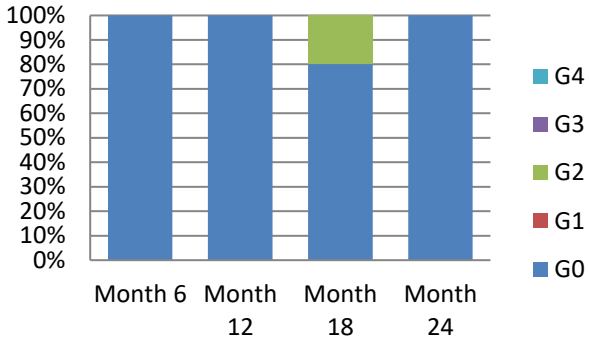
Figure 6-10 Other late CTCAE toxicities (not urinary or lower GI) by time point for prostate and lymph node radiotherapy

Prevalence of late CTCAE toxicities (A), distribution of grades (B), and prevalence of specific CTCAE (C)

A



B



C

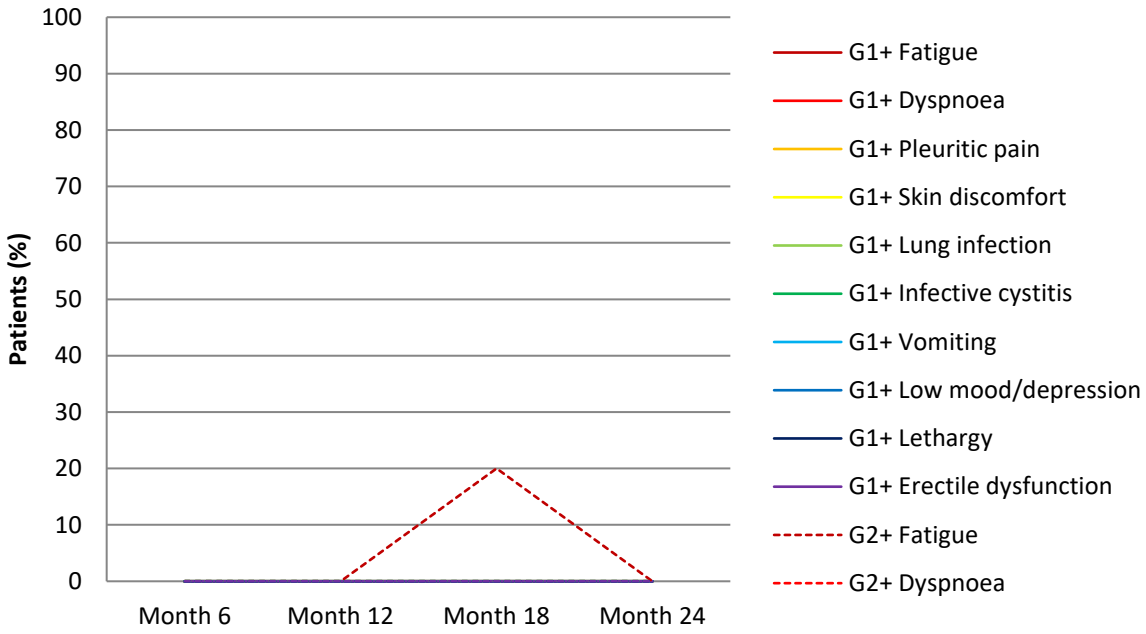
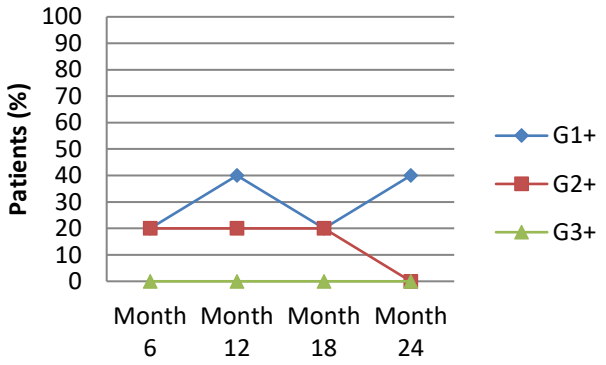


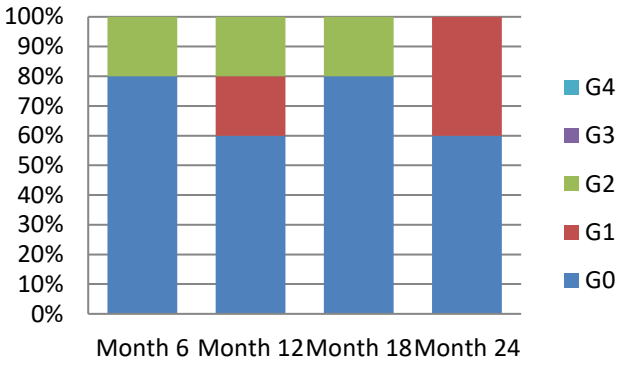
Figure 6-11 Late RTOG toxicity by time point for prostate and lymph node radiotherapy

Prevalence (A) and distribution (B) of urinary toxicity grades. Prevalence (C) and distribution (D) of lower GI toxicity grades

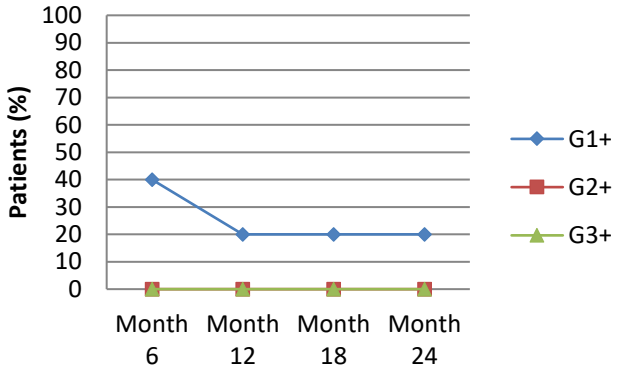
A



B



C



D

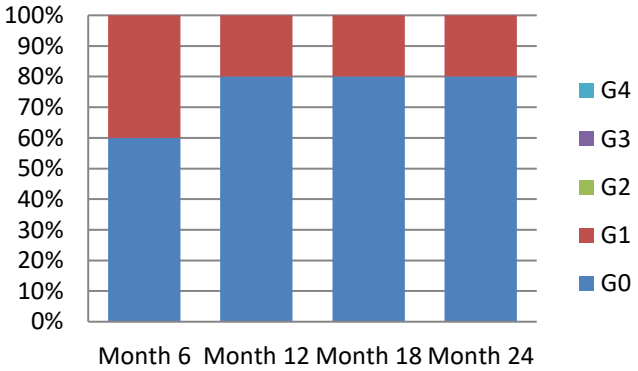
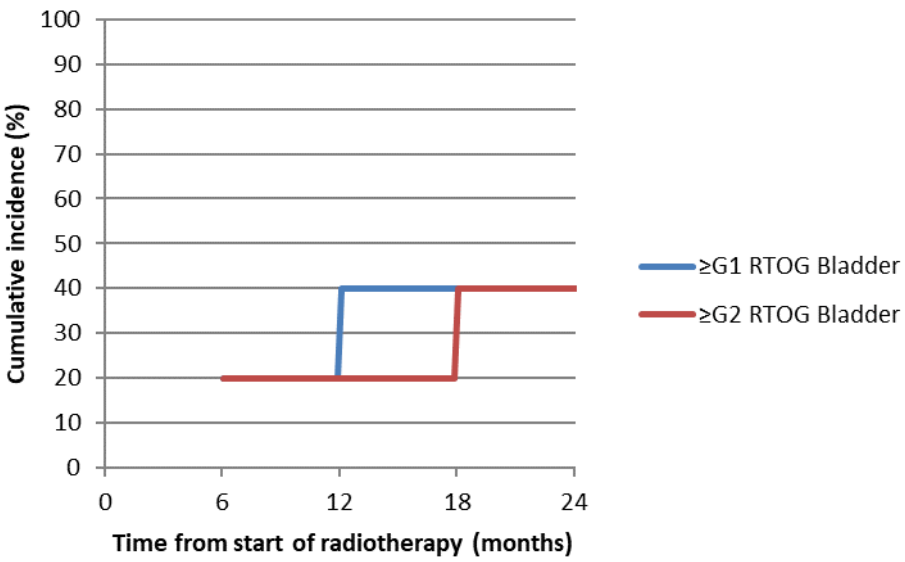


Figure 6-12 Cumulative incidence of late RTOG toxicity by time point for prostate and lymph node radiotherapy

Cumulative incidence of urinary toxicity (A) and lower GI toxicity (B)

A



B

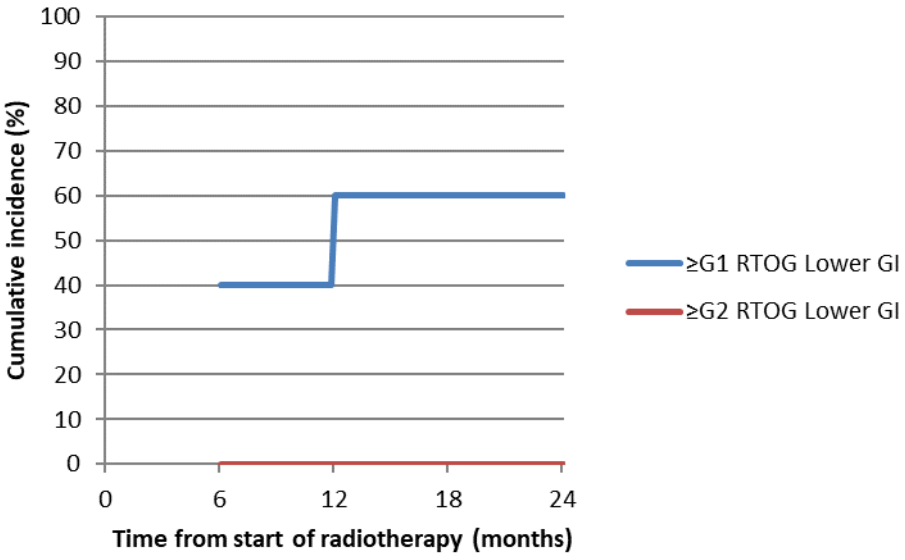
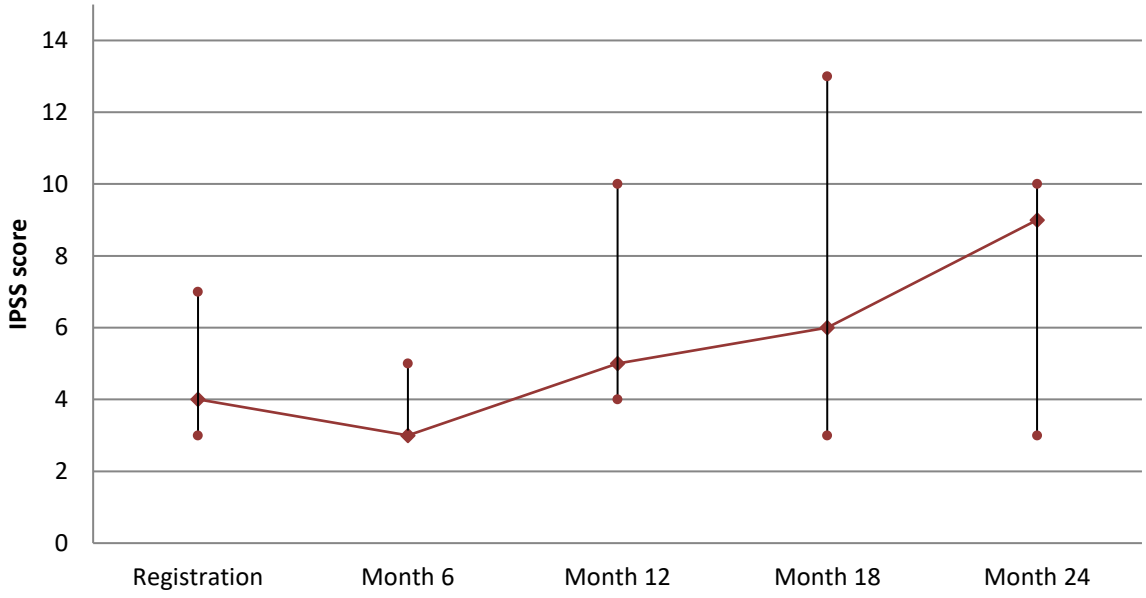


Figure 6-13 IPSS score (A) and IPSS Quality of Life score (B) between registration and month 24 for prostate and lymph node radiotherapy

Upper quartile, median, and lower quartile are plotted

A



B

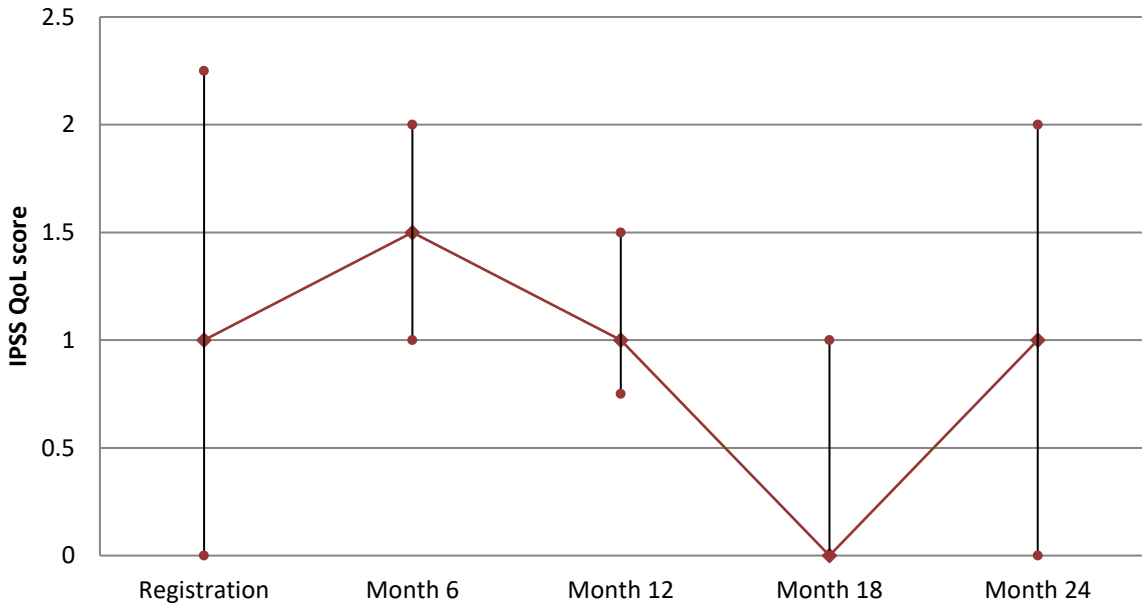
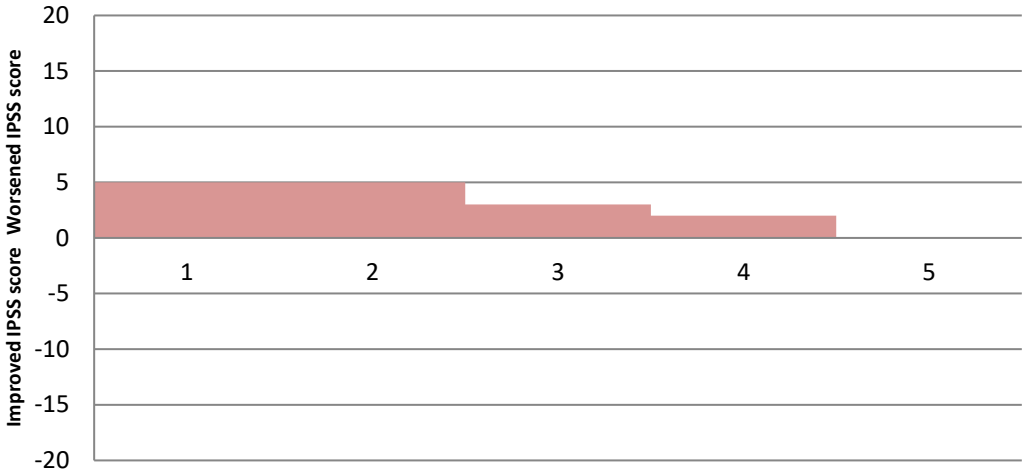


Figure 6-14 Change in IPSS for prostate and lymph node radiotherapy between registration and month 24

Waterfall plot of change in IPSS score (A) and IPSS Quality of Life score (B)

A



B

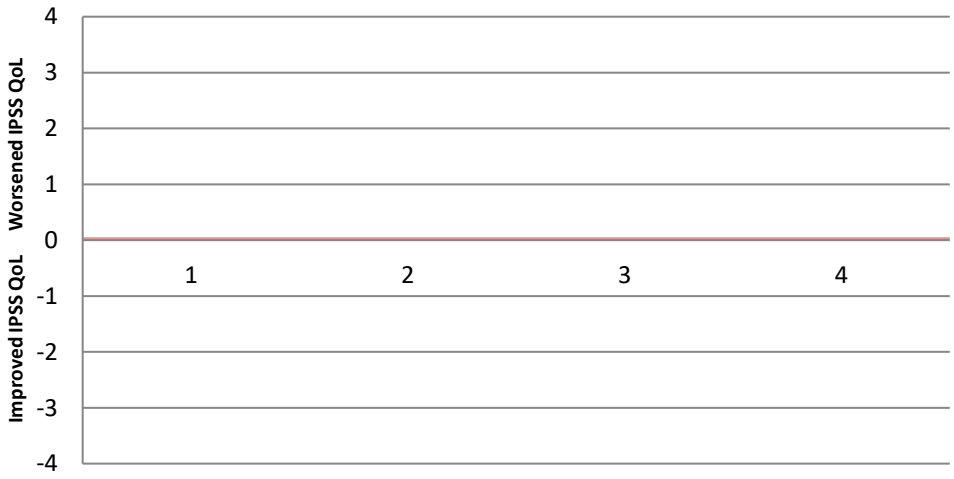


Table 6-1 Performance status (PS) within the prostate only radiotherapy group (to month 24)
Prevalence at registration and month 24 (A) and change in PS between the time points (B)

A

	Registration		Month 24			
	PS 0	**PS 1**	**PS 0**	**PS 1**	**PS 2**	**Unanswered**
No. of pts	**46**	**5**	**40**	**8**	**2**	**1**

B

Change in PS from Registration to Month 24	**No. of patients**
PS 0 to 0	**38**
PS 0 to 1	**6**
PS 0 to 2	**1**
PS 1 to 0	**2**
PS 1 to 1	**2**
PS 1 to 2	**1**
PS 0 to unanswered	**1**

Table 6-2 Performance status (PS) within the prostate and lymph node radiotherapy group (to month 24)

Prevalence at registration and month 24 (A) and change in PS between the time points (B)

A

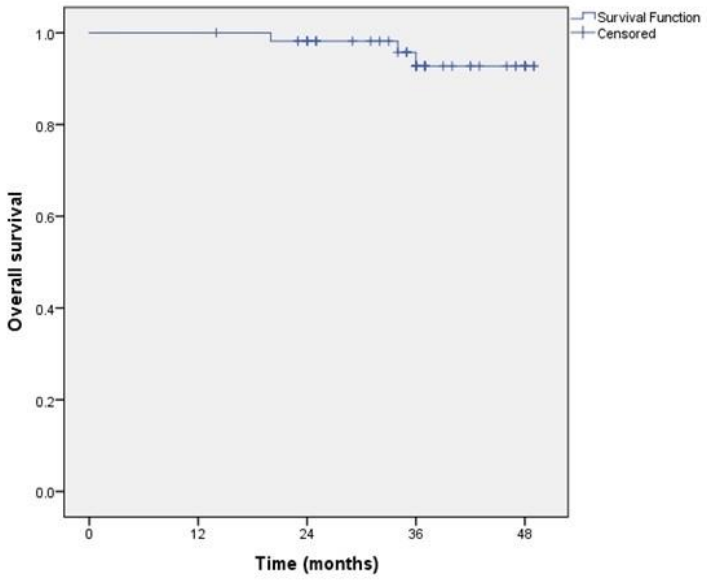
	Registration		Month 24	
	PS 0	**PS 1**	**PS 0**	**PS 1**
No. of pts	**5**	**0**	**5**	**0**

B

Change in PS from Registration to Month 24	**No. of patients**
PS 0 to 0	**5**
PS 0 to 1	**0**
PS 1 to 0	**0**
PS 1 to 1	**0**

Figure 6-15 Kaplan Meier Curve for Overall Survival for all 56 patients

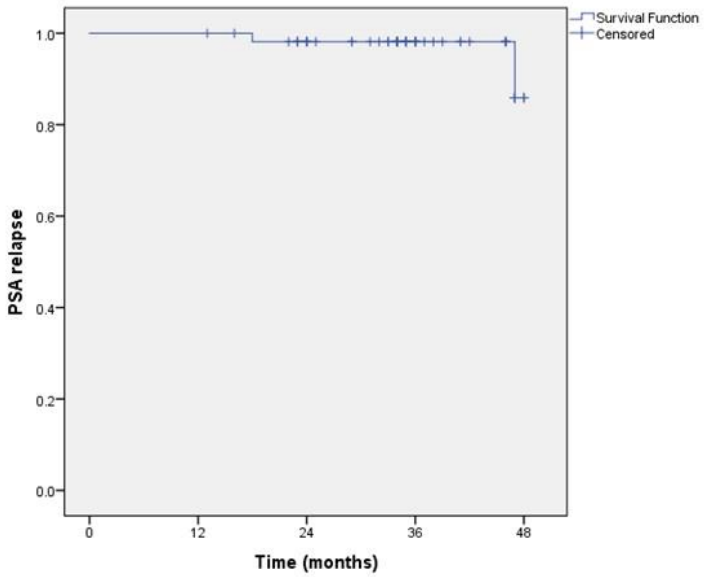
Three patients had died (at 20 months, 34 months, and 36 months)



Numbers at risk	55	55	47	22	2

Figure 6-16 Kaplan Meier curve for PSA relapse (by Phoenix criteria) for all 56 patients

Two patients had PSA relapse (at 18 months and 47 months)



Numbers at risk	55	55	44	17	1

6.5 Discussion

Treatment of clinically node-negative prostate cancer with moderately hypofractionated dose painting radiotherapy to the prostate alone was well tolerated and toxicity generally did not worsen from month 6 to month 24. Prevalence of late G≥2 urinary toxicity was around 6% and was mostly urinary frequency. Prevalence of late G≥2 bowel toxicity was around 2% and was mostly diarrhoea. Only 16% had a deterioration in performance status between registration and month 24.

Treatment of clinically node-positive prostate cancer with dose painting radiotherapy to both the prostate and pelvic lymph nodes was also well tolerated. No patients had late G≥2 urinary or bowel toxicity. The commonest urinary toxicity reported was retention and urgency, and the commonest bowel toxicity reported was diarrhoea and rectal haemorrhage. IPSS score showed an increase from month 6 to month 24 but there was no statistically significant difference between registration and month 24 (of note, an IPSS score of <12 is classed as no or mildly symptomatic only). In comparison, the IPSS QOL score was stable, and there was no deterioration in performance status between registration and month 24.

In comparison to the pilot study, the cumulative incidence of late G≥2 toxicities for prostate only dose painting radiotherapy were higher in this study for both urinary (20% vs. 7%) and bowel (4% vs. 0%) toxicities(161). This may be due to fundamental differences between the studies. The BIOPROP20 protocol offered the addition of ^{18}F choline PET/CT to aid DIL delineation whilst the pilot study did not, but this did not result in larger DILs (median 3.5 ml (range 1.2 ml to 14.9 ml) for this study vs. median 4.3 ml (range 0.46 ml to 15 ml) for the pilot study). The pilot study used a research version of Pinnacle in order to create plans radiobiologically optimised for tumour control probability and normal tissue complication probability as the first step, before re-planning in the clinical treatment planning system whilst attempting to reproduce certain planning parameters from the radiobiologically optimised plan. The mean (and range) of the maximum doses to the rectum achieved by the clinical plans in the pilot study were 56 Gy (53 to 58 Gy), whilst that of this study were 62 Gy (58 to 66 Gy). Therefore this may explain the higher bowel toxicities in this study when compared to the pilot study, although care needs to be taken when comparing outcomes from separate studies with small sample numbers.

In comparison to the CHHiP study, the prevalence of G≥2 RTOG late bladder toxicity at 2 year follow up was higher in this study (6% vs. 2%) but was similar for late bowel toxicity (2% vs. 3%)(10). According to the Fleming-A'Hern design for the BIOPROP20 study which aimed to recruit 50 patients,

if 7 or less patients developed G≥2 toxicity at 2 years, the null hypothesis will be rejected in favour of a 10% complication rate. Although the analysis of this chapter consisted of the 51 patients treated with prostate only dose painting radiotherapy at Clatterbridge Cancer Centre alone, 3 patients had G≥2 urinary toxicity at 2 years (CTCAE and RTOG) and 1 patient had G≥2 bowel toxicity (CTCAE and RTOG). The final statistical analysis for the whole of the BIOPROP20 study is currently pending.

In terms of disease control, 1 patient out of 51 patients (2%) who received prostate only dose painting radiotherapy in this study had biochemical failure by 2 years follow up, whilst 88 out of 1074 patients (8%) who received prostate only radiotherapy in the CHHiP study (60 Gy arm) had biochemical or clinical events by 5 years follow up. This suggests that disease control with dose painting is acceptable at this relatively short follow up time interval, which would be expected given that dose painting should theoretically increase disease control +/- toxicities.

6.6 Conclusion

Late toxicity (up to 2 years follow up) for moderately hypofractionated dose painting radiotherapy for prostate adenocarcinoma appears to be well tolerated and clinically acceptable.

7 Future directions

Current standard of care non-surgical treatment for intermediate and high risk localised or locally advanced prostate cancer is a combination of hormone therapy and radiotherapy, where radiotherapy involves the delivery of a homogenous dose to the whole gland irrespective of the pattern of disease within it. Modern technological advances in imaging technology allow the identification of dominant intraprostatic lesions where there is highest risk of local recurrence, and advances in radiotherapy delivery allow dose escalation to sub-volumes within the target volume. Given that whole organ dose escalation radiotherapy leads to improved biochemical control at a cost of increased toxicity, selective dose escalation by dose painting to these sub-volumes responsible for local failure may lead to improved disease control without a significant increase in toxicity.

This thesis shows that planning and delivery of moderately hypofractionated dose painting radiotherapy to the prostate appear to be both feasible and clinically acceptable with regards to toxicity. However, the data presented here are for 2 years follow up, and given that prognosis is generally good for this group of patients, longer term data is required to assess clinical outcomes including biochemical relapse free survival and overall survival, and to assess for any emergent late toxicity beyond 2 years follow up. Also only 5 patients were treated with both prostate and pelvic nodal radiotherapy, and although the results show that it is technically feasible, larger cohorts will need to be treated in order to allow conclusions to be drawn regarding toxicity.

Dose escalation by external beam radiotherapy is limited by dose to the surrounding organs. HDR brachytherapy provides an alternative method of radiation delivery and although it is an invasive procedure with the associated risks of general anaesthesia, it provides better dose conformity and can deliver higher biologically effective doses. Therefore dose painting by using a combination of external beam radiotherapy and HDR brachytherapy may offer an improved therapeutic ratio.

For radiotherapy planning, the dose descriptors of organs at risk, including bladder and rectum, are based on dose volume histograms. However, these methods lose spatial dose information, and advanced methods such as bladder and rectal dose surface maps would preserve dose distribution data. This may be more useful when assessing plans for dose

painting radiotherapy, as the heterogeneous dose distributions generated can involve focal hot spots with high dose gradients in close proximity to surrounding organs at risk.

With regards to imaging to define the dominant intraprostatic lesions, this thesis has used ^{18}F choline tracer for PET/CT imaging. With the increasing availability and utilisation of PSMA PET/CT, there is strong evidence for its use in identifying disease recurrence after definitive treatment. It would be of interest to investigate whether PSMA performs better than ^{18}F choline in localising dominant intraprostatic lesions for dose painting.

The work contained in this thesis has led to the PIVOTALboost trial which is currently underway. It is a large national multicentre randomised phase III clinical trial for dose painting radiotherapy, where patients with node negative intermediate risk (with at least 2 adverse features including maximum tumour length >6mm, ≥50% biopsy core positive and >50% involved cancer/total biopsy length) or high risk prostate cancer are randomised to prostate boost (whole prostate or focal dose escalation) and pelvic nodal radiotherapy.

8 References

1. Uk CR. Prostate cancer incidence statistics. Cancer Research UK; 2014.

2. Eigl BJ, Gleave ME, Chi KN. The future of systemic therapies for localised prostate cancer. Clin Oncol (R Coll Radiol). 2013;25(8):506-13.

3. Hoskin PJ. Radiotherapy in practice : imaging. 2012.

4. Dulaney CR, Osula DO, Yang ES, Rais-Bahrami S. Prostate Radiotherapy in the Era of Advanced Imaging and Precision Medicine. Prostate Cancer. 2016;2016:4897515.

5. Fantus RJ, Helfand BT. Germline Genetics of Prostate Cancer: Time to Incorporate Genetics into Early Detection Tools. Clin Chem. 2019;65(1):74-9.

6. Gunderson LL, Tepper JE. Clinical radiation oncology. 2016.

7. Carroll PH, Mohler JL. NCCN Guidelines Updates: Prostate Cancer and Prostate Cancer Early Detection. J Natl Compr Canc Netw. 2018;16(5S):620-3.

8. Osses DF, Roobol MJ, Schoots IG. Prediction Medicine: Biomarkers, Risk Calculators and Magnetic Resonance Imaging as Risk Stratification Tools in Prostate Cancer Diagnosis. Int J Mol Sci. 2019;20(7).

9. Cheng HH, Sokolova AO, Schaeffer EM, Small EJ, Higano CS. Germline and Somatic Mutations in Prostate Cancer for the Clinician. J Natl Compr Canc Netw. 2019;17(5):515-21.

10. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol. 2016;17(8):1047-60.

11. Kasivisvanathan V, Emberton M, Ahmed HU. Focal therapy for prostate cancer: rationale and treatment opportunities. Clin Oncol (R Coll Radiol). 2013;25(8):461-73.

12. Khoo V, Loblaw DA. Prostate cancer: current status, new developments and applications in radiotherapy. Clin Oncol (R Coll Radiol). 2013;25(8):449-50.

13. Turkbey B, Mena E, Aras O, Garvey B, Grant K, Choyke PL. Functional and molecular imaging: applications for diagnosis and staging of localised prostate cancer. Clin Oncol (R Coll Radiol). 2013;25(8):451-60.

14. Prestwich RJ, Vaidyanathan S, Scarsbrook AF. Functional Imaging Biomarkers: Potential to Guide an Individualised Approach to Radiotherapy. Clin Oncol (R Coll Radiol). 2015;27(10):588-600.

15. Khoo VS, Padhani AR, Tanner SF, Finnigan DJ, Leach MO, Dearnaley DP. Comparison of MRI with CT for the radiotherapy planning of prostate cancer: a feasibility study. Br J Radiol. 1999;72(858):590-7.

16. Rasch C, Barillot I, Remeijer P, Touw A, van Herk M, Lebesque JV. Definition of the prostate in CT and MRI: a multi-observer study. Int J Radiat Oncol Biol Phys. 1999;43(1):57-66.

17. Roach M, 3rd, Faillace-Akazawa P, Malfatti C, Holland J, Hricak H. Prostate volumes defined by magnetic resonance imaging and computerized tomographic scans for three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys. 1996;35(5):1011-8.

18. Sannazzari GL, Ragona R, Ruo Redda MG, Giglioli FR, Isolato G, Guarneri A. CT-MRI image fusion for delineation of volumes in three-dimensional conformal radiation therapy in the treatment of localized prostate cancer. Br J Radiol. 2002;75(895):603-7.

19. Sridharan S, Dal Pra A, Catton C, Bristow RG, Warde P. Locally advanced prostate cancer: current controversies and optimisation opportunities. Clin Oncol (R Coll Radiol). 2013;25(8):499-505.

20. Alonzi R. Functional Radiotherapy Targeting using Focused Dose Escalation. Clin Oncol (R Coll Radiol). 2015;27(10):601-17.

21. Padhani AR. Dynamic contrast-enhanced MRI in clinical oncology: current status and future directions. J Magn Reson Imaging. 2002;16(4):407-22.

22. Kurhanewicz J, Swanson MG, Nelson SJ, Vigneron DB. Combined magnetic resonance imaging and spectroscopic imaging approach to molecular imaging of prostate cancer. J Magn Reson Imaging. 2002;16(4):451-63.

23. Barentsz JO, Weinreb JC, Verma S, Thoeny HC, Tempany CM, Shtern F, et al. Synopsis of the PI-RADS v2 Guidelines for Multiparametric Prostate Magnetic Resonance Imaging and Recommendations for Use. Eur Urol. 2016;69(1):41-9.

24. Vargas HA, Hotker AM, Goldman DA, Moskowitz CS, Gondo T, Matsumoto K, et al. Updated prostate imaging reporting and data system (PIRADS v2) recommendations for the detection of clinically significant prostate cancer using multiparametric MRI: critical evaluation using whole-mount pathology as standard of reference. Eur Radiol. 2016;26(6):1606-12.

25. von Eyben FE, Kiljunen T, Kangasmaki A, Kairemo K, von Eyben R, Joensuu T. Radiotherapy Boost for the Dominant Intraprostatic Cancer Lesion-A Systematic Review and Meta-Analysis. Clin Genitourin Cancer. 2016;14(3):189-97.

26. Perna L, Fiorino C, Cozzarini C, Broggi S, Cattaneo GM, De Cobelli F, et al. Sparing the penile bulb in the radical irradiation of clinically localised prostate carcinoma: A comparison between MRI and CT prostatic apex definition in 3DCRT, Linac-IMRT and Helical Tomotherapy. Radiother Oncol. 2009;93(1):57-63.

27. Mazzola R, Fersino S, Fiorentino A, Ricchetti F, Giaj Levra N, Di Paola G, et al. The impact of prostate gland dimension in genitourinary toxicity after definitive prostate cancer treatment with moderate hypofractionation and volumetric modulated arc radiation therapy. Clin Transl Oncol. 2016;18(3):317-21.

28. Villeirs GM, Van Vaerenbergh K, Vakaet L, Bral S, Claus F, De Neve WJ, et al. Interobserver delineation variation using CT versus combined CT + MRI in intensity-modulated radiotherapy for prostate cancer. Strahlenther Onkol. 2005;181(7):424-30.

29. Parker CC, Damyanovich A, Haycocks T, Haider M, Bayley A, Catton CN. Magnetic resonance imaging in the radiation treatment planning of localized prostate cancer using intra-prostatic fiducial markers for computed tomography co-registration. Radiother Oncol. 2003;66(2):217-24.

30. Zamboglou C, Drendel V, Jilg CA, Rischke HC, Beck TI, Schultze-Seemann W, et al. Comparison of (68)Ga-HBED-CC PSMA-PET/CT and multiparametric MRI for gross tumour volume detection in patients with primary prostate cancer based on slice by slice comparison with histopathology. Theranostics. 2017;7(1):228-37.

31. Groenendaal G, Moman MR, Korporaal JG, van Diest PJ, van Vulpen M, Philippens ME, et al. Validation of functional imaging with pathology for tumor delineation in the prostate. Radiother Oncol. 2010;94(2):145-50.

32. Fortuin A, Rooij M, Zamecnik P, Haberkorn U, Barentsz J. Molecular and functional imaging for detection of lymph node metastases in prostate cancer. Int J Mol Sci. 2013;14(7):13842-75.

33. Chan J, Syndikus I, Mahmood S, Bell L, Vinjamuri S. Is choline PET useful for identifying intraprostatic tumour lesions? A literature review. Nucl Med Commun. 2015;36(9):871-80.

34. Roach PJ, Francis R, Emmett L, Hsiao E, Kneebone A, Hruby G, et al. The Impact of (68)Ga-PSMA PET/CT on Management Intent in Prostate Cancer: Results of an Australian Prospective Multicenter Study. J Nucl Med. 2018;59(1):82-8.

35. Zschaeck S, Lohaus F, Beck M, Habl G, Kroeze S, Zamboglou C, et al. PSMA-PET based radiotherapy: a review of initial experiences, survey on current practice and future perspectives. Radiat Oncol. 2018;13(1):90.

36. Eiber M, Weirich G, Holzapfel K, Souvatzoglou M, Haller B, Rauscher I, et al. Simultaneous (68)Ga-PSMA HBED-CC PET/MRI Improves the Localization of Primary Prostate Cancer. Eur Urol. 2016;70(5):829-36.

37. Zamboglou C, Thomann B, Koubar K, Bronsert P, Krauss T, Rischke HC, et al. Focal dose escalation for prostate cancer using (68)Ga-HBED-CC PSMA PET/CT and MRI: a planning study based on histology reference. Radiat Oncol. 2018;13(1):81.

38. Afaq A, Gleeson F, Scarsbrook A, Bradley K, Subesinghe M, Macpherson R, et al. UK guidelines on 18F-fluciclovine PET/CT in prostate cancer imaging. Nucl Med Commun. 2019.

39. Van den Bergh L, Koole M, Isebaert S, Joniau S, Deroose CM, Oyen R, et al. Is there an additional value of (1)(1)C-choline PET-CT to T2-weighted MRI images in the localization of intraprostatic tumor nodules? Int J Radiat Oncol Biol Phys. 2012;83(5):1486-92.

40. Souvatzoglou M, Weirich G, Schwarzenboeck S, Maurer T, Schuster T, Bundschuh RA, et al. The sensitivity of [11C]choline PET/CT to localize prostate cancer depends on the tumor configuration. Clin Cancer Res. 2011;17(11):3751-9.

41. Bundschuh RA, Wendl CM, Weirich G, Eiber M, Souvatzoglou M, Treiber U, et al. Tumour volume delineation in prostate cancer assessed by [11C]choline PET/CT: validation with surgical specimens. Eur J Nucl Med Mol Imaging. 2013;40(6):824-31.

42. Giovacchini G, Picchio M, Coradeschi E, Scattoni V, Bettinardi V, Cozzarini C, et al. [(11)C]choline uptake with PET/CT for the initial diagnosis of prostate cancer: relation to PSA levels, tumour stage and anti-androgenic therapy. European journal of nuclear medicine and molecular imaging. 2008;35(6):1065-73.

43. Farsad M, Schiavina R, Castellucci P, Nanni C, Corti B, Martorana G, et al. Detection and localization of prostate cancer: correlation of (11)C-choline PET/CT with histopathologic step-section analysis. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2005;46(10):1642-9.

44. Martorana G, Schiavina R, Corti B, Farsad M, Salizzoni E, Brunocilla E, et al. 11C-choline positron emission tomography/computerized tomography for tumor localization of primary prostate cancer in comparison with 12-core biopsy. J Urol. 2006;176(3):954-60; discussion 60.

45. Testa C, Schiavina R, Lodi R, Salizzoni E, Corti B, Farsad M, et al. Prostate cancer: sextant localization with MR imaging, MR spectroscopy, and 11C-choline PET/CT. Radiology. 2007;244(3):797-806.

46. Piert M, Park H, Khan A, Siddiqui J, Hussain H, Chenevert T, et al. Detection of aggressive primary prostate cancer with 11C-choline PET/CT using multimodality fusion techniques. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2009;50(10):1585-93.

47. Reske SN, Blumstein NM, Neumaier B, Gottfried H-W, Finsterbusch F, Kocot D, et al. Imaging prostate cancer with 11C-choline PET/CT. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2006;47(8):1249-54.

48. Chang JH, Joon DL, Lee ST, Gong SJ, Scott AM, Davis ID, et al. Histopathological correlation of (11)C-choline PET scans for target volume definition in radical prostate radiotherapy. Radiotherapy

and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2011;99(2):187-92.

49. Schmid DT, John H, Zweifel R, Cservenyak T, Westera G, Goerres GW, et al. Fluorocholine PET/CT in patients with prostate cancer: initial experience. Radiology. 2005;235(2):623-8.

50. Kwee SA, Thibault GP, Stack RS, Coel MN, Furusato B, Sesterhenn IA. Use of step-section histopathology to evaluate 18F-fluorocholine PET sextant localization of prostate cancer. Molecular imaging.7(1):12-20.

51. Kwee SA, Wei H, Sesterhenn I, Yun D, Coel MN. Localization of primary prostate cancer with dual-phase 18F-fluorocholine PET. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2006;47(2):262-9.

52. Hartenbach M, Hartenbach S, Bechtloff W, Danz B, Kraft K, Klemenz B, et al. Combined PET/MRI improves diagnostic accuracy in patients with prostate cancer: a prospective diagnostic trial. Clin Cancer Res. 2014;20(12):3244-53.

53. Pinaquy JB, De Clermont-Galleran H, Pasticier G, Rigou G, Alberti N, Hindie E, et al. Comparative effectiveness of [(18) F]-fluorocholine PET-CT and pelvic MRI with diffusion-weighted imaging for staging in patients with high-risk prostate cancer. Prostate. 2015;75(3):323-31.

54. Beheshti M, Imamovic L, Broinger G, Vali R, Waldenberger P, Stoiber F, et al. 18F choline PET/CT in the preoperative staging of prostate cancer in patients with intermediate or high risk of extracapsular disease: a prospective study of 130 patients. Radiology. 2010;254(3):925-33.

55. Yamaguchi T, Lee J, Uemura H, Sasaki T, Takahashi N, Oka T, et al. Prostate cancer: a comparative study of 11C-choline PET and MR imaging combined with proton MR spectroscopy. Eur J Nucl Med Mol Imaging. 2005;32(7):742-8.

56. Budiharto T, Joniau S, Lerut E, Van den Bergh L, Mottaghy F, Deroose CM, et al. Prospective evaluation of 11C-choline positron emission tomography/computed tomography and diffusion-weighted magnetic resonance imaging for the nodal staging of prostate cancer with a high risk of lymph node metastases. Eur Urol. 2011;60(1):125-30.

57. Vallini V, Ortori S, Boraschi P, Manassero F, Gabelloni M, Faggioni L, et al. Staging of pelvic lymph nodes in patients with prostate cancer: Usefulness of multiple b value SE-EPI diffusion-weighted imaging on a 3.0 T MR system. Eur J Radiol Open. 2016;3:16-21.

58. Sankineni S, Brown AM, Fascelli M, Law YM, Pinto PA, Choyke PL, et al. Lymph node staging in prostate cancer. Curr Urol Rep. 2015;16(5):30.

59. Thoeny HC, Barbieri S, Froehlich JM, Turkbey B, Choyke PL. Functional and Targeted Lymph Node Imaging in Prostate Cancer: Current Status and Future Challenges. Radiology. 2017;285(3):728-43.

60. Evangelista L, Briganti A, Fanti S, Joniau S, Reske S, Schiavina R, et al. New Clinical Indications for F/C-choline, New Tracers for Positron Emission Tomography and a Promising Hybrid Device for Prostate Cancer Staging: A Systematic Review of the Literature. Eur Urol. 2016.

61. Poulsen MH, Bouchelouche K, Høilund-Carlsen PF, Petersen H, Gerke O, Steffansen SI, et al. [18F]fluoromethylcholine (FCH) positron emission tomography/computed tomography (PET/CT) for lymph node staging of prostate cancer: a prospective study of 210 patients. BJU international. 2012;110(11):1666-71.

62. Evangelista L, Cimitan M, Zattoni F, Guttilla A, Zattoni F, Saladini G. Comparison between conventional imaging (abdominal-pelvic computed tomography and bone scan) and [(18)F]choline positron emission tomography/computed tomography imaging for the initial staging of patients with intermediate- tohigh-risk prostate cancer: A retrospective analysis. Scand J Urol. 2015;49(5):345-53.

63. Heck MM, Retz M, Bandur M, Souchay M, Vitzthum E, Weirich G, et al. Topography of lymph node metastases in prostate cancer patients undergoing radical prostatectomy and extended lymphadenectomy: results of a combined molecular and histopathologic mapping study. Eur Urol. 2014;66(2):222-9.

64. Joniau S, Van den Bergh L, Lerut E, Deroose CM, Haustermans K, Oyen R, et al. Mapping of pelvic lymph node metastases in prostate cancer. Eur Urol. 2013;63(3):450-8.

65. Abdollah F, Cozzarini C, Sun M, Suardi N, Gallina A, Passoni NM, et al. Assessing the most accurate formula to predict the risk of lymph node metastases from prostate cancer in contemporary patients treated with radical prostatectomy and extended pelvic lymph node dissection. Radiother Oncol. 2013;109(2):211-6.

66. Rahman S, Cosmatos H, Dave G, Williams S, Tome M. Predicting pelvic lymph node involvement in current-era prostate cancer. Int J Radiat Oncol Biol Phys. 2012;82(2):906-10.

67. Eifler JB, Feng Z, Lin BM, Partin MT, Humphreys EB, Han M, et al. An updated prostate cancer staging nomogram (Partin tables) based on cases from 2006 to 2011. BJU Int. 2013;111(1):22-9.

68. Cagiannos I, Karakiewicz P, Eastham JA, Ohori M, Rabbani F, Gerigk C, et al. A preoperative nomogram identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer. J Urol. 2003;170(5):1798-803.

69. Briganti A, Larcher A, Abdollah F, Capitanio U, Gallina A, Suardi N, et al. Updated nomogram predicting lymph node invasion in patients with prostate cancer undergoing extended pelvic lymph node dissection: the essential importance of percentage of positive cores. Eur Urol. 2012;61(3):480-7.

70. Cimino S, Reale G, Castelli T, Favilla V, Giardina R, Russo GI, et al. Comparison between Briganti, Partin and MSKCC tools in predicting positive lymph nodes in prostate cancer: a systematic review and meta-analysis. Scand J Urol. 2017;51(5):345-50.

71. Payne H, Mason M. Androgen deprivation therapy as adjuvant/neoadjuvant to radiotherapy for high-risk localised and locally advanced prostate cancer: recent developments. Br J Cancer. 2011;105(11):1628-34.

72. Wo JY, Zietman AL. Why does androgen deprivation enhance the results of radiation therapy? Urol Oncol. 2008;26(5):522-9.

73. Widmark A, Klepp O, Solberg A, Damber JE, Angelsen A, Fransson P, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. Lancet. 2009;373(9660):301-8.

74. Bourke L, Kirkbride P, Hooper R, Rosario AJ, Chico TJ, Rosario DJ. Endocrine therapy in prostate cancer: time for reappraisal of risks, benefits and cost-effectiveness? Br J Cancer. 2013;108(1):9-13.

75. Mohiuddin JJ, Baker BR, Chen RC. Radiotherapy for high-risk prostate cancer. Nat Rev Urol. 2015;12(3):145-54.

76. Studer UE, Whelan P, Wimpissinger F, Casselman J, de Reijke TM, Knonagel H, et al. Differences in time to disease progression do not predict for cancer-specific survival in patients receiving immediate or deferred androgen-deprivation therapy for prostate cancer: final results of EORTC randomized trial 30891 with 12 years of follow-up. Eur Urol. 2014;66(5):829-38.

77. Lu-Yao GL, Albertsen PC, Moore DF, Shih W, Lin Y, DiPaola RS, et al. Survival following primary androgen deprivation therapy among men with localized prostate cancer. JAMA. 2008;300(2):173-81.

78. Iversen P, Tyrrell CJ, Kaisary AV, Anderson JB, Van Poppel H, Tammela TL, et al. Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of followup. J Urol. 2000;164(5):1579-82.

79. Iversen P, Johansson JE, Lodding P, Kylmala T, Lundmo P, Klarskov P, et al. Bicalutamide 150 mg in addition to standard care for patients with early non-metastatic prostate cancer: updated results from the Scandinavian Prostate Cancer Period Group-6 Study after a median follow-up period of 7.1 years. Scand J Urol Nephrol. 2006;40(6):441-52.

80. Pilepich MV, Winter K, Lawton CA, Krisch RE, Wolkov HB, Movsas B, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. Int J Radiat Oncol Biol Phys. 2005;61(5):1285-90.

81. Roach M, 3rd, Bae K, Speight J, Wolkov HB, Rubin P, Lee RJ, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. J Clin Oncol. 2008;26(4):585-91.

82. Bolla M, Van Tienhoven G, Warde P, Dubois JB, Mirimanoff RO, Storme G, 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(11):1066-73.

83. Denham JW, Steigler A, Lamb DS, Joseph D, Turner S, Matthews J, et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. Lancet Oncol. 2011;12(5):451-9.

84. Bolla M, de Reijke TM, Van Tienhoven G, Van den Bergh AC, Oddens J, Poortmans PM, et al. Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med. 2009;360(24):2516-27.

85. Horwitz EM, Bae K, Hanks GE, Porter A, Grignon DJ, Brereton HD, et al. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. J Clin Oncol. 2008;26(15):2497-504.

86. Zapatero A, Guerrero A, Maldonado X, Alvarez A, Gonzalez San Segundo C, Cabeza Rodriguez MA, et al. High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial. Lancet Oncol. 2015;16(3):320-7.

87. Tree AC, Alexander EJ, Van As NJ, Dearnaley DP, Khoo V. Biological dose escalation and hypofractionation: what is there to be gained and how will it best be done? Clin Oncol (R Coll Radiol). 2013;25(8):483-98.

88. Zhao S, Urdaneta AI, Anscher MS. The role of androgen deprivation therapy plus radiation therapy in patients with non-metastatic prostate cancer. Expert Rev Anticancer Ther. 2016;16(9):929-42.

89. Caram ME, Skolarus TA, Cooney KA. Limitations of Prostate-specific Antigen Testing After a Prostate Cancer Diagnosis. Eur Urol. 2016;70(2):209-10.

90. Nguyen PL, Je Y, Schutz FA, Hoffman KE, Hu JC, Parekh A, et al. Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: a meta-analysis of randomized trials. JAMA. 2011;306(21):2359-66.

91. D'Amico AV, Denham JW, Crook J, Chen MH, Goldhaber SZ, Lamb DS, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. J Clin Oncol. 2007;25(17):2420-5.

92. Juloori A, Shah C, Stephans K, Vassil A, Tendulkar R. Evolving Paradigm of Radiotherapy for High-Risk Prostate Cancer: Current Consensus and Continuing Controversies. Prostate Cancer. 2016;2016:2420786.

93. Ahmed HU, Cathcart P, McCartan N, Kirkham A, Allen C, Freeman A, et al. Focal salvage therapy for localized prostate cancer recurrence after external beam radiotherapy: a pilot study. Cancer. 2012;118(17):4148-55.

94. Ferrera G, Mortellaro G, Mannino M, Caminiti G, Spera A, Figlia V, et al. Moderate hypofractionation and simultaneous integrated boost by helical tomotherapy in prostate cancer: monoinstitutional report of acute tolerability assessment with different toxicity scales. Radiol Med. 2015;120(12):1170-6.

95. Hoskin P. Radiotherapy in practice : external beam therapy2014.

96. Budaus L, Bolla M, Bossi A, Cozzarini C, Crook J, Widmark A, et al. Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. Eur Urol. 2012;61(1):112-27.

97. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys. 1991;21(1):109-22.

98. Dearnaley D, Syndikus I, Sumo G, Bidmead M, Bloomfield D, Clark C, 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(1):43-54.

99. Mangar SA, Sydes MR, Tucker HL, Coffey J, Sohaib SA, Gianolini S, et al. Evaluating the relationship between erectile dysfunction and dose received by the penile bulb: using data from a randomised controlled trial of conformal radiotherapy in prostate cancer (MRC RT01, ISRCTN47772397). Radiother Oncol. 2006;80(3):355-62.

100. Roach M, Winter K, Michalski JM, Cox JD, Purdy JA, Bosch W, et al. Penile bulb dose and impotence after three-dimensional conformal radiotherapy for prostate cancer on RTOG 9406: findings from a prospective, multi-institutional, phase I/II dose-escalation study. Int J Radiat Oncol Biol Phys. 2004;60(5):1351-6.

101. Miralbell R, Molla M, Rouzaud M, Hidalgo A, Toscas JI, Lozano J, 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(1):50-7.

102. Pinkawa M, Siluschek J, Gagel B, Demirel C, Asadpour B, Holy R, et al. Influence of the initial rectal distension on posterior margins in primary and postoperative radiotherapy for prostate cancer. Radiother Oncol. 2006;81(3):284-90.

103. Langen KM, Willoughby TR, Meeks SL, Santhanam A, Cunningham A, Levine L, et al. Observations on real-time prostate gland motion using electromagnetic tracking. Int J Radiat Oncol Biol Phys. 2008;71(4):1084-90.

104. Tanyi JA, He T, Summers PA, Mburu RG, Kato CM, Rhodes SM, et al. Assessment of planning target volume margins for intensity-modulated radiotherapy of the prostate gland: role of daily inter- and intrafraction motion. Int J Radiat Oncol Biol Phys. 2010;78(5):1579-85.

105. Onishi H, Kuriyama K, Komiyama T, Marino K, Araya M, Saito R, et al. Large prostate motion produced by anal contraction. Radiother Oncol. 2012;104(3):390-4.

106. Rudat V, Nour A, Hammoud M, Alaradi A, Mohammed A. Image-guided intensity-modulated radiotherapy of prostate cancer: Analysis of interfractional errors and acute toxicity. Strahlenther Onkol. 2016;192(2):109-17.

107. Ahmed HU, Dickinson L, Charman S, Weir S, McCartan N, Hindley RG, et al. Focal Ablation Targeted to the Index Lesion in Multifocal Localised Prostate Cancer: a Prospective Development Study. Eur Urol. 2015;68(6):927-36.

108. Di Muzio NG, Fodor A, Noris Chiorda B, Broggi S, Mangili P, Valdagni R, et al. Moderate Hypofractionation with Simultaneous Integrated Boost in Prostate Cancer: Long-term Results of a Phase I-II Study. Clin Oncol (R Coll Radiol). 2016;28(8):490-500.

109. Warde P, Mason M, Ding K, Kirkbride P, Brundage M, Cowan R, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Lancet. 2011;378(9809):2104-11.

110. Mason MD, Parulekar WR, Sydes MR, Brundage M, Kirkbride P, Gospodarowicz M, et al. Final Report of the Intergroup Randomized Study of Combined Androgen-Deprivation Therapy Plus Radiotherapy Versus Androgen-Deprivation Therapy Alone in Locally Advanced Prostate Cancer. J Clin Oncol. 2015;33(19):2143-50.

111. Mottet N, Peneau M, Mazeron JJ, Molinie V, Richaud P. Addition of radiotherapy to long-term androgen deprivation in locally advanced prostate cancer: an open randomised phase 3 trial. Eur Urol. 2012;62(2):213-9.

112. James ND, Spears MR, Clarke NW, Dearnaley DP, Mason MD, Parker CC, et al. Failure-Free Survival and Radiotherapy in Patients With Newly Diagnosed Nonmetastatic Prostate Cancer: Data From Patients in the Control Arm of the STAMPEDE Trial. JAMA Oncol. 2016;2(3):348-57.

113. Zelefsky MJ, Yamada Y, Fuks Z, Zhang Z, Hunt M, Cahlon O, et al. Long-term results of conformal radiotherapy for prostate cancer: impact of dose escalation on biochemical tumor control and distant metastases-free survival outcomes. Int J Radiat Oncol Biol Phys. 2008;71(4):1028-33.

114. Kalbasi A, Li J, Berman A, Swisher-McClure S, Smaldone M, Uzzo RG, et al. Dose-Escalated Irradiation and Overall Survival in Men With Nonmetastatic Prostate Cancer. JAMA Oncol. 2015;1(7):897-906.

115. Dearnaley DP, Jovic G, Syndikus I, Khoo V, Cowan RA, Graham JD, et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. Lancet Oncol. 2014;15(4):464-73.

116. Hou Z, Li G, Bai S. High dose versus conventional dose in external beam radiotherapy of prostate cancer: a meta-analysis of long-term follow-up. J Cancer Res Clin Oncol. 2015;141(6):1063-71.

117. Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR, 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(1):67-74.

118. Pollack A, Zagars GK, Starkschall G, Childress CH, Kopplin S, Boyer AL, et al. Conventional vs. conformal radiotherapy for prostate cancer: preliminary results of dosimetry and acute toxicity. Int J Radiat Oncol Biol Phys. 1996;34(3):555-64.

119. Pollack A, Zagars GK, Starkschall G, Antolak JA, Lee JJ, Huang E, 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(5):1097-105.

120. Heemsbergen WD, Al-Mamgani A, Slot A, Dielwart MF, Lebesque JV. Long-term results of the Dutch randomized prostate cancer trial: impact of dose-escalation on local, biochemical, clinical failure, and survival. Radiother Oncol. 2014;110(1):104-9.

121. Peeters ST, Heemsbergen WD, Koper PC, van Putten WL, Slot A, Dielwart MF, 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(13):1990-6.

122. Peeters ST, Heemsbergen WD, van Putten WL, Slot A, Tabak H, Mens JW, 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(4):1019-34.

123. Al-Mamgani A, van Putten WL, Heemsbergen WD, van Leenders GJ, Slot A, Dielwart MF, et al. Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2008;72(4):980-8.

124. Zietman AL, Bae K, Slater JD, Shipley WU, Efstathiou JA, Coen JJ, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. J Clin Oncol. 2010;28(7):1106-11.

125. Beckendorf V, Guerif S, Le Prise E, Cosset JM, Bougnoux A, Chauvet B, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. Int J Radiat Oncol Biol Phys. 2011;80(4):1056-63.

126. Dearnaley DP, Sydes MR, Graham JD, Aird EG, Bottomley D, Cowan RA, 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(6):475-87.

127. Dearnaley DP, Sydes MR, Langley RE, Graham JD, Huddart RA, Syndikus I, et al. The early toxicity of escalated versus standard dose conformal radiotherapy with neo-adjuvant androgen suppression for patients with localised prostate cancer: results from the MRC RT01 trial (ISRCTN47772397). Radiother Oncol. 2007;83(1):31-41.

128. Michalski JM, Moughan J, Purdy JA, Bosch WR, Bahary J, Lau H, et al. Initial Results of a Phase 3 Randomized Study of High Dose 3DCRT/IMRT versus Standard Dose 3D-CRT/IMRT in Patients Treated for Localized Prostate Cancer (RTOG 0126). International Journal of Radiation Oncology • Biology • Physics.90(5):1263.

129. Benjamin LC, Tree AC, Dearnaley DP. The Role of Hypofractionated Radiotherapy in Prostate Cancer. Curr Oncol Rep. 2017;19(4):30.

130. Nahum AE. The radiobiology of hypofractionation. Clin Oncol (R Coll Radiol). 2015;27(5):260-9.

131. Gulliford S, Hall E, Dearnaley D. Hypofractionation trials and radiobiology of prostate cancer. Oncoscience. 2017;4(3-4):27-8.

132. Hoffman KE, Skinner H, Pugh TJ, Voong KR, Levy LB, Choi S, et al. Patient-reported Urinary, Bowel, and Sexual Function After Hypofractionated Intensity-modulated Radiation Therapy for Prostate Cancer: Results From a Randomized Trial. Am J Clin Oncol. 2016.

133. Hoffman KE, Voong KR, Levy LB, Allen PK, Choi S, Schlembach PJ, et al. Randomized Trial of Hypofractionated, Dose-Escalated, Intensity-Modulated Radiation Therapy (IMRT) Versus Conventionally Fractionated IMRT for Localized Prostate Cancer. J Clin Oncol. 2018;36(29):2943-9.

134. Pollack A, Walker G, Horwitz EM, Price R, Feigenberg S, Konski AA, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. J Clin Oncol. 2013;31(31):3860-8.

135. Lee WR, Dignam JJ, Amin MB, Bruner DW, Low D, Swanson GP, et al. Randomized Phase III Noninferiority Study Comparing Two Radiotherapy Fractionation Schedules in Patients With Low-Risk Prostate Cancer. J Clin Oncol. 2016;34(20):2325-32.

136. Catton CN, Lukka H, Gu CS, Martin JM, Supiot S, Chung PWM, et al. Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer. J Clin Oncol. 2017;35(17):1884-90.

137. Aluwini S, Pos F, Schimmel E, van Lin E, Krol S, van der Toorn PP, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial. Lancet Oncol. 2015;16(3):274-83.

138. Sanguineti G, Arcidiacono F, Landoni V, Saracino BM, Farneti A, Arcangeli S, et al. Macroscopic Hematuria After Conventional or Hypofractionated Radiation Therapy: Results From a Prospective Phase 3 Study. Int J Radiat Oncol Biol Phys. 2016;96(2):304-12.

139. Dearnaley D, Hall E. How will the CHHiP trial affect the future of prostate radiotherapy? Expert Rev Anticancer Ther. 2018;18(7):607-9.

140. Dearnaley D, Syndikus I, Gulliford S, Hall E. Hypofractionation for Prostate Cancer: Time to Change. Clin Oncol (R Coll Radiol). 2017;29(1):3-5.

141. Hoffman KE, Voong KR, Pugh TJ, Skinner H, Levy LB, Takiar V, et al. Risk of late toxicity in men receiving dose-escalated hypofractionated intensity modulated prostate radiation therapy: results from a randomized trial. Int J Radiat Oncol Biol Phys. 2014;88(5):1074-84.

142. Arcangeli G, Fowler J, Gomellini S, Arcangeli S, Saracino B, Petrongari MG, et al. Acute and late toxicity in a randomized trial of conventional versus hypofractionated three-dimensional conformal radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys. 2011;79(4):1013-21.

143. Arcangeli S, Strigari L, Gomellini S, Saracino B, Petrongari MG, Pinnaro P, et al. Updated results and patterns of failure in a randomized hypofractionation trial for high-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2012;84(5):1172-8.

144. Lieng H, Pintilie M, Bayley A, Berlin A, Bristow R, Chung P, et al. Long-term outcomes of a phase II trial of moderate hypofractionated image-guided intensity modulated radiotherapy (IG-IMRT) for localized prostate cancer. Radiother Oncol. 2017;122(1):93-8.

145. Aluwini S, Pos F, Schimmel E, Krol S, van der Toorn PP, de Jager H, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): late toxicity results from a randomised, non-inferiority, phase 3 trial. Lancet Oncol. 2016;17(4):464-74.

146. Incrocci L, Wortel RC, Alemayehu WG, Aluwini S, Schimmel E, Krol S, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol. 2016;17(8):1061-9.

147. Cellini N, Morganti AG, Mattiucci GC, Valentini V, Leone M, Luzi S, 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(3):595-9.

148. Arrayeh E, Westphalen AC, Kurhanewicz J, Roach M, 3rd, Jung AJ, Carroll PR, et al. Does local recurrence of prostate cancer after radiation therapy occur at the site of primary tumor? Results of a longitudinal MRI and MRSI study. Int J Radiat Oncol Biol Phys. 2012;82(5):e787-93.

149. Korsager AS, Carl J, Riis Ostergaard L. Comparison of manual and automatic MR-CT registration for radiotherapy of prostate cancer. J Appl Clin Med Phys. 2016;17(3):294-303.

150. Harris VA, Staffurth J, Naismith O, Esmail A, Gulliford S, Khoo V, et al. Consensus Guidelines and Contouring Atlas for Pelvic Node Delineation in Prostate and Pelvic Node Intensity Modulated Radiation Therapy. Int J Radiat Oncol Biol Phys. 2015;92(4):874-83.

151. Hafeez S, Warren-Oseni K, McNair HA, Hansen VN, Jones K, Tan M, et al. Prospective Study Delivering Simultaneous Integrated High-dose Tumor Boost (</=70 Gy) With Image Guided Adaptive Radiation Therapy for Radical Treatment of Localized Muscle-Invasive Bladder Cancer. Int J Radiat Oncol Biol Phys. 2016;94(5):1022-30.

152. Gregoire V, Langendijk JA, Nuyts S. Advances in Radiotherapy for Head and Neck Cancer. J Clin Oncol. 2015;33(29):3277-84.

153. Onal C, Sonmez S, Erbay G, Guler OC, Arslan G. Simultaneous integrated boost to intraprostatic lesions using different energy levels of intensity-modulated radiotherapy and volumetric-arc therapy. Br J Radiol. 2014;87(1034):20130617.

154. Riches SF, Payne GS, Desouza NM, Dearnaley D, Morgan VA, Morgan SC, et al. Effect on therapeutic ratio of planning a boosted radiotherapy dose to the dominant intraprostatic tumour lesion within the prostate based on multifunctional MR parameters. Br J Radiol. 2014;87(1037):20130813.

155. Bossart EL, Stoyanova R, Sandler K, Studenski M, Orman A, Abramowitz M, et al. Feasibility and Initial Dosimetric Findings for a Randomized Trial Using Dose-Painted Multiparametric Magnetic Resonance Imaging-Defined Targets in Prostate Cancer. Int J Radiat Oncol Biol Phys. 2016;95(2):827-34.

156. Kuang Y, Wu L, Hirata E, Miyazaki K, Sato M, Kwee SA. Volumetric modulated arc therapy planning for primary prostate cancer with selective intraprostatic boost determined by 18F-choline PET/CT. Int J Radiat Oncol Biol Phys. 2015;91(5):1017-25.

157. Wong WW, Schild SE, Vora SA, Ezzell GA, Nguyen BD, Ram PC, et al. Image-guided radiotherapy for prostate cancer: a prospective trial of concomitant boost using indium-111-capromab pendetide (ProstaScint) imaging. Int J Radiat Oncol Biol Phys. 2011;81(4):e423-9.

158. Schild MH, Schild SE, Wong WW, Vora SA, Silva AC, Silva AM, et al. Early Outcome of Prostate Intensity Modulated Radiation Therapy (IMRT) Incorporating a Simultaneous Intra-Prostatic MRI Directed Boost. OMICS J Radiol. 2014;3(4).

159. Pinkawa M, Piroth MD, Holy R, Klotz J, Djukic V, Corral NE, et al. Dose-escalation using intensity-modulated radiotherapy for prostate cancer - evaluation of quality of life with and without (18)F-choline PET-CT detected simultaneous integrated boost. Radiation oncology (London, England). 2012;7:14-.

160. Ippolito E, Mantini G, Morganti AG, Mazzeo E, Padula GD, Digesu C, et al. Intensity-modulated radiotherapy with simultaneous integrated boost to dominant intraprostatic lesion: preliminary report on toxicity. Am J Clin Oncol. 2012;35(2):158-62.

161. Onjukka E, Uzan J, Baker C, Howard L, Nahum A, Syndikus I. Twenty Fraction Prostate Radiotherapy with Intra-prostatic Boost: Results of a Pilot Study. Clin Oncol (R Coll Radiol). 2017;29(1):6-14.

162. Feutren T, Herrera FG. Prostate irradiation with focal dose escalation to the intraprostatic dominant nodule: a systematic review. Prostate Int. 2018;6(3):75-87.

163. Shah TT, Peters M, Eldred-Evans D, Miah S, Yap T, Faure-Walker NA, et al. Early-Medium-Term Outcomes of Primary Focal Cryotherapy to Treat Nonmetastatic Clinically Significant Prostate Cancer from a Prospective Multicentre Registry. Eur Urol. 2019;76(1):98-105.

164. Guillaumier S, Peters M, Arya M, Afzal N, Charman S, Dudderidge T, et al. A Multicentre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer. Eur Urol. 2018;74(4):422-9.

165. Ahdoot M, Lebastchi AH, Turkbey B, Wood B, Pinto PA. Contemporary treatments in prostate cancer focal therapy. Curr Opin Oncol. 2019;31(3):200-6.

166. Kovacs A, Pinkawa M. Interventional therapy in malignant conditions of the prostate. Radiologe. 2019;59(Suppl 1):28-39.

167. Zaorsky NG, Palmer JD, Hurwitz MD, Keith SW, Dicker AP, Den RB. What is the ideal radiotherapy dose to treat prostate cancer? A meta-analysis of biologically equivalent dose escalation. Radiother Oncol. 2015;115(3):295-300.

168. Fonteyne V, Villeirs G, Speleers B, De Neve W, De Wagter C, Lumen N, 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(3):799-807.

169. Lips IM, van der Heide UA, Haustermans K, van Lin EN, Pos F, Franken SP, 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. 2011;12:255.

170. Sundahl N, De Meerleer G, Villeirs G, Ost P, De Neve W, Lumen N, et al. Combining high dose external beam radiotherapy with a simultaneous integrated boost to the dominant intraprostatic lesion: Analysis of genito-urinary and rectal toxicity. Radiother Oncol. 2016;119(3):398-404.

171. Pinkawa M, Piroth MD, Holy R, Klotz J, Djukic V, Corral NE, et al. Dose-escalation using intensity-modulated radiotherapy for prostate cancer - evaluation of quality of life with and without (18)F-choline PET-CT detected simultaneous integrated boost. Radiat Oncol. 2012;7:14.

172. Garibaldi E, Delmastro E, Gabriele D, Bresciani S, Russo F, Di Dia A, et al. Clinical and technical feasibility of ultra-boost irradiation in Dominant Intraprostatic Lesion by Tomotherapy: preliminary experience and revision of literature. Panminerva Med. 2016;58(1):16-22.

173. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol. 2017;71(4):630-42.

174. Roach M, Hunt D, Lawton CA, Hsu I, Lustig RA, Seider M, et al. Radiation Therapy Oncology Group (RTOG) 9413: A Randomized Trial Comparing Whole Pelvic Radiation Therapy (WPRT) to Prostate Only (PORT) and Neoadjuvant Hormonal Therapy (NHT) to Adjuvant Hormonal Therapy (AHT). International Journal of Radiation Oncology • Biology • Physics. 2013;87(2):S106-S7.

175. Dearnaley D, Griffin CL, Lewis R, Mayles P, Mayles H, Naismith OF, et al. Toxicity and Patient-Reported Outcomes of a Phase 2 Randomized Trial of Prostate and Pelvic Lymph Node Versus Prostate only Radiotherapy in Advanced Localised Prostate Cancer (PIVOTAL). Int J Radiat Oncol Biol Phys. 2019;103(3):605-17.

176. Amini A, Kavanagh BD, Rusthoven CG. Improved survival with the addition of radiotherapy to androgen deprivation: questions answered and a review of current controversies in radiotherapy for non-metastatic prostate cancer. Ann Transl Med. 2016;4(1):14.

177. Seisen T, Vetterlein MW, Karabon P, Jindal T, Sood A, Nocera L, et al. Efficacy of Local Treatment in Prostate Cancer Patients with Clinically Pelvic Lymph Node-positive Disease at Initial Diagnosis. Eur Urol. 2017.

178. Rusthoven CG, Carlson JA, Waxweiler TV, Raben D, Dewitt PE, Crawford ED, et al. The impact of definitive local therapy for lymph node-positive prostate cancer: a population-based study. Int J Radiat Oncol Biol Phys. 2014;88(5):1064-73.

179. Shinde A, Li R, Glaser S, Amini A. Node-positive Nonmetastatic Prostate Cancer: Time to Reconsider Prognostic Staging? Eur Urol. 2019;75(3):355-7.

180. Norkus D, Karklelyte A, Engels B, Versmessen H, Griskevicius R, De Ridder M, et al. A randomized hypofractionation dose escalation trial for high risk prostate cancer patients: interim analysis of acute toxicity and quality of life in 124 patients. Radiat Oncol. 2013;8:206.

181. Fonteyne V, De Gersem W, De Neve W, Jacobs F, Lumen N, Vandecasteele K, et al. Hypofractionated intensity-modulated arc therapy for lymph node metastasized prostate cancer. Int J Radiat Oncol Biol Phys. 2009;75(4):1013-20.

182. Fonteyne V, Lumen N, Ost P, Van Praet C, Vandecasteele K, De Gersem Ir W, et al. Hypofractionated intensity-modulated arc therapy for lymph node metastasized prostate cancer: early late toxicity and 3-year clinical outcome. Radiother Oncol. 2013;109(2):229-34.

183. Pilepich MV, Krall JM, al-Sarraf M, John MJ, Doggett RL, Sause WT, et al. Androgen deprivation with radiation therapy compared with radiation therapy alone for locally advanced prostatic carcinoma: a randomized comparative trial of the Radiation Therapy Oncology Group. Urology. 1995;45(4):616-23.

184. Roach M, Hunt D, Lawton CA, Hsu I, Lustig RA, Seider M, et al. Radiation Therapy Oncology Group (RTOG) 9413: A Randomized Trial Comparing Whole Pelvic Radiation Therapy (WPRT) to Prostate Only (PORT) and Neoadjuvant Hormonal Therapy (NHT) to Adjuvant Hormonal Therapy (AHT). International Journal of Radiation Oncology • Biology • Physics.87(2):S106-S7.

185. Pommier P, Chabaud S, Lagrange JL, Richaud P, Lesaunier F, Le Prise E, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. J Clin Oncol. 2007;25(34):5366-73.

186. Choudhury A, Arthur C, Malik J, Mandall P, Taylor C, Alam N, et al. Patient-reported outcomes and health-related quality of life in prostate cancer treated with a single fraction of high dose rate brachytherapy combined with hypofractionated external beam radiotherapy. Clin Oncol (R Coll Radiol). 2014;26(10):661-7.

187. Holch P, Henry AM, Davidson S, Gilbert A, Routledge J, Shearsmith L, et al. Acute and Late Adverse Events Associated With Radical Radiation Therapy Prostate Cancer Treatment: A Systematic Review of Clinician and Patient Toxicity Reporting in Randomized Controlled Trials. Int J Radiat Oncol Biol Phys. 2017;97(3):495-510.

188. Jiang Y. Normal Tissue Toxicity Criteria in Radiation Therapy. International Journal of Radiation Oncology Biology Physics. 2013;87(2):S621 - S2.

189. Yoshida K, Yamazaki H, Nakamara S, Masui K, Kotsuma T, Akiyama H, et al. Comparison of common terminology criteria for adverse events v3.0 and radiation therapy oncology group toxicity score system after high-dose-rate interstitial brachytherapy as monotherapy for prostate cancer. Anticancer Res. 2014;34(4):2015-8.

190. Wei JT, Dunn RL, Sandler HM, McLaughlin PW, Montie JE, Litwin MS, et al. Comprehensive comparison of health-related quality of life after contemporary therapies for localized prostate cancer. J Clin Oncol. 2002;20(2):557-66.

191. Basch E, Jia X, Heller G, Barz A, Sit L, Fruscione M, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. J Natl Cancer Inst. 2009;101(23):1624-32.

192. Atkinson TM, Ryan SJ, Bennett AV, Stover AM, Saracino RM, Rogak LJ, et al. The association between clinician-based common terminology criteria for adverse events (CTCAE) and patient-reported outcomes (PRO): a systematic review. Support Care Cancer. 2016;24(8):3669-76.

193. Muanza TM, Albert PS, Smith S, Godette D, Crouse NS, Cooley-Zgela T, et al. Comparing measures of acute bowel toxicity in patients with prostate cancer treated with external beam radiation therapy. Int J Radiat Oncol Biol Phys. 2005;62(5):1316-21.

194. O'Brien PC, Franklin CI, Poulsen MG, Joseph DJ, Spry NS, Denham JW. Acute symptoms, not rectally administered sucralfate, predict for late radiation proctitis: longer term follow-up of a phase III trial--Trans-Tasman Radiation Oncology Group. Int J Radiat Oncol Biol Phys. 2002;54(2):442-9.

195. Zelefsky MJ, Levin EJ, Hunt M, Yamada Y, Shippy AM, Jackson A, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2008;70(4):1124-9.

196. Sutinen E, Nurmi M, Roivainen A, Varpula M, Tolvanen T, Lehikoinen P, et al. Kinetics of [(11)C]choline uptake in prostate cancer: a PET study. Eur J Nucl Med Mol Imaging. 2004;31(3):317-24.

197. Schaefferkoetter JD, Wang Z, Stephenson MC, Roy S, Conti M, Eriksson L, et al. Quantitative 18F-fluorocholine positron emission tomography for prostate cancer: correlation between kinetic parameters and Gleason scoring. EJNMMI Res. 2017;7(1):25.

198. Tau N, Berlin A, Yeung I, Halankar J, Murphy G, Jhaveri KS, et al. Quantitative assessment of dynamic (18)F-flumethycholine PET and dynamic contrast enhanced MRI in high risk prostate cancer. Br J Radiol. 2019;92(1094):20180568.

199. Mathieu C, Ferrer L, Carlier T, Colombie M, Rusu D, Kraeber-Bodere F, et al. Assessment of Lymph Nodes and Prostate Status Using Early Dynamic Curves with (18)F-Choline PET/CT in Prostate Cancer. Front Med (Lausanne). 2015;2:67.

200. Takesh M. Kinetic Modeling Application to (18)F-fluoroethylcholine Positron Emission Tomography in Patients with Primary and Recurrent Prostate Cancer Using Two-tissue Compartmental Model. World J Nucl Med. 2013;12(3):101-10.

201. Chang JH, Joon DL, Lee ST, Gong SJ, Scott AM, Davis ID, et al. Histopathological correlation of (11)C-choline PET scans for target volume definition in radical prostate radiotherapy. Radiother Oncol. 2011;99(2):187-92.

202. Muller SA, Holzapfel K, Seidl C, Treiber U, Krause BJ, Senekowitsch-Schmidtke R. Characterization of choline uptake in prostate cancer cells following bicalutamide and docetaxel treatment. Eur J Nucl Med Mol Imaging. 2009;36(9):1434-42.

203. Fuccio C, Schiavina R, Castellucci P, Rubello D, Martorana G, Celli M, et al. Androgen deprivation therapy influences the uptake of 11C-choline in patients with recurrent prostate cancer: the preliminary results of a sequential PET/CT study. Eur J Nucl Med Mol Imaging. 2011;38(11):1985-9.

204. Giovacchini G, Picchio M, Coradeschi E, Scattoni V, Bettinardi V, Cozzarini C, et al. [(11)C]choline uptake with PET/CT for the initial diagnosis of prostate cancer: relation to PSA levels, tumour stage and anti-androgenic therapy. Eur J Nucl Med Mol Imaging. 2008;35(6):1065-73.

205. Mutanga TF, de Boer HC, Rajan V, Dirkx ML, Incrocci L, Heijmen BJ. Day-to-day reproducibility of prostate intrafraction motion assessed by multiple kV and MV imaging of implanted markers during treatment. Int J Radiat Oncol Biol Phys. 2012;83(1):400-7.

206. Giovacchini G. Do we have to withdraw antiandrogenic therapy in prostate cancer patients before PET/CT with [11C]choline? Eur J Nucl Med Mol Imaging. 2011;38(11):1964-6.

207. Beauregard JM, Beaulieu A. How we read FCH-PET/CT for prostate cancer. Cancer Imaging. 2016;16(1):41.

208. Chang JH, Lim Joon D, Davis ID, Lee ST, Hiew CY, Esler S, et al. Comparison of [(11)C]choline Positron Emission Tomography With T2- and Diffusion-Weighted Magnetic Resonance Imaging for Delineating Malignant Intraprostatic Lesions. Int J Radiat Oncol Biol Phys. 2015;92(2):438-45.

209. A'Hern RP. Sample size tables for exact single-stage phase II designs. Stat Med. 2001;20(6):859-66.

210. Naismith OF, Griffin C, Syndikus I, South C, Mayles H, Mayles P, et al. Forward- and Inverse-Planned Intensity-Modulated Radiotherapy in the CHHiP Trial: A Comparison of Dosimetry and Normal Tissue Toxicity. Clin Oncol (R Coll Radiol). 2019;31(9):600-10.

211. 4. Definition of volumes. J ICRU. 2010;10(1):41-53.

212. Steuber T, Schlomm T, Heinzer H, Zacharias M, Ahyai S, Chun KF, et al. [F(18)]-fluoroethylcholine combined in-line PET-CT scan for detection of lymph-node metastasis in high risk prostate cancer patients prior to radical prostatectomy: Preliminary results from a prospective histology-based study. Eur J Cancer. 2010;46(2):449-55.

213. O'Neill AG, Jain S, Hounsell AR, O'Sullivan JM. Fiducial marker guided prostate radiotherapy: a review. Br J Radiol. 2016;89(1068):20160296.

214. Barry MJ, Fowler FJ, Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol. 1992;148(5):1549-57; discussion 64.

215. CTEP CTEP. 2017 [Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

216. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31(5):1341-6.

217. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

218. Sonn GA, Sadetsky N, Presti JC, Litwin MS. Differing perceptions of quality of life in patients with prostate cancer and their doctors. J Urol. 2013;189(1 Suppl):S59-65; discussion S.

219. Litwin MS, Lubeck DP, Henning JM, Carroll PR. Differences in urologist and patient assessments of health related quality of life in men with prostate cancer: results of the CaPSURE database. J Urol. 1998;159(6):1988-92.

220. Basch E. The missing voice of patients in drug-safety reporting. N Engl J Med. 2010;362(10):865-9.

221. Sydes MR, Spears MR, Mason MD, Clarke NW, Dearnaley DP, de Bono JS, et al. Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol. Ann Oncol. 2018;29(5):1235-48.

9 Appendix

9.1 Risk stratification for prostate cancer (NCCN guidelines 2018)

Risk group	Clinical/Pathological features
Very low	**All of the following:** - **T1c** - **Gleason ≤ 6 / grade group 1** - **PSA < 10 ng/ml** - **< 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core** - **PSA density < 0.15 ng/ml/g**
Low	**All of the following:** - **T1 – T2a** - **Gleason score ≤ 6 / grade group 1** - **PSA < 10 ng/ml**
Intermediate - favourable	**Any of the following:** - **T2b – T2c** - **Gleason score 3 + 4 = 7/ grade group 2** - **PSA 10 – 20 ng/ml** **PLUS percentage of positive biopsy cores < 50%**
Intermediate - unfavourable	**Any of the following:** - **T2b – T2c** - **Gleason 3 + 4 = 7/ grade group 2 or Gleason 4 + 3 = 7/grade group 3** - **PSA 10 – 20 ng/ml**
High	**Any of the following:** - **T3a** - **Gleason score 8 / grade group 4 or Gleason 4+5 = 9/ grade group 5** - **PSA > 20 ng/ml**
Very high	**Any of the following:** - **T3b – T4** - **Primary Gleason pattern 5** - **> 4 cores with Gleason score 8 – 10/ grade group 4 or 5**

9.2 Assessment forms

9.2.1 CTCAE

CTCAE	1	2	3	4
Anal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent interventions indicated
Anal necrosis	-	-	TPN or hospitalisation indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Anal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Rectal haemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterisation indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated

Rectal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated
Cystitis noninfective	Microscopic haematuria; minimal increase in frequency, urgency, dysuria or nocturia; new onset of incontinence	Moderate haematuria; moderate increase in frequency, urgency, dysuria, nocturia or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL	Gross haematuria; transfusion, IV medications or hospitalisation indicated, elective endoscopic, radiologic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated
Urinary fistula	-	Noninvasive intervention indicated; urinary or suprapubic catheter placement indicated	Limiting self care ADL; elective radiologic, endoscopic or operative intervention indicated; permanent urinary diversion indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	-	-
Urinary incontinence	Occasional (e.g. with coughing, sneezing etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g. clamp, collagen injections); operative intervention indicated; limiting self care ADL	-

Urinary retention	Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual	Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated	Elective operative or radiologic intervention indicated; substantial loss of affected kidney function or mass	Life threatening consequences: organ failture; urgent operative intervention indicated
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-

9.2.2 RTOG

RTOG	1	2	3	4
Lower GI	**Increased frequency or change in quality of bowel habits not requiring medication / rectal discomfort not requiring analgesics**	**Diarrhoea requiring parasympatholytic drugs (e.g. Lomotil) / mucous discharge not necessitating sanitary pads / rectal or abdominal pain requiring analgesics**	**Diarrhoea requiring parenteral support / severe mucous or blood discharge necessitating sanitary pads / abdominal distension (flat plate radiograph demonstrates distended bowel loops)**	**Acute or subacute obstruction, fistula or perforation ; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion**
Bladder	**Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication**	**Frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anaestheic**	**Frequency with urgency and nocturia hourly or more frequently / dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic / gross haematuria with / without clot passage**	**Haematuria requiring transfusion / acute bladder obstruction not secondary to clot passage, ulceration or necrosis**

9.2.3 IPSS

IPSS	Not at all	Less than 1 in 5 times	Less than half the time	About half the time	More than half the time	Almost always
Incomplete Emptying: How often have you had the sensation of not emptying your bladder?	**0**	**1**	**2**	**3**	**4**	**5**
Frequency: How often have you had to urinate less than every two hours?	**0**	**1**	**2**	**3**	**4**	**5**
Intermittency: How often have you found you stopped and started again several times when you urinated?	**0**	**1**	**2**	**3**	**4**	**5**
Urgency: How often have you found it difficult to postpone urination?	**0**	**1**	**2**	**3**	**4**	**5**
Weak stream: How often have you had a weak urinary stream?	**0**	**1**	**2**	**3**	**4**	**5**
Straining: How often have you had to strain to start urination?	**0**	**1**	**2**	**3**	**4**	**5**

	None	1 time	2 times	3 times	4 times	5 times
Nocturia: How many times did you typically get up at night to urinate?	**0**	**1**	**2**	**3**	**4**	**5**

9.2.4 IPSS QoL

IPSS QoL	Delighted	Pleased	Mostly satisfied	Mixed	Mostly dissatisfied	Unhappy	Terrible
Quality of life due to urinary symptoms: If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

9.2.5 PS

Performance Status	Criteria
0	**Able to carry our all normal activity without restriction**
1	**Restricted in strenuous activity but ambulatory and able to carry out light work**
2	**Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours**
3	**Symptomatic and in a chair or in bed for greater than 50% of the day but not bedridden**
4	**Completely disabled; cannot carry out any self-care; totally confined to bed or chair**

9.2.6 EPIC

EPIC

The Expanded Prostate Cancer Index Composite

This questionnaire is designed to measure Quality of Life issues in patients with Prostate cancer. To help us get the most accurate measurement, it is important that you answer all questions honestly and completely.

Remember, as with all medical records, information contained within this survey will remain strictly confidential.

Today's Date (please enter date when survey completed): Month_____Day_____Year_____

Name (optional): _____

Date of Birth (optional): Month_____Day_____Year_____

Do Not Mark in This Space

URINARY FUNCTION

This section is about your urinary habits. Please consider **ONLY THE LAST 4 WEEKS**.

1. Over the **past 4 weeks**, how often have you leaked urine?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number) 23/
   About once a week..... 4
   Rarely or never..... 5

2. Over the **past 4 weeks**, how often have you urinated blood?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number) 24/
   About once a week..... 4
   Rarely or never..... 5

3. Over the **past 4 weeks**, how often have you had pain or burning with urination?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number) 25/
   About once a week..... 4
   Rarely or never..... 5

4. Which of the following best describes your urinary control **during the last 4 weeks**?

   No urinary control whatsoever..... 1
   Frequent dribbling..... 2 (Circle one number) 26/
   Occasional dribbling..... 3
   Total control..... 4

Do Not Mark in This Space

5. How many pads or adult diapers <u>per day</u> did you usually use to control leakage **during the last 4 weeks**?

None	0		
1 pad per day	1		
2 pads per day	2	(Circle one number)	
3 or more pads per day	3		27/

6. How big a problem, if any, has each of the following been for you **during the last 4 weeks**?

(Circle one number on each line)

		No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a.	Dripping or leaking urine	0	1	2	3	4	28/
b.	Pain or burning on urination	0	1	2	3	4	29/
c.	Bleeding with urination	0	1	2	3	4	30/
d.	Weak urine stream or incomplete emptying	0	1	2	3	4	31/
e.	Waking up to urinate	0	1	2	3	4	32/
f.	Need to urinate frequently during the day	0	1	2	3	4	33/

7. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?

No problem	1		
Very small problem	2		
Small problem	3	(Circle one number)	34/
Moderate problem	4		
Big problem	5		

Do Not Mark in This Space

BOWEL HABITS

The next section is about your bowel habits and abdominal pain.
Please consider **ONLY THE LAST 4 WEEKS**.

8. How often have you had rectal urgency (felt like I had to pass stool, but did not) **during the last 4 weeks**?

More than once a day	1		
About once a day	2		
More than once a week	3	(Circle one number)	42/
About once a week	4		
Rarely or never	5		

9. How often have you had uncontrolled leakage of stool or feces?

More than once a day	1		
About once a day	2		
More than once a week	3	(Circle one number)	43/
About once a week	4		
Rarely or never	5		

10. How often have you had stools (bowel movements) that were loose or liquid (no form, watery, mushy) **during the last 4 weeks**?

Never	1		
Rarely	2		
About half the time	3	(Circle one number)	44/
Usually	4		
Always	5		

11. How often have you had bloody stools **during the last 4 weeks**?

Never	1		
Rarely	2		
About half the time	3	(Circle one number)	45/
Usually	4		
Always	5		

Do Not Mark in This Space

12. How often have your bowel movements been painful **during the last 4 weeks**?

Never..... 1
Rarely..... 2
About half the time..... 3 (Circle one number) 46/
Usually..... 4
Always..... 5

13. How many bowel movements have you had on a typical day **during the last 4 weeks**?

Two or less..... 1
Three to four..... 2 (Circle one number) 47/
Five or more..... 3

14. How often have you had crampy pain in your abdomen, pelvis or rectum **during the last 4 weeks**?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 48/
About once a week..... 4
Rarely or never..... 5

15. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Urgency to have a bowel movement	0	1	2	3	4	49/
b. Increased frequency of bowel movements.....	0	1	2	3	4	50/
c. Watery bowel movements.....	0	1	2	3	4	51/
d. Losing control of your stools.....	0	1	2	3	4	52/
e. Bloody stools	0	1	2	3	4	53/
f. Abdominal/ Pelvic/Rectal pain...	0	1	2	3	4	54/

16. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**?

No problem..... 1
Very small problem..... 2
Small problem..... 3 (Circle one number) 55/
Moderate problem..... 4
Big problem..... 5

Do Not Mark in This Space

SEXUAL FUNCTION

The next section is about your **current** sexual function and sexual satisfaction. Many of the questions are very personal, but they will help us understand the important issues that you face every day. Remember, THIS SURVEY INFORMATION IS COMPLETELY **CONFIDENTIAL**. Please answer honestly about **THE LAST 4 WEEKS ONLY**.

17. How would you rate each of the following during the last 4 weeks? (Circle one number on each line)

	Very Poor to None	Poor	Fair	Good	Very Good	
a. Your level of sexual desire?	1	2	3	4	5	56/
b. Your ability to have an erection?	1	2	3	4	5	57/
c. Your ability to reach orgasm (climax)?	1	2	3	4	5	58/

18. How would you describe the usual QUALITY of your erections **during the last 4 weeks**?

None at all 1
Not firm enough for any sexual activity 2
Firm enough for masturbation and foreplay only ..... 3 (Circle one number) 59/
Firm enough for intercourse 4

19. How would you describe the FREQUENCY of your erections **during the last 4 weeks**?

I NEVER had an erection when I wanted one 1
I had an erection LESS THAN HALF the time I wanted one 2
I had an erection ABOUT HALF the time I wanted one ..... 3 (Circle one number) 60/
I had an erection MORE THAN HALF the time I wanted one 4
I had an erection WHENEVER I wanted one 5

20. How often have you awakened in the morning or night with an erection **during the last 4 weeks**?

Never 1
Less than once a week 2
About once a week ..... 3 (Circle one number) 61/
Several times a week 4
Daily 5

Do Not Mark in This Space

21. **During the last 4 weeks**, how often did you have <u>any</u> sexual activity?

Not at all	1		
Less than once a week	2		
About once a week	3	(Circle one number)	62/
Several times a week	4		
Daily	5		

22. **During the last 4 weeks**, how often did you have sexual intercourse?

Not at all	1		
Less than once a week	2		
About once a week	3	(Circle one number)	63/
Several times a week	4		
Daily	5		

23. Overall, how would you rate your ability to function sexually **during the last 4 weeks**?

Very poor	1		
Poor	2		
Fair	3	(Circle one number)	64/
Good	4		
Very good	5		

24. How big a problem **during the last 4 weeks**, if any, has each of the following been for you?
(Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Your level of sexual desire	0	1	2	3	4	65/
b. Your ability to have an erection	0	1	2	3	4	66/
c. Your ability to reach an orgasm	0	1	2	3	4	67/

25. Overall, how big a problem has your sexual function or lack of sexual function been for you **during the last 4 weeks**?

No problem	1		
Very small problem	2		
Small problem	3	(Circle one number)	68/
Moderate problem	4		
Big problem	5		

Do Not Mark in This Space

HORMONAL FUNCTION

The next section is about your hormonal function. Please consider **ONLY THE LAST 4 WEEKS**.

26. **Over the last 4 weeks**, how often have you experienced hot flashes?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 69/
About once a week..... 4
Rarely or never..... 5

27. How often have you had breast tenderness **during the last 4 weeks**?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 70/
About once a week..... 4
Rarely or never..... 5

28. **During the last 4 weeks**, how often have you felt depressed?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 71/
About once a week..... 4
Rarely or never..... 5

29. **During the last 4 weeks**, how often have you felt a lack of energy?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 72/
About once a week..... 4
Rarely or never..... 5

30. How much change in your weight have you experienced **during the last 4 weeks**, if any?

Gained 10 pounds or more.....1
Gained less than 10 pounds 2
No change in weight..... .....3 (Circle one number) 73/
Lost less than 10 pounds 4
Lost 10 pounds or more.....5

Do Not Mark in This Space

31. How big a problem **during the last 4 weeks**, if any, has each of the following been for you?
(Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Hot flashes	0	1	2	3	4	74/
b. Breast tenderness/enlargement	0	1	2	3	4	75/
c. Loss of Body Hair	0	1	2	3	4	76/
d. Feeling depressed	0	1	2	3	4	77/
e. Lack of energy	0	1	2	3	4	78/
f. Change in body weight	0	1	2	3	4	79/

Overall Satisfaction

32. Overall, how satisfied are you with the treatment you received for your prostate cancer?

Extremely dissatisfied..... 1
Dissatisfied..... 2
Uncertain..... 3 (Circle one number) 80/
Satisfied..... 4
Extremely satisfied..... 5

THANK YOU VERY MUCH!!

Is choline PET useful for identifying intraprostatic tumour lesions? A literature review

***Chan J**, Syndikus I, Mahmood S, Bell L, Vinjamuri S.*

Nucl Med Commun. 2015 Sep;36(9):871-880

Review article

Nuclear Medicine Communications

Is choline PET useful for identifying intraprostatic tumour lesions? A literature review

Joachim Chan[a], Isabel Syndikus[a], Shelan Mahmood[b], Lynn Bell[c] and Sobhan Vinjamuri[d]

More than 80% of patients with intermediate-risk or high-risk localized prostate cancer are cured with radiation doses of 74–78 Gy, but high doses increase the risk for late bowel and bladder toxicity among long-term survivors. Dose painting, defined as dose escalation to areas in the prostate containing the tumour, rather than to the whole gland, minimizes dose to normal tissues and hence toxicity. It requires accurate identification of the location and size of these lesions, for which functional MRI is the current gold standard. Many studies have assessed the use of choline PET in staging newly diagnosed patients. This review will discuss important imaging variables affecting the accuracy of choline PET scans, how choline PET contributes to tumour identification and is used in radiotherapy planning and how PET can improve the patient pathway involving prostate radiotherapy. In summary, the available literature shows that the accuracy of choline PET improves with higher tracer doses and delayed imaging (although the optimal uptake time is unclear), and tumour identification by MRI is improved by the addition of PET imaging. We propose future research with prolonged choline uptake time and multiphase imaging, which may further improve accuracy. *Nucl Med Commun* **36:871–880**

Nuclear Medicine Communications 2015, 36:871–880

Keywords: choline, dose painting, PET, prostate cancer, radiotherapy

Departments of [a]Clinical Oncology, [b]Nuclear Medicine, [c]Radiotherapy, Clatterbridge Cancer Centre NHS Foundation Trust, Wirral and [d]Department of Nuclear Medicine, Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, UK

Correspondence to Joachim Chan, Clatterbridge Cancer Centre NHS Foundation Trust, Clatterbridge Road, Bebington, Wirral CH63 4JY, UK
Tel: +44 151 334 1155; fax: +44 151 482 7821;
e-mail: joachim.chan@clatterbridgecc.nhs.uk

Received 30 March 2015 Revised 30 March 2015 Accepted 6 April 2015

Introduction

Currently, prostate radiotherapy treats the whole gland with a uniform dose because the prostate is a small mobile organ, multifocal disease is common and because tumour nodules are sometimes difficult to define even with modern functional MRI [1,2]. Higher doses have been shown to significantly improve control in patients with localized disease; in the RT01 trial, 74 Gy resulted in 55% of patients having biochemical progression-free survival at 10 years of follow-up, whereas 64 Gy resulted in only 43% of patients showing progression-free survival [3]. However, these doses were associated with an increased risk for complications to adjacent organs, with severe bowel symptoms reported in 8 and 6% of patients, respectively [4]. Many patients survive for years after biochemical relapse and may die from causes other than prostate cancer; hence, attention to treatment toxicity and quality of life is of paramount importance.

Technological advancements in planning and treatment delivery of external beam radiotherapy have allowed better dose coverage of the target volume and reduction of normal tissue doses. Dose-painting radiotherapy increases the dose to tumour nodules within the prostate, whereas it limits the dose to adjacent normal tissues, which reduces toxicity and long-term side effects [5,6]. This is a good option for patients with bulky local disease (diameter > 5 mm) with high-grade histology, as they are at a higher risk for local relapse following standard radiotherapy [7]. Accurate identification of the tumour nodules is a prerequisite: if tumour nodules are not detected (low sensitivity of imaging), dose painting may not improve local control, whereas treatment of normal prostate with high-dose radiation will increase toxicity unnecessarily (low specificity of imaging).

Functional multiparametric MRI is commonly used to identify tumour foci [8,9]. Another option is PET, usually in the form of PET/computed tomography (CT) [10]. The benefit of PET/CT over MRI for radiotherapy planning is its ease of use in commercially available planning systems, as no additional fusion steps are required.

The general use of choline PET in prostate cancer has already been reviewed in an article published in this journal last year [11]; however, it did not expand upon local tumour staging within the prostate. Hence, this review will perform the following:

(1) Analyse the evidence from the literature on the use of choline PET imaging in identifying tumour foci within a prostate that has not received definitive treatment, and identify PET imaging variables that are shown to affect accuracy.
(2) Discuss the value added by choline PET imaging to MRI of the prostate.

DOI: 10.1097/MNM.0000000000000338

(3) Discuss the use of choline PET imaging for delineating areas for intraprostatic radiotherapy boost.
(4) Discuss how PET imaging can alter the patient pathway for radiotherapy if used routinely in the clinical setting.

Material and methods

We conducted a PubMed search using the following terms: PET[All Fields] AND ('prostatectomy'[MeSH Terms] OR 'prostatectomy'[All Fields]) AND ('anatomy and histology'[Subheading] OR ('anatomy'[All Fields] AND 'histology'[All Fields]) OR 'anatomy and histology'[All Fields] OR 'histology'[All Fields] OR 'histology'[MeSH Terms], and we selected studies that had used choline PET to identify tumour foci within the prostate, while using histology as the reference standard, in confirmed cancers that had not received definitive treatment previously. PET analysis data of patients who did not fit these criteria were excluded if the study involved a mix of patients, such as those in remission following definitive treatment. There were 10 articles for ^{11}C-choline PET and six articles for ^{18}F-choline PET. We also conducted a search for studies that had used both choline PET and MRI to identify tumour foci before prostatectomy by using the terms PET [All Fields] AND ('magnetic resonance imaging'[MeSH Terms] OR ('magnetic'[All Fields] AND 'resonance'[All Fields] AND 'imaging'[All Fields]) OR 'magnetic resonance imaging'[All Fields] OR 'mri'[All Fields]) AND ('prostate'[MeSH Terms] OR 'prostate'[All Fields]). Five relevant studies were found. Finally, we conducted a further search for studies that had used choline PET in radiotherapy planning using the terms PET[All Fields] AND ('prostate'[MeSH Terms] OR 'prostate'[All Fields]) AND ('radiotherapy'[Subheading] OR 'radiotherapy'[All Fields] OR 'radiotherapy'[MeSH Terms]). Overall, we also referred to and will discuss studies included in hand-searched review articles that are of interest.

Results

Patient cohorts

Studies that had analysed the histopathology of prostatectomy specimens included patients who had on average a lower risk score and smaller cancers compared with a typical high-risk radiotherapy cohort. It is therefore likely that the sensitivity in the group of radiotherapy patients is better than the published results. There was still a wide spread of clinical and pathological staging parameters in the studies: the Gleason score ranged from 2 to 10 and prostate specific antigen ranged from 0.2 to 462. Some of the patients had received neoadjuvant hormone therapy before scanning [12] or neoadjuvant chemotherapy [13] before prostatectomy, which may have reduced tracer uptake or the size of the tumour areas in the prostate [14,15]. Some studies had considered only tumour foci above a certain size on histological analysis, such as 5 mm diameter [16,17] or 1 cm^3 [13], resulting in higher accuracy compared with those without a minimal size criterion. These studies are more relevant to imaging before dose-painting radiotherapy as smaller tumour nodules and very low-grade lesions (Gleason score ≤ 6) do not require boost doses for control.

PET and PET/CT scanners used

Most studies had used Siemens Biograph (Siemens Medical, Erlangen, Germany) or GE Discovery (General Electric Medical Systems, Waukesha, Wisconsin, USA) scanners. Not all studies described the image reconstruction methods. Some had used iterative reconstruction with differing ordered subset expectation maximization (OSEM) algorithms, filters and reconstruction matrices (such as studies by Giovacchini and colleagues [12,13,16]).

Image acquisition protocols – ^{11}C-choline PET

Studies that had correlated ^{11}C-choline PET uptake with prostate histopathology are summarized in Table 1. The majority of studies had used static emission scanning only, and all of these had used early imaging, from 2 to 10 min after injection of the tracer [12,16–23]. Only one study had used dynamic imaging, beginning immediately after tracer injection and continued over 60 min [13].

The accuracy of static scans generally improves with increasing tracer uptake time (from 61.1% at 2 min [16] to 84% at 5–10 min [17]) and with increasing tracer doses (370 MBq gave an accuracy of 59.6% [12]; 370–555 MBq gave an accuracy of 71–72.5% [20,21]; 1112± 131 MBq gave an accuracy of 84% [17]). A short uptake time is not necessarily improved by a higher tracer dose: 740–1000 MBq ^{11}C-choline and an uptake time of 2 min gave an accuracy of 61.1% [16]. Emission detection duration ranged from 3 to 7 min per bed position. The dose of tracer used in the study that had scanned with a 3 min duration (1112 ± 131 MBq) was higher than that used in the studies that had scanned over a longer duration, potentially compensating for the short emission detection duration [17]; there are no specific data on the accuracy of identifying general malignancy in the study that detected emission for 7 min.

Image analysis protocols – ^{11}C-choline PET

For the image analysis method, visual correlation performed well for determining sextant involvement, with Farsad *et al.* [20] and Testa *et al.* [22] both reporting broadly similar sensitivities (66 and 55%) and specificities (81 and 86%). The results of using various standardized uptake value (SUV) thresholds to identify malignant segments were mixed (Table 2). Despite the relatively narrow range of the SUV_{max} threshold (2.5–2.9), specificity varied (42.6–87%), with no clear pattern, although sensitivity was more consistent (71.6–81%). Of note, Reske *et al.* [17] reported a sensitivity and specificity of 75 and 95%, respectively, with an SUV_{max} threshold of 3.05 when only tumour foci greater than 5 mm in

Table 1 Studies correlating ^{11}C-choline PET and histopathology (all used PET/CT, except Chang and colleagues, who used PET and transmission scanning)

Reference	*N*	Correlation method	Uptake time	Tracer dose	Scan sequence	Tumour size	Optimal method of tumour identification	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Van den Bergh *et al.* [16]	49	By octants	2 min	740–1000 MBq	Static over 5 min	> 5 mm diameter	Threshold of SUV_{max} 2.7	77.4	44.9	ND	ND	61.1
Souvatzoglou *et al.* [18]	43	By laterality[d]	5 min	682 ± 75 MBq	Static 3D over 3 min	Not specified	Not specified but highest choline uptake correlates with malignant segments in 79% of patients	ND	ND	ND	ND	ND
Bundschuh *et al.* [19]	20	By manual delineation	5 min	544–773 MBq	Static over 3–5 min	Mean 3.3 cm^3 (0.4–12.5 cm^3)	Fixed threshold SUV value of 4.9 ± 1.8 or variable threshold SUV_{max} of 75.8 ± 14%	ND	ND	ND	ND	ND
Giovacchini *et al.* [12][a]	19	By sextants	5 min	370 MBq	Static 2D over 4 min	Not specified	Threshold of SUV_{max} 2.5	71.6	42.6	64.0	51.3	59.6
Farsad *et al.* [20]	36	By sextants	5 min	370–555 MBq	Static over 5 min	Not specified	Only visual analysis performed	66	81	87	55	71
Martorana *et al.* [21][b]	43	By individual nodules and sextants	5 min	370–555 MBq	Static over 5 min	Not specified	Visual analysis by sextants	65.6	84.2	87.7	58.8	72.5
Testa *et al.* [22]	26	By sextants	5 min	370–555 MBq	Static over 5 min	Not specified	Threshold of SUV_{max} 2.9	72	65	ND	ND	72
Piert *et al.* [23]	14	Using ex-vivo MRI and block-face photography	5 min	700 MBq	Static over 7 min	0.03–12.6 cm^3	Not specified, but the tumour-to-normal tissue ratio identified aggressive disease better than absolute values	ND	ND	ND	ND	ND
Reske *et al.* [17]	26	By 36 segments	5–10 min	1112 ± 131 MBq	Static over 3 min	> 5 mm diameter	Threshold of SUV_{max} 2.65	81	87	86	83	84
Chang *et al.* [13][c]	8	At voxel level	Immediately	370 MBq	Dynamic over 60 min	≥ 1 cm^3	Relative SUV thresholding of 60%	79 ± 13	72 ± 17	ND	ND	ND

3D, three dimensional; 2D, two dimensional; *N*, number of patients; ND, not defined.
[a]Only patients who had radical prostatectomy in the study are included in this table (of these, seven of 19 patients had undergone hormone therapy previously).
[b]Unclear whether patients from the study by Farsad and colleagues are included.
[c]All patients received chemotherapy before prostatectomy.
[d]Merged consecutive axial slices due to partial volume effect.

Table 2 Sensitivity and specificity of ^{11}C-choline PET for identifying malignancies with varying SUV_{max} threshold values

Reference	n	Number of segments per prostate	Total number of segments analysed	SUV_{max} threshold	Sensitivity (%)	Specificity (%)
Giovacchini et al. [12]	19	6	114	2.5	71.6	42.6
Reske et al. [17]	26	36	936	2.65	81	87
Van den Bergh et al. [16]	49	24	1176	2.7	77.4	44.9
Testa et al. [22]	26	6	156	2.9	72	65

n, number of patients.

diameter were considered. A 60% SUV_{max} threshold (as a percentage within the region of interest – i.e. prostate) gave the best volume overlap between imaging and histology, as reported by Park *et al.* [24] (provided tumour volume is $\geq 4\,cm^3$ – i.e. sphere of 2.0 cm diameter) and Chang *et al.* [13], although it was not statistically significant in the latter study, with only eight patients imaged. Of interest, Souvatzoglou *et al.* [18] found that the highest choline uptake occurred in large unifocal tumours, whereas smaller or rind-shaped or multifocal tumours could be missed.

In summary, the available evidence suggests that ^{11}C-choline PET imaging improves with increasing uptake time and tracer dose, although more studies would be useful to confirm the former. In addition, further data are required to show whether emission time affects imaging accuracy.

Image acquisition protocols – ^{18}F-choline PET

There are comparatively fewer studies correlating ^{18}F-choline PET uptake and prostate histopathology, as summarized in Table 3. However, a higher proportion involved imaging at multiple time points. The earliest static imaging was performed with an uptake time of 2 min, which had a poor performance because of tracer uptake in areas of benign prostatic hyperplasia [25]. An early scan with an uptake time of 10 min achieved a sensitivity and specificity of 64 and 90%, respectively [26]. Similar values were achieved with imaging at 48 min [27], and they decreased with imaging at 60 min [28]. However, one study found that delayed (uptake time of 60 min) imaging did improve differentiation between benign and malignant sextants when compared with early imaging [29]. The longest uptake time was 90–120 min [30]. Although this study primarily analysed lymph node involvement, it found a correlation between sextants with highest tracer uptake and those with maximal tumour infiltration, which was also found by another study [26].

Image analysis protocols – ^{18}F-choline PET

Two studies, both with delayed imaging protocols, found that visual analysis tended to provide high sensitivity (91 and 90%) but low specificity (44 and 62%), with high positive predictive value (86 and 84%) but low negative predictive value (57 and 73%) [27,28]. An SUV_{max} threshold of 3.4 provided the highest documented accuracy of 81% [27].

In summary, the accuracy of ^{18}F-choline PET improves with delayed imaging (60–90 min). Further studies on this and quantitative analysis of dynamic imaging would be of interest.

Limitations of these studies comparing PET imaging and histopathology

These results may be influenced by the number of prostate segments used for correlation analysis between imaging and histology. For instance, some studies divided the prostate into only six segments [12,22], whereas others divided the prostate into 36 segments [17]. Statistically, small segment numbers will increase accuracy, whereas large numbers will increase the statistical power of the analysis. Both a small and a very large number of segments are not very useful clinically for dose-painting planning as there is either not enough information about the location of the tumour nodules or, alternatively, it is difficult to locate the segments on planning scans.

Use of step-section histopathology from the subsequent prostatectomy as a reference standard has inherent problems, with sample deformation and shrinkage before analysis [19,23,31,32]. Therefore, the coordinates of the histological segments may not match exactly with those of the imaging segments, potentially allowing errors when correlation between the two is attempted. Although most studies did not specifically account for this, some factored this into their analysis [19] and devised sophisticated fusion coregistration techniques [23], thereby lending more weight to their conclusions.

Is there any added value of choline PET imaging in MRI of the prostate?

T2-weighted (T2w) and diffusion-weighted (DWI) MRIs are the current standards for identifying tumour nodules within the prostate and have been used in the Focal lesion ablation microboost in prostate cancer randomized trial [33,34]. A comparative study of choline PET with MRI would involve performing both imaging techniques on the same patient, with histopathology as the reference standard (Table 4). We have not considered magnetic resonance spectroscopy in this review as it is not routinely performed in clinical practice and did not perform better than T2w MRI in a multiobserver study [35].

For ^{11}C-choline PET, a short uptake time of 2 min resulted in lower accuracy (61.6%) compared with T2w

Table 3 Studies correlating ^{18}F-choline PET and histopathology (all studies used ^{18}F-fluorocholine except Hartenbach and colleagues, who used ^{18}F-fluoroethylcholine)

Reference	*n*	Correlation method	Uptake time (sequence and time per bed position)	Tracer dose	Tumour size	Optimal method of tumour identification	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Schmid *et al.* [25]	10	Subjective visual correlation	2 min (static over 3 min)	214 ± 14 MBq	Not specified	PET correlated with histopathology in 1 patient only	ND	ND	ND	ND	ND
Kwee *et al.* [26][a]	15	By sextants	10 min (2D static over 7 min)	3.3–4 MBq/kg	Mean 4.9 ml	Threshold of SUV_{max} 5.6	64	90	ND	ND	72
Kwee *et al.* [29][b]	26	By sextants	7 min (2D static over 7 min), then 60 min (2D static over 7 min)	3.3–4 MBq/kg	Not specified	Mean malignant-to-benign ratio increased from 1.4 on initial scan to 1.8 on delayed scan	ND	ND	ND	ND	ND
Hartenbach *et al.* [27][c]	38	Direct analysis	Immediately (dynamic over 10 min), then 48 min (static over 3 min), then 71 min (static over 6 min)	3.3 MBq/kg	Not specified	Threshold of SUV_{mean} 3.4	63	90	83	76	81
Pinaquy *et al.* [28]	47	By sextants	Immediate (dynamic over 15 min), then 60 min (static over 2.5 min)	4 MBq/kg	Not specified	Threshold of SUV_{max} 4	60	78	ND	ND	ND
Beheshti *et al.* [30]	132	By sextants	1 min (dynamic over 8 min), then 10 min (2D static over 4 min), then 90–120 min (2D static over 4 min)	4.07 MBq/kg	Not specified	Only visual analysis performed (highest SUV sextant had maximal tumour infiltration)	ND	ND	ND	ND	ND

[a] Study included a combination of patients with newly confirmed diagnosis and recurrent prostate cancer patients; two of the patients had undergone hormone therapy previously. [b] All studies used PET/CT except that by Kwee and colleagues (a) and (b), and Hartenbach and colleagues (c).
2D, two dimensional; *N*, number of patients; ND, not defined.

MRI (70.2%) [16]. However, with a longer uptake time of 5 min, the accuracy of PET improved and exceeded that of T2w MRI [22,36]. A separate study performed both MRI and ^{11}C-choline PET scanning in 17 patients [37] (14 patients have already been described [23]). Although this study did not compare the accuracy of tumour localization between PET and MRI in relation to histology, PET and MRI together could identify aggressive disease better than either modality alone.

For ^{18}F-choline PET, one study found that DWI MRI is better than both T2w MRI and PET (with 60 min uptake time) for tumour localization and local evaluation [28]. These studies that performed the imaging as separate modalities and subsequently fused the scans for analysis can have registration errors. However, the study by Hartenbach *et al.* [27] did achieve optimal spatial and temporal coregistration by performing both scans while keeping the patient on the same imaging table with the urinary catheter and endorectal coil *in situ* throughout, and also used fiducial markers. The accuracy of T2w MRI was 60%, that of PET (uptake time of 48 min) was 81%, and that of combined PET and MRI was 88%. Of interest, studies have shown that integrated PET/MRI scanners may generally improve the identification of significant prostate cancer [37,38]. One study showed that accuracy was slightly higher for MRI (76%) compared with ^{18}F-choline PET/MRI (75%) for the whole prostate, although PET/MRI was significantly more accurate (83%) compared with MRI (78%) when considering only the peripheral zone [39]. Another study showed that cancer was detected in 80% of patients by ^{18}F-choline PET, in 83.3% of patients by MRI, and in 93.3% by PET/MRI [40]. It should be noted that the study performing DWI MRI [28] had used endorectal coils for signal reception, which can affect the accuracy by causing image deformation [8,27,32,41,42].

Overall, the evidence suggests that ^{11}C-choline PET/CT with longer uptake time has superior accuracy to T2w MRI alone, whereas ^{18}F-choline PET/CT with late image acquisition has superior accuracy to T2w MRI and functional MRI alone. The combination of PET and MRI (as PET/CT and MRI, or integrated PET/MRI) is better than either imaging modality.

Use of choline PET for outlining boost volumes for radiotherapy

Choline PET has already been used to investigate intraprostatic dose escalation radiotherapy in theoretical modelling studies. The overlap between PET tumour areas defined by different SUV_{max} threshold levels and malignant histology was investigated to define intraprostatic target volume [24] using the PET sequencing protocol published by Piert *et al.* [23]. They concluded that an SUV_{max} threshold of 60% within the prostate provided the best overlap with histology using a sophisticated registration technique, although only four patients

Table 4 Studies correlating both choline PET/CT and MRI (1.5 T) with histopathology

Reference	*n*	Correlation method	PET tracer	PET tracer uptake time (sequence and duration)	PET tracer dose	MRI techniques for prostate analysis	Tumour size	PET sensitivity (%)	PET specificity (%)	PET accuracy (%)	MRI sensitivity (%)	MRI specificity (%)	MRI accuracy (%)	Conclusion
Van den Bergh *et al.* [16]	49	By octants	^{11}C-choline	2 min (static over 5 min)	740–1000 MBq	T2w spin echo	> 5 mm diameter	77.4	44.9	61.6	33.5	94.6	70.2	For octant localization, PET (threshold SUV_{max} of 2.7) was more sensitive but less specific than MRI
Testa *et al.* [22]	26	By sextants	^{11}C-choline	5 min (static over 5 min)	370–555 MBq	T2w spin echo – endorectal coil used	Not specified	55	86	67	54	75	61	For sextant localization, PET was more accurate than MRI
Yamaguchi *et al.* [36]	20	By laterality	^{11}C-choline	5 min (static over 5 min)	370 MBq	T2w spin echo – endorectal coil used	Not specified	81	ND	ND	≤ 60	ND	ND	For laterality localization, ^{11}C-choline was superior to MRI
Pinaquy *et al.* [28]	47	By sextants	^{18}F-fluorocholine	Immediately (dynamic over 15 min), then 60 min (static over 2.5 min)	4 MBq/kg	T2w, DWI, DCE	Not specified	60	76	ND	72	69	ND	For sextant localization, SUV_{max} threshold of 4 had higher specificity but lower sensitivity than DWI MRI
Hartenbach *et al.* [27]	38	By direct analysis	^{18}F-fluoroethycholine	Immediately (dynamic over 10 min), then 48 min (static over 2 min), then 71 min (static over 6 min)	3.3 MBq/kg	T2w spin echo – endorectal coil used	Not specified	90	62	81	73	31	60	For direct correlation with histology, PET visual analysis was more accurate than MRI, but improved to 88% when combined

DCE, dynamic contrast enhancement imaging; DWI, diffusion-weighted; *N*, number of patients; ND, not defined; T2w, T2-weighted.

were analysed, as only tumours measuring 4 cm^3 or more were included. Chang *et al.* [43] also performed a radiobiological modelling planning study using ^{11}C-choline with data acquired over 60 min, which showed that both 60 and 70% SUV_{max} thresholds could be used for semi-automatic contouring of boost areas while adhering to predetermined dose constraints.

Several dose-painting studies were conducted by Pinkawa and colleagues [10,14] using simultaneous boost volumes defined by PET/CT: in 2009 and 2010, they published two treatment-planning studies including 12 and 66 prostate cancer patients, respectively, who underwent integrated PET/CT imaging 1 h after injection of 178–355 MBq ^{18}F-choline. They used a tumour-to-background SUV_{max} ratio of more than 2 to define the dose escalation volume, on the basis of the results from previous studies [17,20,26,29]. In 2012, they reported that they had treated 46 patients using this technique, and preliminary results did not show significantly increased toxicity [44].

At our centre, we have been treating patients with dose-painting radiotherapy in the Biologically Optimised IMRT for Prostate Radiotherapy (BIOPROP) study series (NCT02125175) for several years using MRI, and more recently have incorporated visual analysis of ^{18}F-choline PET/CT imaging into the radiotherapy planning process [45]. Our experience has shown that PET imaging can often help outline tumour lesions when they are difficult to define on MRI alone (Fig. 1).

How PET imaging may alter the patient pathway for radiotherapy if used routinely in the clinical setting

In current practice, newly diagnosed, histologically confirmed intermediate and high-risk patients with localized disease (PSA ≥ 10, Gleason score ≥7, clinical staging T2b–T4) are staged with pelvic T2w and functional MRI as well as a bone scan [46]. If localized, the main curative options are radical prostatectomy or radiotherapy. Radiotherapy is commonly used for high-risk patients, providing good outcomes. For standard radiotherapy planning, the clinician outlines treatment volumes on a planning CT scan, and a therapeutic dose of 74–78 Gy is delivered to the whole prostate in 37–39 fractions over 7.5–8 weeks [47]. It is standard practice to treat these patients with neoadjuvant hormone therapy around 3 months before as well as during radiotherapy, which in a meta-analysis has been shown to improve survival compared with radiotherapy alone [48]. It is not recommended to start hormone therapy shortly before treatment, as it might result in prostate volume changes during the course of radiotherapy.

If PET/CT is performed, the CT component can be directly used for radiotherapy planning, with dose escalation to the tumour foci without additional image fusion, which would be required with MRI. As discussed, hormone therapy reduces prostate volume and tracer uptake significantly. Therefore, if patients are scanned before hormone therapy, the tumour foci may be more easily detectable, although the subsequent prostate and tumour volumes at the time of radiotherapy may be smaller because of incurring cell death and apoptosis. It would therefore be necessary to use a second CT scan for the planning. However, if patients are scanned after starting hormone therapy, the tumour volumes will have, in our experience, a lower uptake, and the volume might not be representative of the original volume.

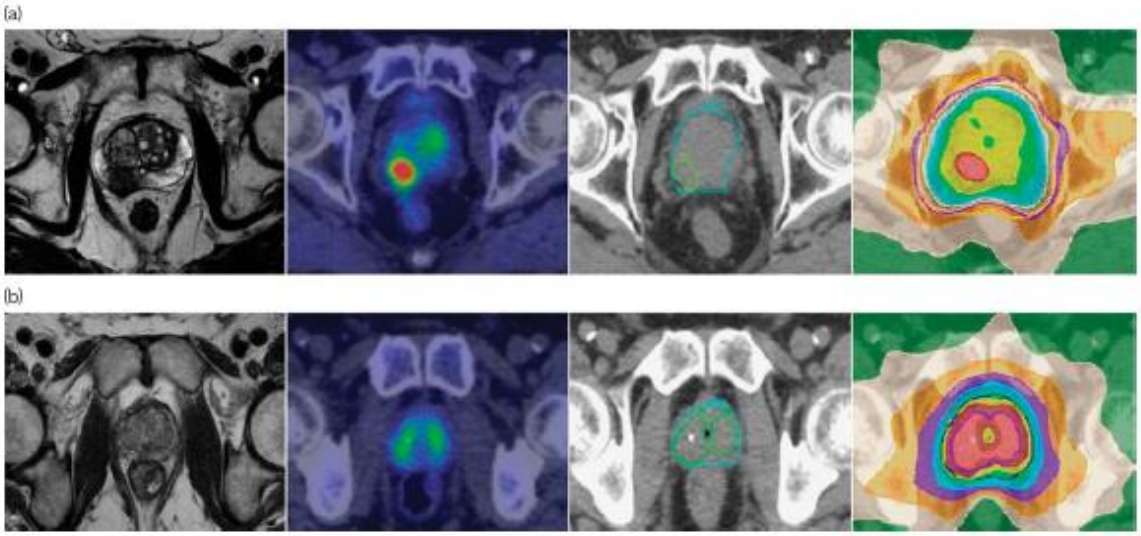
Patients suitable for dose-painting radiotherapy have around 20–40% risk for positive lymph node disease in surgical series using extended lymph node resection, even if the pelvic MRI staging scans are normal [49,50]. Rather than treating all patients with pelvic node radiotherapy, which increases bowel toxicity significantly, a staging PET scan could be used to identify those with pelvic lymph node or metastatic disease [51], and the patient can be managed appropriately. For example, we have identified positive uptake in lymph nodes of normal morphological size in several patients within our PET study series, and a recent meta-analysis found that choline PET/CT results directly changed the management plan for a third of patients [11]. Sensitivity has been reported as being generally low (^{11}C-choline at 41.4% and ^{18}F-choline at 33%), but specificity is high (^{11}C-choline at 99.8% and ^{18}F-choline at 92%) [51,52].

Discussion

Radiotherapy is universally accepted as the most effective nonsurgical treatment strategy for cancer. At present, the standard management strategy for intermediate-risk or high-risk localized prostate cancer patients in the UK is radiotherapy with hormone therapy. Over the last 10 years, radiotherapy computer planning and treatment technology have progressed significantly. Intensity-modulated radiotherapy techniques and image-guided radiotherapy can reduce toxicity and give rise to opportunities for more intensive, risk-adapted treatments. If advances in radiotherapy technology, such as dose painting, can be used to safely escalate the radiation dose delivered to key areas of risk within the prostate, there is potential for improved outcomes for patients. Functional imaging with PET contributes in this regard.

This is the first published review specifically on ^{11}C-choline and ^{18}F-choline PET scanning protocols for the identification of intraprostatic tumour foci and their imaging performance. These studies demonstrate the numerous variables that might have influenced the results, including uptake time, dose of tracer injected, total acquisition time, scanning sequence used (static and dynamic), and image reconstruction methods. The studies varied in how images were correlated to histology or to a different imaging modality, such as the degree of

Fig. 1



T2w MRI, ^{18}F-choline PET with an uptake time of 60 min, radiotherapy outlining (blue, prostate; green, tumour) and radiation dose distribution of two patients scanned at our centre. (a) A 79-year-old man with T3b, PSA 25.6, and Gleason 3+3 disease, for whom MRI and PET correspond well for tumour identification. (b) A 70-year-old man with T2c, PSA 16.4, and Gleason 3+4 disease, for whom the tumour could not be clearly identified on MRI alone, and both MRI and PET allowed the dose escalation area to be defined.

segmentation used (e.g. by broad anatomical terms or by sophisticated coregistration techniques).

Overall, a longer uptake time and an increasing tracer dose can generally improve accuracy. A previous review article concluded that more prospective ^{11}C-choline PET data are required to identify accurate PET tissue delineating processes [53]. Another review concluded that the overall performance of ^{18}F-choline is not clear and that there is a need for a standardized scanning protocol to be developed [54].

For the purposes of dose-painting radiotherapy, imaging should identify tumour foci with high accuracy (it may be argued especially more so for specificity, given that a treatment dose is already planned for the whole prostate [16]). The majority of these correlation studies did not define the gross tumour borders, but used prostate segments (e.g. sextants). This is relevant for providing a useful indication of tumour location, but normally dose painting requires a delineated volume rather than a segment location.

A concern with intraprostatic dose escalation radiotherapy is the inadvertent treatment of a nonmalignant region because of false-positive imaging results [33]. For example, tracer uptake has been seen in 29% of sextants with high-grade intraepithelial neoplasia only and no malignancy [22]. From our experience, PET uptake in malignant lesions identified on MRI increases with uptake time, and thus an improved imaging protocol can reduce these issues.

It is generally agreed that SUV is influenced by hormone therapy [12,14,15]. However, there is conflicting evidence on the correlation between SUVs and some key prognostic factors such as the Gleason score and PSA levels, although most studies suggest that no relationship exists [12,14,16–21, 26,29,30,55,56]. For instance, Breeuwsma *et al.* [57] found that there was no correlation between absolute ^{11}C-choline uptake and cell proliferation by Ki-67 labelling in prostate cancer in a small sample of 18 patients, and yet Piert *et al.* [23] suggested that the $SUV_{max/mean}$ tumour-to-background ratio did significantly increase with the Ki-67 labelling index. Furthermore, Chang *et al.* [58] found that a combination of DWI MRI and ^{11}C-choline PET did achieve significant correlations with the Gleason score. Therefore, although a combination of MRI and choline PET may improve the accuracy of tumour outlining [59], the SUVs are unable to contribute to radiotherapy planning dose calculations. Of note, Van den Bergh *et al.* [16] showed that a combination of PET/CT and T2w MRI increases sensitivity but decreases specificity, whereas Testa *et al.* [22] showed that a combination of PET/CT, T2w MRI, and magnetic resonance spectroscopy increases both.

Further research on the use of choline PET for tumour identification should yield promising results. For ^{11}C-choline PET, studies involving multiphase imaging may be of use as they have not been performed before, as may more studies

on dynamic imaging. For ^{18}F-choline PET, quantitative data from dynamic imaging would be of interest, as well as performing even more delayed imaging given that differentiation between benign and malignant segments has been shown to improve with uptake time [29]. Furthermore, integrated PET/MRI may provide further evidence on the added benefit of PET over MRI and, using 3 T MRI machines, image deformation would be minimized as endorectal coils may be omitted. All of this would contribute to identifying an optimal PET scanning sequence with which to outline tumour lesions for radiotherapy dose escalation.

Conclusion

A review published by this journal last year has discussed the use of choline PET in general imaging for prostate cancer [11]. Current evidence set out in this article shows that the accuracy of ^{18}F-choline PET/CT for staging of newly diagnosed prostate cancer is improved by increasing the tracer dose and by delaying scanning (the optimal uptake time is unclear). It also shows the increased accuracy achieved when PET imaging is combined with MRI, compared with MRI alone. Ultimately, it is likely that the most accurate tumour outlining will result from a combination of multiparametric MRI and PET scanning [22,27,37].

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Karavitakis M, Ahmed HU, Abel PD, Hazell S, Winkler MH. Reviews tumor focality in prostate cancer: implications for focal therapy. *Nat Publ Gr* 2010; **8**:48–55.
2 Tanderup K, Olsen DR, Grau C. Dose painting: art or science? *Radiother Oncol* 2006; **79**:245–248.
3 Dearnaley DP, Jovic G, Syndikus I, Khoo V, Cowan RA, Graham JD, *et al.* Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2014; **15**:464–473.
4 Syndikus I, Morgan RC, Sydes MR, Graham JD, Dearnaley DP. MRC RT01 collaborators. Late gastrointestinal toxicity after dose-escalated conformal radiotherapy for early prostate cancer: results from the UK Medical Research Council RT01 trial (ISRCTN47772397). *Int J Radiat Oncol Biol Phys* 2010; **77**:773–783.
5 Nahum AE, Uzan J. (Radio)biological optimization of external-beam radiotherapy. *Comput Math Methods Med* 2012; **2012**:329214.
6 Niyazi M, Bartenstein P, Belka C, Ganswindt U. Choline PET based dose-painting in prostate cancer – modelling of dose effects. *Radiat Oncol* 2010; **5**:23.
7 Cellini N, Morganti AG, Mattiucci GC, Valentini V, Leone M, Luzi S, *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.
8 Bauman G, Haider M, Van der Heide UA, Ménard C. Boosting imaging defined dominant prostatic tumors: a systematic review. *Radiother Oncol* 2013; **107**:274–281.
9 van Lin ENJT, Futterer JJ, Heijmink SWTPJ, van der Vight LP, Hoffmann AL, van Kollenburg P, *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.
10 Pinkawa M, Attieh C, Piroth MD, Holy R, Nussen S, Klotz J, *et al.* Dose-escalation using intensity-modulated radiotherapy for prostate cancer – evaluation of the dose distribution with and without ^{18}F-choline PET-CT detected simultaneous integrated boost. *Radiother Oncol* 2009; **93**:213–219.
11 von Eyben FE, Kairemo K. Meta-analysis of (11)C-choline and (18)F-choline PET/CT for management of patients with prostate cancer. *Nucl Med Commun* 2014; **35**:221–230.
12 Giovacchini G, Picchio M, Coradeschi E, Scattoni V, Bettinardi V, Cozzarini C, *et al.* [^{11}C]choline uptake with PET/CT for the initial diagnosis of prostate cancer: relation to PSA levels, tumour stage and anti-androgenic therapy. *Eur J Nucl Med Mol Imaging* 2008; **35**:1065–1073.
13 Chang JH, Joon DL, Lee ST, Gong SJ, Scott AM, Davis ID, *et al.* Histopathological correlation of (11)C-choline PET scans for target volume definition in radical prostate radiotherapy. *Radiother Oncol* 2011; **99**:187–192.
14 Pinkawa M, Holy R, Piroth MD, Klotz J, Nussen S, Krohn T, *et al.* Intensity-modulated radiotherapy for prostate cancer implementing molecular imaging with ^{18}F-choline PET-CT to define a simultaneous integrated boost. *Strahlenther Onkol* 2010; **186**:600–606.
15 Beheshti M, Haroon A, Bomanji JB, Langsteger W. Fluorocholine PET/computed tomography: physiologic uptake, benign findings, and pitfalls. *PET Clin* 2014; **9**:299–306.
16 Van den Bergh L, Koole M, Isebaert S, Joniau S, Deroose CM, Oyen R, *et al.* Is there an additional value of ^{11}C-choline PET-CT to T2-weighted MRI images in the localization of intraprostatic tumor nodules? *Int J Radiat Oncol Biol Phys* 2012; **83**:1486–1492.
17 Reske SN, Blumstein NM, Neumaier B, Gottfried H-W, Finsterbusch F, Kocot D, *et al.* Imaging prostate cancer with ^{11}C-choline PET/CT. *J Nucl Med* 2006; **47**:1249–1254.
18 Souvatzoglou M, Weirich G, Schwarzenboeck S, Maurer T, Schuster T, Bundschuh RA, *et al.* The sensitivity of [^{11}C]choline PET/CT to localize prostate cancer depends on the tumor configuration. *Clin Cancer Res* 2011; **17**:3751–3759.
19 Bundschuh RA, Wendl CM, Weirich G, Eiber M, Souvatzoglou M, Treiber U, *et al.* Tumour volume delineation in prostate cancer assessed by [^{11}C]choline PET/CT: validation with surgical specimens. *Eur J Nucl Med Mol Imaging* 2013; **40**:824–831.
20 Farsad M, Schiavina R, Castellucci P, Nanni C, Corti B, Martorana G, *et al.* Detection and localization of prostate cancer: correlation of (11)C-choline PET/CT with histopathologic step-section analysis. *J Nucl Med* 2005; **46**:1642–1649.
21 Martorana G, Schiavina R, Corti B, Farsad M, Salizzoni E, Brunocilla E, *et al.* ^{11}C-choline positron emission tomography/computerized tomography for tumor localization of primary prostate cancer in comparison with 12-core biopsy. *J Urol* 2006; **176**:954–960. discussion 960.
22 Testa C, Schiavina R, Lodi R, Salizzoni E, Corti B, Farsad M, *et al.* Prostate cancer: sextant localization with MR imaging, MR spectroscopy, and ^{11}C-choline PET/CT. *Radiology* 2007; **244**:797–806.
23 Piert M, Park H, Khan A, Siddiqui J, Hussain H, Chenevert T, *et al.* Detection of aggressive primary prostate cancer with ^{11}C-choline PET/CT using multimodality fusion techniques. *J Nucl Med* 2009; **50**:1585–1593.
24 Park H, Meyer CR, Wood D, Khan A, Shah R, Hussain H, *et al.* Validation of automatic target volume definition as demonstrated for ^{11}C-choline PET/CT of human prostate cancer using multi-modality fusion techniques. *Acad Radiol* 2010; **17**:614–623.
25 Schmid DT, John H, Zweifel R, Cservenyak T, Westera G, Goerres GW, *et al.* Fluorocholine PET/CT in patients with prostate cancer: initial experience. *Radiology* 2005; **235**:623–628.
26 Kwee SA, Thibault GP, Stack RS, Coel MN, Furusato B, Sesterhenn IA. Use of step-section histopathology to evaluate ^{18}F-fluorocholine PET sextant localization of prostate cancer. *Mol Imaging* 2008; **7**:12–20.
27 Hartenbach M, Hartenbach S, Bechtloff W, Danz B, Kraft K, Klemenz B, *et al.* Combined PET/MRI improves diagnostic accuracy in patients with prostate cancer: a prospective diagnostic trial. *Clin Cancer Res* 2014; **20**:3244–3253.
28 Pinaquy J-B, De Clermont-Galleran H, Pasticier G, Rigou G, Alberti N, Hindie E, *et al.* Comparative effectiveness of [(18) F]-fluorocholine PET-CT and pelvic MRI with diffusion-weighted imaging for staging in patients with high-risk prostate cancer. *Prostate* 2014; **75**:323–331.
29 Kwee SA, Wei H, Sesterhenn I, Yun D, Coel MN. Localization of primary prostate cancer with dual-phase ^{18}F-fluorocholine PET. *J Nucl Med* 2006; **47**:262–269.
30 Beheshti M, Imamovic L, Broinger G, Vali R, Waldenberger P, Stoiber F, *et al.* ^{18}F choline PET/CT in the preoperative staging of prostate cancer in patients with intermediate or high risk of extracapsular disease: a prospective study of 130 patients. *Radiology* 2010; **254**:925–933.
31 Korporaal JG, van den Berg CAT, Groenendaal G, Moman MR, van Vulpen M, van der Heide UA. The use of probability maps to deal with the

uncertainties in prostate cancer delineation. *Radiother Oncol* 2010; **94**:168–172.
32 Zaidi H, El Naqa I. PET-guided delineation of radiation therapy treatment volumes: a survey of image segmentation techniques. *Eur J Nucl Med Mol Imaging* 2010; **37**:2165–2187.
33 Kitajima K, Murphy RC, Nathan MA, Sugimura K. Update on positron emission tomography for imaging of prostate cancer. *Int J Urol* 2014; **21**:12–23.
34 Lips IM, Van Der Heide UA, Haustermans K, Van Lin ENJT, Pos F, Franken SPG, *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* 2011; **12**:255.
35 Bittencourt LK, Hausmann D, Sabaneeff N, Gasparetto EL, Barentsz JO. Multiparametric magnetic resonance imaging of the prostate: current concepts. *Radiol Bras* 2014; **47**:292–300.
36 Yamaguchi T, Lee J, Uemura H, Sasaki T, Takahashi N, Oka T, *et al.* Prostate cancer: a comparative study of ^{11}C-choline PET and MR imaging combined with proton MR spectroscopy. *Eur J Nucl Med Mol Imaging* 2005; **32**:742–748.
37 Park H, Wood D, Hussain H, Meyer CR, Shah RB, Johnson TD, *et al.* Introducing parametric fusion PET/MRI of primary prostate cancer. *J Nucl Med* 2012; **53**:546–551.
38 Wetter A, Nensa F, Schenck M, Heusch P, Püppel T, Bockisch A, *et al.* Combined PET imaging and diffusion-weighted imaging of intermediate and high-risk primary prostate carcinomas with simultaneous [^{18}F] choline PET/MRI. *PLoS One* 2014; **9**:e101571.
39 De Perrot T, Rager O, Scheffler M. Potential of hybrid ^{18}F-fluorocholine PET/MRI for prostate cancer imaging. *Eur J Nucl Med Mol Imaging* 2014; **41**:1744–1755.
40 Kim Y, Cheon GJ, Paeng JC, Chung J, Kim EE, Lee DS. Usefulness of MR-assisted metabolic volumetric parameters provided by simultaneous ^{18}F-fluorocholine PET/MRI for primary prostate cancer characterization. *Eur J Nucl Med Mol Imaging* 2015. [Epub ahead of print].
41 Wang H, Vees H, Miralbell R, Wissmeyer M, Steiner C, Ratib O, *et al.* ^{18}F-fluorocholine PET-guided target volume delineation techniques for partial prostate re-irradiation in local recurrent prostate cancer. *Radiother Oncol* 2009; **93**:220–225.
42 Groenendaal G, Moman MR, Korporaal JG, van Diest PJ, van Vulpen M, Philippens ME, van der Heide UA. Validation of functional imaging with pathology for tumor delineation in the prostate. *Radiother Oncol* 2010; **94**:145–150.
43 Chang JH, Lim Joon D, Lee ST, Gong SJ, Anderson NJ, Scott AM, *et al.* Intensity modulated radiation therapy dose painting for localized prostate cancer using ^{11}C-choline positron emission tomography scans. *Int J Radiat Oncol Biol Phys* 2012; **83**:e691–e696.
44 Pinkawa M, Piroth MD, Holy R, Klotz J, Djukic V, Corral NE, *et al.* Dose-escalation using intensity-modulated radiotherapy for prostate cancer – evaluation of quality of life with and without (18)F-choline PET-CT detected simultaneous integrated boost. *Radiat Oncol* 2012; **7**:14.
45 Vinjamuri S, Uzan J, Riley A, Mayles P. ^{18}Fluoro-ethyl choline PET CT for radiobiologically optimised prostate dose-painting (BIOPROP). *Radiother Oncol* 2012; **103**:S335.
46 National Institute for Clinical Excellence. *Prostate cancer: diagnosis and treatment*. London: National Institute for Clinical Excellence; 2014.
47 The Royal College of Radiologists. *Radiotherapy dose-fractionation*. London: The Royal College of Radiologists; 2006.
48 Bria E, Cuppone F, Giannarelli D, Milella M, Ruggeri EM, Sperduti I, *et al.* Does hormone treatment added to radiotherapy improve outcome in locally advanced prostate cancer?: meta-analysis of randomized trials. *Cancer* 2009; **115**:3446–3456.
49 Rahman S, Cosmatos H, Dave G, Williams S, Tome M. Predicting pelvic lymph node involvement in current-era prostate cancer. *Int J Radiat Oncol Biol Phys* 2012; **82**:906–910.
50 Roach M 3rd, Marquez C, Yuo HS, Narayan P, Coleman L, Nseyo UO, *et al.* Predicting the risk of lymph node involvement using the pre-treatment prostate specific antigen and Gleason score in men with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 1994; **28**:33–37.
51 Kjölhede H, Ahlgren G, Almquist H, Liedberg F, Lyttkens K, Ohlsson T, Bratt O. ^{18}F-fluorocholine PET/CT compared with extended pelvic lymph node dissection in high-risk prostate cancer. *World J Urol* 2014; **32**:965–970.
52 Schiavina R, Scattoni V, Castellucci P, Picchio M, Corti B, Briganti A, *et al.* ^{11}C-choline positron emission tomography/computerized tomography for preoperative lymph-node staging in intermediate-risk and high-risk prostate cancer: comparison with clinical staging nomograms. *Eur Urol* 2008; **54**:392–401.
53 De Bari B, Alongi F, Lestrade L, Giammarile F. Choline-PET in prostate cancer management: the point of view of the radiation oncologist. *Crit Rev Oncol Hematol* 2014; **91**:234–247.
54 Bauman G, Belhocine T, Kovacs M, Ward A, Beheshti M, Rachinsky I. 18F-fluorocholine for prostate cancer imaging: a systematic review of the literature. *Prostate Cancer Prostatic Dis* 2012; **15**:45–55.
55 Würschmidt F, Petersen C, Wahl A, Dahle J, Kretschmer M. [^{18}F] fluoroethylcholine-PET/CT imaging for radiation treatment planning of recurrent and primary prostate cancer with dose escalation to PET/CT-positive lymph nodes. *Radiat Oncol* 2011; **6**:44.
56 Sutinen E, Nurmi M, Roivainen A, Varpula M, Tolvanen T, Lehikoinen P, Minn H. Kinetics of [(11)C]choline uptake in prostate cancer: a PET study. *Eur J Nucl Med Mol Imaging* 2004; **31**:317–324.
57 Breeuwsma AJ, Pruim J, Jongen MM, Suurmeijer AJ, Vaalburg W, Nijman RJ, de Jong IJ. In vivo uptake of [^{11}C]choline does not correlate with cell proliferation in human prostate cancer. *Eur J Nucl Med Mol Imaging* 2005; **32**:668–673.
58 Chang JH, Lim Joon D, Lee ST, Hiew C-Y, Esler S, Gong SJ, *et al.* Diffusion-weighted MRI, ^{11}C-choline PET and ^{18}F-fluorodeoxyglucose PET for predicting the Gleason score in prostate carcinoma. *Eur Radiol* 2014; **24**:715–722.
59 Turkbey B, Pinto PA, Choyke PL. Imaging techniques for prostate cancer: implications for focal therapy. *Nat Rev Urol* 2009; **6**:191–203.

Effect of androgen deprivation therapy on intraprostatic tumour volume identified on ^{18}F choline PET/CT for prostate dose painting radiotherapy

***Chan J**, Carver A, Brunt JNH, Vinjamuri S, Syndikus I*

British Journal of Radiology 2017 March 90(1071), 20160818

BJR

Received: 20 October 2016 | Revised: 5 December 2016 | Accepted: 14 December 2016
https://doi.org/10.1259/bjr.20160818

Cite this article as:
Chan J, Carver A, Brunt JNH, Vinjamuri S, Syndikus I. Effect of androgen deprivation therapy on intraprostatic tumour volume identified on ^{18}F choline PET/CT for prostate dose painting radiotherapy. *Br J Radiol* 2017; **90**: 20160818.

FULL PAPER

Effect of androgen deprivation therapy on intraprostatic tumour volume identified on ^{18}F choline PET/CT for prostate dose painting radiotherapy

[1]JOACHIM CHAN, MBBS, BSc, [1]ANTONY CARVER, PhD, [1]JOHN N H BRUNT, PhD, [2]SOBHAN VINJAMURI, MD and [1]ISABEL SYNDIKUS, MD

[1]Radiotherapy Department, Clatterbridge Cancer Centre NHS Foundation Trust, Bebington, UK
[2]Nuclear Medicine Department, Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, UK

Address correspondence to: Dr Joachim Chan
E-mail: *Joachim.chan@clatterbridgecc.nhs.uk*

Objective: Prostate dose painting radiotherapy requires the accurate identification of dominant intraprostatic lesions (DILs) to be used as boost volumes; these can be identified on multiparametric MRI (mpMRI) or choline positron emission tomography (PET)/CT. Planning scans are usually performed after 2–3 months of androgen deprivation therapy (ADT). We examine the effect of ADT on choline tracer uptake and boost volumes identified on choline PET/CT.

Methods: Fluoroethylcholine (^{18}F choline) PET/CT was performed for dose painting radiotherapy planning in patients with intermediate- to high-risk prostate cancer. Initially, they were performed at planning. Owing to low visual tracer uptake, PET/CT for subsequent patients was performed at staging. We compared these two approaches on intraprostatic lesions obtained on PET using both visual and automatic threshold methods [prostate maximum standardized uptake value (SUV_{max}) 60%] when compared with mpMRI.

Results: PET/CT was performed during ADT in 11 patients (median duration of 85 days) and before ADT in 29 patients. ADT significantly reduced overall prostate volume by 17%. During ADT, prostate SUV_{max} was lower although it did not reach statistical significance (4.2 *vs* 6.6, $p = 0.06$); three patients had no visually identifiable PET DIL; and visually defined PET DILs were significantly smaller than corresponding mpMRI DILs ($p = 0.03$). However, all patients scanned before ADT had at least one visually identifiable PET DIL, with no significant size difference between MRI and visually defined PET DILs. In both groups, threshold PET produced larger DILs than visual PET. Both PET methods have moderate sensitivity (0.50–0.68) and high specificity (0.85–0.98) for identifying MRI-defined disease.

Conclusion: For visual contouring of boost volumes in prostate dose painting radiotherapy, ^{18}F choline PET/CT should be performed before ADT. For threshold contouring of boost volumes using our PET/CT scanning protocol, threshold levels of above 60% prostate SUV_{max} may be more suitable. Additional use of PET with MRI for radiotherapy planning can significantly change the overall boost volumes compared with using MRI alone.

Advances in knowledge: For prostate dose painting radiotherapy, the additional use of ^{18}F choline PET with MRI can significantly change the overall boost volumes, and PET should be performed before hormone therapy, especially if boost volumes are visually identified.

INTRODUCTION

Higher radiation doses to the whole prostate have been shown to improve biochemical relapse free survival for prostate cancer but at the cost of increased rectal toxicity.[1] Dose painting radiotherapy boosts tumour volumes [dominant intraprostatic lesions (DILs)] whilst delivering the standard dose to the rest of the prostate. Cohort studies have demonstrated outcomes without increased toxicity.[2–5] These DILs have been contoured using a co-registered multiparametric MRI (mpMRI) in several studies such as Dose EscaLation to Intraprostatic tumour Nodules in localised prostate Cancer (DELINEATE) (ISRCTN04483921), Hypofractionated External beam Image-Guided Highly Targeted radiotherapy (HEIGHT) (NCT01411332) and Focal Lesion Ablation Microboost In Prostate Cancer (FLAME) trials.[6]

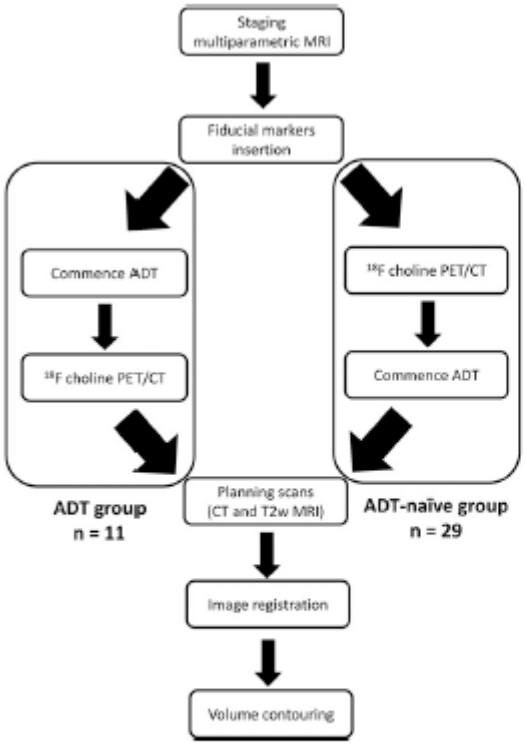
An alternative imaging modality for identifying lesions is the positron emission tomography CT scan (PET/CT). The standard treatment protocol for patients of intermediate and high risks combines several months of neoadjuvant androgen deprivation therapy (ADT) prior to radiotherapy. One option is for the PET/CT scan to be performed before

ADT (*i.e.* at staging), which will allow outlining of the original boost volume. However, this can complicate co-registration of the PET with planning CT since 2–3 months of ADT can reduce the overall prostate size by around 10–20%. Another option is for the PET/CT to be performed during ADT. This would allow the CT component of the scan to be used for planning, reducing the requirement for image co-registration and the number of scans performed. Studies have used this second option, but there are no data available to quantify the effects of ADT on the intraprostatic tracer uptake and boost volume sizes.[2]

Different isotopes have been used to radiolabel choline as a tracer for prostate cancer.[7] There is more evidence for the use of ^{11}C choline, where automatic contouring by using the threshold of $SUV_{60\%}$ was found to result in the best correlation with pathology in the only study that has systematically analysed different threshold methods.[8] However, fluoroethylcholine (^{18}F choline) has the advantage of a longer half-life which allows its use at centres without an onsite cyclotron and permits use of imaging protocols involving prolonged uptake times.[9] Currently, there is no available evidence for the best threshold to use for ^{18}F choline.

The Biologically Optimised Intensity Modulated Radiotherapy for Prostate Radiotherapy clinical trial (NCT02125175) investigating dose painting by contours used both MRI [staging mpMRI and planning T_2 weighted MRI (T2w MRI)] and ^{18}F choline PET/CT to define the boost volumes.[5] In the study development phase, patients had PET/CT imaging at planning whilst on ADT ("ADT group"). As visual tracer uptake was noted to be low for the first 10 patients, subsequent patients had PET/CT imaging at staging before ADT ("ADT-naïve group"). By using the tumour volumes defined on MRI as the reference standard, we have retrospectively analysed these scans to quantify the effect of ADT on the tumour volumes on PET, identified either by manual contouring (visual method) or automatic contouring (threshold method of 60% of prostate maximum SUV).

Figure 1. Sequence of imaging in both groups. ^{18}F choline, fluoroethylcholine; ADT, androgen deprivation therapy; PET, positron emission tomography; T2w, T_2 weighted.



METHODS AND MATERIALS

Patient groups

The Biologically Optimised Intensity Modulated Radiotherapy for Prostate Radiotherapy clinical trial had been approved by the local ethics committee, and all patients had provided written informed consent. All patients had histologically confirmed intermediate- or high-risk prostate adenocarcinoma, T2a–T4 N0 disease on staging mpMRI, and a negative bone scan. Patients who had received ^{18}F choline PET/CT were identified and separated into either the ADT group or the ADT-naïve group (Figure 1). The only difference in protocol between the two groups was whether ADT was started before or after the PET/CT. In all patients, fiducial markers were inserted in the prostate prior to PET/CT, planning MRI and planning CT.

Imaging protocol

All patients were scanned with the same PET/CT imaging protocol. The patients fasted for at least 4 hours before imaging and were asked to drink 500 ml of water before an intravenous injection of 370 MBq of ^{18}F choline. A static pelvic scan performed at 90 min post injection in a single bed position over 10 min with a GE Discovery™ 690 PET/CT scanner (GE Medical Systems, Milwaukee, WI) was used. Images were reconstructed using the iterative line of response algorithm. Standardized uptake values (SUVs) were corrected for body weight. Prior to planning T2w MRI and planning CT, patients emptied their bowels with a mini enema and drank 300 ml of water. These scans were acquired with an indwelling 12-gauge soft Foley urethral catheter. The planning MRI was performed with turbo spin echo thin slice acquisition using a Philips Intera 1.5-T MRI scanner with phased array coils. The planning CT was performed by a Philips Brilliance wide-bore scanner, giving a 3-mm slice width.

Boost volume outlining protocol

On ProSoma (OSL Oncology Systems Limited, UK), the PET/CT and planning T2w MRI images were rigidly co-registered to the planning CT using fiducial markers and catheter. The whole prostate was contoured on both PET/CT and planning CT. The identification of DILs on MRI was performed by two radiation oncologists together by contouring on the planning T2w MRI whilst using the staging MRI (anatomical T2w and functional diffusion-weighted imaging) for reference. The identification of DILs on PET was performed visually ("visual PET") by the two radiation oncologists on ProSoma and automatically using the threshold method ["threshold PET"—threshold was 60% of prostate maximum SUV (SUV_{max})] on Mirada (Mirada Medical

Table 1. Patient demographics

		ADT group	ADT-naïve group
Number of patients		11	29
Age (years)[a]		63 (49–76)	68 (50–77)
PSA (ng ml^{-1})[a]		16.6 (10.9–28.6)	9.0 (3.6–39.4)
ADT duration before PET/CT (days)[a]		85 (42–193)	–
High risk[b]		11	25
Gleason score	6	0	1
	7	7	21
	8, 9	4	7
TNM staging	T2a	0	5
	T2b, c	4	6
	T3a, b	7	18

ADT, androgen deprivation therapy; PET, positron emission tomography; PSA, prostate-specific antigen.
[a]Median and range.
[b]Risk stratification as per prostate cancer: diagnosis and management (2014), the National Institute for Health and Care Excellence guidelines CG175.

Limited, Oxford, UK) where SUV_{max} uptake data was also collected. All information was available at the time of contouring (including pathology and other imaging).

Boost volume analysis

To unite the structures from both ProSoma and Mirada systems, the contours were imported into ARIA v. 11 (Varian Medical Systems, Palo Alto, CA) which displayed the registered images along with all structures. Data on DIL volumes were collected from ARIA. In order to account for registration errors between the primary data set (planning CT) and the secondary data sets (MRI or PET), a 5-mm isotropic expansion margin was performed around the prostate contours and the DIL contours within ARIA. Correlation analyses were used with these expanded volumes, with four different metrics used.[8] Dice similarity coefficient (DSC) was defined according to the following formula: $DSC = 2 \times A \cap B/(A + B)$, where A and B are the volumes of the MRI-defined and PET-defined DIL contours and $A \cap B$ is the volume of the overlapping volumes. Sensitivity, specificity and Youden index were calculated according to the following formulas: sensitivity = TP/(TP + FN); specificity = TN/(TN + FP); Youden index = sensitivity + specificity − 1, where TP is the overlapping volume between MRI and PET contours; FP is the PET contour excluding the MRI contour; FN is the MRI contour excluding the PET contour; and TN is the planning CT prostate contour excluding MRI and PET contours.

Statistical analysis

SPSS® v. 22.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) was used for statistical analysis. Owing to the skewed distribution of the contour volumes and SUV uptake values (kurtosis of up to 8.5 and 5.2, respectively), they were reported by median and range, with two-tailed significance testing using Wilcoxon signed-rank test. As the distribution of the correlation analyses tended to normal distribution (kurtosis were all well below 3 except for DSC between MRI and threshold PET during ADT which was 3.3), they were reported by mean ± standard deviation with two-tailed significance testing using independent t-test.

RESULTS

There were 11 patients in the ADT group (all were on 150 mg of bicalutamide once a day orally) and 29 patients in the ADT-naïve group (Table 1). Within the groups, the number of patients who were already on concomitant medications that may affect prostate volume was one and two, respectively (doxazosin only).

Table 2. Prostate and dominant intraprostatic lesion (DIL) volumes.

		ADT group		ADT-naïve group	
		Median	Range	Median	Range
Prostate volumes/ml	PET/CT	38.02	26.01 to 60.30	47.02	25.92 to 84.38
	Planning CT	36.92	25.63 to 64.96	39.07	18.07 to 82.96
	% change	0.03%	−5.79 to 7.73	−16.94%	−50.86 to 9.67
DIL volumes/ml	MRI	1.98	0.53 to 17.83	2.17	0.68 to 10.45
	Visual PET	1.34	0.36 to 6.41	2.62	0.65 to 8.77
	Threshold PET	4.81	1.12 to 10.68	3.71	0.20 to 18.35

ADT, androgen deprivation therapy; PET, positron emission tomography.

Table 3. Number of dominant intraprostatic lesions (DILs) identified

	n	ADT group	ADT-naïve group
Number of patients with *n* MRI DILs	0	0	1
	1	11	25
	2	0	3
Number of patients with *n* visual PET DILs	0	3	0
	1	7	20
	2	1	9
Number of patients with *n* threshold PET DILs	0	0	0
	1	10	21
	2	1	6
	3	0	1
	4	0	1

ADT, androgen deprivation therapy; PET, positron emission tomography.

There was no significant change in prostate volume between PET/CT and planning CT scans for the ADT group (median 0.03%, $p = 0.89$), but there was a significant reduction in the ADT-naïve group (median −16.9%, $p < 0.01$, Table 2).

The prostate SUV_{max} was lower in the ADT group (median 4.2, range 2.7–12.0) than in the ADT-naïve group (median 6.6, range 4.1–18.6), although it did not reach statistical significance (Mann–Whitney *U* test; $p = 0.06$).

In the ADT group, all patients had one MRI lesion, but three patients had no visually identifiable PET lesions. In the ADT-naïve group, 28 patients had at least 1 MRI lesion, 1 patient had no MRI lesions that could be confidently contoured and all patients had at least one visually identifiable PET lesion (Table 3).

In both groups, the median DIL volumes on MRI were small (1.98 and 2.17 ml), but there was a large variation between patients (0.53–17.83 ml, Table 2). Per individual patient, the visual PET lesions were significantly smaller than the MRI lesions in the ADT group (median reduction of 63%, $p = 0.03$) but not in the ADT-naïve group (median reduction of 5%, $p = 0.84$). The threshold PET lesions were generally larger than the MRI lesions in both groups, but this varied between patients and was not statistically significant (median increase of 60%, $p = 0.33$ and median increase of 20%, $p = 0.19$).

The correlation analyses showed that both visual and threshold PET have a moderate sensitivity (0.50–0.68) and a high specificity (0.85–0.98) for identifying MRI-defined disease (Table 4). There was a trend for the PET DILs (especially visually defined) to correlate better with the MRI DILs in the ADT-naïve group.

DISCUSSION

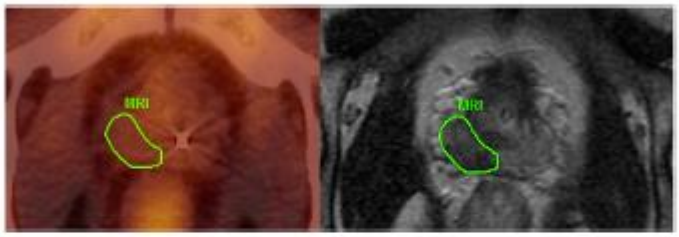
Although the observation of reduced tracer uptake in patients on ADT has previously been described, our article is the first to have quantified this effect.[10] If the PET/CT was performed during ADT, the prostate SUV_{max} was lower although it did not

Table 4. Comparison between dominant intraprostatic lesions (DILs) and prostate (with 5-mm margin)

		ADT group[a]	ADT-naïve group[a]	*p*-value[b]
PET/CT *vs* planning CT prostate (+5 mm)	DSC	0.86 ± 0.05	0.86 ± 0.06	–
MRI *vs* visual PET DIL (+5 mm)	DSC	0.56 ± 0.11	0.61 ± 0.15	0.41
	Sensitivity	0.50 ± 0.11	0.68 ± 0.18	0.12
	Specificity	0.98 ± 0.03	0.92 ± 0.08	<0.05
	Youden	0.48 ± 0.10	0.60 ± 0.20	0.11
MRI *vs* threshold PET DIL (+5 mm)	DSC	0.49 ± 0.15	0.51 ± 0.15	0.72
	Sensitivity	0.64 ± 0.22	0.63 ± 0.25	0.99
	Specificity	0.85 ± 0.14	0.87 ± 0.11	0.63
	Youden	0.48 ± 0.20	0.50 ± 0.21	0.80

ADT, androgen deprivation therapy; DSC, dice similarity coefficient; PET, positron emission tomography.
[a]Mean ± standard deviation.
[b]Independent *t* test (two-tailed).

Figure 2. A patient who had positron emission tomography/CT during androgen deprivation therapy. No dominant intraprostatic lesion could be identified visually.



reach statistical significance, and over a quarter of patients had no visually identifiable PET boost volumes (Figure 2). If PET/CT was performed when ADT-naïve, all patients had at least one visually identifiable PET boost volume and two patients had three to four threshold-identified PET boost volumes. These additional volumes tended to be small (0.1–0.3 ml) and, in practice, would be omitted from the total boost volume.

For the patients who were ADT-naïve at PET/CT imaging, visually identified PET boost volumes were similar in size to those seen on MRI, whilst those identified in patients who were on ADT were significantly smaller (Figures 3 and 4). This suggests that choline tracer uptake in malignant lesions is reduced by ADT on PET imaging, and therefore, ADT should ideally be commenced after imaging has been performed. This effect might also be found for PET imaging with other tracers such as prostate-specific membrane antigen, which is increasingly used for identifying sites of recurrence following radical treatment.

Although it would be expected that a similar effect should be found for boost volumes contoured by the threshold PET method, our results have not shown this. This may be because the threshold level of SUV_{max} 60% is too low for our PET imaging protocol, resulting in generally larger boost volumes which may have obscured any effect from ADT.

Although it did not reach statistical significance, the correlation between threshold PET boost volumes and MRI boost volumes were generally poorer than with the visual PET method. This is likely to be because clinicians had access to all relevant clinic details at the time of visual contouring, as per real life clinical practice. The overall DSC values were the highest for visual PET in the ADT-naïve group (Figure 5).

Our data have also shown that around two and a half months of ADT can reduce the overall prostate volume by 17%, albeit with significant interpatient variation. When both PET/CT and planning CT were performed during ADT, the prostate volumes were similar although there were differences of up to 7.7%, which reflects the difficulty in contouring pelvic soft tissue on CT. Despite the reduction in prostate size from ADT, the DSC between the prostate volumes were the same between the two groups (0.86) which may suggest that the variation due to the change in size is on the same scale as the variation due to difficulty contouring on CT. Rigid co-registration of the PET/CT and planning CT using the fiducial markers and catheter was generally uncomplicated.

The duration of ADT before PET/CT was performed varied from 42 to 193 days, in part due to the busy clinical schedule of our nuclear medicine department. Although it is not clear in the literature the duration of ADT at which the effect on prostate volume size is maximal, this variability may have influenced volume reduction. The ADT used in this study was bicalutamide, an antiandrogen. Other ADTs commonly used in clinical practice include luteinizing hormone-releasing hormone agonists which may be expected to have a larger effect on SUV_{max} and intraprostatic lesion reduction.

For this study, we had used a standard injected activity of 370 MBq of ^{18}F choline, as opposed to a dose calibrated to the patient's weight. This is because when we first introduced

Figure 3. A patient who had positron emission tomography (PET)/CT during androgen deprivation therapy. The dominant intraprostatic lesion identified visually by PET is smaller than the corresponding lesion identified by MRI.

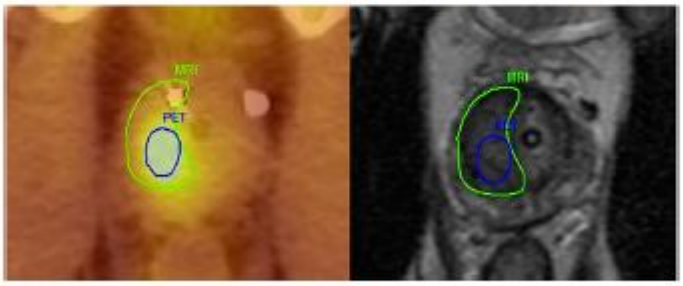
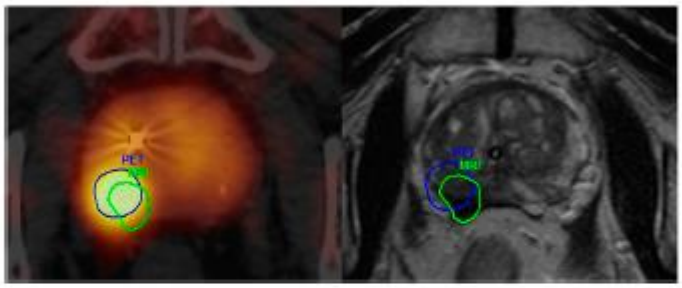


Figure 4. A patient who had positron emission tomography (PET)/CT before androgen deprivation therapy. The dominant intraprostatic lesion identified visually on PET overlaps the corresponding lesion identified on MRI.



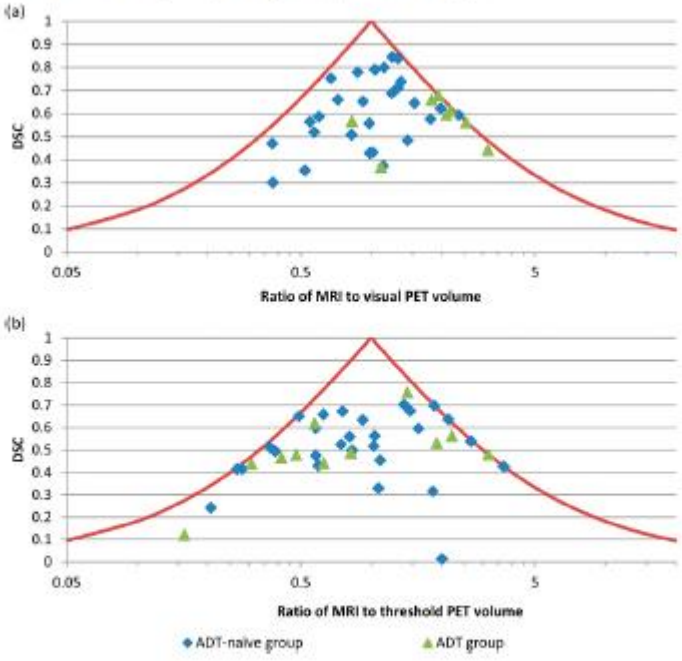
^{18}F choline imaging in our department, we were unsure about the optimum time of imaging, *i.e.* whether delayed imaging at 90 min would be appropriate. Hence, we injected the maximum activity possible under the regulations. Since this study was conducted, there is more evidence for weight-based reduction of injected activity which we have now adopted.

MRI and nuclear medicine specialists were not directly involved in contouring for this study, as radiotherapy contouring is principally performed by radiation oncologists in the UK. Therefore, our results are directly relevant to potential clinical practice.

There are differing views about the benefit of the addition of ^{11}C choline PET/CT with MRI to detect intraprostatic tumours.[11,12] However, Hartenbach et al[13] showed the increased accuracy of using ^{18}F choline PET/MRI (a scanning protocol with a comparatively prolonged tracer uptake time) for identifying intraprostatic tumour compared with MRI alone. It may be the prolonged uptake time possible with using ^{18}F choline which allows better differentiation between malignant and benign prostate tissue.

Owing to the lack of available literature identifying the optimal threshold level for ^{18}F choline PET/CT, we used the threshold

Figure 5. Distribution of dice similarity coefficient (DSC) values between (a) MRI and visual positron emission tomography (PET) and (b) MRI and threshold PET (the red line depicts the maximum DSC achievable with the given differences between the MRI and PET dominant intraprostatic lesion volumes). ADT, androgen deprivation therapy.



level of SUV_{max} 60% which was identified by Chang et al[8] to provide the best correlation between ^{11}C choline PET and pathology. However, there are key differences between their methodology and ours, including the radioisotope used, registration method and the defined standard (histology *vs* MRI) for comparison.

It is acknowledged that there is a substantial difference in the number of patients between the two groups in our retrospective study and that each group individually constitutes a small sample size. However, the DIL correlation methodology deployed here followed that in the published work (involving a smaller number of subjects than in either of our groups) of Chang et al.[8]

A limitation of our retrospective study is that the patients were not randomized into the two groups, but instead the groups were recruited in sequence. This should not have resulted in differing group characteristics as the inclusion criteria were constant throughout. However, subjective visual identification of DILs may have changed over time with increasing experience in analysing choline PET/CT imaging. Furthermore, there was a lack of the gold standard comparison with cross-sectional histology. It should be noted that surgical series may often include patients with lower risk, and histology samples distort significantly after preparation and mounting. An alternative to cross sectional histology is template biopsies, which would have offered an accurate assessment of the location and size of significant high-grade tumour. Overall, any visual method is by definition subjective, and therefore the conclusions from this article will ideally be confirmed by other research groups using different PET/CT imaging protocols. Further studies are required to determine whether the addition of PET for the planning process will ultimately improve clinical treatment outcomes.

CONCLUSION

For visual contouring of boost volumes in prostate dose painting radiotherapy, ^{18}F choline PET/CT should be performed before ADT. For threshold contouring of boost volumes using our PET/CT scanning protocol, threshold levels of >60% of prostate SUV_{max} may be more suitable. The location and size of PET boost volumes can vary to that of the MRI boost volumes, and therefore the additional use of PET with MRI for radiotherapy planning can significantly change the overall boost volumes compared with using MRI alone. However, further studies are required to determine whether the addition of PET for the planning process will ultimately improve clinical treatment outcomes. Similar effects of ADT on PET/CT using other tracers, such as prostate-specific membrane antigen, may exist.

REFERENCES

1. Dearnaley DP, Sydes MR, Graham JD, Aird EG, Bottomley D, Cowan RA, et al. Escalated-dose *versus* control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2014; **15**: 464–73. doi: https://doi.org/10.1016/S1470-2045(14)70040-3
2. Pinkawa M, Piroth MD, Holy R, Klotz J, Djukic V, Corral NE, et al. Dose-escalation using intensity-modulated radiotherapy for prostate cancer—evaluation of quality of life with and without (18)F-choline PET-CT detected simultaneous integrated boost. *Radiat Oncol* 2012; **7**: 14. doi: https://doi.org/10.1186/1748-717X-7-14
3. Dolezel M, Odrazka K, Vaculikova M, Vanasek J, Sefrova J, Paluska P, et al. Dose escalation in prostate radiotherapy up to 82Gy using simultaneous integrated boost: direct comparison of acute and late toxicity with 3D-CRT 74 Gy and IMRT 78Gy. *Strahlenther Onkol* 2010; **186**: 197–202. doi: https://doi.org/10.1007/s00066-010-2065-x
4. Fonteyne V, Villeirs G, Speleers B, De Neve W, De Wagter C, Lumen N, 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. doi: https://doi.org/10.1016/j.ijrobp.2008.01.040
5. Uzan J, Nahum AE. Prostate dose-painting radiotherapy and radiobiological guided optimisation enhances the therapeutic ratio. *Clin Oncol (R Coll Radiol)* 2016; **28**: 165–70. doi: https://doi.org/10.1016/j.clon.2015.09.006
6. Lips IM, van der Heide UA, Haustermans K, van Lin EN. 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* 2011; **12**: 255. doi: https://doi.org/10.1186/1745-6215-12-255
7. Evangelista L, Brigantib A, Fanti S. New clinical indications for F/C-choline, new tracers for positron emission tomography and a promising hybrid device for prostate cancer staging: a systematic review of the literature. *Eur Urol* 2016; **12**: 161–75.
8. Chang JH, Joon DL, Lee ST, Gong SJ, Scott AM. Histopathological correlation of (11)C-choline PET scans for target volume definition in radical prostate radiotherapy. *Radiother Oncol* 2011; **99**: 187–92. doi: https://doi.org/10.1016/j.radonc.2011.03.012
9. Chan J. Is choline PET useful for identifying intraprostatic tumour lesions? A literature review. *Nucl Med Commun* 2015; **36**: 871–80. doi: https://doi.org/10.1097/MNM.0000000000000338
10. Giovacchini G. Do we have to withdraw antiandrogenic therapy in prostate cancer patients before PET/CT with [11C]choline? *Eur J Nucl Med Mol Imaging* 2011; **38**: 1964–6. doi: https://doi.org/10.1007/s00259-011-1926-6
11. Van den Bergh L, Koole M, Isebaert S, Joniau S, Deroose CM, Oyen R, et al. Is there an additional value of (1)(1)C-choline PET-CT to T2-weighted MRI images in the localization of intraprostatic tumor nodules? *Int J Radiat Oncol Biol Phys* 2012; **83**: 1486–92. doi: https://doi.org/10.1016/j.ijrobp.2011.10.046
12. Chang JH, Lim Joon D, Davis ID, Lee ST, Hiew CY, Esler S, et al. Comparison of [(11)C]choline positron emission tomography with T2- and diffusion-weighted magnetic resonance imaging for delineating malignant intraprostatic lesions. *Int J Radiat Oncol Biol Phys* 2015; **92**: 438–45. doi: https://doi.org/10.1016/j.ijrobp.2015.02.004
13. Hartenbach M, Hartenbach S, Bechtloff W, Danz B, Kraft K, Klemenz B, et al. Combined PET/MRI improves diagnostic accuracy in patients with prostate cancer: a prospective diagnostic trial. *Clin Cancer Res* 2014; **20**: 3244–53. doi: https://doi.org/10.1158/1078-0432.CCR-13-2653

Hypofractionated dose painting IMRT for intermediate to high risk localised prostate cancer: treatment with 20 fractions

***Chan J**, Rowntree T, Brunt J, Howard L, Syndikus I.*

International Journal of Radiation Oncology, Biology, Physics 2016, Volume 96, Number 2S, E239

Author Disclosure: **P. Alexidis**: None. **J.P. Christodouleas**: None. **J.E. Bekelman**: None. **N. Vapiwala**: None. **P.E. Gabriel**: None.

2581

Hypofractionated Dose Painting Intensity Modulated Radiation Therapy for Intermediate- to High-Risk Localized Prostate Cancer: Treatment With 20 Fractions

J. Chan, T. Rowntree, J.N. Brunt, L. Howard, and I. Syndikus; *Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, United Kingdom*

Purpose/Objective(s): The CHHiP trial has shown non-inferiority of 60Gy/20# schedule compared to conventional 74Gy/37# for biochemical control at 5 years. Prostate dose-painting (boosting intra-prostatic tumor volumes, standard dose to prostate outside boost volume) may improve biochemical relapse-free survival similar to whole organ dose-escalation, whilst avoiding increased associated toxicity. We present dose painting radiation therapy results for a phase II trial: intermediate to high risk patients treated with 60Gy/20# and concurrent 68Gy boost to intra-prostatic lesions.

Materials/Methods: Patients had a multi-parametric MRI and ^{18}F choline PET/CT prior to androgen deprivation (ADT), and planning MRI and CT following 2 months' ADT. Registration used fiducial markers. Intra-prostatic boost volumes were outlined by combining visually identified lesions on MRI and PET. Rotational IMRT planning was performed using Pinnacle software. Patients with unexpected regional lymph node PET uptake also received pelvic radiation therapy with boost. Toxicity evaluation was performed with CTCv.4.0 and RTOG scale. Endpoint was acute toxicity at 18 weeks.

Results: Fifty-three patients were planned and treated, 5 with concurrent pelvic radiation therapy. Median age and PSA was 67 years (range 50-77) and 10.0ng/ml (3.9-39.4), 13 patients had intermediate and 40 had high risk disease. For all patients, median prostate boost volume was 13.5ml (range 8.1-33.1). Median prostate dose excluding boost was 61.0Gy. Median intra-prostatic boost dose was 68.1Gy. In pelvic radiation therapy group, lymph node dose of 45Gy with boost to 50Gy was achievable, as were normal tissue dose volume constraints (bladder, urethra, rectum and bowel) (Table). Grade 2 urinary toxicity at baseline was 12%, increasing to 26% during radiation therapy and 1 patient had grade 3 toxicity (RTOG). At week 18, the results were back to baseline. Bowel toxicity was modest: 12% developed grade 1 and 5% grade 2 during radiation therapy, with 5% with grade 1 and 2 at 18 weeks.

Conclusion: Prostate radiation therapy with hypofractionated dose painting schedule of 60Gy/20# with 68Gy boost to intra-prostatic lesions was well tolerated in this cohort study.

Abstract 2581; Table 1.

		Dose painting to prostate only (n = 48)	Dose painting to prostate and LN (n = 5)
		Median (Range)	Median (Range)
Prostate without boost (Gy)	D2%	66.4 (64.1-69.0)	66.2 (64.7-67.6)
	D50%	61.0 (60.4-61.7)	61.0 (60.9-61.2)
	D98%	58.1 (57.2-59.0)	58.0 (57.1-58.3)
Prostate boost volume (Gy)	D2%	70.1 (69.0-71.0)	70.3 (69.2-71.0)
	D50%	68.1 (66.2-68.9)	67.2 (66.8-68.5)
	D98%	60.9 (59.2-64.2)	62.0 (59.5-64.6)
LN without boost (Gy)	D50%		45.2 (45.1-45.7)
	Min. dose		35.7 (35.5-40.0)
LN boost volume (Gy)	D50%		51.0 (50.1-51.4)
	Min. dose		48.6 (46.4-49.0)
Rectum (%)	V48.6	15.0 (9.1-33.3)	17.8 (6.0-18.3)
	Max. dose	62.3 (58.2-66.4)	62.8 (61.6-64.6)
	Mean dose	21.6 (15.0-32.3)	29.0 (23.1-33.9)
Bladder (%)	V48.6	11.2 (3.1-31.9)	19.8 (9.3-26.9)
	Max. dose	63.4 (60.7-67.1)	64.1 (62.5-65.4)
	Mean dose	18.2 (7.1-35.9)	39.6 (32.5-42.2)

Author Disclosure: **J. Chan**: None. **T. Rowntree**: None. **J.N. Brunt**: None. **L. Howard**: None. **I. Syndikus**: None.

2582

Natural History of Progression After Biochemical Failure Following Postoperative Radiation Therapy in Prostate Cancer

V. Tumati,[1] D.E. Spratt,[2] W.C. Jackson,[2] F.Y. Feng,[2] C. Roehrborn,[1] Y. Lotan,[1] D.A. Pistenmaa,[1] A.M. Laine,[1] M.R. Folkert,[1] R. Hannan,[1] and N.B. Desai[1]; *[1]University of Texas Southwestern Medical Center, Dallas, TX, [2]University of Michigan, Ann Arbor, MI*

Purpose/Objective(s): Post-operative radiation therapy (PORT) is an effective treatment for appropriately selected prostate cancer patients after radical prostatectomy (RP). The natural history of disease after biochemical recurrence (BCR) following PORT has not been well described. This study examined the clinical course of patients who underwent PORT and experienced a BCR.

Materials/Methods: A retrospective multi-institutional study was performed on 608 consecutive men who received PORT following RP between 1986 and 2013. BCR was defined as a rise in PSA of 0.2 ng/mL or greater above the PSA nadir followed by a sequentially equal or higher PSA. Two hundred ninety-seven men had a BCR and formed the study cohort. Actuarial estimates of freedom from BCR, freedom from castration resistant prostate cancer (CRPC), prostate cancer specific survival (PCSS), overall survival (OS), local, regional, and distant recurrence (DM) were determined using the Kaplan-Meier method. Castrate resistance was defined as ≥2 episodes of rising PSA with testosterone <50 ng/ml. Statistical analysis was performed using log-rank and Cox proportional hazard testing.

Results: The median follow-up from time of BCR was 72 months. Actuarial 72 months, local recurrence, regional recurrence, DM, CRPC PCSS, and OS were 5%, 8%, 40%, 29%, 81%, and 75%, respectively. Median time to DM and to OS after BCR were 107 and 154 months, respectively. For men who developed DM after BCR, subsequent median OS and PCSS were 59 and 67 months, respectively. On univariate analysis, pre-PORT PSA > 0.4 (P = .03), T stage > T2c (P = .019), N+ (P = 0.05), and whole pelvic RT (P = 0.01) were associated with worse OS. On multivariate analysis only pre-PORT PSA >0.4 remained significantly associated with worse OS (HR 1.7 P = 0.04). A total of 203 men received ADT after BCR, of whom 69 received immediate ADT within 3 months of BCR. Of the men who developed CRPC, 45 went on to receive 2nd generation ADT, 29 received chemotherapy, 2 received sipuleucel-T, and 7 received radium-223.

Conclusion: Men who suffer BCR after PORT have a long survival, with high rates of PCSS. However, 6-years after BCR 40% of patients will have developed metastatic disease, despite the frequent use of ADT, and nearly 20% will have died from prostate cancer. Given these high rates of distant failure, further systemic intensification of therapy is warranted with PORT in men with prostate cancer, particularly in those with baseline adverse features such as pre-PORT PSA >0.4.

Author Disclosure: **V. Tumati**: None. **D.E. Spratt**: None. **W.C. Jackson**: None. **F.Y. Feng**: None. **C. Roehrborn**: None. **Y. Lotan**: None. **D.A. Pistenmaa**: None. **A.M. Laine**: None. **M.R. Folkert**: None. **R. Hannan**: None. **N.B. Desai**: None.

2583

Patterns of Lymph Node Failure After Dose-Escalated Radiation Therapy in Patients Who Did Not Undergo Pelvic Lymph Node Irradiation: Implications for Extended Pelvic Lymph Node Coverage

D.E. Spratt,[1,2] H.A. Vargas,[3] Z.S. Zumsteg,[4] J. Golia Pernicka,[3] J. Osborne,[3] S.M. McBride,[2] M.A. Kollmeier,[2] X. Pei,[2] and M.J. Zelefsky[2]; *[1]University of Michigan, Ann Arbor, MI, [2]Memorial Sloan Kettering Cancer Center, New York, NY, [3]Memorial Sloan Kettering, New York, NY, [4]Cedars-Sinai Medical Center, Los Angeles, CA*

Purpose/Objective(s): Clinical trials evaluating the benefit of pelvic radiation therapy in the radiotherapeutic management of patients with higher risk prostate cancer have limited the superior field border to the S1/S2 or L5/S1 interspace. However, imaging and surgical series have demonstrated a high frequency of prostatic lymph node (LN) drainage beyond these

Hypofractionated dose painting IMRT using 20 fractions for intermediate and high-risk localised prostate cancer: Two-year outcome data (BIOPROP20, NCT02125175)

*Syndikus I, **Chan J**, Rowntree T, Howard L, Staffurth J*

Journal of Clinical Oncology 37, no.7_suppl (March 01, 2019) 59-59

PROSTATE CANCER-LOCALIZED DISEASE

Hypofractionated dose painting IMRT using 20 fractions for intermediate to high-risk localized prostate cancer: Two-year outcome data (BIOPROP20, NCT02125175).

Isabel Syndikus, Joachim Kwok-Chiu Chan, Thelma Rowntree, Laura Howard, John Staffurth

Show More

Abstract Disclosures

Abstract

59

Background: Prostate dose painting (boosting intra-prostatic tumour volumes) may improve biochemical relapse-free survival similar to whole organ dose-escalation without the associated increased toxicity. We present a pre-defined secondary endpoint of 2 year outcome for patients at one of two UK centres in a phase II trial (BIOPROP20) on dose-painting radiotherapy for intermediate to high risk patients treated with 60Gy/20# and concurrent 68Gy boost. **Methods:** Pinnacle software was used for VMAT planning and boost volumes were outlined by ^{18}F choline PET/CT and mpMRI. Patients with positive lymph nodes also had concurrent pelvic radiotherapy of 45Gy with boost to 50Gy. Patients were followed up until year 2 with PSA and toxicity scores. **Results:** Overall 56 patients were treated, 5 with pelvic radiotherapy. Median age and PSA was 67.5 years (range 50 - 77) and 10.0ng/ml (3.9 - 39.4). All patients had tumour volumes > 10mm diameter on pre-biopsy mpMRI. 13 and 43 patients had intermediate and high risk disease. Median % LN risk was 18% (15 - 40). ADT duration was 6 months, 2 years, and 3 years for 42, 5, and 9 patients. At the 2 year follow up review, no grade 3 late toxicity was observed. For prostate only dose painting, grade 2 GU and GI toxicity was noted in 6% and 2% respectively. For prostate and nodal dose painting, no grade 2 toxicity was noted. Median IPSS score was 5 and 9, and median PSA was 0.3 and 0.1, in the two groups respectively. 1 patient had biochemical and metastatic relapse at 18 months (prostate, pelvic nodes and bone metastasis) and 1 patient had died of unrelated disease. **Conclusions:** Prostate radiotherapy with hypofractionated dose painting schedule of 60Gy/20# with 68Gy boost to intra-prostatic lesions was well tolerated at 2 years follow up. Clinical trial information: NCT02125175.

At 2 year followup		Prostate (n = 50)			Prostate and node (n = 5)	
		n	[%]		n	[%]
Remains on adjuvant ADT			6	12%	3	60%
Biochemical relapse			1	2%	0	0%
Late CTCAE toxicity grade	Urinary	0	23	46%	2	40%
		1	24	48%	3	60%
		2	3	6%	0	0%
	Bowel	0	43	86%	3	60%
		1	2	12%	2	40%
		2	1	2%	0	0%

Oral Presentations

International

June 2015 — Dose painting radiotherapy for high risk prostate cancer: delayed ^{18}F-choline PET/CT imaging before neo-adjuvant hormone therapy improves detection rates
Chan J*, Mahmood S, Brunt J, Vinjamuri S, Syndikus I.*
Biology-Guided Adaptive Radiotherapy 13th Acta Oncologica Symposium (BiGART2015) – Aarhus, Denmark

National

June 2017 — Hypofractionated dose painting IMRT for intermediate to high risk prostate cancer: treatment with 20 fractions
Chan J*, Jackson R, Rowntree T, Brunt J, Howard L, Syndikus I.*
UKCRO (UK Radiological and Radiation Oncology Congress) 2017 – Manchester, UK

Poster Presentations

International

Feb 2019 — Hypofractionated dose painting IMRT using 20 fractions for intermediate to high risk localised prostate cancer: 2 year outcome data
Syndikus I, ***Chan J****, Rowntree T, Howard L, Staffurth J*
GU ASCO 2019

May 2017 — Impact of ^{18}F choline PET scan acquisition time on delineation of GTV in prostate cancer
Parkinson C, ***Chan J****, Syndikus I, Marshall C, Staffurth J, Spezi E*
ESTRO 2017

Sept 2016 — Hypofractionated dose painting IMRT for intermediate to high risk localised prostate cancer: treatment with 20 fractions
Chan J*, Rowntree T, Brunt J, Howard L, Syndikus I.*
ASTRO 2016