The value of elective pelvic lymph node radiotherapy in high risk prostate cancer

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Author’s Declaration

I declare as sole author of this thesis that the work presented here represents my personal research conducted as a clinical research fellow at the Institute of Cancer Research and The Royal Marsden NHS Foundation Trust between 2015 and 2018. The tables and figures contained herein are my own work unless credited otherwise.

Atia Khan

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Abstract

High risk prostate cancer patients carry a high risk of microscopic pelvic lymph node (PLN) disease; however, the clinical benefit of elective PLN radiotherapy remains unproven due conflicting results from clinical trials. This thesis investigates methods of improving the PLN control achieved with IMRT, while maintaining acceptable levels of toxicity.

My first aim was to determine the rates of disease control for patients treated in the RMH Phase I/II IMRT trial. A similar anatomical pattern of disease relapse was seen in all trial cohorts with a low rate (6%) of PLN relapse. The majority of PLN relapses occurred outside the radiation field occurred at the proximal common iliac nodes. 50% of relapses occurred within the radiation field and no clear dose gradient or favoured site was seen.

My second aim was to determine the coverage provided by the PIVOTAL trial PLN contouring guidelines. The contours covered 66% of Choline PET-CT identified PLN. The common iliac nodal group was the site most poorly covered and I considered the implications on bowel dosimetry of modifying the standard PLN to improve coverage.

My third aim was to determine if the dose-volume constraints developed in the IMRT trial and used in the PIVOTAL trial could be refined any further to improve the toxicity profile of pelvic IMRT. Using the bowel dose cube data and late toxicity results for the PIVOTAL trial cohorts, I found no clear correlation between radiation dose to any part of the bowel and late RTOG toxicity that suggested modification of dose constraints.

In conclusion, the current target volumes and planning constraints are associated with a favourable late toxicity profile. Further PLN control might be achieved by covering the upper common iliac nodes. However, the impact of PLN IMRT needs to be evaluated in the context of recent developments in treatment intensification using systemic therapies which may treat microscopic nodal disease.

List of Abbreviations

ADT	Androgen deprivation therapy
BED	Biologically equivalent dose
Ch-PET	Choline PET CT scan
CI	Confidence interval
CTV	Clinical target volume
DVH	Dose volume histogram
DWI	Diffusion weighted imaging
ePLND	Extended pelvic lymph node dissection
EBRT	External beam radiation
EUA	European Urology Association
EQD2	Equivalent dose in 2Gy per fraction
GI	Gastro-intestinal
GTV	Gross target volume
GU	Genito-urinary
Gy	Gray
IBDQ	Inflammatory bowel disease questionnaire
IGRT	Image guided radiotherapy
IMRT	Intensity modulated radiotherapy
LHRHa	Luteinising-hormone releasing hormone agonist
LNI	Lymph node involvement
MpMRI	Multiparametric MRI
OAR	Organ at risk
PLN	Pelvic lymph node
PLND	Pelvic lymph node dissection
PORT	Prostate only radiotherapy
PSA	Prostate specific antigen
PTV	Planning target volume
QOL	Quality of life
RMH	Royal Marsden Hospital
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
WPRT	Whole pelvic radiotherapy

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Chapter 1 introduction:

This chapter will introduce the current definitions and treatment paradigms for high risk prostate cancer and the role of elective pelvic lymph node treatment in this patient group. I will outline the current methods for pelvic lymph node staging, and the evidence for refining pelvic lymph node radiotherapy. My thesis aims to explore methods to refine pelvic lymph node radiotherapy in order to improve its efficacy while maintaining acceptable toxicity.

1.1 Determining Risk in prostate cancer

The term “high risk prostate cancer” describes disease that carries a high risk of local recurrence, distant metastases and risk of dying from prostate cancer. This is despite the cancer being localised at diagnosis and treated in accord with current guidelines (1). There are several definitions of what constitutes “high risk” summarised in table 1 and they are all are based upon the diagnostic features of index PSA, T stage and Gleason score, as these are independent predictors of biochemical failure after definitive treatment for prostate cancer.

D’Amico first categorised patients into risk groupings based upon the endpoint of PSA failure and defined “high risk” as; clinical T stage of cT2c or more, Gleason score of ≥8 or PSA >20ng/ml (2). This definition has now been adopted by the American Urological Association (3). Other histological features beyond the Gleason grade play an important part in determining risk, such as the volume of cancer detected. This was included in the Cancer of the Prostate Risk Assessment (CAPRA) score, which was developed to account for the percentage of biopsy cores involved with cancer at diagnosis and was first published in 2005 (106). The CAPRA score was initially developed using pathology and clinical data from men in the USA undergoing radical prostatectomies (RP) without any adjuvant treatment to predict disease recurrence. Since then, it has been validated in multiple independent studies including radiation cohort studies and for other clinical endpoints such as cancer specific mortality (107).

One of the limitations of risk classification systems is that there can be significant variation in the risk within each grouping, and between groupings (108).

Nomograms are prediction models based on multivariable statistical models that calculate the continuous probability of a clinical outcome and represent it graphically. There are several online computerised nomograms such as the Memorial Sloane Kettering nomograms. However, most of the popularly used tools are those developed and validated for lower risk patients undergoing radical prostatectomy (RP) or post RP. A review by Raymond et al in 2017 appraised all the available tools for men undergoing radiation treatment (including brachytherapy) for prostate cancer. 97 predictive tools were identified, of which 66 were newly developed and 31 were validations of previously published tools. The authors limited their search to studies post 2007 to account for changes in in radiation modality but all expect 5 studies included data from patients treated as far back as the 1990's when radiation doses to the prostate were lower. Therefore, how relevant these tools might be in the era of modern radiotherapy is unknown. Other criticisms included short follow up periods (defined as a mean or median of >5 years) leading to bias, lack of external validation in 65% and no reported accuracy in 57% (109).

Table 1. Definitions of high risk prostate cancer

Organisation	High risk definition	Outcomes
American Urologic Association (3)	**Pre op PSA >20ng/ml and/or Gleason score of 8-10, and/or clinical stage ≥T2c**	
European Association of Urology (5)	**Pre-op PSA >20ng/ml and/or Gleason 8-10 and/or clinical stage ≥T3a**	
Radiation Therapy Oncology Group (6)	**High risk: T1-2 and Gleason 8-10, or T3 or N1 and Gleason 7** **Very high risk: T3 or N1 and Gleason 8-10**	**High risk; 10-year DSS =62%** **Very high risk; 10-year DSS = 34%**
National Comprehensive Cancer Network (version 2, 2014) (7)	**High risk: Pre-op PSA >20ng/ml, Gleason 8-10 or clinical stage T3a** **Very high risk: T3b-T4**	

In 2014 a new prostate cancer grading system was developed during the International Society of Urological Pathology (ISUP) Consensus conference with changes to the assignment of Gleason pattern based on pathology (136). The new system assigns grade groups from 1-5 and was validated in two separate cohorts of men treated for prostate cancer with surgery or radiotherapy. Both validation studies found that the new grade groups predicted the risk of recurrence after primary treatment (137,138).

Certain architectural tumour patterns may also have strong adverse implications. Intraductal carcinoma is accounts for only 1.3% of all prostate cancers but is an important histological feature to recognise as it is more frequently seen in higher risk groups (139). When found in radical prostatectomy specimens it is often associated with other high risk features such as high Gleason grade, large tumour volume, advanced T stage or lymph node metastases and is an independent adverse prognostic factor associated with biochemical recurrence and decreased progression free survival (140). It is also an independent risk factor for early biochemical recurrence in patients undergoing radiation treatment (141). There is also some data to suggest that tumours with this pathology have increased genomic instability and might be more likely to harbour somatic and/or germline alterations in mismatch repair genes, homologous DNA repair or germline BRCA2 mutations (142). The cribiform variant of grade group 4 is also associated with worse outcomes in several studies with a reported increased risk for metastatic disease, biochemical failure and disease specific mortality in patients treated with surgery (143).

Genetic information is also helping to further define prostate cancer risk more accurately than using clinical information alone. At present there are three commercially developed genetic expression panels available; Prolaris, Oncotype DX and Decipher. These three panels contain a total of 85 genes with virtually no overlap between the tests and there is also no data comparing the tests in the same patient groups. All the panels have been initially developed to add prognostic information after radical prostatectomy. Some studies have also performed the tests on pre surgical biopsies to use in the context of risk prediction pre-treatment, in particular to guide patients considering active surveillance. One of the limitations of this is that the dominant lesion; that is the most aggressive

lesion that is most likely to be the driver for metastatic disease is not always the one biopsied. The dominant lesion may not be easy to identify in multifocal disease and 10-15% of clinically significant cancers are invisible on MRI (110).

That said, retrospective data is emerging to suggest that the genetic information available from these commercial assays may provide valuable information beyond what can be gained from the already available risk stratifications and nomograms. A study using 4 multicentre cohorts with a total of 6928 prostate cancer patient used Decipher panel defined risk categories to re-classify the NCCN risk groupings. The patients were initially classified into NCCN groupings of low, intermediate and high risk, and then further subclassified using genomic information into 6 groups; very low, low, favourable intermediate, unfavourable intermediate, high risk and very high risk. This six-tiered system was then converted back into a new three tier clinical-genomic risk grouping. A total of 33.4% of the total trial population had their risk group reclassified using the genomic information. A retrospective training cohort with a median follow up of 8 years and was used to assess the risk of metastatic disease using the NCCN classification and then again using the clinical-genomic risk groupings. The findings were then validated in another separate retrospective cohort and confirmed that the clinical-genomic risk groupings had far greater ability to discriminate 10-year rates of distant metastases than the traditional NCCN groupings (111).

The cell cycle progression score (CCP) is a prognostic RNA signature based on the average expression level of 31 CCP genes. IT has been shown to predict biochemical recurrence after prostatectomy and cancer specific mortality in men undergoing observation (129,130). The CCP score was retrospectively tested on biopsy specimens of 141 men who had been diagnosed with prostate cancer between 1991 and 2006 and treated with external beam radiation and had a median follow up of 4.8 years. The CPS score significantly predicted for biochemical recurrence independently of the standard variables of PSA, Gleason score and percentage of positive cores (131).

At present the recommendations are that these assays may be offered in situations where the results can be considered alongside routine clinical factors

to help inform management decisions, but there is no evidence that they can improve cancer specific outcomes or quality of life (110).

1.2 Treatment for high risk prostate cancer

Evidence from clinical trials has established several important treatment goals for high risk cancer prostate patients in order to maximise local and distant disease control (8).

1.2.1 Treatment of the primary tumour

Treatment of the primary tumour is essential for local control and the prevention of metastatic seeding (1, 9). The Scandinavian watchful waiting versus surgery trial was published in 2005 following 10 years follow up and demonstrated that prostate cancer specific mortality was nearly halved (Hazard ratio (HR) R=0.56, 95% CI 0.36-0.88) in patients receiving surgery (10). Following this, two trials demonstrated that the addition of prostate radiotherapy (RT) to androgen deprivation therapy (ADT) improved overall survival and prostate cancer specific mortality. The first was the Scandinavian SPCG-7/SFUO-3 study which reported results in 2009 (11). Patients with locally advanced disease were randomised to receive treatment with ADT alone or ADT with RT. There was an improvement in overall survival of around 10% at 10 years and a decrease in the cumulative incidence of prostate cancer specific mortality from 23.9% to 11.9% (11). The second trial was the Intergroup Canadian/ MRC UK PRO7 trial which randomised 1205 patients with locally advanced prostate cancer (T3 and T4) to lifelong ADT vs ADT and radiation to the prostate and pelvis (12). At a median follow up of 8 years overall survival was significantly improved in the patients allocated to ADT+RT (HR, 0.70; 95% CI, 0.57 to 0.85; P < .001). Additionally, deaths from prostate cancer were significantly reduced by the addition of RT to ADT (HR, 0.46; 95% CI, 0.34 to 0.61; P < 0.001) (12).

1.2.2 Dose escalation of prostate radiotherapy

The trials described above which established the survival benefit of combing ADT with external beam radiation used doses of 65-70Gy, which are not reflective of the modern dose escalation used in clinical practice. Further improvement in local control and biochemical control has been demonstrated with escalating radiation dose to the prostate in all risk groups. The following trials established a benefit in high risk patients. The RTO1 trial first published in 2007 (15) demonstrated that conformal dose escalated radiotherapy to the prostate improved biochemical progression free survival. At a median follow up of 10 years (16) the biochemical progression free survival was 43% in the control group that received 64Gy in 32 fractions (95% CI 38-38) and 55% in the dose escalated group that received 74Gy in 37 fractions (95% CI 50-61) (HR=0.69, 95% CI 0.56-0.84, p=0.0003). No overall survival benefit was seen and an increase in late bowel toxicity was seen in the dose escalated group. In 2006, Peeters et al (13) published a multicentre trial in 669 patients, of which 55% had high risk disease. The patients were randomised between 68Gy and 78Gy to the prostate. Patients also received ADT. There was an improvement in biochemical failure rates with dose escalation at a median follow up of 5 years (64% vs 54%, HR=0.74, p=0.02) (13). No improvement in clinical failure rates or overall survival was seen. Another study by Kuban et al (14), randomised 301 patients, of which 34% had high risk disease between 70Gy or 78Gy to the prostate in 2Gy per fraction and 46Gy to the pelvic nodes. Patients did not receive any ADT. At a median follow up of 9 years the high-risk patients receiving 78Gy to the prostate had an improved biochemical relapse free survival (79% vs 59%, p=0.018), decreased rates of distant failure (4% vs 19%, $p<0.05$) and decreased risk of death from prostate cancer (4% v 16%, p=0.05). Zelefsky published a large retrospective series of 2047 patients treated with a range of radiation doses in 2008. 37% of the cohort had NCCN defined high risk disease and 52% of the total cohort received neoadjuvant short course ADT. The patients received a range of radiation doses from 66Gy to 86.4Gy. Radiation dose had an impact on biochemical control in the high-risk patients and the 5 year PSA relapse free survival was 71%, 66%, 61% and 40% in patients who received 86.4Gy, 81Gy, 75.6Gy and 70.2Gy respectively. The impact was most significant when comparing the outcomes in patients who received >86.4Gy v 75.6Gy (p=0.05).

Dose was also a significant predictor of distant metastatic free survival in the high risk group and the dominant effect was seen in patients treated with >81Gy v 70.2Gy. No overall survival benefit was seen in any risk group (112).

Dose escalation of the whole prostate gland with external beam radiotherapy is limited by an increased dose to the surrounding normal tissues and a resultant increase in toxicity. Therefore, other radiation modalities have been investigated. Low dose rate (LDR) or high dose rate (HDR) brachytherapy boosts to the prostate in conjunction with external beam radiotherapy and ADT allow for dose escalation to the whole prostate gland. This has been demonstrated in multiple randomised trials to improve biochemical control compared to EBRT and ADT alone, but does result in increased toxicity.

A small study randomised patients with T2 and T3 disease to EBRT alone (n=53, 66Gy in 33 fractions) or EBRT (n=51, 40Gy in 20 fractions) with an Iridium implant delivering 35Gy over 48 hours. All patients were surgically staged as N0. After a median follow up of 8.2 years a significant improvement in the biochemical rate was seen in the brachytherapy group (29% vs 61%, HR 0.42, p=0.0024). Toxicity was recorded up to 18 months post treatment and a non significant trend towards increased gastrointestinal toxicity was seen in the brachytherapy group (132). In the UK, a study by Hoskin randomised 218 intermediate and high risk node negative patients to EBRT alone (n=108, 55Gy in 20 fractions) or EBRT (n=110, 35.75Gy in 13 fractions) and HDR brachytherapy boost of 2 x8.5Gy in 24 hours. NA ADT was administered to 76% of the group and planned for 6 months in intermediate risk patients and 3 years in high risk patients. At a follow up of 85 months reported in 2012, the EBRT +HDR group had a significant improvement in relapse free survival, with a 33% reduction in the risk of recurrence (p=0.01). The rates of severe late urinary and rectal toxicity were similar in both groups (133). A population based study using 12,745 patients identified from the SEER database in the US compared the prostate cancer specific mortality (PCSM) in those treated with EBRT alone and EBRT and brachytherapy or brachytherapy alone. Patients had high risk disease with Gleason score 8-10, or Gleason grade 4-5, T1-T3N0M0 stage. The median follow up was 6.4 years and the authors reported that treatment with brachytherapy alone with EBRT was associated with a significant reduction in PCSM compared with patients treated with EBRT alone

(HR 0.77, 95% CI 0.66-0.99) (134). The ASCENDE-RT trial compared two methods of dose escalation using either LDR brachytherapy boost or an EBRT boost to 78Gy. 398 men with intermediate or high risk disease were included in the study which reported an improved biochemical free progression at 9 years of 83% vs 62% (log rank p<o.001) in favour of the LDR boost arm. There was a trend for increased gastrointestinal toxicity in the brachytherapy arm (135).

1.2.3 Systemic therapy

1.2.3.1 Androgen Deprivation Therapy

There have been numerous trials that have explored the role of neoadjuvant and adjuvant androgen deprivation therapy with prostate radiotherapy demonstrating benefits to this combination. Short course neoadjuvant ADT has been demonstrated to improve biochemical control, metastatic disease free survival and overall survival in intermediate and high risk disease. In the context of high risk prostate cancer, long term adjuvant ADT demonstrates additional benefits. One of the earliest and largest trials was RTOG 85-31 which randomised 977 locally advanced patients with cT3 or node positive disease to radiation alone (60-70Gy) or radiation and ADT (Goserelin, starting in the last week of RT and continued indefinitely). At 10 years the arm with additional ADT had rates of local control (23% vs 38%, p<0.0001), distant metastases (24% vs 39%, p<0.0001), disease specific survival (16% vs 22%, p=0.0052) and overall survival (49% vs 39%, p=0.002) (17). Additionally, the EORTC 22863 trial randomised 415 men with T3-T4 disease or T1-T2 disease and poorly differentiated histology to radiation alone (70Gy to the prostate and 50Gy to the pelvis) vs radiation and concurrent and adjuvant ADT using an LHRH analogue and cyproterone acetate for 3 years in total. Again, the arm with radiotherapy and ADT had improved rates of local failure (16.4% vs 1.7%, p<0.0001), distant metastases (29.2% vs 9.8%, p<0.0001), disease specific survival (74% vs 40%, p<0.0001) and overall survival (78% vs 62%, p=0.0002) (18).

Three large randomised controlled trials (RTOG 9202 (19), DART01/05 (20) and EORTC22961 (21) have also demonstrated that a longer course (28-36 months) of ADT improves overall survival compared to short course (4-6 months) ADT in

combination with radiotherapy. RTOG 92-02 was designed to detect an absolute 10% improvement in disease-free survival with long course ADT. 1554 patients with T2c-T4 disease and a PSA <150ng/ml were randomised to a short course of ADT (starting 2 months pre-RT and ending at the end of RT) and long course ADT (starting 2 months pre-RT and continuing for 2 years post RT. Radiotherapy was to the prostate and pelvic nodes. At 10 years there was a significant benefit in favour of the long course of ADT for multiple endpoints such as local failure (22.2% v 12.3%, p<0.00001), disease free survival (22.5% v 13.2% p<0.0001), disease specific survival (83.9% v 88.7%, p=0.0042) and distant metastases 22.8% v 14.8% (p<0.0001). An unplanned subset analysis for patients with Gleason 8-10 disease also revealed a significant improvement in overall survival (45% v 32%, p=0.006) but this was not seen in the whole trial cohort (19). The DART 01/05 trial was conducted in Spain and randomised 355 patients with NCCN intermediate to high risk disease between long and short course ADT. All patients received high dose RT at 76-82Gy and were additional randomised to receive either 4 months of ADT (Goserelin) alone (2 months pre-RT and 2 months during RT) or an additional 24 months of ADT. The primary endpoint was biochemical disease-free survival at 5 years which was significantly improved in the long course ADT group (90% v 81%, HR 1.88) and additional improvements in the 5 year metastatic free survival (94% v83%, HR 2.31) and overall survival (95% v 86% HR 2.48) (20). The EORTC 22961 trial was designed to compare 6 months of ADT with 3 years of ADT and in high risk patients receiving RT. 970 patients with high risk disease defined as T1c-T2b N1/N2 or T2c-T4 N0-N2 and PSA up to 40 x above the upper limit of normal were randomised. After a median follow up of 6.4 years a survival benefit was found in favour of the long course ADT group with a reported 5-year overall mortality of 15.2% v 19.0%, HR 1.42 (21).

There have also been two meta-analyses published. The first was published in 2010 by Cuppone and included 5 trials (113). The authors concluded that a longer duration of ADT improves biochemical control with an absolute benefit of 10.1%, local recurrence with an absolute benefit of 11.7% and distant metastases with an absolute benefit of 11.5%. They also reported a trend for improved cancer specific survival. The second by Sasse was published in 2012 and included data from 10 trials (114). The authors concluded that there was

significant benefit in overall survival and disease-free survival when long course ADT was combined with RT, particularly when more than 1 year of goserelin was used.

1.2.3.2 Docetaxel

The large Medical Research Council (MRC) STAMPEDE trial published data for the standard arms vs two additional systemic therapy arms in 2015. The 2962 men included either had metastatic disease (1817, 61%), node positive disease (448, 15%) or were high risk stage N0M0 (697, 24%), or previously treated with local therapy (165, 6%). The patients were randomised 2:1:1:1 between standard of care (SOC), SOC + Zolendronic acid, SOC+ Docetaxel 75mg/m2, or SOC+ Zolendronic acid +Docetaxel. The standard of care was at least 2 years of ADT plus (and mandatory RT at a later time point) in N0M0 patients and optional RT in the N+M0 arm. The Docetaxel chemotherapy was commenced within 12 weeks of ADT initiation and given as six 3-weekly cycles with prednisolone 10mg daily. After a median follow up of 43 months (IQR 30-60 months), the patients treated with Docetaxel (+/- Zolendronic acid) showed an improvement in overall survival (HR 0.78, 95%CI 0.66-0.93, p=0.006). While the improvement was most pronounced in the metastatic patient group, but there was also a clear failure free survival improvement (HR 0.6, 95% CI 0.45-0.8, p=0.283x10-3) in the non-metastatic patient group. Fewer deaths occurred in the non-metastatic patient group, which meant that any statements about overall survival in this subgroup were underpowered at the time of reporting and further follow up was required (22). Several other trials such as GETUG12, CHAARTED and RTOG 0521, investigating the early use of docetaxel in the high risk and metastatic patient population have recently been published. A meta-analysis of the pooled results found no overall survival benefit with the use of Docetaxel in non-metastatic patients, but failure free survival was improved with the addition of Docetaxel (HR=0.7, 95% CI 0.61-0.81, p<0.0001) was reported as an absolute improvement in the failure free rate of 8% (23).

Abiraterone

The STAMPEDE trial also published its results with the early use of abiraterone vs ADT alone in 2017. A total of 1917 patients were included in the analysis of which 878 had locally advanced non metastatic disease. Patients with node negative non-metastatic disease had mandatory radiotherapy to the prostate at 6-9 months after starting ADT. All patients without metastatic disease had at least 2 years of ADT. Abiraterone was given at a dose of 1000mg with 5mg of prednisolone daily and continued till progression in patients with metastatic disease and for 2 years (unless progression occurred before then) in the non-metastatic patients. A significant improvement in failure free survival was seen in all types of patients receiving additional abiraterone and the reported 3 year failure free rate was 75% V 45% (HR for failure 0.29, 95% CI 0.25-0.34, p<0.001). The overall survival of the whole cohort was also significantly improved at 83% v 76% (HR for death 0.63, 95% CI 0.52-0.76, p<0.001) (115).

In summary, the current treatment of high risk prostate cancer includes dose escalated radiotherapy to the primary tumour. Alongside this systemic therapy with long course ADT improves overall and disease specific survival in patients with high risk prostate cancer. Additional systemic therapy with the early use of Docetaxel chemotherapy or Abiraterone improves progression free survival.

1.3 The role of pelvic lymph node treatment in high risk patients

Below I will outline the rationale and evidence for and against pelvic nodal radiation in this group of patients. I will also outline the current methods for pelvic lymph node staging and estimating pelvic nodal risk in order to plan treatment.

1.3.1 The rationale for treating pelvic lymph nodes

The treatment of local nodal stations with a high risk of micro-metastatic disease is well established in head and neck (24), rectal (25), breast (26) and gynaecological malignancies (27). Extended pelvic lymph node dissections performed in clinically node negative patients with high risk prostate cancer

confirm the presence of lymph node metastases in 30-40% of patients (28). Logically, if left untreated the lymph node metastases should result in a poorer disease related outcomes and several of the historical trials that demonstrated the benefit of radiation and long term ADT in high risk patients used whole pelvic radiation to cover the pelvic nodes (18, 19, 21, 29).

Historically node positive prostate cancer patients were felt to have a prognosis similar to that of patients with systemic metastases and were treated with palliative intent with lifelong ADT. While there have never been any randomised trials performed, recently, there have been at least two significant publications suggesting the benefit of treating this patient group with whole pelvic RT (WPRT).

The STAMPEDE trial published a cohort analysis of patients recruited into the standard of care arm of the trial that had non-metastatic disease (30). All patients had ADT for at least 2 years. Patients with N1 disease could have radiotherapy at the discretion of the clinician, who could also choose between PORT and WPRT. The trial recommendations for RT were conformal or IMRT techniques and a recommended dose to the prostate was 74Gy in 2Gy per fraction or the equivalent using a hypofractionated schedule. The optional pelvic dose was 46-50Gy in 2Gy per fraction or equivalent. If using IMRT the suggested pelvic dose was 55Gy in 37 fractions. Data was available for 177 node positive patients and the failure free survival was significantly improved in the patients who received radiotherapy compared to those that didn't (adjusted HR, 0.35, 95% CI 0.19-0.65) with a 2 year failure free survival rate of 88% (95% CI 77-94%) vs 64% (95% CI 51-75%). These results held even after adjustment for Gleason score, Log transformed index PSA, age and WHO performance status at presentation. In the 71 node positive patients who received radiotherapy, 82% had treatment to the prostate and pelvis (30).

Another recent large retrospective series of 3540 node positive patients from the US SEER database was published in 2015 (31). Patients treated with ADT and RT were younger, with a lower comorbidity score, higher Gleason grade, lower PSA and more often clinical stage T2/T3 than T4, than patients treated with ADT alone. After propensity score matching, 318 patients remained in each group for analysis. There was a 50% decrease in the risk of five year all-cause mortality in

patients treated with radiotherapy and ADT versus ADT alone (HR 0.50, 95% CI 0.37-0.67, p<0.001, crude OS rate 71.5% vs 53.2%). There was no information about the duration of ADT, radiation doses or treatment volume (31)

With this growing body of evidence that WPRT and ADT can improve outcomes in patients with clinically node positive disease, it would therefore be logical to expect that the same treatment in patients with a high risk of microscopic nodal disease might also carry a benefit, albeit smaller in magnitude.

1.3.2 Retrospective Data

There have been multiple retrospective trials comparing the outcomes of patients treated with prostate only RT (PORT) vs WPRT and the results have been mixed (summarised in table 2). There are several methodological issues such as differences in the characteristics of the treated patient populations for example risk groupings. There are also variations in the radiation doses and delivery techniques, and differences in treatment with ADT. The most significant issue is that selection bias likely resulted in younger, fitter patients with more aggressive disease being treated with WPRT. The main trials published in the post PSA era using external beam alone are summarised in table 2 (32-36). One of the largest, most recent retrospective series was by Amini et al (37). The US national cancer database was used to identify 14,817 node negative prostate cancer patients treated with radiotherapy between 2004 and 2006. Baseline characteristics of PSA, Gleason score and T stage were available and overall 64% of patients had Gleason ≥8, 42% had PSA >20 and 17% had T stage of ≥T3. Patients were categorised into two groups; PORT or WPRT which described patients who had all or most of the pelvis treated with a boost to the prostate. Information about radiation modality (3DCRT vs IMRT) was available for 7034 (47%) patients. Androgen deprivation therapy was received by 77% of the whole cohort but there was no information about the type or duration of treatment. The authors reported that the patients receiving WPRT were younger (p=0.015), had a higher T stage (p<0.001), PSA (p=0.006), Gleason score (p<0.001) and overall greater number of risk factors (p<0.001). The WPRT group were also more likely to receive ADT (p<0.001) or a brachytherapy boost (p<0.001). Nonetheless the group used multivariate analysis and propensity score matching to attempt to

account for this selection bias. At a median follow up of 82 months (range 2-122 months) the group reported that the addition of WPRT had no survival benefit. Additionally, on recursive partitioning analysis (RPA) no subgroup of patients could be identified where the addition of WPRT carried a survival benefit. No information is available on the database about local or distant disease control, biochemical failure or cancer specific survival. The addition of androgen deprivation therapy (HR=0.92, p=0.33) and combination of external beam radiotherapy with a brachytherapy boost (HR=0.71, P<0.001) were associated with an increase in overall survival. However, the authors accepted that despite the RPA methods used, the selection bias of patients with higher risk features being treated with WPRT may have masked any improvements in cancer specific and overall survival. Furthermore as longer course androgen deprivation therapy carries a survival advantage in the high risk population, the lack of detail about treatment duration means we do not know if this was a confounding factor (37).

Table 2. Summary of the retrospective trials published in the post PSA era evaluating prostate only radiotherapy (PORT) vs whole pelvic radiotherapy (WPRT) using external beam radiation. OS=overall survival, NA=neo-adjuvant, ADT=androgen deprivation therapy, Int=internal, ext.=external, 3D-CRT=Three dimensional conformal

Study	Population	Androgen Deprivation therapy	Prostate RT	Pelvic Lymph node RT	Key findings
Seaward 1998 (32) n=201	**WPRT=117 PORT=84 LNI risk ≥ 15% (Partin)**	**NA ADT for 4 months or less. 32% of WPRT group 26% of PORT group**	**Median dose 70.1Gy/1.8Gy in WPRT group 71.9Gy/l.8Gy in PORT group 49% 3D-CRT, 51%=4 field box**	**Standard - top of L5/S1 and posteriorly covering sacrum Dose unknown**	**Benefit in median progression free survival in favour of WPRT at median follow up of 32 months. 34.3 months v21.0 months (P=0.0001)**
Pan 2002 (33) n=263	**WPRT=176 PORT=87 LNI risk >5% and l≤15% (Partin)**	**~20% received NA ADT in both groups**	**60-80Gy 3D CRT (# size not stated)**	**Standard – top of L5/S1, posteriorly to sacrum. Dose =45Gy**	**Benefit for WPRT, most pronounced in intermediate risk group: Biochemical relapse free survival was 90% vs 81% at 2 years (p=0.02). No difference in low and high risk groups**
Aizer 2009 (36) n=277	**WPRT=68 PORT=209 LNI≥ 15% (Roach)**	**NA and concurrent ADT for 12-24 months. In 92% of PORT and 99% of WPRT group**	**Median dose = 75Gy in 1.8Gy per fraction 3DCRT=35% IMRT=65%**	**Standard field up to L5/S1, covering pre-sacral nodes posteriorly, Dose= 45Gy in 1.8-2Gy, 4 field technique**	**4-year biochemical relapse free survival improvement in favour of WPRT of 86% vs 69%. P=0.02**

Study	Population	Androgen Deprivation therapy	Prostate RT	Pelvic Lymph node RT	Key findings
Milecki 2009 (34) n=162	**WPRT=70** **PORT=92** **High risk disease = Gleason >7 or PSA >20ng/ml or T3 disease**	**WPRT = NA ADT for 2-12 months, then long term ADT for median duration of 28 months.** **PORT = long term ADT starting at end of RT, median duration of 28 months**	**Median 70.2Gy in 1.8-2Gy per fraction** **3D-CRT**	**4 field box covering obturator, int./ext. iliac and pre-sacral LN** **Dose =46.4Gy in 1.8-2Gy** **4 field technique**	**5-year biochemical relapse free survival benefit in favour of WPRT 53% vs 40%, p=0.07** **No OS benefit seen.**
Mantini 2011 (35) n=72	**WPRT=34** **PORT=38** **LNI > 30%** **(stage T2c/T3/T4 and/or Gleason ≥7 and /or PSA≥20)**	**Based on risk - 2 months NA and concurrent only, or long term for 1 year**	**70.2-73.8Gy in 1.8Gy**	**Standard field above L5/S1.** **Post cover of sacral nodes to S3** **Or 3D CRT planned** **Dose= 45Gy in 1.8-2Gy**	**4 year biochemical relapse free survival benefit in favour of WPRT in patients with LNI risk of >30%.** **87.9% vs 70.4%, p=0.03.**
Amini 2015 (37) n=14,817	**WPRT=7606** **PORT=7211** **High risk (T3/Gleason 8-10, PSA 20)**	**Unknown**	**Unknown**	**Unknown**	**No difference in OS at 7 years, 72.0% vs 73.2%, P=0.006** **Biochemical relapse free survival and prostate cancer specific mortality not known**

1.3.3 Randomised data

To date there have been three published prospective randomised controlled trials investigating the benefit of elective pelvic radiotherapy and all of them have been negative.

1.3.3.1 RTOG-7706

The first was the RTOG-7706 trial published in 1988. This was conducted in the pre-PSA era and patients were staged as N0 either with a laparotomy (25%) or lymphangiogram (75%). Only 5% of either treatment arm received any androgen deprivation therapy. 484 patients were randomised between the two groups and results were reported with a median follow up of 7 years. The prostate was treated to 60Gy and the pelvic nodes to 45Gy in 1.8-2Gy per fraction with a 4-field technique. The authors found no statistically significant benefit in overall survival or relapse-free survival between the PORT and WPRT groups (38).

1.3.3.2 RTOG-9413

This was followed by the RTOG-9413 trial. The aim of this trial was to test two hypotheses; Firstly; that ADT and whole pelvic radiotherapy improved progression free survival (PFS) compared to ADT and PORT. Secondly to test the hypothesis that neo-adjuvant ADT (NA-ADT, commencing 2 months before RT and during RT) and RT (regardless of field) improved PFS by at least 10% compared to RT followed by adjuvant ADT (beginning just after RT). The trial was designed to detect a 10% difference in the 5 year PFS between the two groups (WPRT vs PORT and NA-ADT vs A- ADT) with a significant level of 0.025 and power of 80% and the target sample size for the trial was 1200 patients.

The ADT consisted of a monthly LHRHa and flutamide for a total of four months. The radiation dose to the prostate was 70.2Gy in 1.8Gy per fraction. WPRT consisted of a conventional four field box technique with a minimum unblocked field size of 16.16cm and treated to a dose of 50.4Gy in 1.8Gy per fraction (Equivalent to 48Gy in 2Gy per fraction using an α/β of 1.5-3 for prostate).

A failure event for PFS was defined as local progression, regional/nodal failure, distant failure, biochemical failure, or death due to any cause. The trial was designed in the early 1990's prior to the established definition of PSA failure as the nadir plus 2ng/ml, and was defined as two consecutive and significant rises separated by at least one month. Secondary endpoints included overall survival, local failure, distant metastases and PSA failure. Eligible patients had to have a LNI risk of >15% based on the Roach formula. They were randomised in a 1:1:1:1 fashion between all four treatment groups and stratified for PSA (<30 or ≥ 30) T stage and Gleason score.

The first results were published in 2003 after a median follow up 59 months. At this point a statistically significant improvement in PFS of the WPRT cohort compared to the PORT cohort (54.2% vs 47%, p=0.02) was seen. No difference was reported in overall survival or failure free survival between the patients treated neoadjuvant and adjuvant hormones (39). However, an update after a median follow up of 6.6 years showed no statistically significant difference in OS or PFS between the WPRT and PORT groups and the two androgen deprivation groups. While the trial was not powered to compare each of the four arms, the authors reported an overall survival advantage for the neoadjuvant ADT and WPRT arm compared to the three other arms. The WPRT and adjuvant ADT arm had the poorest survival of all four groups. The authors hypothesised that there may be a sequence dependent interaction between ADT and radiation in the lymph nodes which is T cell mediated to account for this result. A supportive study demonstrated T cell infiltration in the prostate at the initiation of ADT treatment leading to an increase in apoptosis which peaked 3-4 weeks into the treatment (40). The trial authors hypothesised that if this same process occurs inside involved nodes it may lead to an increase in cancer cell death before radiation in the NA-ADT arm, making the WPRT more effective at the radiation doses given. However, it does not explain why the A-ADT and WPRT would have an outcome worse than the two other PORT groups. There was no difference in biochemical recurrence or prostate cancer specific survival between the four arms, but there was a trend towards an improved outcome in both for the NA-ADT+WPRT group. Late GU (≥ grade 3) toxicity did not differ between the four arms, but there was an increase in ≥Grade 3 late GI toxicity between the four arms, as the rate was 5% in the neo-adjuvant ADT +WPRT arm compared to 1%

in the PORT+NA-ADT arm, 2% in the PORT+A-ADT arm and 2% in the WPRT+A-ADT arm (41).

Criticisms of RTOG-9413

There are several trial design features which have been heavily criticised and may have contributed to the negative results. Firstly, the overall treatment of patients in the trial would be considered under treatment by today's standards. Patients were treated with only short course ADT (and some patients only in the adjuvant setting) and radiation dose to the prostate would also be considered inadequate. Both of these factors may have led to treatment failures that masked any benefit of WPRT. The trial was designed in 1993 when little was known about the significance of a rising PSA post treatment and the currently used definition of biochemical failure post RT (of nadir PSA +2ng/ml) had yet to be established. The end point of PFS was therefore picked and also included death from any cause. This may have masked any true differences between the group as a reported 27% of failure events were recorded as "death from any cause" or "clinical features of progression that proceeded biochemical failure". This was recognised by the authors and the updated results at 10 years included analysis based on the recognised definition of biochemical failure which was also negative (41). Another major criticism was that the trial was underpowered to detect a benefit in the order of 10% in favour of WPRT. The risk of lymph node involvement in the trial cohort was assessed via the Roach score and reported as 15-35% in 25% of participants and >35% in 75% of participants. This meant that true proportion of patients with PLN disease in the trial may have only been too small to detect a difference between the treatment groups.

The RTOG is currently conducting a new randomised phase III trial (RTOG 09-24, NCT01368588) in which patients with high risk or locally advanced prostate cancer are treated with ADT and PORT or WPRT (43).

1.3.3.3 GETUG-01

The most recent published randomised study was the GETUG-01 trial. In this trial 444 pts with T1b-T3N0 prostate cancer were randomly assigned to receive PORT (66-70Gy in 2Gy per fraction) or WPRT (46Gy to the pelvic nodes). The

pelvic irradiation technique was a four-field box to cover the low common iliac nodes, internal iliac and external iliac nodes. The top border lay between S1 and S2. Later modifications included an increase in the prostate dose from 66Gy to 70Gy after March 2000 following the publication of dose escalation studies. Two other schemes were also introduced; 1.8Gy/fraction treating to a total dose of 68.4Gy to the prostate and 46.8 to the pelvis (EQD2 of 44-45Gy using α/β of 1.5-3Gy), and 2.25Gy per fraction, treating four fractions a week to a total dose of 45Gy to the pelvis ((EQD2 of 47-48Gy using α/β of 1.5-3Gy and assuming no time factor) and 65.25Gy to the prostate.

The trial defined high risk patients as having T3 disease and/or Gleason ≥7 and/or PSA≥3x the upper limit of normal (which for most labs was 4ng/ml). Patients were stratified according to "high" and "low" risk groups according to this definition and approximately 21% of the patients were low risk. Androgen deprivation therapy was only authorised for patients classified as having "high risk disease" and consisted of 4-8 months of neoadjuvant and concomitant treatment with an LHRHa. ADT was received by around 60% of patients in both arms. According to the Roach formula of (2/3PSA) + [(Gleason score-6) x10] 51% of the prostate and pelvic group and 57% of the prostate only group had a low risk (<15%) of lymph node involvement. The study was powered to detect a 15% improvement (60-75%) in the 5 year PFS in favour of WPRT. The definition of PFS included local, distant or nodal progression, biochemical progression or death from any cause.

The early results were published in 2007 (44) with a median follow up of 42 months. The study was negative as the 5 year PFS and OS were similar in both groups. There was a small but insignificant increase in the acute GI toxicity assessed by the LENTSOMA scale and a trend towards increased mild GI toxicity (RTOG) in the WPRT arm. No difference in the quality of life was observed between the groups. The PFS results were also similar for patients stratified into high and low risk groups using the trial definition.

The results were updated after a median follow up pf 11.4 years and there remained no difference in the OS and PFS between the two groups. However, in the patients stratified as low risk there was a trend towards an improvement in

event free survival in favour of WPRT (77.2% (95% CI 63.8-88.4) vs 62.5% (95% CI 47.0-78.1%) at 10 years, p=0.1778). A further post hoc subgroup analysis was performed by dividing the patients up into risk of lymph node involvement <15% vs ≥15% according to the Roach formula. This analysis demonstrated a significant event free survival improvement with WPRT in patients with a LNI risk of <15% (82.2% vs 60.7% at 10 years, P=0.0058) and this was most pronounced in those patients who had not received ADT (45).

Criticism of GETUG-01

There are several limitations that may account for the negative results seen in the GETUG trial. Firstly over 50% of the trial population had a low risk of LNI, which meant that it was significantly underpowered to detect a benefit for WPRT. Secondly, the other treatments used may have resulted in progression which might have masked any benefit of WPRT. Namely the low doses of radiation to the prostate and selective use of ADT in high risk patients. Lastly, the limited pelvic field which would have missed the upper pre-sacral and lower common iliac nodes would be considered inadequate to cover potential nodal disease.

1.3.4 Summary of trial data

In summary there have been three randomised controlled trials that have failed to unequivocally demonstrate a benefit for whole pelvic radiation over prostate only radiation.

1.4 Pelvic lymph node detection

1.4.1 Prostate lymphatics

The lymphatic drainage pathway for the prostate is complex and takes four routes. The first main route of drainage is laterally to the obturator nodes and from here there may be spread on to the middle and lateral chains of the external iliac nodes. The second most common route is to the internal iliac nodes along the branches of the internal iliac vessels. Thirdly some drainage occurs along an anterior route, via nodes that are anterior to the bladder and on to the internal iliac nodes. Finally there is a posterior route to the peri-rectal and pre-sacral

nodes anterior to the sacral promontory and up to the medial chain of the common iliac nodes (46).

1.4.2 Sentinel lymph node sampling

Sentinel lymph node procedures have become routine for malignancies such as breast cancer, melanoma and penile cancer. The procedure helps to establish which clinically node negative patients would benefit from a more extensive nodal dissection and the results from various studies show it to be a promising diagnostic tool. However, there is no consensus on the definitions and technical aspects of performing the procedure in prostate cancer and the technique is not routinely recommended (47).

1.4.3 Pelvic Lymph node dissection

Pelvic lymph node dissection at the time of radical prostatectomy (RP) remains primarily a staging procedure and is the most accurate method of assessing lymph node spread from prostate cancer. However, its accuracy depends upon the anatomical extent of pelvic nodes dissected. A standard dissection (PLND) would include removal of the obturator and external iliac nodes. This is now widely regarded as an inadequate staging assessment and doesn't address all of the lymphatic drainage pathways of the prostate outlined above. A larger operation would be an extended pelvic lymph node dissection (ePLND). This would additionally include the removal of the internal iliac (hypogastric) nodes and some surgeons would also include the pre-sacral and common iliac nodal groups (48). In a study by Heck et al (49), 52 intermediate and high risk patients underwent ePLND with a detailed mapping of the dissected node locations. The majority (70%) of positive lymph nodes were in the obturator and external iliac regions that are covered by a standard PLND, however the internal iliac and common iliac areas accounted for 16% and 13% of positive lymph nodes respectively. Also, 11% of node positive patients had disease in the common iliacs alone, with no other site of PLN detectable. The group therefore recommended that an ePLND should include the common iliacs up to the ureteral crossing at the least. Another study used Single photon emission (SPECT) fused with CT or MRI to detect lymphatic drainage sites in patients in clinically node

negative patients who had had received an intra-prostatic injection of Tc-99 colloid. Patients then underwent ePLND and a gamma probe was used intraoperatively to identify and resect the nodes. In total 317 lymph nodes were identified in the 34 patients studied. The external iliac and obturator areas which would be the only nodes resected in the limited PLND accounted for only 38% (n=120) of these nodes. The remaining nodes were found in the internal iliac (n=81), pre-sacral/para-rectal (n=26), common iliac (n=50), para-aortic (n=38) and inguinal (n=2) regions. A standard ePLND including the internal iliac nodes would have accounted for 63% of all the nodes identified. The authors suggested a balance should be sought between capturing all of the draining nodes and the potential increase risks and toxicity associated with more extensive surgery, so they also recommended the template of the ePLND be extended to where the ureters cross the common iliac artery, which would remove around 50% of the nodes along the common iliac vessels and 75% of all of the nodes identified (50). There are controversies about the rate of surgical complications according to the extent of dissection. Some studies finding comparable toxicity rates and others finding considerably more toxicity (48) with an ePLND. Both PLND and ePLND however are invasive, require a hospital stay and are inevitably associated with additional risks to the patient.

Irrespective of the extent of lymphadenectomy, there are two consistent findings in the published surgical data. Firstly, that with increasing risk stratification, the yield of positive nodes at surgery increases. Lymph node metastases are detected in approximately 5-6%, 20-25% and 30-40% of low, intermediate and high risk patients respectively (28). Secondly, that the number of lymph node metastases identified increases linearly with the extent of dissection performed (51).

In summary, the EUA and NCCN guidelines both recommend an ePLND rather than a PLND for the assessment of pelvic lymph nodes. Guidelines recommend that ePLND should be offered to all high risk patients and any intermediate risk patients who have >2-5% risk of lymph node involvement according to the Roche equation and are undergoing a radical prostatectomy. However, there is currently no consensus about which nodal groups should be included and what is an ideal nodal yield (5, 7). In the UK there is no consensus on the use of ePLND and it is

controversial whether a 2-5% LN involvement risk justifies the extra morbidity of additional surgery.

1.4.4 The therapeutic benefit of pelvic lymph node dissection

At present, the clinical benefit of lymph node dissection remains unproven, with no randomised data available and conflicting results from retrospective data (52). One of the difficulties in interpreting the data is the stage migration that occurs. If patients undergo a PLND and are found to have positive nodes, they will probably have a lower burden of disease compared to patients who are clinically node positive and may well have better outcomes. Similarly, the patients who are staged pN0 after a nodal dissection have had a more thorough assessment leading to stage migration and are more likely to be genuinely N0 than patients who are clinically N0; again improving outcomes for both N0 and N+ surgically staged patients – the “Will Rogers” phenomenon (53).

The potential clinical benefit of an ePLND over a standard PLND in node negative patients is currently being investigated in a prospective randomised trial called the SEAL study (54). Patients are being randomised to a limited PLND with removal of approximately 10-14 nodes, or an ePLND with removal of approximately 20 nodes, including the common iliac nodes. The primary outcome is biochemical relapse free survival and the secondary outcomes include overall survival and comparison of treatment related morbidity.

1.4.5 Adjuvant treatment for pN+ patients

In the past, on finding positive nodes upon frozen section, a radical prostatectomy was often abandoned. However, as already discussed there is emerging data to suggest that the N1 population is diverse group of patients who do not universally have a poor prognosis. Surgical series show that patients with a low volume of nodal disease have significantly higher survival rates compared with patients who have high volume nodal disease, irrespective of the adjuvant treatment they receive (55, 56).

A single small randomised trial has shown a survival advantage for immediate hormone therapy (orchidectomy) after radical prostatectomy in pN1 patients after

a median follow up of 7.1 years (57). As a result, the EAU guidelines recommend offering adjuvant ADT to improve biochemical control, cancer specific survival and overall survival (5). There is also retrospective data to support the use of post-operative radiation in this group of patients. In a large retrospective study by Abdollah et al (58), based on surgical data from two centres, 1,107 patients were identified as pN1 following radical prostatectomy and ePLND. All patients received lifelong adjuvant ADT and 35% also went on to receive adjuvant radiotherapy to the prostate bed. It is not clear what proportion of these patients also had pelvic radiation. On multivariable analysis, adjuvant radiotherapy was associated with an improvement in cancer specific mortality (HR 0.37; $P < 0.001$). When patients were stratified by risk, two groups benefited from adjuvant radiotherapy; firstly, patients with ≤ 2 positive lymph nodes, Gleason score 7 -10, pT3b/pT4 stage, or positive surgical margins (HR= 0.30; $P = 0.002$); secondly, patients with 3-4 positive lymph nodes (HR=0.21; $P =0.02$), regardless of other tumour characteristics (58). Therefore, the EAU Guidelines recommends that patients with a low volume of nodal disease (<2 nodes, with no extranodal extension), clear margins and a low post-operative PSA (<0.1) can be offered observation as an alternative to radiation (5).

1.5 Imaging methods to stage pelvic lymph nodes

1.5.1 Standard CT and MRI

There are several features used to identify pathological lymph nodes on conventional imaging; the first of which is size. A study by Vinnicombe et al (59), based on staging lymphograms and CT in men surveyed for early stage testicular cancer at the Royal Marsden Hospital, established the normal pelvic LN size (maximum short axis diameter) on CT should be 7mm for the internal iliac nodes, 8mm for obturator, 9mm for common iliac and 10mm for external iliac nodes. A later study by the same group found that MRI could detect smaller normal nodes than CT. Taking the 95th centile values and accepting a false positive rate of 5%, the upper limit for the normal maximum short axis diameter in the pelvic nodes on MRI should be 4mm for common iliac and obturator nodes, 5mm for external iliac and internal iliac nodes. (60). Therefore, nodes larger than 8mm in short axis on CT or MRI should be regarded as enlarged. Another suspicious feature is shape, as round or irregularly shaped nodes are more likely to be

malignant than oval nodes (61). Nodes frequently enhance with intravenous contrast; if this enhancement is more avid this is suspicious of malignancy. Lastly, location is important; so that nodes in the typical lymphatic drainage sites for prostate cancer are treated with greater suspicion that nodes outside of these areas (62).

Unfortunately, none of these characteristics are reliable and, standard CT and MRI are still limited in their diagnostic capabilities for pelvic lymph node metastases. Size in particular is not a reliable indicator of prostate cancer involvement; with studies estimating 80% of metastatic nodes are smaller than the threshold of 8mm (63, 64). In a study performed in patients undergoing radical prostatectomy and lymph node dissection (65), 76 positive lymph nodes and 96 negative lymph nodes were identified and measured. The mean axial size for positive nodes was 0.8cm (range 0.2 to 0.65cm) and 1.0cm (range 0.2-2.2cm) for negative nodes. In 56 metastatic nodes (74%) the axial size was less that 1cm and in 20 (26%) it was 5mm or less. The pre-operative CT scans for these patients did not identify any nodes larger than 1.5cm, which was the size criteria used to identify positive nodes in the study. However, 6(8%) and 19(12%) of patients with and without LN metastases respectively had nodes 1.5cm or greater in axial dimension.

In a meta-analysis of CT and MRI for diagnosing malignant nodes the threshold for size considered positive ranged from 0.5-2cm. There was little difference in the performance of MRI and CT in lymph node staging. The pooled sensitivity was 42% for CT and 39% for MRI and the pooled specificity was 82% for both methods. There was a trend (but not significant) improvement in diagnostic performance if the threshold for considering a node pathological was under 1cm, but understandably, specificity declined as the size threshold dropped. Conversely, specificity was much improved if the size criteria was over 1.5cm (64) . The authors concluded that round nodes with a short axis >8mm and oval nodes with a short axis >10mm should be considered metastatic.

1.5.2 Multiparametric and Diffusion weighted MRI

Diffusion weighted imaging and multiparametric MRI has improved the assessment of prostate tumours within the gland, but has not been extensively investigated for the detection of LN metastases (66). Multiparametric MRI (mpMRI) plays an important role in the management of patients with prostate cancer. It contains T1- and T2-high-resolution weighted imaging, diffusion-weighted imaging (DWI), dynamic contrast-enhanced (DCE) and other functional MRI techniques. DWI provided information on tissue cellular density and membrane integrity while DCE enabled visualization of vascular permeability and perfusion. The incorporation of these newer sequences allows functional tissue information to supplement the anatomic information provided by T1W and T2W sequences. There are several small studies showing promising results for detecting lymphadenopathy with mpMRI (67-69) however, it has not been extensively investigated for the detection of prostate cancer lymph node metastases and the results need confirmation in larger multicentre prospective trials, ideally with histologically validation. Furthermore, the techniques need standardisation and the expertise needs to be widely available for this to be of routine clinical use in staging (66).

1.5.3 MRI lymphography

This technique uses a lymph node specific contrast agent; ferumoxtran-10 to detect metastases in normal sized lymph nodes. This is an intravenous contrast agent that consists of ultra-small particles of superparamagnetic iron oxide. The agent is transported to lymph nodes by macrophages after extravasation and causes nodes to have low signal intensity on T2 weighted MRI scans. Metastases in lymph nodes block the accumulation of the iron particles and therefore the signal intensity of these nodes remains high on T2 weighted MRI (63). The technique appeared promising and in a study by Harisinghani in 80 patients with T1-T3 prostate cancer, MRL was used to identify possible malignant nodes. 75 patients had PLND and 5 had a CT guided biopsy for histological confirmation of the pathological nodes. The reported sensitivity of the technique was 90.5% and specificity was 97.8%. However again, smaller nodes posed a problem so that if they were less than 5mm in size, sensitivity dropped to 40%

although specificity was still 98% (70). These results were later confirmed by a group in the Netherlands who performed a larger multicentre study in 375 intermediate and high-risk patients. All patients underwent a PLND or a CT guided biopsy and the reported sensitivity was 82% and specificity was 93% (63). Unfortunately production of ferumoxtran10 has been stopped and it is currently unavailable (66) and there have been problems with allergic reactions and other practical issues that have also limited its introduction into routine clinical practice (71).

1.5.4 PET-CT

Positron Emission Tomography (PET) combined with CT gives both molecular and anatomical data in a single imaging session. It uses an intravenously injected tracer labelled with a positron emitting isotope which is taken up by tumour cells. Subsequent emission of the positron within the tumour cells yields a pair of 511keV gamma photons that is detected by the PET scanner and reconstructed into a 3D image when co-registered with the CT images. Several PET tracers have been developed for use in prostate cancer and even more are in development. They are most commonly used in the setting of biochemical recurrence post RP (or RT) as they detect macroscopic recurrences at relatively low PSA levels with a greater sensitivity than conventional imaging techniques and can guide salvage treatment. Most of the available published data is therefore in this setting rather than the primary staging setting. Below are summarised three of the most commonly used PET tracers in clinical practice, with emphasis on the available data to support their use in the primary staging setting.

1.5.5 Choline-PET

Uptake of choline is increased in prostate cancer cells and 11C-labelled or 18F labelled Choline has been most comprehensively studied in the assessment of prostate cancer.

There have been multiple studies investigating the diagnostic performance of choline PET CT (see table 3). However, the results have been very variable, with sensitivity ranging from 0-100% and specificity ranging from 80-100%. It has

been suggested that this variability might be due to differences in the selection of patients, nuclear physicist experience, inter-clinic and inter-operator skills, equipment factors, validation reference methods and size of the lymph node metastases (66, 72). A systematic review and meta-analysis conducted in 2013 reported a pooled sensitivity of 49.2% and specificity of 95% for the detection of metastatic lymph nodes (73). In one of the largest studies by Beheshti et al (74), 130 patients underwent a PET-CT scan at diagnosis. Patients then went on to have a radical prostatectomy with extended pelvic lymph node dissection, or radical radiotherapy. Patients who did not have surgery and were diagnosed with PET positive nodes received follow up scans to confirm sites of disease with either persistent or increased uptake with corresponding morphological changes on CT, or decreased uptake with clinically regressive changes after treatment. The reported sensitivity and specificity for all the patients were 45% and 96% respectively. However, in lymph nodes of at least 5mm diameter, the sensitivity was 66% and specificity was 96%. The average diameter of the true positive LN was significantly larger than that of the false negative LNs (15mm vs. 4.0mm, p=0.0001), which the authors felt reflected the limited spatial resolution of the PET scanners which was about 4.8mm (74). In this study, the staging PET CT lead to a change in clinical management in 15% for whole group, and this increased to 20% if only the high risk patients were considered (74).

In another study, staging PET-CT was compared to MRI and was found to have superior sensitivity and specificity for identifying LN metastases (75). Several other smaller studies have compared the performances of Choline PET with MRI for the identification of nodal disease and found PET CT to be more sensitive and specific (76-78).

Presently however, the value and role of choline-PET in the staging of prostate cancer patients remains unclear due to rather variable performance and poor sensitivity. It is not recommended in the EUA guidelines for initial staging as it does not reach clinically acceptable diagnostic accuracy for the detection of LN metastases (7).

Table 3. Studies evaluating the use of Choline PET in pelvic lymph node detection at diagnosis

Study	Tracer/imaging	Participants	LN positivity criteria	Verification method	Sensitivity (LN or region based)	Specificity (LN or region based)
de Jong et al 2003 (79) Prospective	**11C-Choline PET**	**n=66**	**PET: uptake above background**	**PLND (n=43) Follow up PSA (n=23)**	**80.0%**	**96.0%**
Hacker et al 2006 (80) Prospective	**18F-Choline PET-CT**	**n=20 Intermediate or high risk**	**PET: uptake above background CT: no fatty hilum, round shape, >10mm diameter, contrast enhancement**	**ePLND**	**10.0%**	**80.0%**
Husarik et al 2008 (81) Retrospective	**18F-Choline PET-CT**	**n=43**	**PET: uptake above background CT: not specified**	**PLND (n=23) PSA follow up (n=18) Targeted lymphadenectomy (n=2)**	**33.0%**	**100% (in pts who had surgery)**
Schiavina et al 2008 (82) Prospective	**11C-Choline PET-CT**	**n=57 Intermediate or high risk**	**Only based upon PET: uptake above background**	**ePLND**	**60.0%**	**97.6%**
Steuber et al 2010 (83) Prospective	**18F-Choline PET-CT**	**n=20 >20% LNI risk**	**PET: uptake above background CT: short axis >10mm**	**ePLND**	**0%**	**100.0%**
Poulsen et al 2010 (84) Prospective	**18F-Choline PET-CT**	**n=25 intermediate or high risk**	**PET: uptake above background CT: not specified**	**PLND**	**100%**	**95.0%**
Beheshti et al 2010 (74) Prospective	**18F-Choline PET-CT**	**n=130 Intermediate or high risk**	**PET: uptake above background CT: short axis>10mm, no fatty hilum, round shape, contrast enhancement**	**Follow up imaging (n=15) ePLND (n=108)**	**45.0%, 66% in pts with pN ≥5mm**	**96%, 96.0% in pts with pN ≥5mm**

Study	Tracer/imaging	Participants	LN positivity criteria	Verification method	Sensitivity (LN or region based)	Specificity (LN or region based)
Budiharto et al 2011 (78) Prospective	**11-Choline PET-CT**	**n=36 10-35% LNI risk**	**PET: uptake above background CT: not specified**	**ePLND**	**42.9%**	**81.1%**
Contractor et al 2011 (85) Prospective	**11C-Choline PET and PET-CT**	**n=28**	**PET: uptake above background PET-CT: uptake above background and any size on CT.**	**ePLND**	**PET=40.7% PET-CT =51.9%**	**PET=98.4% PET-CT =98.4%**
Poulson et al 2012 (86) Prospective	**18-F Choline PET-CT**	**n=210**	**PET: uptake above background CT: not specified**	**PLND**	**56.2%**	**94.0%**
Vag et al 2014 (87) Prospective	**11C-Choline PET-CT**	**n=33 intermediate or high risk**	**PET: uptake above background CT: size (not specified)**	**ePLND**	**69.7%**	**90.5%**
Kjolhede et al 2014 (88) Prospective	**18F-Choline PET-CT**	**n=112 high risk**	**PET: uptake above background CT: not specified**	**ePLND**	**33.0%**	**92.0%**
Heck et al 2014 (87) Prospective	**11-C Choline PET-CT**	**n=33 intermediate or high risk**	**PET: uptake above background CT: not specified**	**ePLND**	**62.0%**	**96.0%**
Van den Berg et al 2015 (89) Prospective	**11-C Choline PET-CT**	**n=75 LNI risk of ≥10% but <35% from partin tables**	**PET: uptake above background**	**ePLND**	**8.2%**	**98.8%**
Pinaquy et al 2015 (90) Prospective	**18-F Choline-PET CT**	**n=47 intermediate or high risk**	**PET: uptake above background**	**PLND**	**56.0%**	**98.0%**

1.5.6 PSMA-PET

Prostate specific membrane antigen (PSMA) is a transmembrane protein found in normal prostate cells. Neoplastic transformation of prostatic tissue results in the transfer of PSMA from the apical membrane to the luminal surface of ducts and this overexpression on the cell membrane makes it an excellent target for molecular imaging. Additionally, there is greater PSMA expression in high Gleason grade or castrate resistant disease (91). Several small radiopharmaceutical agents have been developed for the targeting of PSMA and can be labelled with differing agents for use in imaging, radio-guided surgery and targeted endo-radiotherapy (92).

At present, PSMA-PET based imaging is proving particularly useful in the setting of post-surgical recurrence, where it is more sensitive than conventional imaging at detecting sites of disease even with low PSA levels (93) and is recommended for use by the EAU (116). PSMA-PET also appears to be more accurate than current standard imaging at diagnosing lymph node metastases in the primary diagnostic setting. In a study of 130 intermediate and high risk patients, 68Ga-PSMA PET was used to identify positive lymph nodes. Patients then underwent radical prostatectomy with ePLND and the reported sensitivity and specificity were 68.3% and 99.1% respectively (94). The authors found that in the positive lymph nodes that were not picked on imaging, the tumours were either PSMA negative or disease was found in a single lymph node. Other studies using 68Ga-PSMA PET have also reported high specificity (95, 96) and a meta-analysis with histopathology as standard of reference reported combined sensitives of 80% and specificities of 97% at lesion level and 86% and 86% at patient level, either at initial staging or biochemical recurrence (93). Although sensitivity is limited as smaller lymph nodes may still be missed (97) and PSMA-PET is therefore not yet recommended for routine use in staging.

1.5.7 Fluciclovine PET CT

18F-fluciclovine is a non naturally occurring amino acid analogue radiotracer. Its transport Is primarily mediated by the sodium dependent amino acid transporter system (ASC) and the sodium independent system (LAT1). Both of these amino

acid transporter systems are overexpressed in in prostate cancer and upregulated with androgen stimulation. In the primary staging setting a study was performed in 40 high risk prostate cancer patients with negative bone scans, who were eligible for surgery. The patients had undergone conventional imaging in the form of pelvic MRI (n=28) or CT abdomen/pelvis (n=12) and all had undergone investigational Fluciclovine PET CT. Radical prostatectomy and ePLND was carried out in all patients. Histologically confirmed lymph nodes were seen in 21/40 (53.5%) patients and correctly detected in 13/21 (61.9%) of patients with PET and 9/21 (42.9%) with conventional imaging. On region analysis, fluciclovine PET CT had 57.5% sensitivity and 98.2% specificity, compared with conventional imaging which had 19.2% sensitivity and 95.6% specificity (117). The majority of studies using this PET tracer have been performed in the setting of biochemical recurrence and it has been approved by the Food and Drug Administration in the US for the detection of recurrent disease. In comparison with other PET tracers in this setting it appears to be superior to Choline PET (118) and inferior to PSMA (119) in detecting recurrent metastatic disease in patients with biochemical recurrence post surgery.

1.5.8 Summary of radiological LN detection

In summary, current standard radiological techniques for detecting pelvic lymph node metastases in prostate cancer are insufficiently sensitive. New techniques are being developed that are promising but are not yet ready for introduction into routine clinical practice.

1.6 Tools for estimating lymph node involvement (LNI) risk

In the absence of appropriately sensitive radiological tests, several nomograms and predictive tables have been developed to estimate the risk of pelvic lymph node involvement and guide management of prostate cancer patients. Most have been developed and validated using limited PLND data for the purpose of guiding the decision to offer PLND in patients undergoing radical prostatectomy. Most studies have included data from PLND rather than ePLND and are therefore are felt to underestimate the true prevalence of lymph node involvement due to the limited nodal areas sampled (48). The Partin tables were created using the pre-operative PSA, clinical stage and Gleason scores of patients undergoing radical

prostatectomies to predict pathological stage at surgery. The original tables were based on data from 1982 to 1991 in the pre-PSA era. Since the advent of PSA testing there have been changes to the clinical and pathological stages of men diagnosed with prostate cancer, and updates to the Gleason scoring system, therefore the tables have been updated with more contemporary surgical data. In a single institution study, data from 5629 men undergoing radical prostatectomy and PLND between 2006 and 2011 was used to create the tables. Clinical and preoperative PSA data was used to predict the risk of organ confined disease, extra-prostatic extension, seminal vesicle invasion and lymph node invasion. The predicted risk of LNI in the cohort was 0.6% and was found to be 1% on surgical pathology. The authors concluded that this updated Partin table was sufficiently accurate in predicting LNI and seminal vesicle involvement (98).

The Cagiannos nomogram was developed in 2003 based on data from 7014 patients treated with radical prostatectomy across 6 institutions, again using preoperative PSA, clinical stage and biopsy Gleason grade. The rate of LNI was 3.7% and the negative predictive value of the nomogram was 0.99 when predicting $\leq 3\%$ or less chance of positive lymph nodes (120). This nomogram is suggested for use by the NCCN guidelines to discriminate between patients who should or shouldn't be offered a PLND. Two other nomograms in north America have also been developed; the Godoy (121) and the MSKK (122). The Briganti nomogram was based on a European cohort of patients who underwent radical prostatectomy and an ePLND with a median number of nodes removed of 14. The initial nomogram was based on the PSA, clinical stage and biopsy Gleason sum, and reported an accuracy of 78.6% (123). This was later updated to include the percentage of positive cores in a more contemporary group of 588 patients treated at a single tertiary centre and reported an accuracy of 87.6% (124).

A head to head comparison of the four most commonly used nomograms (Briganti, MSKCC, Cagiannos and Godoy) was performed using the SEER database in the US. 19,775 patients who underwent radical prostatectomy and PLND with complete staging information were included. Overall the median number of lymph nodes removed was 6(3-11) and 1,131 men had LNI (5.7%). The four nomograms were compared for multiple criteria and were very similar in sensitivity (89-90%), specificity (45-47%), positive predictive value (8.5-9.2%)

and negative predictive value (all 98.7%) (125). That said, apart from the Cagiannos tool, the three other tools showed significant differences between the predicted and observed rates of LNI once the probability was greater than 30%, suggesting less accuracy in higher risk patients. A limitation of the analysis was that the most up to date Briganti nomogram from 2017 was not used as the information needed regarding the percentage of cores with lower and higher grade disease was not available in the database. Despite this, the authors concluded that the Cagiannos and Briganti nomograms had the best performance overall based on the decision curve analysis.

For the population of patients undergoing radiotherapy, the Roach formula was derived from the Partin tables as a tool to predict the risk of pelvic lymph node involvement and guide the selection of patients that might benefit from elective pelvic nodal RT. The formula is: Lymph node involvement risk (LNI) %= 2/3PSA + (Gleason score-6) x10. When initially developed, a calculated score of ≥15% corresponded with an observed nodal incidence of 40% and a score of <15% corresponded with an observed nodal incidence of 6%. Therefore Roach recommended extending the radiation field to cover pelvic lymph nodes in patients with a Roach score of ≥15% (99). With PSA screening, cancers are now detected earlier, with a lower index PSA and clinical stage. Reclassification of the Gleason scores has also led to an overall upgrade in combined scoring. This shift to earlier stages may have reduced the risk of occult nodal metastases and several validation studies using contemporary surgical data have found that the score over-predicts the risk of lymph node involvement (100). However, these studies have used limited PLND to stage pelvic nodes and in a study by Abdollah using ePLND in 3115 patients, the accuracy of the Roach formula was 80.3% (101). An obvious limitation to the formula is that it doesn't incorporate any information about the volume of disease, either in the form of T stage or the extent of histological involvement, the latter of which is now a well established risk factor for LNI in men undergoing surgery (126).

More recent developments are focusing on predicting LNI risk with genetic information. In a series of 320 prostate cancer patients, Cao et al examined the clinical and pathological data of 320 prostate cancer patients from the Cancer Genome Atlas database and identified a 7 gene signature that is associated with

a high risk of LNI (based on pathological confirmation). A risk score was calculated and patients were divided into high and low risk groups based on their score. Using this genetic risk information alongside the clinical stage, primary Gleason score, PSA and secondary Gleason score, they developed a nomogram for predicting LNI risk. While this was developed in a small cohort of patients and has not yet been externally validated, it provides interesting information about the 7 top hub genes that appear to be closely related to LNI in prostate cancer (127). Lee and colleagues evaluated the performance of the Decipher test in predicting lymph node invasion using a contemporary cohort of 1987 patients treated with radical prostatectomy and a retrospective cohort of 25 surgical patients who were all node positive on pathology. On multivariate analysis, adjusting for Gleason score, extra-prostatic extension and seminal vesicle invasion, Decipher had an odds ratio of 1.42 (95% CI 1.19-1.7, $p<0.001$) for per 10% increase in score for predicting the presence of LNI. Examining the retrospective cohort, they also found an overall concordance in Decipher risk group scores of 71% between the RP, LN specimens and prostate biopsy. This improved to 86% when the biopsy core with the highest Gleason grade and percentage of tumour involved was selected, suggesting that Decipher testing pre-treatment could be used as a tool for predicting LNI (128).

1.7 Improving whole pelvic radiation

The use of classical WPRT may have been suboptimal because of limitations in patient selection, target volume definition and radiation dose (66).

1.7.1 Target volume definition

One of the main criticisms of both randomised controlled trials was that pelvic radiation delivery was inadequate and may have led to under treatment or geographical miss of involved nodes. In support of this theory this was another subset analysis of the RTOG-9413. The 325 patients who had been in the two NA-ADT were reviewed to see if overall pelvic field size related to outcomes. The PORT patients in this group were sorted into two groups: PO with a radiation field size less than the median (10x11cm) or Mini-pelvis (MP) with a radiation field size

≥ the median. The four-year disease-free survival was 60% for the WPRT group, 48% for MP group and 40% for the PO group (p=0.0023). The incidence of grade-3 GI toxicity also increased with field size and was 4.5%, 1.5% and 0 for the WPRT, MP and PO groups respectively (42). The GETUG-01 trial was criticised for the small pelvic field used, which did not cover most of the common iliacs, pre-sacral and anterior external iliac nodes therefore may not have proved to be adequate PLN treatment. From surgical and imaging studies there is a clear indication of the most commonly involved PLN sites. These are the obturator and external iliac nodes, followed by the internal iliac and common iliac nodes. Less commonly involved sites include the pre-sacral and peri-rectal nodes.

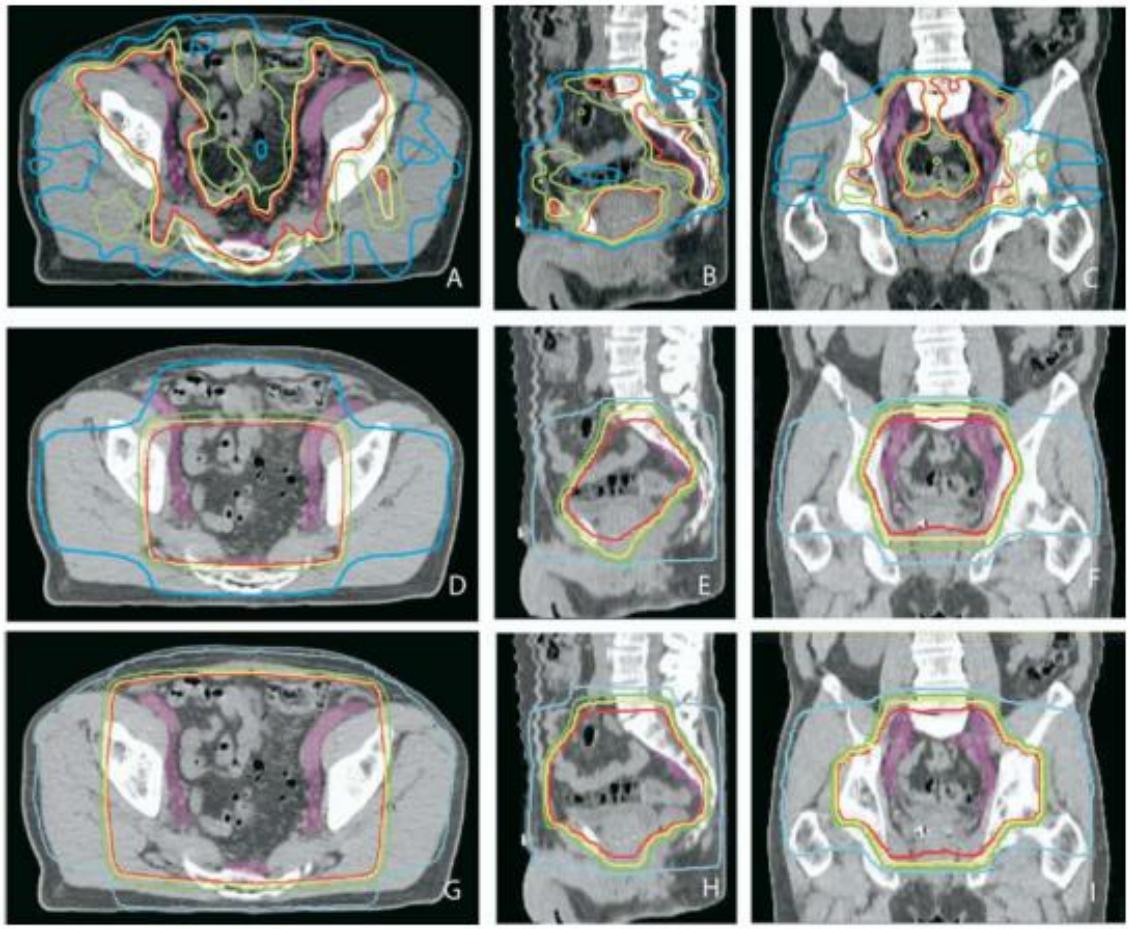
1.7.2 Developments in radiation delivery and dose

The majority of the retrospective trials and all three randomised controlled trials exploring WPRT (38-45) used a traditional four field box technique for radiation delivery. This consisted of anterior, posterior and two lateral radiation fields placed on orthogonal films using bony landmarks. For the anterior and posterior fields, the superior border of the field in most of the studies was placed at the L5/S1 junction, the lateral margins were 1.5-2cm lateral to the widest point of the bony pelvic inlet margin and the inferior border was at the ischial tuberosities. For the lateral fields, posteriorly the pre-sacral nodes were included down to S3 and anteriorly the field was placed anterior to the pubic symphysis. No target definition was required and wedges could be applied to the lateral fields to shape the posterior edge of the beam and reduce the rectal dose.

3D-CRT gained popularity in the 1990s following improvements in computing and imaging that allowed for dose calculations on 3D image sets. Target volumes need to be outlined on the planning CT. These can consist of the “Gross Tumour Volume” (GTV), which if surrounded by a margin of tissue to account for microscopic tumour spread, is called a “Clinical Target Volume” (CTV). This term also describes potential sites of microscopic cancer in the absence of gross visible tumour, as is the case when electively irradiating the pelvic lymph nodes. Finally, a further margin is applied to account for internal organ movement or set

up inaccuracies and the resultant volume is called a “Planning Target Volume” (PTV). Normal tissues adjacent to the target volumes are called organs at risk (OAR) and also need to be outlined (102). Once the CTV and PTV are defined, a beam arrangement could be applied to best cover the PTV while avoiding the normal tissues. As with 2D treatment, wedges could be used but additionally multi-leaf collimators within the treatment machine could be applied to closely conform the beam to the shape of the target, or avoid an organ at risk.

Figure 1. Diagram from Wang-Cheesboro et al (103). Dose distributions for pelvic radiation delivered using IMRT (panels A, B, C) 3D-CRT (panels D, E, F) and conformal fields (panels G, H, I). Shaded pink structures are pelvic LN clinical target volumes.



Intensity Modulated radiotherapy (IMRT) describes treatment with multiple beams that have modulation of intensity across each field. This creates greater conformity and sculpting of dose around the target and away from OARs. Nutting et al (104) published the first planning study for pelvic IMRT in 2000. Planning CT data for 10 patients undergoing prostate radiation at the Royal Marsden

Hospital were used and pelvic lymph node target volumes were outlined along with the surrounding OARS (small bowel, colon, bladder and rectum). Optimised conventional and 3D-CRT plans were then produced and compared to an inverse planned IMRT plan. There was a significant reduction in the mean percentage volume of bowel and colon irradiated to >45Gy using IMRT compared to 3D-CRT (5.3% vs 18.3%, $p<0.001$). Rectal and bladder volumes irradiated to >90% of the prescription dose were also significantly reduced from 50.5% and 52.2% with 3D-CRT to 5.8% and 7.0% with IMRT respectively ($p<0.001$). Other studies have also demonstrated the superiority of IMRT over 3D-CRT in reducing dose to OARS with pelvic IMRT (103) and figure 1 above illustrates the reduced radiation field resulting in reduced dose to the OARS as treatment becomes more conformal from the field technique to 3D-CRT and then IMRT. The property of reducing dose to organs at risk was then exploited to explore escalating dose to the pelvic lymph nodes in the ICR/RMH Pelvic IMRT study described in detail in Chapter 2 (105). As outlined above, dose escalation to the prostate is a key component of improving local control and biochemical relapse free survival in prostate cancer, so it can be hypothesised that escalating dose to the pelvic lymph nodes may also improve the outcomes from WPRT.

1.8 Thesis aims and hypotheses

In summary at present there is evidence to support the use of dose-escalated radiotherapy to the prostate, long course ADT and additional systemic therapy in patients with high risk node negative prostate cancer. Surgical data confirms the incidence of metastatic spread to local pelvic lymph nodes increases with prostate cancer risk and there is emerging evidence to support the use of pelvic radiotherapy in node positive patients. Current radiological tools for the detection of pelvic nodal disease are improving but insufficiently sensitive for routine use.

The benefit of pelvic radiation in clinically node negative high risk patients remains uncertain. The three randomised clinical trials exploring the benefit of pelvic radiation in this patient group were limited by methodological issues which included radiation techniques that may have left involved pelvic nodal tissue uncovered due to the limited field size chosen and the 4 field techniques used to deliver treatment. Secondly the limited sparing of adjacent organs at risk using these conventional techniques prohibited dose escalation. Pelvic IMRT can

reduce dose to adjacent organs at risk, may improve coverage of pelvic nodal tissue and permit dose escalation. This thesis aims to explore methods of refining pelvic IMRT with the aim of improving nodal coverage and limiting associated toxicity.

My thesis aims

1) My first hypothesis is that dose escalated pelvic IMRT would be associated with a low rate of pelvic nodal relapse and that patterns of recurrence will lead to a rationale for target volume modifications. To explore this hypothesis, I will first establish the anatomical patterns of disease relapse. Secondly, I will map out pelvic nodal relapses with respect to the radiotherapy treatment field to see if modifications are required.

2) My second hypothesis is that pelvic nodes identified by choline-PET CT on first presentation of high risk prostate cancer would be covered by the PIVOTAL trial contouring guidelines. To explore this hypothesis, I will identify a group of patients who positive pelvic nodes identified on choline-PET and evaluate the proportion of cases where the CTV and PTV based on the contouring guidelines cover identified nodal disease. Secondly, I will consider modifications to the CTV to improve coverage and their impact on organs at risk.

3) My third hypothesis is that dose volume data and late toxicity results from the PIVOTAL trial can be used to refine the currently used bowel dose constraints. To explore this hypothesis, I will firstly establish any correlation between the late toxicity and radiation dose to bowel. Secondly to establish if any anatomical subtype of bowel in particular associated with the development of late toxicity.

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Chapter 2 Efficacy and outcomes of pelvic IMRT in the phase I/II IMRT trial

2.1 Introduction

The Pelvic lymph node target volume is a complex shape that moves anterior to posterior as it ascends through the pelvis. Is also forms a U shape medial to the bony anatomy in the mid pelvis. Additionally, the organs at risk, (particularly the small bowel) lie in close proximity throughout the pelvis. Traditional radiation techniques have had limited capabilities to spare the adjacent organs at risk and this has proven a barrier to exploring dose escalation. Furthermore, there is evidence that target coverage is also limited using 3D-CRT; In a planning study, one group found that 3D-CRT under covered pelvic nodes prescribed a dose of 45Gy by 25% (1).

Intensity-modulated radiotherapy (IMRT) can achieve greater conformity with concave shaped dose distributions. Therefore, it optimizes the delivery of radiation to irregularly shaped volumes to improve target coverage and simultaneously spare adjacent organs at risk (1, 2).

At the RMH a planning study was undertaken to compare the dose distributions to organs at risk achieved with prostate and pelvic IMRT versus 3D conformal and conventional radiotherapy in a series of ten patients. The dose to the pelvis was 50Gy in 2Gy per fraction. They found the volume of bowel that received more than 45Gy when using 9-field IMRT was 5.3% versus 18.3% using 3D-CRT ($p<0.001$). Furthermore, the volume of rectum and bladder irradiated to more than 90% of the prescription dose was reduced from 50% and 52.2% to 5.8% and 7.0% respectively. IMRT also resulted in an increase in the volume of low dose irradiation received by all of the pelvic organs. It was hypothesised that the significant reduction in the volume of bowel irradiated above tolerance should result in lowering the acute and long term bowel side effects seen (2).

The next step was to evaluate this technique in a Phase I dose escalation trial, with the aim of increasing the pelvic nodal dose but keeping bowel side-effects at a low and acceptable level. Dose escalation has been linked with increased disease control in prostate cancer (3-6) and it has been suggested that one of the reasons the two previous randomised controlled trials (38,39) testing whole pelvis versus prostate only radiotherapy failed to show any benefit was the limited dose to the pelvic nodes.

The low α/β ratio of prostate cancer (7, 8) also makes hypofractionation an attractive option for treatment, with recent data demonstrating equivalent outcomes to standard dose schedules treating the prostate alone (8). Dose escalation and hypofractionation have not been adequately evaluated for pelvic lymph node (PLN) radiotherapy (RT) , with limited data available from small case series (3-5, 9).

Therefore, the aim of this study was to test the feasibility of using IMRT to deliver PLN RT to patients with high risk prostate cancer, using conventional dose escalated and hypofractionated schedules.

I was not involved in any part of the trial design or patient recruitment but was personally involved in the clinical follow-up of many of the trial patients in a Research Oncology Clinic at the Royal Marsden Hospital from 2014- 2017. My contribution to the study was to review in detail the follow-up of all patients in the trial from electronic patient records to update and clarify data on the clinical report forms and trial record database. Specifically, I reviewed all clinical follow up data regarding disease relapse and reviewed dates and causes of death where clarity was required. I also reviewed all available baseline demographic data using electronic records to ensure accuracy and to find missing data where possible. I performed this collection and organisation of the data for subsequent analysis and interpretation presented in this thesis. I undertook this work jointly with Dr Miguel Ferreira who was responsible for the toxicity data and was joint first author with him on the subsequent peer reviewed paper (13). For this MD chapter, I was solely responsible for the collection of detailed data and mapping of patterns of relapse and when necessary reviewed relevant imaging with Dr Aslam Sohaib, Consultant Uro-Radiologist.

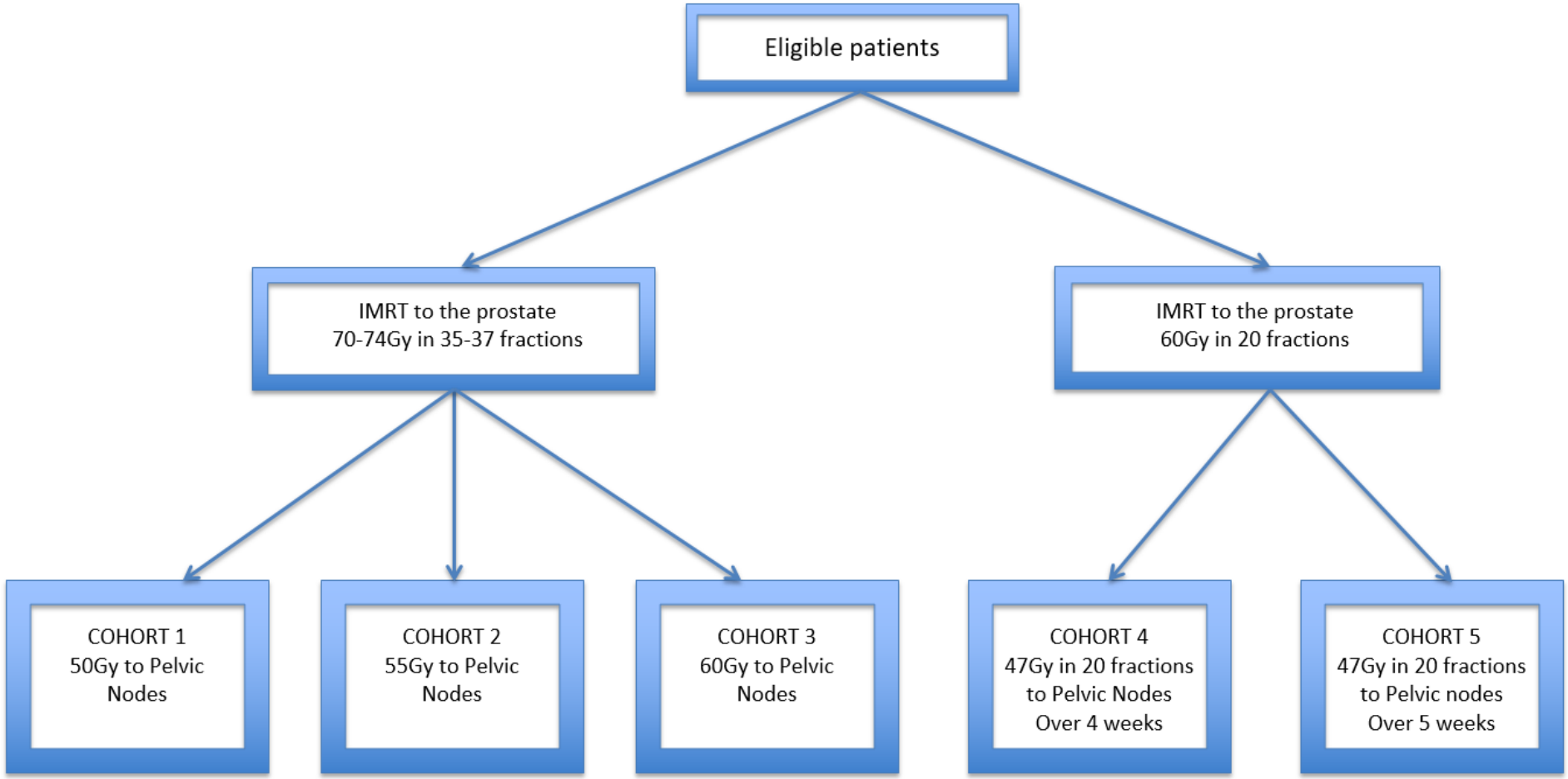
2.2 Methods

2.2.1 IMRT Trial

The IMRT Trial was a single-centre phase I/II study of IMRT to irradiate the prostate and pelvic lymph nodes (PLN) in patients with advanced localised prostate cancer. Eligible patients had high risk prostate cancer with the following features; T3b/T4 or node positive disease, Gleason score ≥8 or ≥ 2 risk factors, or an estimated risk of nodal metastases of >30% based on the Roach formula (10, 11). Post-prostatectomy patients (T2-T3a, N0) with extensive Gleason score ≥8 disease, seminal vesicle or lymph node involvement were also eligible. Patients unsuitable for radical radiotherapy or with a history of pelvic surgery or inflammatory bowel disease were excluded. Staging investigations included PSA, histological diagnosis, radiological or surgical lymph node assessment and staging MRI, CT, or bone scan.

Patients were sequentially assigned to receive conventionally-fractionated IMRT to the prostate and seminal vesicles (70-74Gy in 35-37 fractions), and 50Gy, 55Gy or 60Gy (Cohorts 1,2 and 3 respectively) to the pelvic lymph nodes (PLN) concomitant over 7-7.4 weeks. An integrated boost of 5Gy was given to radiologically suspicious PLN. Two further cohorts then received hypofractionated IMRT, with 60Gy (20 fractions) delivered to the prostate and seminal vesicles and 47Gy to the PLN in either 4 (5 days/week, cohort 4) or 5 weeks (4 days/week, Cohort 5). An integrated boost of 4Gy was given to radiologically suspicious PLN. Patients were initially treated in a 4-week schedule (cohort 4), which was later modified to a 5-week schedule (cohort 5) because of acute GI toxicity. Patients irradiated post-prostatectomy received 64Gy in 32 fractions in cohorts 1 and 2, 65Gy in 35 fractions in cohort 3 and 55Gy in 20 fractions in cohorts 4 and 5. Figure 2 shows the trial schema with all 5 cohorts.

Figure 2. Trial schema



2.2.2 Rationale for choice of dose levels

The pelvic LN dose for cohort 1 was chosen to be close to the standard PLN dose of 45Gy in 25F or 46Gy in 23F. The aim was to achieve an iso-effective dose on bowel and the dose calculation was made using an alpha/beta ratio of 3Gy (40). For efficient use of resource, a single phase treatment technique was chosen which took advantage of the dose painting possibility using IMRT methods.

A dose level of 50Gy in 35F was conservatively selected for cohort 1 which included the first patient treated with IMRT in the UK. Dose was escalated in 5Gy increments to 60Gy in 37F (equivalent to 54-56 Gy in 2Gy F for a/b of 3Gy) considerably in excess of conventional doses. The 2Gy equivalent dose to an involved LN treated to 65 Gy was about 62Gy or 60Gy for a/b of 3.0 and 1.5Gy respectively. For the hypofractionated cohort the 47Gy in 20F was intermediate between the 55Gy and 60Gy groups giving a 2Gy equivalent dose of about 50Gy and 52Gy for a/b of 3.0Gy and 1.5Gy respectively, again considerably (about 9-13%) in excess of conventional fractionated pelvic treatment. These calculations make the assumption there is no time factor in prostate cancer or normal tissue response (41). Appendix 7 contains a table outlining the dose fractionation schedule.

2.2.3 Treatment

Patients received long course (2-3 years) androgen deprivation therapy (ADT) and completed at least 6 months of treatment before radiotherapy was commenced. Patients underwent planning CT-scans with a comfortably full bladder and empty rectum. From 2011, sodium citrate enemas were used for patients with rectal dilatation. CTV1 included the prostate and any radiologically involved seminal vesicle, with a margin of 8mm posteriorly and 10mm in all other directions to create PTV1. CTV2 included PLN and uninvolved seminal vesicles and a uniform margin of 5mm was applied to create PTV2. CTV3 included any radiologically involved lymph nodes and uniform margin of 5mm was applied to create PTV3. All organs-at-risk were contoured as solid organs, by defining the outer wall of rectum, bowel and bladder. The rectum was contoured from the anus (usually at the level of the ischial tuberosities or 1cm below the lower margin

of the PTV whichever was more inferior) to the recto-sigmoid junction. The bowel was outlined separately, excluding rectum and extending 2cm above the superior extent of PTV2. The bladder was outlined from base to dome. Inverse radiotherapy planning was performed for all patients using mandatory normal tissue dose-constraints. Treatment verification was performed offline using bony anatomy for registration.

2.2.4 Follow up

PSA was measured 6-monthly for 8 years after the start of ADT and annually thereafter. The nadir PSA was the lowest level recorded post radiotherapy. Biochemical failure was defined according to the Phoenix consensus guidelines as a PSA value greater than the nadir plus 2ng/ml. Local recurrence was confirmed on MRI pelvis or biopsy and post-prostatectomy patients (n=34) were excluded from this endpoint. Distant relapse was confirmed on MRI, CT scan, bone scan, or choline PET-CT scan. The timing and modality of imaging was based on clinical discretion and available resource.

2.2.5 Statistics

The primary endpoint of the trial was late RTOG toxicity assessed 2 years after radiotherapy. Secondary endpoints included assessment of all toxicity scales during follow-up and disease recurrence. Patients were stratified by total bowel volume outlined (<450cc vs. ≥450cc). For each dose level stratified by bowel volume, at least 15 men were treated and followed up for at least 1 year. If 0 of 15 men had a grade ≥3 RTOG complication, then a ≥20% grade ≥3 toxicity rate was excluded with one sided significance level 0.05. As the dose to the initial cohort was modest, patients in the low bowel volume group were recruited to the second dose level after 7 men had ≥12 months of follow-up, provided none of these had recorded a grade 3 or higher complication. For other cohorts and bowel volume groups, recruitment continued at that level until such time as 15 men had been treated and followed up for at least one year. This strategy ensured that the low bowel volume group moved to the higher dose cohorts in advance of the high bowel volume group. Because recruitment continued in each cohort and bowel volume group until such time as the required total of men had reached ≥12

months of follow-up, in all cases the eventual sample size in each group exceeded the required total to an extent which varied according to the recruitment rate over time.

In cohorts 3 and 4, a further dose expansion phase was planned, with a target sample size of 103 patients (of any bowel volume) evaluable at 2 years in order to rule out a late grade 2 or over (grade 2+) bowel toxicity rate of ≥25%, using a one-sided alpha 0·05 and power of 80% with an assumed true rate of toxicity not more than 15%. The sample size was expanded to a total of 123 in each of cohort 3 and 4 to allow for an expected drop-out rate of 16% by 2 years. However, due to high levels of acute bowel toxicity observed in cohort 4 (4-weekly schedule), the treatment schedule was amended to 5 weeks (cohort 5) with a target of 123 patients.

Efficacy was assessed using Kaplan-Meier methods to calculate length of disease control (defined as a composite endpoint of biochemical progression, local or lymph node/pelvic recurrence, or distant metastasis, or recommencement of androgen deprivation therapy), length of local disease control, length of distant disease control, disease specific, and overall survival from start of radiotherapy. For disease specific and overall survival, patients were censored at the date they were last known to be alive. Rates at 2, 5 years and 10 years were calculated with 95% CI. The data was extracted in September 2015 and analysed using STATA v13.1.

Univariable Cox regression on length of disease control was performed using factors of dose cohort, N-stage (N0 vs. N1-3), baseline PSA (log transformed), clinical T-stage (grouped as T1/T2; T3a; T3b+) and Gleason score (grouped as ≤6; 7; ≥8). Forward and backward stepwise selection methods were used to combine significant factors ($p<0·05$ on univariable analysis) into a multivariable model and produce adjusted hazard ratios with 95% CI.

2.3 Hypothesis and aims

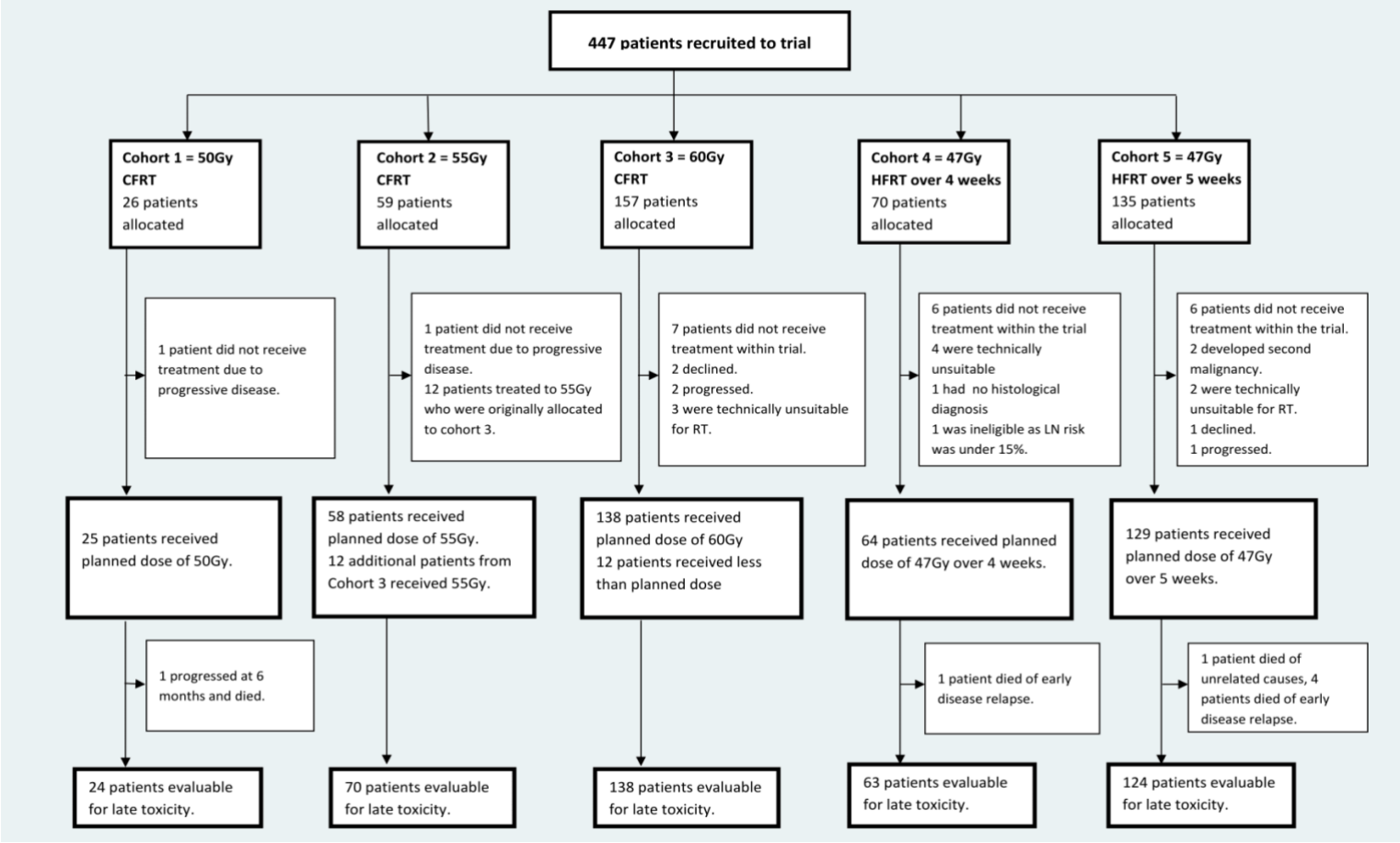
The aim of this chapter was to characterise the patterns of disease relapse in patients treated with pelvic IMRT in this trial.

Hypothesis; Dose escalated pelvic IMRT achieves a low rate of pelvic lymph node relapse, with relapses occurring outside the target volume.

Key objectives; The following objectives test the hypothesis:

1) To establish the anatomical pattern of disease relapse in all trial patients.
2) To correlate pelvic lymph node relapses with respect to the planned radiation treatment volume in order to establish if a dose response effect is evident.

Figure 3. Consort diagram of trial profile RT= radiotherapy, LN=lymph node, CFRT=conventionally fractionated radiotherapy, HFRT= Hypofractionated radiotherapy



2.4 Results

Between Aug 9, 2000 and June 9, 2010, 447 male patients were recruited to cohorts 1-5. 426 patients were treated according to protocol and data was available for efficacy and relapse pattern assessment. Data for 419 patients was available for late toxicity assessment (Figure 3). Data for disease control was available for 426 patients at the time of analysis.

At the time of analysis the median follow up length for the whole cohort was 7.6 years. However, as the trial cohorts had been recruited to in a sequential manner cohort 1 had a median follow up of 13.9 years, whereas cohorts 4 and 5 which were the last to recruit had a median follow up of 7.1 and 5.7 years respectively.

The demographics of the trial participants are shown in table 4 below. The median age was 65 years (IQR: 60-70) with a median presenting PSA of 21·4ng/ml (10·2-42·8). 46% of patients had clinical T3/T4 disease, 54% had Gleason 8 or over scores, and 17% had PLN involvement based upon radiological staging. 92% of the trial cohort had NCCN high risk disease. Cohort 1 had a higher proportion of patients with adverse features than cohorts 2-5, particularly the presenting PSA and proportion of radiologically staged N1 patients.

The median duration of adjuvant hormone therapy was 35 months (33-37 months) and 95% of patients were on hormone therapy for more than 24 months. 73% of patients were treated with LHRH analogues and 20% required long term combined androgen blockade. Thirty-four patients (8%) underwent a radical prostatectomy prior to entering the trial and of these, 23 (5%) had also had the pelvic lymph nodes sampled.

The acute and late toxicity results and final primary endpoints of the trial are reported and have been published (12, 13). The late toxicity and efficacy publication is contained in the appendix, along with the trial protocol (appendix 1, 2 and 3).

Table 4. Patient demographics. Data are n (%) or median (IQR) unless otherwise stated. NCCN=National Comprehensive Cancer Network. PSA = prostate-specific antigen. ADT = androgen deprivation therapy. CT = Computed Tomography. MRI = magnetic resonance.

	Cohort 1 50Gy (n=25)	Cohort 2 55Gy (n=70)	Cohort 3 60Gy (n=138)	Cohort 4 47Gy/4wks (n=64)	Cohort 5 47Gy/5wks (n=129)	Cohorts 1-5 n=426
Median length of follow up in years	13.9	11.2	9.0	7.1	5.7	7.6
Median Age at Diagnosis in years (IQR)	63 (56-67)	62 (57-67)	65 (59-69)	66 (62-72)	67 (62-71)	65 (60-70)
PSA at Diagnosis Median (IQR)	39.1 (24.7-78.0)	25.4 (12.4-44.7)	24.5 (10.2-47.1)	15.4 (8.5-31.4)	18 (8.1-37.9)	21.4 (10.2 – 42.8)
Nadir Pre RT PSA Median (IQR)	0.5 (0.1- 1.2)	0.4 (0.1-1.2)	0.5 (0.1-1.1)	0.4 (0.1- 1.0)	0.6 (0.2-1.2)	0.5 (0.1 -1.2)
Gleason Score						
Gleason 6/7	13(52%)	34(48%)	60 (43%)	22(35%)	56(44%)	185(44%)
Gleason 8	4 (16%)	17 (24%)	29 (21%)	13(20%)	11(9%)	74(17%)
Gleason 9/10	6 (24%)	16 (22%)	48 (35%)	28(44%)	60(47%)	158(37%)
Unknown	2(8%)	3 (4%)	1(1%)	1(2%)	2(2%)	9(2%)
CT/MR N Stage						
N0	16 (64%)	49 (70%)	115 (83%)	51(80%)	110(85%)	341 (80%)
N1-3	9 (36%)	14 (20%)	22 (16%)	11(17%)	18(14%)	74 (17%)
Unknown	0 (0%)	7 (10%)	1 (1%)	2(3%)	1(1%)	11 (3%)
Clinical T Stage						
cT1/T2	8(32%)	23(33%)	60(43%)	6(9%)	42(32%)	156 (37%)
cT3	17 (68%)	34 (49%)	57 (41%)	17(27%)	56(43%)	192 (45%)
cT4	0 (0%)	2 (3%)	3 (2%)	0(0%)	1(1%)	6 (1%)
Unknown	0(0%)	11(16%)	18 (13%)	13(20%)	30(23%)	72 (17%)
MRI T stage						
MRI T1/T2	2 (8%)	6(9%)	30(21%)	7(11%)	25(20%)	70 (17%)
MRI T3	13(52%)	34 (49%)	74 (54%)	30(47%)	78(60%)	229 (54%)
MRI T4	2(8%)	3 (4%)	6 (4%)	1(2%)	4(3%)	16 (4%)
Unknown	8 (32%)	27 (39%)	28 (20%)	26(41%)	22(17%)	111 (26%)

	Cohort 1 50Gy (n=25)	Cohort 2 55Gy (n=70)	Cohort 3 60Gy (n=138)	Cohort 4 47Gy/4wks (n=64)	Cohort 5 47Gy/5wks (n=129)	Cohorts 1-5 n=426
Pathological T stage	n=0	n=7	n=16	n=4	n=6	n=34
T1/T2	0	1(13%)	1(6%)	1(25%)	2(33%)	5(15%)
T3a/b	0	7(77%)	14(82%)	2(50%)	4(67%)	27(79%)
T4	0	0	0	0	0	0
Unknown	0	0	1(6%)	1(25%)	0	2(6%)
Pathological N stage		n=5	n=13	n=3	n=2	n=23
N1	0	2(40%)	3(23%)	0(0%)	0(0%)	5(22%)
Roach Formula – LN involvement risk						
<15%	1 (4%)	2 (3%)	10 (7%)	5(8%)	12(9%)	30 (7%)
15-≤29%	4 (16%)	25(36%)	32 (23%)	16(25%)	24(19%)	101(24%)
≤30%	18(72%)	40(57%)	95(69%)	42(66%)	91(71%)	286 (67%)
Unknown	2 (8%)	3 (4%)	1 (1%)	1(2%)	2 (2%)	9(2%)
NCCN risk group						
Low/Intermediate	1 (4%)	1(1%)	8(6%)	6(10%)	6(5%)	22(6%)
High	24 (96%)	67(96%)	126 (91%)	55 (86%)	118(91%)	390 (92%)
Unknown	0(0%)	2(3%)	4 (3%)	3(5%)	5(4%)	14 (3%)
Hormone Therapy (ADT)						
LHRHa and short term anti-androgen	9(36%)	44(63%)	99(72%)	53(83%)	104(81%)	309(73%)
150mg Bicalutamide	1(4%)	9(13%)	15(11%)	3(5%)	4(1%)	32(8%)
Combined Androgen Blockade	15(60%)	17(24%)	24(17%)	8(12%)	21(16%)	85(20%)
≤12 months	1(4%)	4(6%)	1(1%)	1(2%)	0(0%)	7(2%)
>12-≤48 months	16(64%)	50(71%)	111(82%)	54(84%)	116(90%)	347(82%)
>48 months	3(12%)	6(9%)	10(7%)	2(3%)	24(6%)	24(6%)
Died/progressed on ADT	5(20%)	10(14%)	16(12%)	7(11%)	10(8%)	48(11%)

2.4.1 Disease control

Disease control was calculated from the beginning of radiotherapy. Biochemical progression, local or distant relapse confirmed by clinical imaging or biopsy, or treatment with salvage hormones for presumed but unconfirmed disease relapse were all considered as events. Patients without events were censored at the last known date of follow-up. The total number of events was equal to 168 (39.4%), of which 128 (76.2%) had biochemical progression alone as a first event. 38 (22.6%) had evidence of local or distant disease relapse at the time of biochemical recurrence and 2 (1.2%) patients had disease relapse in the absence of biochemical recurrence. One had a cystoprostatectomy which showed viable remnant prostate cancer and the remaining relapsed at multiple sites with a non-PSA producing prostate cancer.

Only events after the start of radiotherapy were included and any PSA rise on neoadjuvant hormones was ignored. One patient met the criteria for biochemical progression but his PSA subsequently reduced to <2 without treatment so he was defined as an aberrant failure and this was not included as an event.

Due to the varying length of median follow up in each cohort, data was reported at 5 years post radiation to give more comparable results between the non-randomised groups. The biochemical/clinical failure-free rate was 71% (95% CI 66-75%) at 5 years for the whole group, with 38%, 61%, 70%, 80%, and 78% remaining recurrence free in cohorts 1-5 respectively (figure 4). The disease specific survival at 5 years was 92% (95% CI 89-94%) for the whole group and 79%, 88%, 92%, 97% and 95% for cohorts 1-5 respectively (figure 5). Overall survival for the whole cohort was 87% (95% CI 84-90%) at 5 years and 76%, 87%, 86% 89% and 91% for cohorts 1-5 respectively (figure 6).

Figure 4. Disease control from the start of radiotherapy

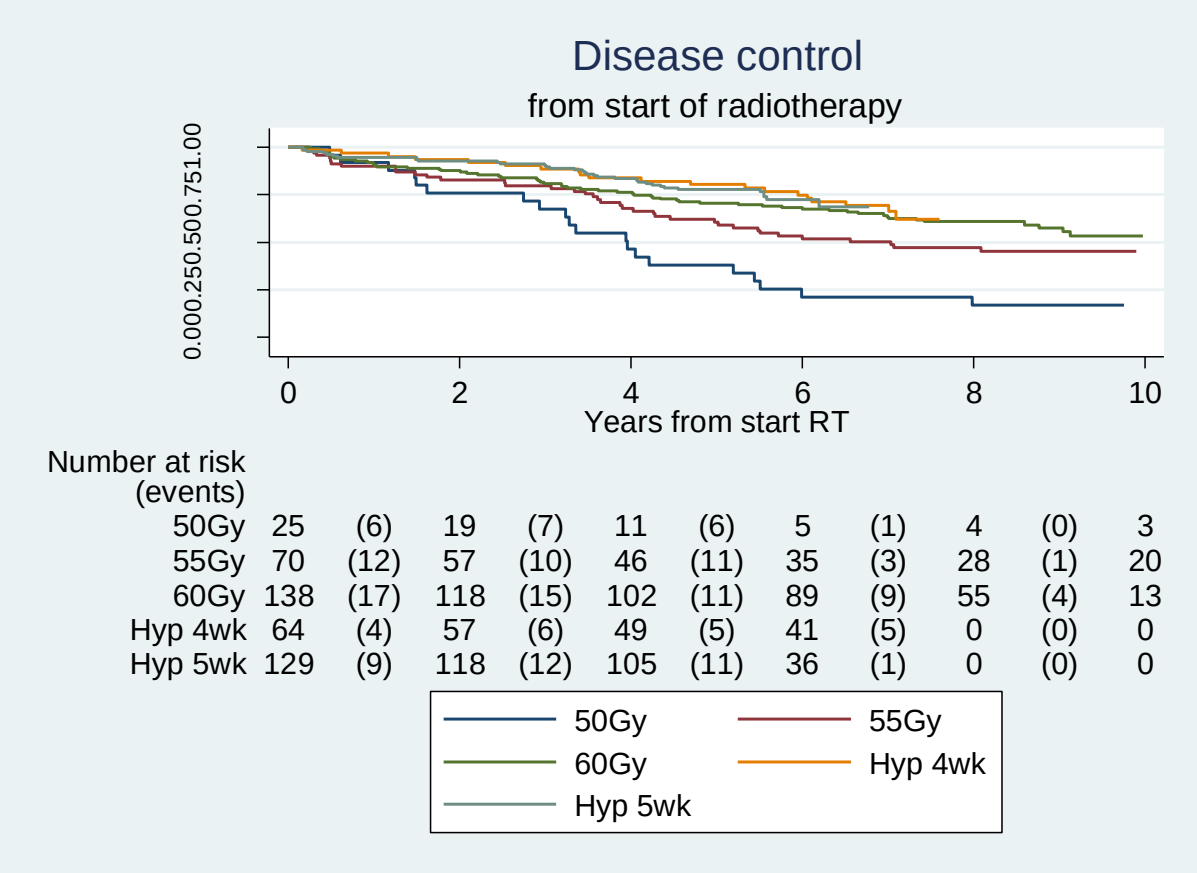


Figure 5. Disease specific survival from the start of radiotherapy

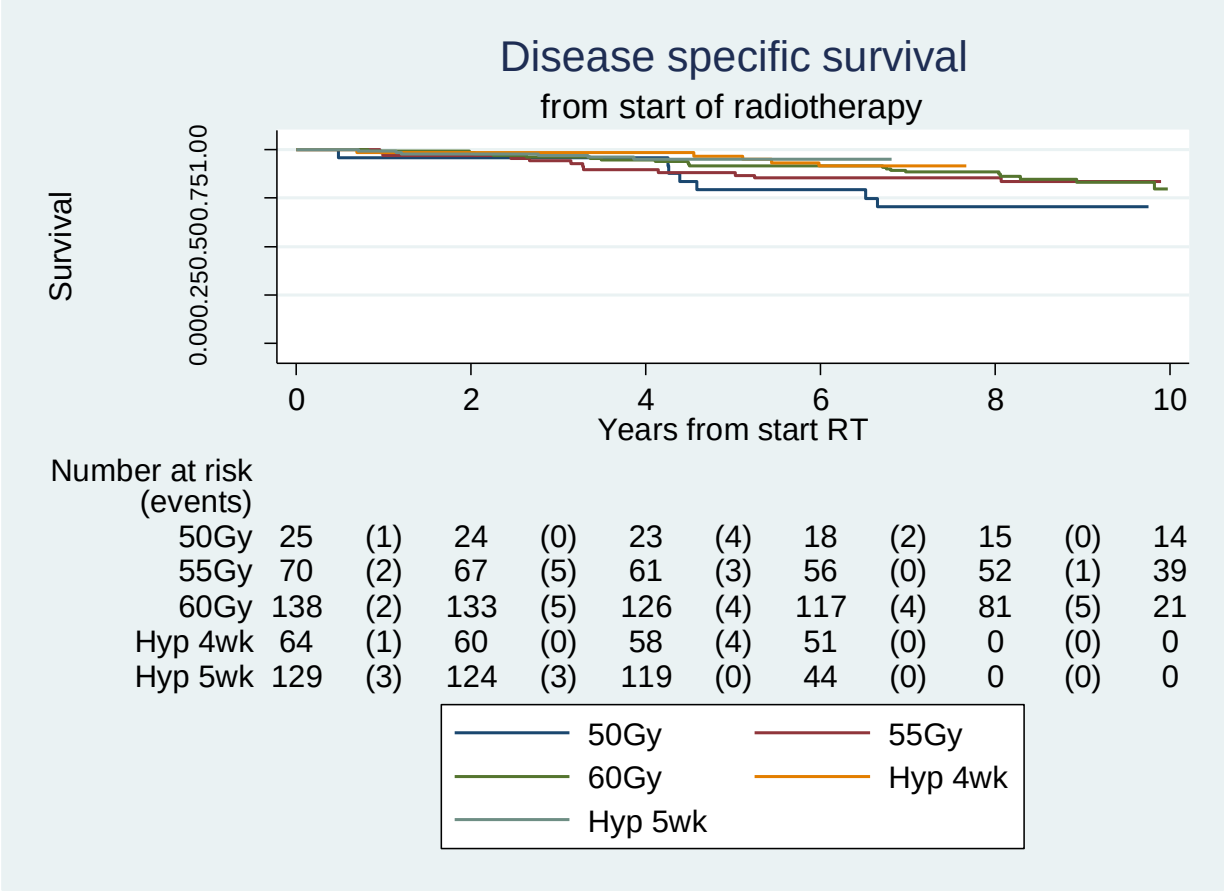
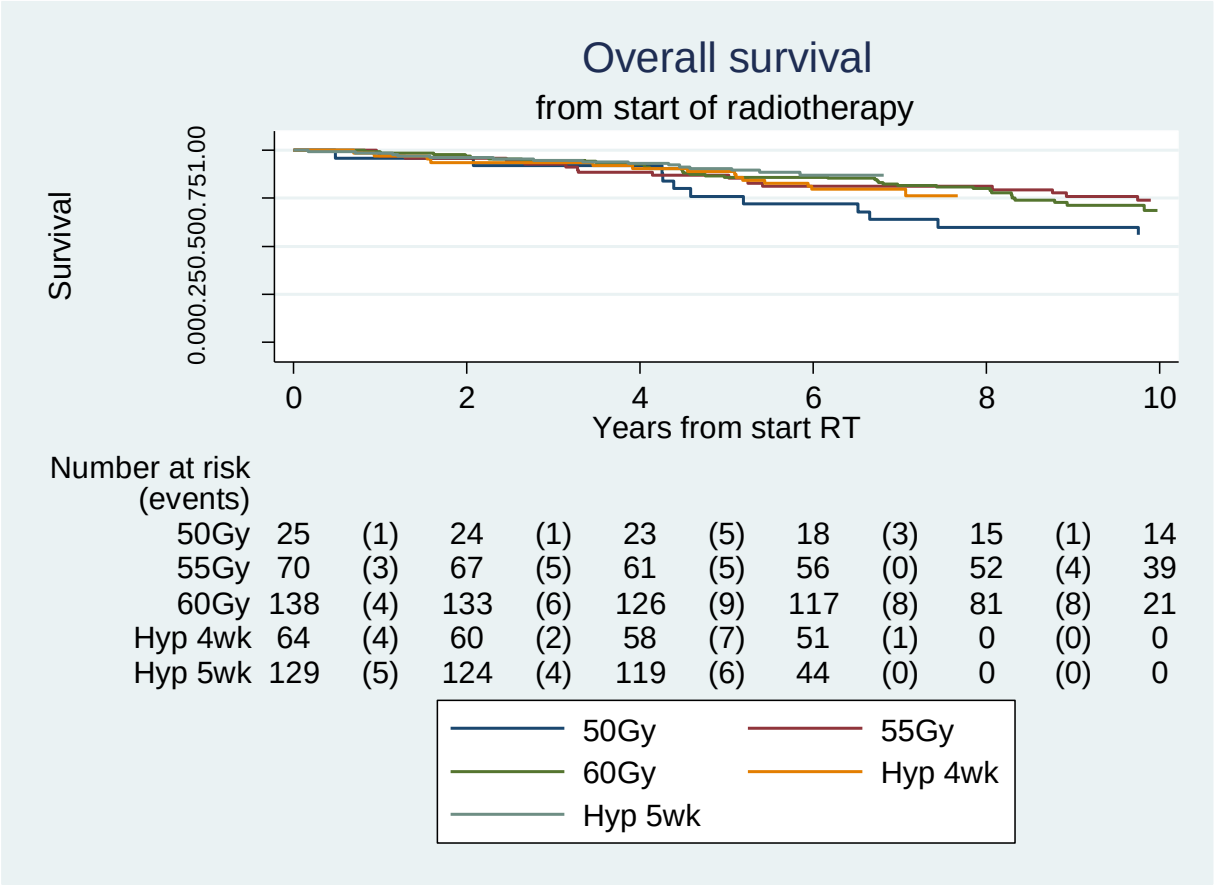


Figure 6. overall survival from the start of radiotherapy



Multivariate analysis revealed pre-treatment PSA level (p=0.004), PLN involvement (p=0.02), T stage (p=0.05), and dose cohort (p=0.05) as factors associated with duration of disease control. The analysis was performed on 326 of the 426 patients within the trial as they had all of the requisite data available.

Table 5. Multivariate cox regression analysis for length of disease control

Factor	Levels	Hazard Ratio (95% CI)	p-value
Dose Cohort	**Cohort 1 - 50Gy** **Cohort 2 - 55Gy** **Cohort 3 - 60Gy** **Cohort 4 - Hyp. 4wk** **Cohort 5 - Hyp. 5wk**	**1 (NA)** **0.71 (0.40, 1.26)** **0.45 (0.26, 0.80)** **0.50 (0.25, 1.01)** **0.45 (0.24, 0.84)**	**0.05**
Log max, pre-treatment PSA	**Continuous. ng/ml**	**1.30 (1.08, 1.57)**	**<0.01**
Clinical T-stage	**T1/T2** **T3a** **T3b+**	**1 (NA)** **1.22 (0.78, 1.91)** **1.70 (1.11, 2.60)**	**0.05**
Radiological N stage	**N0** **N+**	**1 (NA)** **1.65 (1.09, 2.48)**	**0.02**

2.4.2 Patterns of relapse

At the time of analysis there were 41/426 (10%) confirmed relapses within the prostate. Only 8 patients had histological confirmation of local relapse, the remaining 33 patients were diagnosed on the basis of MRI imaging. 26/426 (6%) patients had PLN recurrences and 39/426 (9%) relapsed in distant nodal groups. 99/426 (23%) patients relapsed at other metastatic sites. The results of each cohort are shown in table 6.

For all cohorts the commonest site of relapse was distant metastases. Cohorts 1 and 2 had a high proportion of local relapse compared to the other cohorts and for all the cohorts pelvic and non-pelvic lymph node relapse was the least common site. The greatest proportion of patients (80% of the cohort)

experienced relapse at any site for cohort 1 and the least relapsed in cohort 5 (26% of the cohort).

Table 6. Frequency of relapse at each site for cohorts 1-5

Site of relapse	Cohort 1 n=25	Cohort 2 n=70	Cohort 3 n=138	Cohort 4 n=64	Cohort 5 n=129	Cohort 1-5 n=426
Local	**6 (24%)**	**11 (16%)**	**12 (9%)**	**3 (5%)**	**9 (7%)**	**41(10%)**
PLN	**3 (12%)**	**5 (7%)**	**9 (6%)**	**3 (5%)**	**6 (5%)**	**26(6%)**
Non-pelvic LN	**3 (12%)**	**12 (17%)**	**12 (9%)**	**5 (8%)**	**7 (5%)**	**29 (9%)**
Other distant sites	**13 (52%)**	**25 (36%)**	**34 (25%)**	**9 (14%)**	**18 (14%)**	**99 (23%)**
Any disease relapse/BR	**20 (80%)**	**39 (56%)**	**56 (41%)**	**20 (31%)**	**33 (26%)**	**168 (39%)**
Median Follow up (years)	**13.9**	**11.2**	**9.0**	**7.1**	**5.7**	**7.6**

Local= prostate relapse on MRI +/-biopsy, PLN=any pelvic nodes between the common iliac (defined as nodes below the aortic bifurcation) and inguinal lymph node groups, Non-pelvic LN = above lymph nodes above the common iliac nodes, other distant metastatic sites = bone and visceral metastases. Patients may have more than one site of relapse, therefore results are >100% per cohort. Any disease relapse/BR = all patients that experienced biochemical recurrence or clinical disease relapse, including patients commenced on hormone therapy prior to radiological detection of disease relapse sites.

2.4.3 Pelvic LN recurrences

26 out of 426 (6%) patients were identified as having a pelvic LN relapse at the time of analysis. 16/26 (62%) of the patients were N0 at diagnosis and the remaining 10 were N1. Therefore, the pelvic lymph node failure rate was 13.5% (10/74 relapsed in pelvis) in the node positive patients and 4.5% (16/352 relapsed in pelvis) in the node negative/NX patients. Of the 26 patients, 4 were treated in cohort 1 (50Gy), 4 in cohort 2 (55Gy), 9 in cohort 3 (60Gy), 3 in cohort 4 (40Gy in 4 weeks) and 6 in cohort 5 (40Gy in 5 weeks).

Figure 7 shows the pattern of disease relapse in all 26 patients with recurrent pelvic lymph nodes. Sites of relapse were classified as lymph nodes outside the pelvis (other lymph node metastases), relapse within the prostate (local) and distant metastases at sites outside the lymph nodes. Only 11.5% (3/26) had an isolated relapse within the pelvis with no other sites of disease. These were patients 8, 9 and 12 (see tables 9 and 10). 54% (14/26) had lymph node metastases outside of the pelvis, either in isolation (6/26) or in combination with distant metastases (7/26) or local relapse (1/7). None of the patients had a combination of disease in the prostate, other lymph nodes and distant metastatic disease.

Figures 8 show the pattern of disease relapse in the 16 node negative and 10 node positive patients respectively. All three of the patients with isolated pelvic lymph node relapse were stage N0 at diagnosis. The remaining N0 patients had distant metastases (8/16), lymph nodes outside the pelvis (6/16) and local relapse (6/16).

In comparison none of the 10 N1 patients had an isolated PLN relapse and only one had a local relapse. They either had disease in lymph nodes outside the pelvis (8/10) or at distant metastatic sites (5/10).

Figure 7. Pattern of Disease in 26 Patients with Pelvic LN Relapse

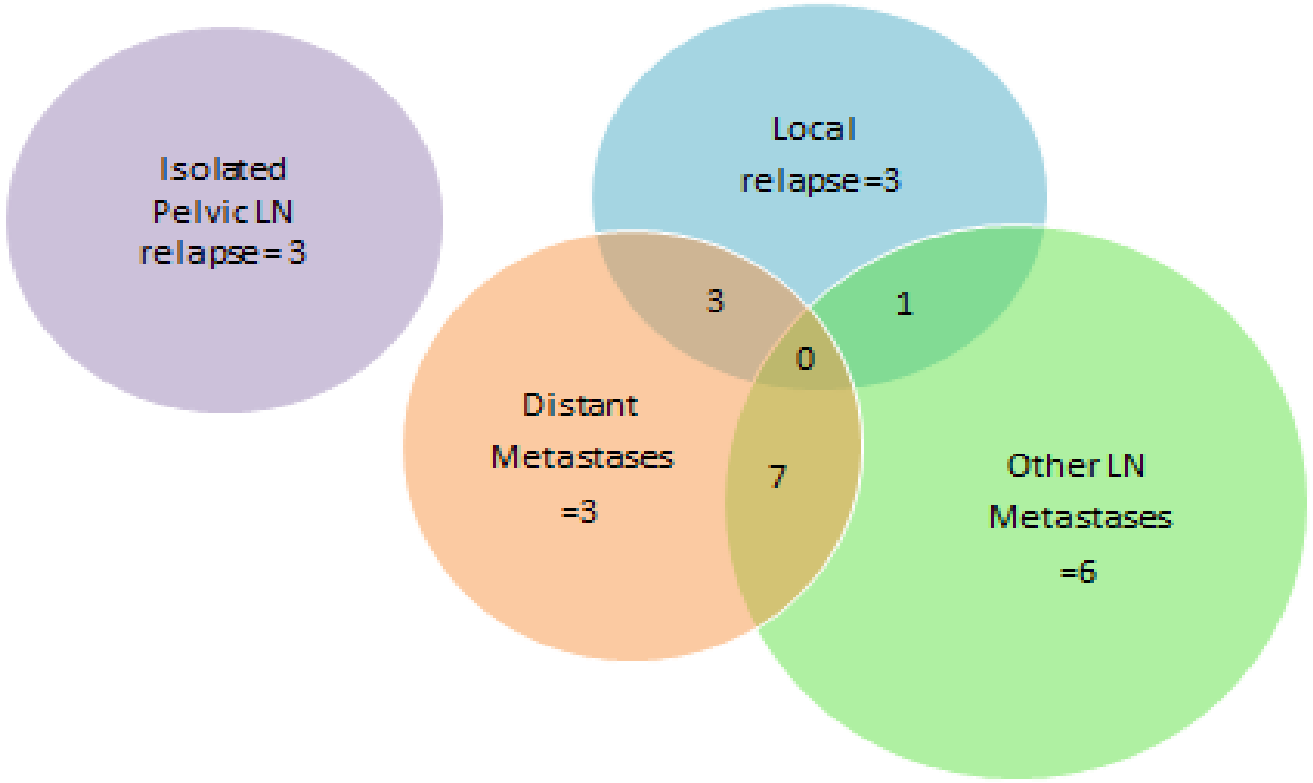
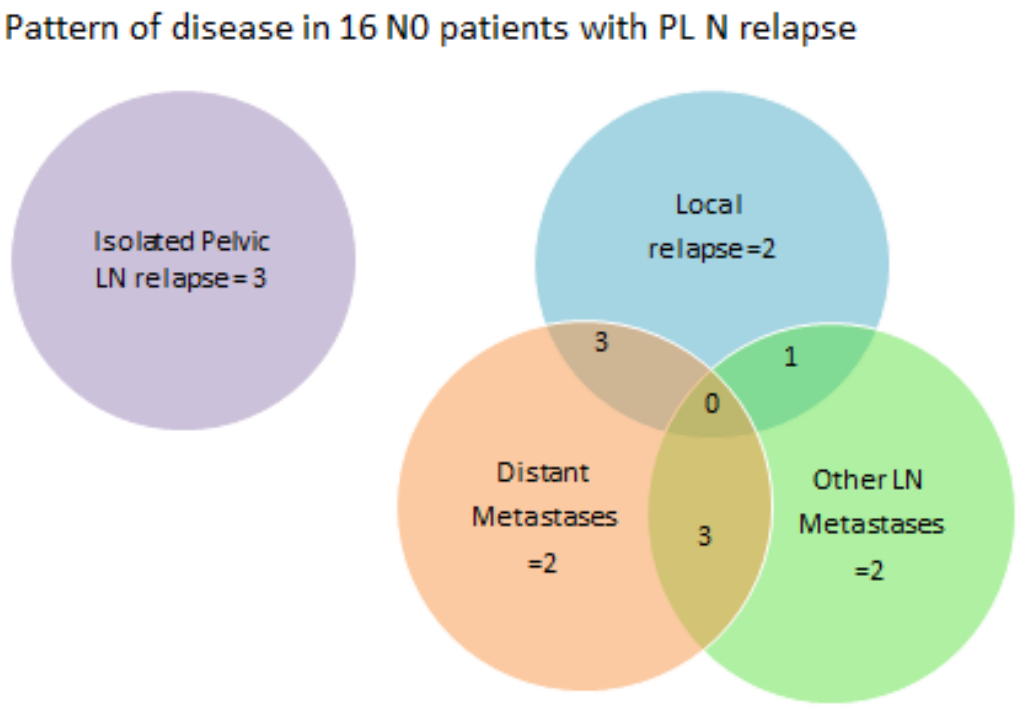


Figure 8. Pattern of disease in 16 patients who were N0 stage at diagnosis and 10 patients who were N1 at diagnosis and subsequently relapsed in the pelvic lymph nodes



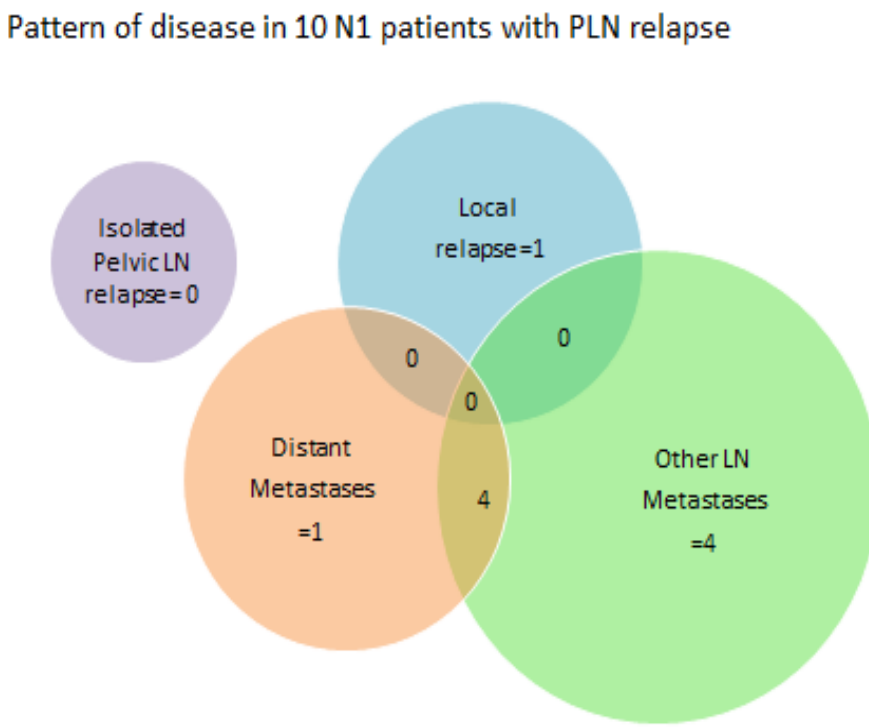


Table 7. First site of recurrence for 26 patients with PLN relapse

First sites of recurrence	Node negative n=16	Node positive n=10	Total n=26
PLN alone	**5**	**4**	**9 (35%)**
PLN and other nodal sites	**3**	**4**	**7 (27%)**
PLN and local	**3**	**1**	**4 (15%)**
PLN and distant metastases +/-local +/-other nodal sites	**3**	**1**	**4 (15%)**
Distant metastases +/- other nodal sites	**2**	**0**	**2 (9%)**

Twenty four (92%) patients relapsed within the pelvic nodes at first relapse. Nine patients (35%) relapsed in the pelvic nodes alone and patients with a combination of prostate and pelvic nodal disease at first relapse accounted for 50% of the group.

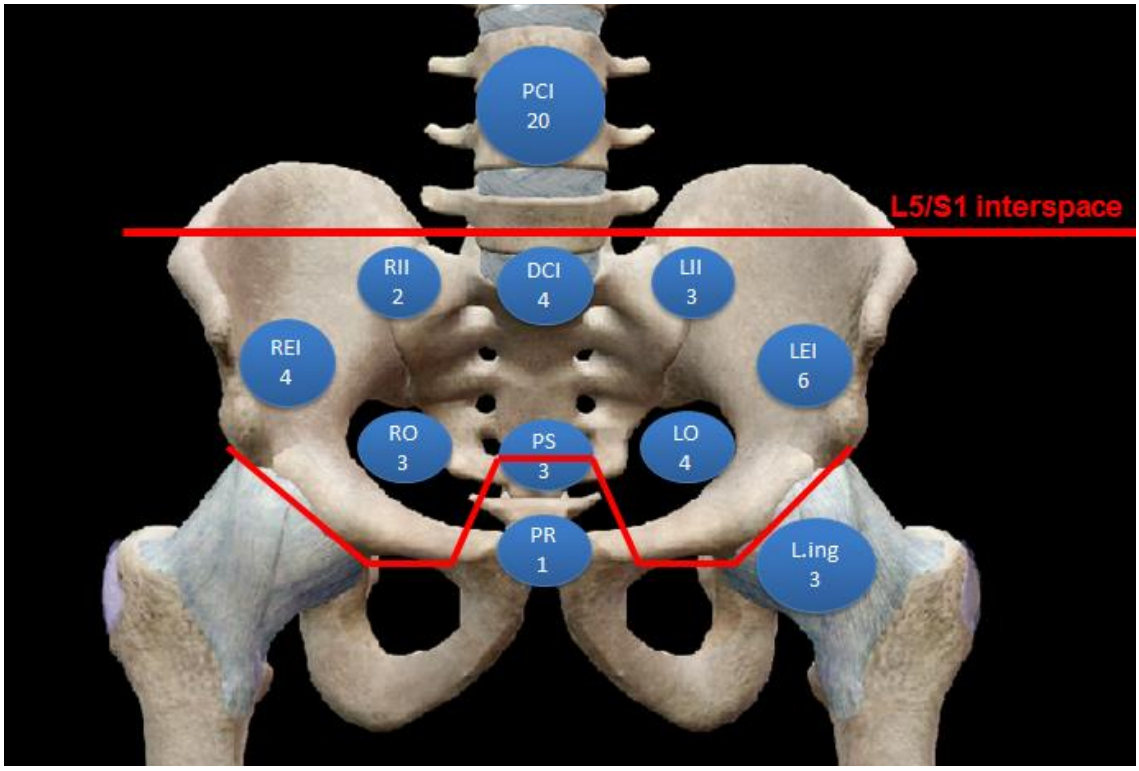
2.4.4 Sites of pelvic relapse

Twenty-five patients had had pelvic relapse diagnosed on the basis of re-staging scans. The remaining 1 patient had a pelvic lymph node dissection for rectal cancer and was incidentally found to have metastatic prostate cancer deposits inside the pelvic LN specimens. The patient had not had a biochemical relapse and no suspicious LN had been visible on the preoperative scans. The exact location of the positive pelvic lymph node was therefore not possible to determine.

Of the remaining 25 patients, the scans that diagnosed recurrence were available for review for 23 patients. These scans were reviewed by a consultant radiologist (Dr Aslam Sohaib) or nuclear medicine specialist (Dr Sue Chua) to confirm the anatomical sites of lymph node relapse using the standard RTOG pelvic lymph node nomenclature.

Figure 9 shows the frequency with which each pelvic LN site was involved by relapsed disease for each of the 25 patients with radiological evidence of pelvic lymphadenopathy. The recurrence sites are marked out with respect to an estimation of the radiation field borders.

Figure 9. Frequency of PLN site involvement with disease relapse



PCI=proximal common iliac node, L5/S1, DCI= distal common iliac below L5/S1, LII/RII=Left/Right internal iliac, L/REI=Left/Right external iliac, PS=pre-sacral, PR=peri-rectal, LO/RO=Left/Right obturator, L.Ing=Left/Right inguinal. The red lines mark out the extent of the pelvic radiation field and which nodal sites fall in and outside it.

For the 25 patients with radiological evidence of pelvic recurrence, 53 sites of node involvement were identified. The out of field recurrences (displayed in figure 8 above as above or below the red line) accounted for 49% (26/53). The commonest out of field site was the proximal common iliac lymph nodes which were positive in 20/26 patients. These lie just above the top border of the radiation field at the L5/S1. The remaining sites involved were the peri-rectal (1), inguinal (3) and low pre-sacral nodes (2).

The remaining 51% (27/53) of involved sites were within the radiation field and appear to be distributed more evenly across all the sites, but overall more nodes identified on the left (13) than the right (9). The external iliac nodes were most commonly involved site, followed by the obturators. There was one pre-sacral node that was in field.

Tables 8 and 9 show the demographics and site of pelvic lymph node group involvement for the 16 node negative and 10 node positive patients that had pelvic relapses. Overall 11 patients had pelvic lymph node relapse entirely outside of the radiation field at the proximal common iliac nodes which lay above L5/S1 (5/10 stage N1 patients and 6/16 N0 patients). Nine patients had pelvic lymph node relapse sites inside and outside the radiation field (5/16 N0 and 4/10 N1). Five patients had relapse within the radiation field alone (4/16 N0 and 1/10 N1). Of the 10 N1 patients, both relapse imaging and staging imaging was available for 6 patients. Comparing the distribution of pelvic nodes on the baseline staging scans and relapse scans of these 6 patients, it was apparent that only 2/6 patients relapsed at the original site of pelvic lymph node disease (patients 18 and 22 table 9) the remaining 4 (patients 21, 24, 25, 26) all relapsed at the common iliacs just outside the radiation field.

Table 8. Demographics and nodal sites of involvement for each of the 16 stage N0 patients who had pelvic recurrence

Patient number	Gleason score	Index PSA ng/ml	Radiological/ path T stage	Cohort	PCI	DCI	L II	R II	L EI	R EI	LO	RO	L ing	R ing	PS	PR
1	3+4	56	T3b	50Gy												
2	4+4	16.5	T3a	50Gy												
3	3+4	53	T3a	55Gy												
4	3+4	168	T3a	55Gy												
5	4+4	100	T3b	55Gy												
6	5+4	7.2	pT3b	60Gy												
7	4+4	112	T2c	60Gy	pathology only											
8	4+5	6	T2c	60Gy												
9	4+3	99.5	T3a	60Gy												
10	3+4	36	T4	60Gy												
11	4+5	13.6	T3b	Hyp 4week												
12	5+4	7.7	T3b	Hyp 4week												
13	3+4	39.8	T3b	Hyp 5week												
14	5+4	12	T3b	Hyp 5week												
15	4+5	26	T3b	Hyp 5week												
16	4+5	122	T4	Hyp 5week												

PCI=proximal common iliac node, L5/S1, DCI= distal common iliac below L5/S1, LII/RII=Left/Right internal iliac, L/REI=Left/Right external iliac, PS=pre-sacral, PR=peri-rectal, LO/RO=Left/Right obturator, L/R Ing=Left/Right inguinal. The red and blue blocks represent lymph node involvement at that site for each patient. Red blocks signify nodal groups outside the radiation field and blue blocks signify nodal groups within the radiation field. The information was based on specialist radiologist review of the recurrence imaging in 23/25 cases and radiological reports in the remaining 2 cases.

Table 9. Demographics and nodal sites of involvement for each of the 10 stage N1 patients who had pelvic recurrence

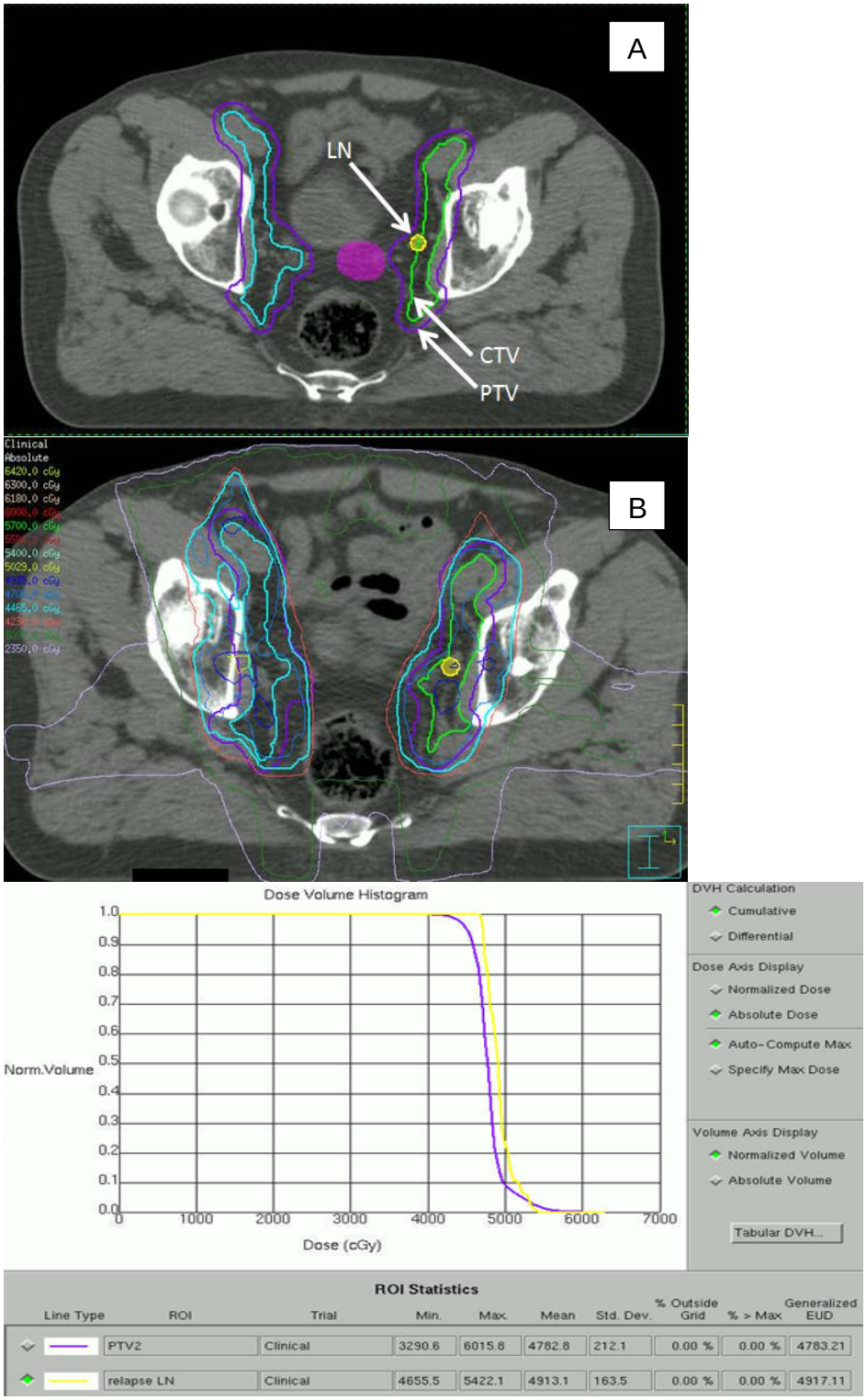
Patient number	Gleason score	Index PSA	Radiological/ path T stage	Cohort	Nodes at diagnosis	PCI	DCI	LII	RII	LEI	REI	LO	RO	lIng	Ring	PS	PR
17	4+5	29	T3a	50Gy	unknown												
18	3+4	65.8	T2b	55Gy	RO												
19	4+5	28	T4	55Gy	CI,LEI, LO, PR												
20	3+4(5)	40	T3a	60Gy	RII, RO												
21	4+3	180	T3a	60Gy	LO												
22	3+4(5)	133	T3b	60Gy	Multiple												
23	4+5	57	T3b	60Gy	Multiple												
24	4+3	10.8	T3b	Hyp 4wk	LII												
25	3+4	46.5	T3a	Hyp 5week	REI												
26	5+3	5.9	pT3a	hyp 5week	RII												

PCI=proximal common iliac node, L5/S1, DCI= distal common iliac below L5/S1, LII/RII=Left/Right internal iliac, L/REI=Left/Right external iliac, PS=pre-sacral, PR=peri-rectal, LO/RO=Left/Right obturator, L/R Ing=Left/Right inguinal. The red and blue blocks represent lymph node involvement at that site for each patient. Red blocks signify nodal groups outside the radiation field and blue blocks signify nodal groups within the radiation field. The information was based on specialist radiologist review of the recurrence imaging in 23/25 cases and radiological reports in the remaining 2 cases.

Radiation plans were available for 18 of the 26 patients (9/10 N1 patients and 9/16 N0 patients). The remaining 8 patients did not have plans available as they had not been stored in digital form. Ten of the plans were held in Pinnacle and the remaining 8 were held in Eclipse. The aim of this analysis was to review the relapses that occurred within or partially within the pelvic radiation field, so nine radiation plans were not included as the patients only had disease outside of the radiation field at the proximal common iliacs. Of the remaining 9 plans, dose information was available for 7 patients.

The radiation plans for these 7 patients were fused with the recurrence diagnostic imaging (CT, PET CT or MRI) using a rigid registration method based on the bony anatomy of the pelvis and lower lumbar spine. Once fused, the recurrent lymphadenopathy was identified and outlined on the planning CT dataset. This was done with CTV, PTV and plan isodoses switched off to avoid any bias. Once completed, the mean dose to the recurrent lymph node volume was then calculated and recorded. An example is shown below in figure 10 and the results are shown in table 10.

Figure 10**.** Example of fusion and co-registration of diagnostic PET CT scan and planning scan



Panel A. shows the RT planning scan of patient 12, which has been fused with the diagnostic CT scan and the recurrent left obturator LN has been outlined. The CTV and PTV are then switched on. Panel B shows the radiotherapy plan isodose lines (of note, not the same axial slice of planning scan seen in panel A) and the panel below shows the DVH and mean dose to the PTV (purple, labelled PTV2) and recurrent left obturator LN (yellow, labelled relapse LN).

Table 10. Recurrent PLN dose information

Patient	N stage	LN site at diagnosis	Cohort	Cohort dose to PLN EQD2	Site of PLN recurrence	In or out of PTV	Mean dose to recurrent node	EQD2 of mean dose to recurrent node
9	N0	n/a	60Gy/35#	55.9Gy	PS PS	In borderline	62Gy 39.3Gy	57.3Gy 36.3Gy
12	N0	n/a	47Gy/20# 4 weeks	51.3Gy	LO	in	49.1Gy	53.6Gy
13	N0	n/a	47Gy/20# 5 weeks	51.3Gy	R.PCI REI	out in	7.2Gy 49Gy	7.8Gy 53.5Gy
14	N0	n/a	47Gy/20# 5 weeks	51.3Gy	L.PCI R.PCI LEI RO LO L.Ing	out out borderline in in out	11.3Gy 3.4Gy 32Gy 46.5Gy 47.1Gy 19.2	12.3Gy 3.71Gy 34.9Gy 50.8Gy 51.4Gy 21Gy
18	N1	RO	55Gy/35#	48.8Gy	RO	in	52.8Gy	45.9Gy
24	N1	LII	47Gy/20# 4weeks	51.3Gy	L.PCI	borderline	31.4Gy	34.3Gy
22	N1	L.DCI L.DCI LEI LO	60Gy/35#	55Gy	L.DCI L.DCI LEI LO	in in in in	62.7Gy 65.2Gy 61.8Gy 65.2Gy	57.9Gy 62.7Gy 57.1Gy 62.8Gy

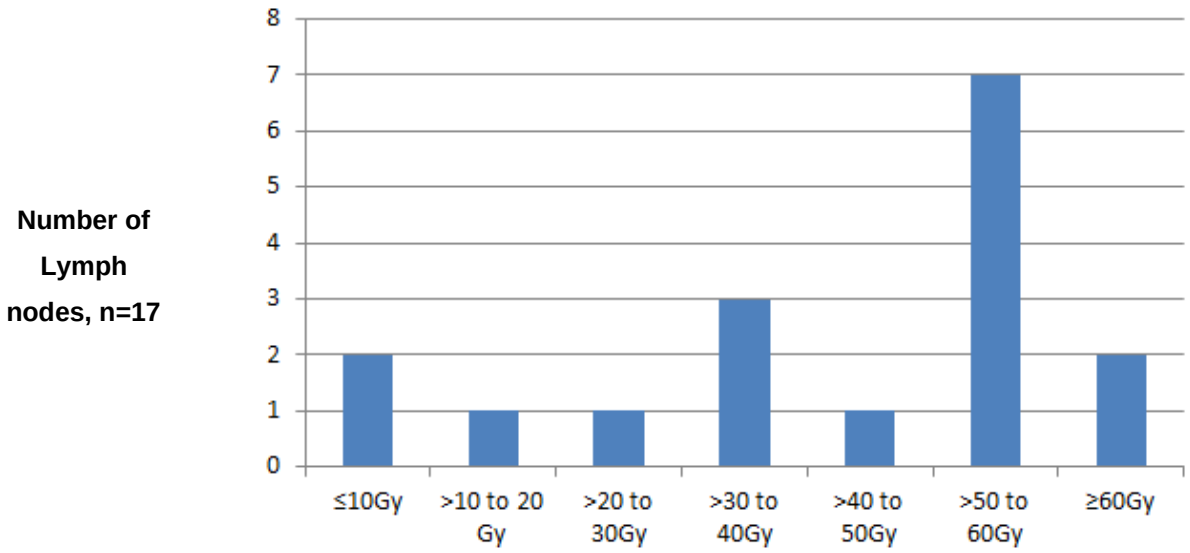
Overall, dose information was available for 17 lymph node recurrences in 7 patients. Four relapses occurred just outside the PTV. These were in the proximal common iliac region. Three relapses were partially covered by the PTV. In two of these cases the nodes were in locations not covered by the radiation field (low pre-sacral and proximal common iliac) and the remaining node was in the external iliac group, but lay just anterior to the field.

The 2Gy equivalent dose for each cohort was calculated using an α/β of 1.8Gy for prostate cancer (7, 8) assuming there is no time factor. The mean dose received by the tissue at each nodal recurrence was also converted to the 2Gy equivalent for comparison. Of note, patient 8 was treated within Cohort 2 (55Gy in 35#) but due to issues with bowel dose was only prescribed 52.5Gy.

Table 11. 17 recurrent pelvic nodes categorised into dose groups for patients staged N0 and N1 at diagnosis

Dose to PLN volume in EQD2 using α/β of 1.8Gy for prostate			
Stage	**≥40Gy**	**<40Gy - >10Gy**	**≤10Gy**
N0	**5**	**4**	**2**
N1	**5**	**1**	**0**
Total	**10**	**5**	**2**

Figure 11. number of lymph nodes recurring in differing dose regions



Both table 11 and figure 11 demonstrate that the majority of lymph node recurrences in the N0 and N1 patients occurred in regions of the pelvis receiving over 50Gy in EQD2. A few nodes occurred in each of the lower dose regions that were outside or partially covered by the PTV. Within the scope of this data with a relatively small number of infield lymph recurrences and relatively small range of delivered dose there did not appear to be any clear dose response relationship.

2.5 Discussion

The IMRT Trial was a single-centre phase I/II study of IMRT to irradiate the prostate and pelvic lymph nodes (PLN) in patients with advanced localized prostate cancer. 426 patients were sequentially treated 5 cohorts. Cohorts 1,2 and 3 received 70-74Gy in 35-37 fractions to the prostate and 50Gy, 55Gy or 60Gy to the PLN. Two additional hypofractionated cohorts were treated with 60Gy in 20 fractions to the prostate and 47Gy to the PLN in either cohort 4 (5 days/week) or cohort 5 (4 days/week). All patients were treated with long course hormone therapy.

2.5.1 Patterns of disease relapse

My aim was to establish the patterns of disease relapse in the whole trial cohort. Distant metastatic disease outside the lymph nodes was the most common site of relapse in all cohorts (23%) and local recurrence was the second most common site of relapse with an overall rate of 10%. The overall the rate of pelvic relapse was low at 6% for the whole group, 13.5% (10/74) for the node positive patients and 4.5% (16/352) for the node negative patients.

To my knowledge there is limited published data about the rate of pelvic lymph node relapse following prostate and pelvic lymph node radiotherapy, or patterns of relapse. In one recent publication of a retrospective series, 2694 patients with localised node negative prostate cancer were treated with prostate only radiotherapy (at least 75.6Gy) and short course ADT. 474 patients with clinical disease recurrence had a median follow up of 9.25 years. The 8 year cumulative incidence pelvic failure rate was 3.9% (95% CI 8.6-11.2) for the whole cohort. Despite a lack of pelvic radiotherapy, this is similar to the failure rate seen in our node negative cohort of 4.5%. Similar to our cohort, the rate of local relapse was 9.9% (95% CI 8.6-11/2%). However, the rate of upper abdominal lymph nodes and bone metastases were 1.6% (95% CI 1.1-2.2%) and 6.5% (95% CI 5.4-7.9%) respectively. This may be a reflection of the patient cohort where 50% of the cohort was NCCN low or intermediate risk (17).

2.5.2 Pelvic relapses

Pelvic recurrence was an early event in the disease relapse course, as 92% of the patients who recurred in the pelvic nodes had evidence of recurrence at this site at the first sign of clinically detectable disease relapse. This suggests there is micro-metastatic disease, perhaps present at diagnosis, which is not sterilised by the radiation, as opposed to new spread to the pelvic nodes following a local recurrence or retrograde spread from upper abdominal nodes.

Within the radiation field, there wasn't a site that was a hot spot for recurrences. The most frequent sites were the external iliacs with 10 recurrences (Right=4 and left=6), followed by the obturators with 7 recurrences (right=3, left=4). This may just reflect the fact that these are the two most common draining sites of the prostate and are therefore most likely to have lymph node involvement (18), rather than some failure of treatment in the area. On examination of the radiation plans for patients with in-field recurrence, 59% of the recurrent nodes occurred within the PTV and received the full intended PTV dose. Given the good nodal control rate for the whole cohort, this suggests that these patients had radio-resistant disease, and rather than benefit from dose escalation, need some other modality of treatment. Multivariate analysis found dose to the pelvic lymph nodes was also statistically significant for disease control. However, the wide and overlapping confidence intervals for the hazard ratios lead me to approach these results with caution. Patients were only stratified on the basis of bowel volume rather than disease characteristics and cohort 1 had a higher rate of adverse features such as higher median index PSA and a higher proportion of N1 patients. This was the smallest cohort with only 25 patients and the first to be recruited into within the trial. Looking at table 2 this cohort had the longest follow up at 13.9 years. While this cohort did have the highest rate of pelvic relapse (12%) compared to the other cohorts, it also had the highest rate of patients with metastatic disease (cohort 1=52%, all cohorts= 23%) and local relapse (cohort 1= 24%, all cohorts =10%). Both these sites of disease relapse are not related to the radiation dose received by the pelvic nodes and contributed significantly more to the overall poor results of the cohort.

In conclusion, there is not enough evidence to support the hypothesis that pelvic lymph node dose escalation using IMRT is associated with a reduced lymph node recurrence rate or overall disease control. However, the patterns of recurrence which I have demonstrated supports my second hypothesis that modification of the pelvic LN target volume is appropriate and should include the proximal common iliac lymph node chains.

There were fewer recurrences that were borderline (20-40Gy) and aside from the node in the left external iliac region, all occurred in nodal areas that the contours did not intend to cover, suggesting little needs to be improved in the contouring and planning process for the nodal groups we aimed to cover. However, the commonest site of relapse was just outside the radiation field at the proximal common iliacs. These were involved in 80% (20/26) of the patients with pelvic relapse and were the sole sight of relapse in 42% (11/26). This raises the question about whether these nodes ought to be included in the radiation field. Certainly, from this data, it would be the only change to the planned pelvic radiation that might have reduced the rate of pelvic relapse. However, covering these nodes may well change the toxicity profile of pelvic radiation. Ideally this toxicity profile should be better understood before exposing entire cohorts of patients to potentially reduce the risk of pelvic recurrence which might have occurred in 11/426 (2.6%) patients in this study. Any modifications should take into account other treatment intensification methods that may reduce the rate of distant metastases and local relapse would be likely to have a more significant impact on overall disease control.

2.5.3 Limitations

During the study follow up period, diagnostic imaging was ordered at the discretion of the clinician and therefore may have introduced bias into our results in several ways. Protocolisation for when to image, how often and with which scans was lacking. Therefore, some patients may have been more frequently investigated or with more sensitive imaging modalities such as a choline PET CT and MRI of the pelvis, rather than a CT and bone scan. They may have been screened for metastatic disease more often if the initial imaging didn't demonstrate sites of clinical recurrence. Secondly, prostate biopsy in patients with suspected local recurrence was not protocolised and

therefore practice varied which may have lead to the under or overestimation of local recurrence rates. To ensure that all sites of radiological relapse were captured thoroughly I reviewed serial imaging results for each patient, beyond those organised at first relapse and documented in the trial case report forms. Therefore, if a patient had progressive disease involving other sites it was picked up. However, in patients where no further imaging was conducted or scans were no longer available for review, I used reports of diagnostic imaging. For the pelvic relapses in particular, due to archiving methods there were limitations in the availability of the baseline, relapse imaging and radiotherapy planning scans which meant that the evaluation of relapsed nodes with respect to the radiation field could only be performed in 7 of the 26 patients.

When evaluating the dose received to each recurrent lymph node sites, the fusion process may have introduced a small margin of error. But it is unlikely that this would have changed the results seen. Due to the age of the radiation plans I was only able to review 50% of the patients with infield recurrence. The missing plans were for patients recruited in to the trial at earlier time points and therefore treated in cohorts 1 and 2 receiving a lower pelvic dose. It is therefore a possibility that review of this data may have found a different pattern of field recurrences to that reported.

2.5.4 Future directions

When considering the whole cohort with the aim of improving their outcomes, the most striking data is the high rate of distant relapse. This is to be expected in such a high risk cohort and while long course androgen deprivation therapy remains the standard of care, there is emerging data to support additional systemic therapy in this patient group. The Stampede trial analysis of patients who had been offered 6 cycles of docetaxel chemotherapy as well as standard of care long term androgen deprivation therapy had a survival advantage compared to standard of care alone. The study cohort included metastatic patients and high risk non metastatic patients (40%) who had at least two of the following; T3/T4 disease, Gleason 8-10 or PSA ≥40ng/ml. While the survival analysis in the non-metastatic group is presently underpowered as too few events have occurred in the available follow-up period, there was a clear advantage in median failure free survival (20 vs. 37 months, HR 0.61, 95% CI 0.53-0.7, p=0.413x10^{-}13) (19). A further arm of the STAMPEDE trial has also found a

significant improvement in PFS in the high risk non-metastatic setting in men treated with 2 years of abiraterone alongside ADT compared to ADT alone (43).

The second most common site of relapse was within the prostate. Dose escalation up to 76-80Gy in 2Gy conventionally fractionated radiotherapy has been proven to improve biochemical control in a number of studies, but does come at the cost of increased toxicity (20-24). Beyond this, further dose escalation strategies include high dose rate brachytherapy; which minimises dose to the surrounding normal tissues and also exploits the low α/β ratio of prostate cancer which should make it more sensitive to large radiation doses per fraction (25, 26).

Several trials have demonstrated an increase in biochemical control in both intermediate and high risk prostate cancer with the use of EBRT in combination with either high dose rate brachytherapy (27, 28) or low dose rate brachytherapy (29) as methods to dose escalate.

Another alternative is to apply a focal boost to the prostate at the site of an identified dominant lesion using IMRT, thereby escalating dose to the highest risk part of the prostate only. The technique is dependent upon the identification of a dominant prostate lesion on multi-parametric MRI (30, 31). At present, two trials in the UK have used this technique; the DELINEATE trial (32) which is currently recruiting at a single centre. It has a conventionally fractionated arm boosting the dominant prostate nodule to 82Gy in 37 fractions and a hypofractionated cohort boosting up to 67Gy in 20 fractions. The other is boosting up to 86Gy in a conventionally fractionated cohort and 68Gy in a hypofractionated cohort, with acceptable early toxicity results (33, 34). In the Netherlands the FLAME trial randomised intermediate to high risk patients between 77Gy in 35F to the whole prostate (n=287) and a dose escalated arm where patients receive an additional integrated boost of up to 95Gy to the multiparametric MRI defined tumour site within the prostate. Thus far the trial has published the toxicity results up to 2 years post treatment and there doesn't appear to be any additional GI or GU toxicity seen in patients treated in the focal boost arm compared to the standard arm (42).

What remains to be seen is how these prostate dose escalation techniques compare to each other and what additional benefit will be gained by combining them with pelvic radiotherapy. Furthermore, what will be the cost in additional toxicity? The current PIVOTAL boost trial will hopefully address these questions. It is a phase III multicentre four arm randomised controlled trial looking of prostate and pelvic radiotherapy versus prostate alone with or without a prostate boost. The four treatment arms that patients can be randomised to are; A. prostate IMRT alone, B. prostate and pelvic IMRT, C. prostate IMRT and prostate boost, D. prostate and pelvic IMRT with prostate boost. The boost can be delivered with IMRT or HDR brachytherapy and depends upon availability at the participating centres and a suitable boost volume being identified on MRI. The primary objective of the trial is to assess whether pelvic lymph node radiotherapy with or without dose escalation to the prostate with HDR brachytherapy to the whole gland, HDR incorporating a focal boost, or focal boost IMRT can lead to improved biochemical control with similar levels genitourinary and bowel side effects experienced by patients (35)

The future is leading to more treatment intensification of radiation and systemic therapy for patients with high risk localised prostate cancer. This is promising in terms of improving long term disease control and survival for this group of patients. But with increased survivorship, care needs to be taken to understand the long term toxicity risks, particular when adding together several new treatment modalities.

Another approach will be to learn more about how to risk stratify patients in order to offer a more personalised approach to treatment. In the aforementioned analysis by Zumsteg (17); the authors noted that many patients' cancers seemed to have a "tropism" for a particular anatomic compartment, and would not spread to other compartments for some years. In their multivariate analysis they found that the anatomic pattern of recurrence was the most important predictor of prostate cancer specific mortality after clinical disease relapse. As patients with visceral disease had worse outcomes that those patients with lymph node or bone only disease. In another series of 1003 patients with node positive prostate cancer treated with radical prostatectomy and extended pelvic lymph node dissection, the patterns of recurrence were described after a median follow up of 6.4 years. They found that the first site of recurrence was an independent predictor for cancer specific mortality, and patients

who recurred with skeletal metastases (HR=2.08; p=0.04) or visceral metastases (HR=4.22; p=0.01) had a higher risk of cancer specific mortality than those patients with local and nodal relapse (36) This is often seen in clinical practice and lends weight to the argument that the high risk prostate cancer group is heterogeneous in its behaviour and pattern of spread.

Ideally future clinical trials will prospectively gather material for potential biomarkers and genetic signatures to determine if these patterns of behaviour can be identified at diagnosis. Information about risk of developing distant metastases, recurrent local disease, radio-resistance or a propensity to spread to the pelvic nodes will help us to prioritise and identify which of the available treatments will have the biggest impact on the patient's clinical disease course.

2.6 Conclusions

This study showed that PLN recurrence was rare following prostate and pelvic IMRT with long course androgen deprivation therapy. When pelvic recurrence occurred, it was often the earliest site of clinically detectable disease, and isolated pelvic recurrences at first relapse were seen in a third of relapsing patients. The clinical pattern was of small volume metastatic disease outside or just beyond the pelvic radiation field (particularly at the proximal common iliacs) or within the field, suggesting radio-resistance or inadequate dose. Rates of metastatic disease and local relapse were comparatively higher than nodal relapse; therefore, treatment intensification to address this is going to have the most clinically significant impact for this group of patients. The high risk localised prostate cancer patients are a heterogeneous group with varying clinical outcomes, despite similar diagnostic features (37). Future work to enable us to predict cancer behaviour is key and will help us to refine our treatment plans for individual patients accordingly.

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Chapter 3 Evaluating pelvic lymph node target contouring guidelines using Choline PET CT

For this chapter I designed the study with the help of the Professor Wim Oyen and Dr Sue Chua who decided upon the criteria for ch-PET positivity and reviewed all imaging with me. Clare Griffin, senior statistician at the clinical trials and statistics unit of the institute of cancer research provided advice about the required sample size. All patient identification, data collection, documentation and interpretation was my work.

3.1 Background

3.1.1 Defining the clinical target volume in pelvic lymph node radiotherapy;

The aim of IMRT is to cover the target as closely as possible to minimise the radiation dose to adjacent organs at risk. In order to achieve this increasingly conformal treatment without geographically missing the target, accurate volume definition is crucial (1).

3.1.2 Which lymph nodes to cover?

When defining the target in elective pelvic lymph node (PLN) IMRT several factors need to be considered. The first is deciding which lymph nodes groups should be covered. Surgical pelvic lymph node dissections have provided the earliest data about the extent of microscopic nodal metastases from prostate cancer. However, as outlined in chapter 1, this data is limited to the anatomical areas sampled in a traditional surgical dissection. A standard pelvic lymph node dissection only removes the external iliac and obturator nodes. An extended dissection would additionally involve removal of the internal iliac nodes and some may include the common iliac nodes. As a result, there is little surgical data about micro-metastases in other pelvic lymph node groups such as the pre sacral and para-rectal nodes, as these areas are not traditionally included in a dissection.

Data from sentinel LN (2) and MR lymphography (3) studies have demonstrated that microscopic disease can exist in lymph node groups as far as the proximal common iliac, para aortic, pre-sacral and para-rectal regions. Most PLN contouring guidelines aim to cover the distal common iliac, external iliac, internal iliac and obturator nodes (4-6) which are the most commonly involved sites.

3.1.3 Method for creating PLN CTV

The next consideration is the technique used to create a PLN clinical target volume (CTV). Small pelvic nodes are not readily identifiable on conventional CT imaging, so surrogate anatomical structures are used to create a CTV in the space that lymph nodes potentially occupy. Anatomical studies have demonstrated that lymph nodes lie adjacent to major blood vessels and studies performed using lymphotropic nano-particle enhanced magnetic resonance imaging (LNMRI) have defined the spatial distribution of nodal tissue in relation to the vessels at different anatomic levels in the pelvis. Table 12 summarises these studies and the margin around vessels needed to cover ~95% of identified nodes (7-9).

Through the upper pelvis the spatial relationship between the nodes and vessels is predictable and the majority of nodes are located within a certain distance from the vessels. As the main vessels divide in the lower pelvis the relationship between the vessels and nodes becomes less consistent; for example, around the small branches of the internal iliac vessels at the pre-sacral region. Additionally, in these areas vessels become more difficult to locate on imaging and even a larger margin around them fails to encompass the majority of nodes. For the pre-sacral nodes Dinniwell et al (7) found a 20mm expansion was required to cover 95% of nodes detected in the pre-sacral area and Taylor et al (9) found that even a 15mm expansion only covered 42% of nodes at the sacrum. In practical terms a balance needs to be sought between maximising PLN coverage with a larger CTV and maintaining a safe dose to the surrounding organs at risk. Therefore, for most PLN CTV guidelines pre-sacral lymphatic tissue is encompassed by creating a 10-20mm margin adjacent to the anterior sacrum rather than the nearest visible vessels. Similarly, the obturator and

medial internal iliac lymphatic tissue along the pelvic sidewall is covered by a margin along the bony pelvic sidewall.

Table 12. studies describing the location of pelvic lymphadenopathy with respect to adjacent vascular structures and recommendations for pelvic lymph node CTV.

PA=para-aortic, CI=common iliac, EI=External iliac, II=Internal iliac, Obt=obturator, PS=pre-sacral nodes

Study	Patients	Number of nodes	Summary of findings	PLN CTV recommendations
Shih et al, 2005 (8)	**18 prostate cancer pts** **Pre-treatment =10** **recurrent disease =8**	**69**	**15mm margin around vessels covered 95% of nodes**	**20mm margin around vessels to create CTV (expanded from 15mm to encompass whole node)** **No edit off muscle, bone or bowel suggested**
Taylor et al, 2005 (9)	**cervix cancer = 12** **endometrial cancer = 8**	**1216**	**10mm margin covered 100% of nodes at all locations** **(Apart from the lateral EI=65%, PS=43%)**	**Uniform 7mm margin around vessels (encompasses average of 87.7% of nodes) round vessels, PS strip = 10mm, Pelvic sidewall strip =18mm to cover obturators** **Edit off bone and muscle but not bowel**
Dinniwell et al, 2009 (7)	**55 patients** **prostate cancer = 36** **bladder cancer= 9** **endometrial cancer = 5** **cervix cancer =5**	**1670**	**PA=9.4mm, CI=8.2mm, II=13.2mm, EI=11.5mm, Obt=20.8mm, PS=20.8** **Margin around vessel that covers 95% of lymphatic tissue at each location.**	**Aiming for 90% coverage with margins around vessels of:** **PA= 12mm, CI and II=10mm, EI=9mm,** **Obt=22mm, PS=12mm** **No edit off muscle, bone or bowel suggested**

3.1.4 IMRT PLN contouring guidelines

A detailed lymph node contouring instruction manual was developed for the pelvic IMRT study, based upon the description of the lymph node areas at risk from surgical series using extended pelvic lymph node dissections (10). This is contained in appendix 4.

The guidelines used a free hand drawing technique and did not specify that a fixed distance from bone or vessel be applied. For consistent CTV's to be achieved using the guidelines, direct supervision from an experienced clinician was required until the technique had been mastered. This made the guidelines less suitable for use outside of the department.

3.1.5 Development of the PIVOTAL PLN CTV guidelines

Following on from the safety data obtained from the IMRT trial (11), the PIVOTAL was planned to further test the 60Gy in 37# IMRT trial cohort in a multicentre setting. This was a randomised Phase II trial of prostate and PLN RT versus prostate only radiotherapy in patients with advanced localised prostate cancer. To achieve consistent PLN CTV's between different centres the trial team needed to develop new contouring guidelines. The aim was to produce similar target and OAR coverage as had been achieved with the RMH guidelines, but to provide clarity in instruction, so that previous experience was not essential for to reproducing the desired CTV.

The RTOG had also produced PLN contouring guidelines (5) that were based on a vascular expansion technique and made use of radiotherapy planning software margin expansion and editing capabilities, rather than freehand drawing. Initially the PIVOTAL trials team considered using the RTOG guidelines. However, when compared to the RMH guidelines there were several factors that made them unsuitable. Firstly there were differences in target coverage, secondly they lacked sufficient detail in the instruction and thirdly they were not at that time supported by any trial safety data. Therefore, it was decided by the group to adapt the existing RMH guidelines using a similar vascular expansion technique

outlined in the RTOG methods. The resultant modifications of the RMH guidelines produced larger CTV volumes than the original RMH and RTOG techniques. This raised concerns in the trial group that the increase in bowel irradiation might result in increased rates of toxicity. In order to mitigate the CTV encroachment over bowel, a further step in the guidelines was added. The bowel volume was given an isotopic margin using the planning software, to create a bowel expansion margin (BEV). The PLN CTV was then edited back to exclude the BEV. The only exception where the CTV was not edited back from the BEV was over blood vessels and where there may be “small white dots” that could represent sub centimetre suspicious lymph nodes. This method created a final PLN PTV that had equal (or less) overlap with bowel in comparison to the PLN PTV’s created using the RMH technique (6).

The final PIVOTAL contouring guidelines can be summarised as follows; the distal common iliac nodes are covered from the bottom of L5 downwards. The pelvic vessels are identified on the planning CT scan and contoured. An isotropic 7mm expansion is created using the planning software to create a volume. This volume is edited off muscle, bone, bladder and rectum and the BEV to create a final PLN CTV. Along the sacrum, where the internal iliac vessels further divide, a 12mm width strip is drawn to cover the pre-sacral nodes down to the S3/4 junction. An 18mm strip is drawn along the bony pelvic side wall to connect the internal and external iliac nodes as well as cover the obturator nodes up to 1cm above the pubic bone. The external iliac nodes are covered to the top of the femoral heads which typically act as a surrogate for the inguinal ligament. Both the pre-sacral strips and obturator strips are flush against bone and edited off any nearby muscle, bladder, rectum and BEV. The full PIVOTAL contouring instructions and planning target margins are in appendix 5.

The PITVOTAL guidelines cover a similar PLN group to the RTOG guidelines; however, the methodology for creating and editing PLN contours differs, with a more comprehensive description of outlining for all levels in the pelvis. In clinical practice anatomical variations in the size of the pelvis, vasculature and bowel patterns may affect the resultant CTV created and therefore the coverage of nodes. Additionally, editing the contours due to the location of the BEV may result in poorer CTV coverage. I wanted to investigate how well these contours cover

PLN disease in clinical practice, to define any locations where coverage is consistently poor and consider modifications that might improve lymph node coverage.

3.1.6 Choline PET identified PLN disease

Conventional imaging with CT and MRI mainly relies upon lymph node enlargement to detect metastatic disease and is not sufficiently sensitive for detecting low volume nodal involvement (12, 13). 18F Choline PET-CT (Ch-PET) has a pooled sensitivity of 49% and specificity of 95% on meta-analysis (14). While the overall sensitivity is still low, it appears more sensitive than conventional imaging at picking up metastases in normal sized lymph nodes and has been found to be superior to MRI in head to head comparisons using histological verification (15-17). MR Lymphography would have been an ideal imaging technique to use but unfortunately this is not in routine clinical use. One study used both MR Lymphography (MRL) and Ch-PET imaging to detect PLN in patients with prostate cancer. MRL detected significantly more positive lymph nodes overall. However, in nodes that were ≥ 7mm there was good correlation between the two imaging modalities as 22 and 26 LN were detected by Ch-PET and MRL respectively (18). Other new imaging techniques that may be even more sensitive such as PMSA PET were not available at RMH at the time of this study.

18F labelled Choline PET-CT (Ch-PET) scans have been used in clinical practice at RMH since 2012. In the context of disease staging it has been used to detect small volume metastatic disease that may otherwise be missed on conventional imaging in high risk prostate cancer patients. This meant that there was a readily available bank of patients that had received PLN IMRT, who may have had PLN disease identified on Ch-PET scan as part of their diagnostic work up.

3.2 Hypothesis and aims

The aim of this chapter was to establish how well the developed PIVOTAL pelvic nodal contouring guidelines would cover pelvic lymph nodes in patients with prostate cancer.

Hypothesis; 75% of pelvic lymph nodes are covered by the PIVOTAL pelvic nodal contours

The following objectives test the hypothesis;

1) identify a group of prostate cancer patients with positive pelvic node positive disease identified on Choline-PET CT who had undergone prostate and PLN RT.

2) Establish the proportion of cases where a CTV (and PTV) based on the PIVOTAL contouring guidelines cover Ch-PET the identified PLN disease?

2) Consider any modifications to the CTV (and PTV) which might consistently improve PLN coverage and how they impact organs at risk?

3.3 Methods

3.3.1 Patient selection

I designed the study however the criteria used to describe Ch-PET positive lymph nodes was decided upon by the two nuclear medicine consultants who reviewed all the imaging; Professor Wim Oyen and Dr Sue Chua. Clare Griffin, senior statistician at the clinical trials and statistics unit of the institute of cancer research provided advice about the required sample size. All patient identification, data collection, documentation and interpretation was my work.

Radiotherapy records were used to identify prostate cancer patients who received radical radiotherapy to the prostate and PLN at the Royal Marsden Hospital in Sutton. From September 2012 to June 2016, 258 pts were identified. Patients staged as N0 on imaging, or who had metastatic disease, distant lymphadenopathy (including para-aortic disease) or co-existing second primary

cancers were excluded. 90 patients remained that were staged N1 based on imaging studies reviewed in multidisciplinary meetings. 52/90 patients were N1 based on CT or MRI alone and the remaining 38 patients were staged N1 on the basis of pre-treatment Ch-PET imaging.

3.3.2 Choline-PET CT imaging

The Ch-PET images were acquired using a Siemens Biograph 64 True Point PET-CT (Siemens Medical Solutions). Approximately 60 min after the intravenous administration of F-18-choline, a half body, low-dose, unenhanced CT extending from the base of the skull to the mid-thigh was recorded for purposes of attenuation correction and anatomical localisation. Subsequently, F-choline-emission data were acquired from the base of the skull to the mid-thigh. Lymph nodes with moderate or high F-choline accumulation in excess of physiologic uptake were identified as positive. Lymph nodes with low F-choline uptake, defined as just above adjacent blood pool activity were considered equivocal if structurally larger than 1cm (table 13).

Patients were commenced on androgen deprivation therapy after their PET CT scans had been performed and 6-12 months later underwent a planning CT scan for their radiotherapy treatment. Scans were performed in the supine position with immobilisation using knee rests and ankle stocks. CT images were acquired on a large bore CT (Philips Medical, Cleveland OH, USA) at 2.5mm intervals. The standard upper border was the bottom of the L1 vertebra and the lower border was 2cm below the ischial tuberosities.

3.3.3 Radiological review of Choline-PET CT positive pelvic lymph node disease

The Ch-PET CT scans were initially reported routinely by a nuclear medicine specialist. For the purposes of this study all the scans were re- reviewed by two consultant specialists, Professor Wim Oyen and Dr Sue Chua. They had previously agreed upon set criteria for which nodes would be described as unequivocally positive outlined in table 13. Uptake was quantitively described by comparing the intensity with patient physiological landmarks that are known to have high uptake, such as the liver and salivary glands. Visible nodes were

described as having low, moderate or high uptake without reference to the specific standard uptake value (SUV) measurement. Using a fixed SUV threshold to identify a positive node was not appropriate due to the well documented issues of inter-patient variation in biodistribution and kinetics and the potential technical errors of entering weight FCH dose and injection and imaging time, all of which can influence the SUV measurement (38). Using the CT images nodes were measured in the maximum short axis dimension and were assigned a score. So for example, a node that was definitely positive and between 5 and 10mm in size would have a score of 4A. All positive or equivocal nodes were assigned to a lymph node station with respect to the RTOG guidelines (5). This methodology was in keeping with the methods used in most published studies using Ch-PET to identify pelvic lymph nodes in prostate cancer patients outlined in table 3 of chapter 1.

Table 13. scoring criteria used for defining positive nodes on Choline PET-CT and recording size

Score	Description
1 = Benign	**No uptake on Choline PET and structurally normal in size and appearance on CT/MR**
2 = Likely benign	**Low uptake on Choline PET – just above background adjacent physiological uptake and structurally normal in size and appearance on CT/MRI.**
3 = Equivocal	**Low uptake on Choline PET – just above background adjacent physiological uptake and structurally larger than normal size (>10mm) without any other features suspicious of metastases.**
4 = Positive	**Moderate or high uptake on Choline PET and/or enlarged nodes (>10mm) with structurally abnormal appearance.**
Size (short axis)	
A	**5 to ≤10mm**
B	**11 to ≤20mm**
C	**≥ 21mm**

All 38 pre-treatment Ch-PET CT scans were reviewed and all nodes scoring 3 (equivocal) or 4 (positive) were recorded. The first 10 scans were jointly reviewed by both consultants to confirm consistency. Thereafter only ambiguous cases were jointly reviewed. From the 38 Ch-PET scans, 6 patients were found to have only equivocal nodes in the pelvis leaving 32 cases identified for the next steps of the study.

3.3.4 Mapping of PET positive nodes onto PIVOTAL based PLN CTV.

The next step was to map each positive node onto the patients planning CT scan and assess its position with respect to a PIVOTAL based PLN CTV. For each patient, I recreated a pelvic LN CTV on the planning CT scan (Pinnacle version 8.0) using the PIVOTAL contouring method. I was blinded to the previously drawn pelvic LN CTV. A standard CTV to PTV margin of 5mm was applied. The previously contoured bowel volume was carefully checked for accuracy and that its superior border was 2cm above the PLN PTV. The accuracy of the PIVOTAL LN contouring was reviewed by a supervising clinician (Professor Dearnaley) for the initial 5 cases.

3.3.4.1 Co-registration of Choline PET CT with radiotherapy planning CT scan

Subsequently, the CT component of the Ch-PET scan was co-registered with the planning scan using a rigid registration method based on the bony anatomy of the pelvis and lumbar spine. The vessels are the closest soft tissue structure to the PLN CTV and are considered fixed in location. Therefore, the quality of the co-registration was checked by how well the outlined vessels overlapped at the areas closest to the positive nodes. Any displacement was measured and the one case where a displacement of less than 5mm could not be achieved was excluded due to inadequate fusion.

There were some limitations to this registration method. Firstly, there were variations in patient positioning. Ch-PET scans are performed with patients lying on a concave couch, allowing for curvature of the back. Whereas planning CT scans are performed on a flat top couch with knee and ankle supports that resulting in a lower back contour that is flush with the couch. Overall this results in differences in the position of the pelvis. Secondly patients are scanned for radiotherapy with a comfortably full bladder and with an empty bladder for Ch-PET scans. In some cases the full bladder appeared to displace the vessels

laterally. Lastly, planning CT scans have 1.25mm slices whereas the Ch-PET CT slices are 3mm thick which can also contribute to mismatched appearances.

3.3.4.2 . Contouring PET positive pelvic nodes on planning CT

Once a satisfactory fusion had taken place, the Ch-PET positive nodes were contoured onto the planning CT with the CTV and PTV contours switched off. With the CTV and PTV then switched back on, the position of the nodes relatives to these volumes was recorded and scored as below to reflect the degree of coverage. A further case was excluded at this point as it was too difficult to accurately locate the lymphadenopathy on the CT component of the Ch-PET.

Figure 12. Colour code used to describe PLN coverage by CTV and PTV. A score of 1-3 was classified as sufficiently covered by the contours

1	**Node fully covered by CTV+PTV**
2	**Node partly covered by CTV and fully covered by PTV**
3	**Node outside CTV but covered by fully by PTV**
4	**Node outside/partly covered by CTV and partly covered by PTV**
5	**Node outside of CTV+PTV**

3.3.5 Statistical considerations

The table below shows the number of nodes needed to be analysed in order to demonstrate lymph node coverage of 70-85% with 95% confidence intervals of 5-10%. We aimed to identify 60-70 nodes which would allow us to confirm 75-80% coverage with 95% confidence intervals of 10%. Patients were sequentially identified and recruited until the requisite number of lymph nodes was identified.

Table 14. Number of nodes needed to demonstrate PLN coverage of 70-85% with 95% confidence intervals of either 5% or 10%

Expected proportion of coverage	95% confidence interval	Number needed
85%	**80-90%**	**196**
85%	**75-95%**	**49**
80%	**70-90%**	**62**
75%	**65-85%**	**73**
70%	**60-80%**	**81**

3.4 Results

3.4.1 Demographics

A total of 32 patients were evaluated. All patients had consented to their radiotherapy related data and imaging to be used for research purposes at the point of treatment consent. Patient demographics are shown in table 15. The majority of the population had high risk or very high risk disease on NCCN classification with Gleason ≥8 in 50%, T3b/T4 disease in 62% and a median/mean PSA of 30/50.1ng/ml.

Table 15. Demographics of the 32 patients with positive pelvic lymph nodes on pre-treatment Choline PET CT scan

Demographics (n=32)			
Age (years)		**Index PSA (ng/ml)**	
Mean	**67.4**	**Mean**	**50.1**
Median	**65.5**	**Median**	**30**
Range	**62-73**	**Range**	**15-60**
Tumour Stage (MRI)		**Gleason score**	
T2a	**1(3%)**	**6**	**1(3%)**
T2b	**1(3%)**	**7(3+4)**	**4(13%)**
T2c	**3(9%)**	**7(4+3)**	**10(31%)**
T3a	**7(22%)**	**8**	**3(9%)**
T3b	**17(53%)**	**9**	**13(41%)**
T4	**3(9%)**	**unknown**	**1(3%)**
	NCCN group		
	Intermediate	**2(6%)**	
	High risk	**10(31%)**	
	Very High risk	**20(63%)**	

NCCN guidelines (version 3, 2016); Intermediate risk = T2b-T2c, or Gleason 7 or PSA 10-20, High risk = T3a, or Gleason 8-10, or PSA >20. Very high risk = ≥T3b-T4, primary Gleason 5, or ≥5 cores of Gleason 8-10.

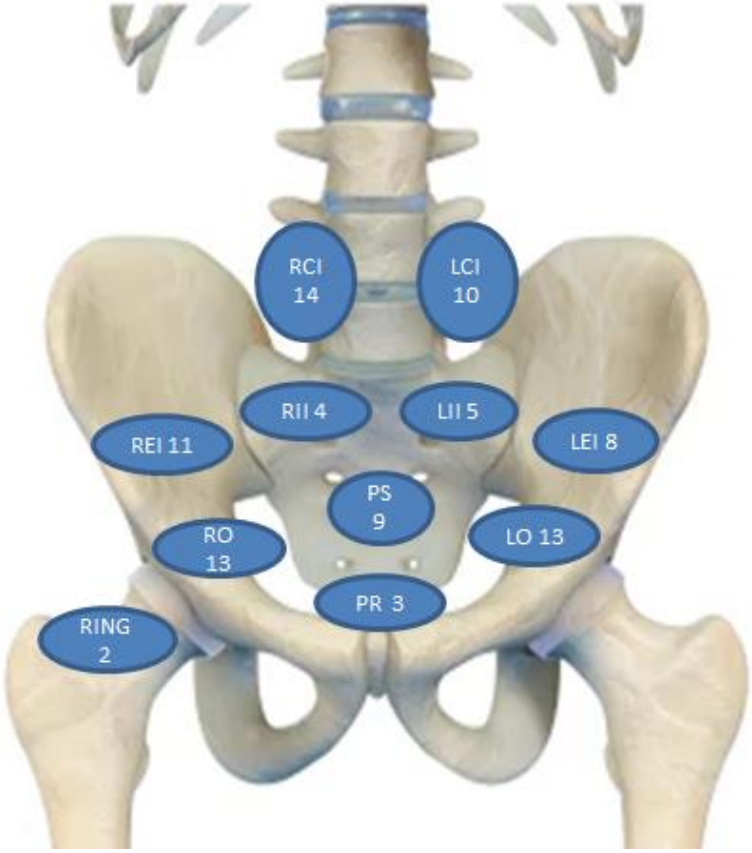
3.4.2 Location and distribution of PET positive lymph nodes

In total 92 positive nodes and 15 equivocal nodes were identified. Table 16 describes the location and size of the positive (4A-C) and equivocal (3A) pelvic nodes identified on Ch-PET according to the criteria described. Patients with positive nodes in the para-aortic region had been excluded at the initial screening stage. Otherwise, the positive nodes were found in an expected distribution (Figure 13), with highest numbers in the obturator (53%) common iliac (34%), external iliac (34%) and internal iliac (25%) regions. The nodes were also evenly distributed between the left and right sides of the pelvis. Overall, there were 12/32 (35%) of patients with a single positive lymph node on Ch-PET. The median number of nodes detected per patient was 2 (IQR 1-3) and the mean was 2.4 nodes. 85% (78/92) of the nodes were ≤10mm in size so were unlikely to have been identified as malignant on conventional CT and MRI based on size criteria (19, 20).

Table 16. Size and location of positive and equivocal nodes identified on staging Choline PET-CT scan in 32 patients with prostate cancer

Lymph node station	Positive Nodes					Equivocal Nodes
	5 - ≤10mm	11- ≤20mm	≥ 21mm	Total	No of pts with station involved (%)	
Left common Iliac	9	1	0	10	11/32 (34%)	3
Right common Iliac	14	0	0	14		4
Left external iliac	7	0	1	8	11/32 (34%)	0
Right external iliac	8	3	0	11		1
Left internal iliac	4	1	0	5	8/32 (25%)	2
Right internal iliac	3	0	1	4		0
Left obturator	10	3	0	13	17/32 (53%)	1
Right obturator	11	1	1	13		3
Pre-sacral	8	1	0	9	5/32 (16%)	0
Peri-rectal	3	0	0	3	3/32 (9%)	1
Left inguinal	0	0	0	0	2/32 (6%)	0
Right inguinal	1	1	0	2		0
Total	78	11	3	92		15

Figure 13. Distribution of the 92 positive pelvic lymph nodes found on choline PET CT scans in 32 patients



RCI=right common iliac, LCI=Left common iliac, RIII=Right internal iliac, LII=Left internal iliac, REI=Right external iliac, LEI=left internal iliac, PS=pre-sacral, RO=Right obturator, LO=Left obturator, PR=Peri-rectal, RING=Right inguinal

3.4.3 PLN Coverage using PIVOTAL contouring instructions

Table 17 shows the results of the nodal mapping for each of the 30 patients. In total I was able to map out 83 Ch-PET positive nodes in 30 patients. 2 patients were excluded due to poor fusion between the planning scan and PET CT.

For each patient, the total number of nodes is recorded as well as their location. Each node is assigned a colour on the table to describe how well the node has been covered by the PLN target volumes. Nodes coloured light and dark green are well covered whereas nodes coloured red or orange are partially covered or uncovered by the target volumes.

The table shows that 100% of nodes in the external iliac and obturator regions are covered by the contours and 94% of the nodes in the internal iliac region. In total forty-two nodes were fully covered by the CTV and PTV (score 1) and 13 nodes were partially covered by the CTV and fully covered by the PTV (score 2). Therefore, a total of 55 nodes (66%) were adequately covered using the PIVOTAL PLN contouring guidelines. Figure 14 shows some examples of nodes that were well covered by the CTV and PTV. In contrast, the 28 poorly covered nodes were all concentrated in locations; firstly, the common iliac area, where only 10% of nodes were covered, then the pre-sacral, peri-rectal and inguinal regions. Ten nodes were in some part covered by the CTV and PTV (score 4) and 18 nodes were completely uncovered by the CTV and PTV (score 5).

Table 17. Nodes mapped at each nodal station per patient

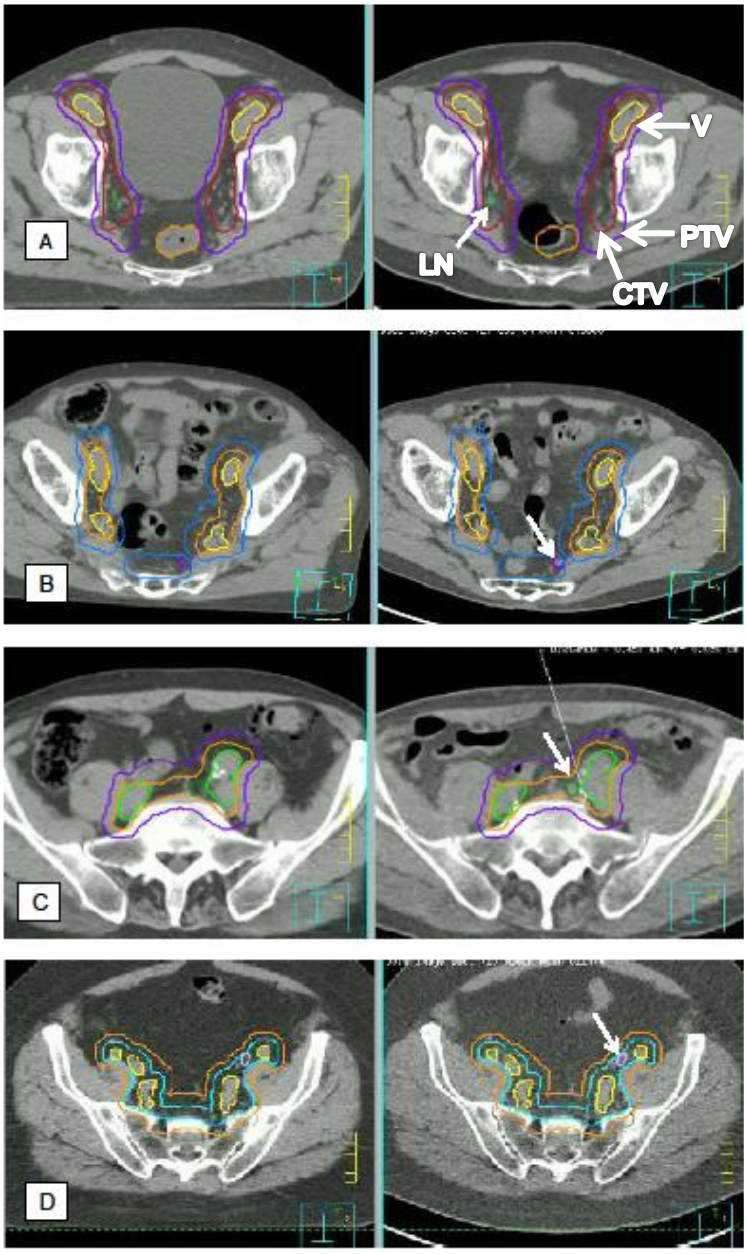
Patient No	Total no of nodes	Nodal Stations										
		LCI	RCI	LEI	REI	LII	RII	LO	RO	PS	PR	R.Ing
1	3									1		
2	1											
3	3											
4	1											
5	3											
6	4									1 2		
7	1											
8	1											
9	4		L4									
10	1											
11	1									3		
12	2											
13	1											
14	7	L4 L5	L4									
15	9	L4 L4	L5 L5 L5									
16	2											
17	5		L5									
18	1		L5									
19	1											
20	1											
21	8	L5	L5 L4/5									
22	2	L5	L5									
23	3	L4/5	L5									
24	1											
25	1											
26	2											
27	3			5								
28	2											
29	4	L5/S1								4		
30	5											
nodes mapped on planning scan	83	9	12	8	10	4	4	12	11	9	3	1
nodes seen on Choline PET	92	10	14	8	11	5	4	13	13	9	3	2
nodes covered by PIVOTAL (%)	55/83 (66%)	2/21 (10%)		17/18 (94%)		8/8 (100%)		23/23 (100%)		5/9 (56%)	1/3 (33%)	0/1 (0%)

1	Node fully covered by CTV+PTV
2	Node partly covered by CTV and fully covered by PTV
3	Node outside CTV but covered by fully by PTV
4	Node outside/partly covered by CTV and partly covered by PTV
5	Node outside of CTV+PTV

L4, mid L4/5, L5 and L5/S1 describes the top vertebral level of the uncovered common iliac nodes. Nodes labelled 1-5 were within the radiation field but not covered by the PTV; 1=PS node anterior to PTV, 2=PS node below PTV (S4), 3=PS node medial to PTV, 4=PS node below PTV (S5), 5=LEI node below PTV

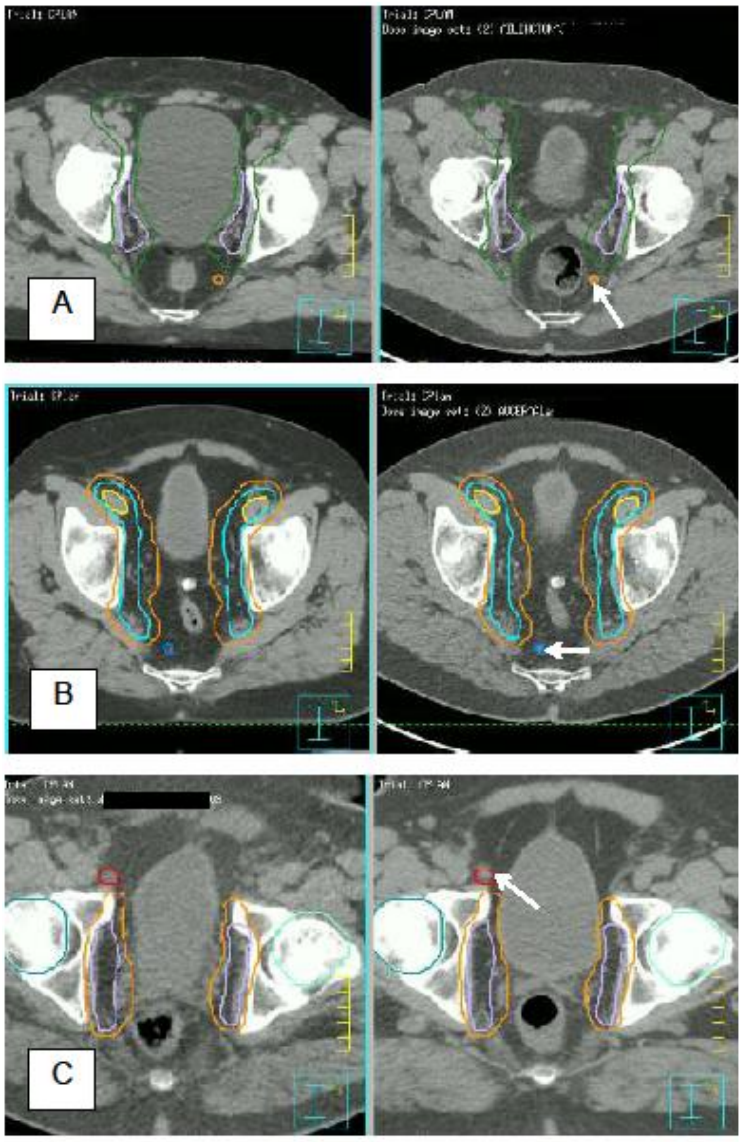
Figure 14. Planning CT scans (left) and corresponding Choline PET scans (right) showing examples of nodes covered by radiation contours.

A. obturator node, B. pre-sacral node, C. common iliac node, D. external iliac node



Arrows point to nodes outlined on Ch-PET CT scans (LN), Yellow/green outlined structures are vessels (labelled V) and surrounded by outlines of the CTV and PTV.

Figure 15. Choline PET and corresponding planning CT scans showing nodes uncovered by radiation contours. A. peri-rectal node B. Pre-sacral node and C. right inguinal node. Arrows indicate position of LN.



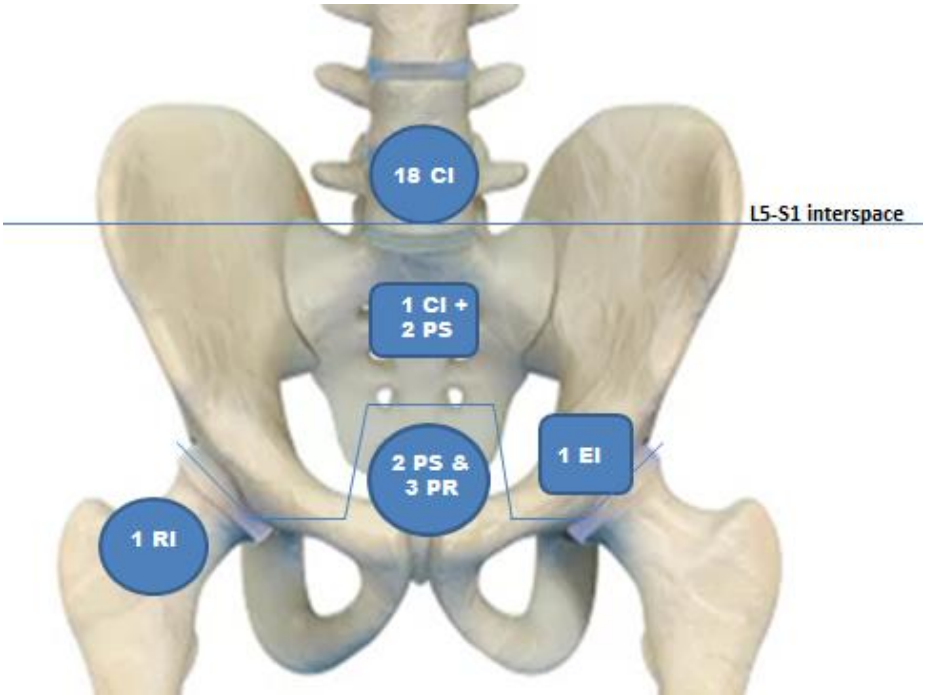
3.4.4 Where did coverage fail?

There were 28 uncovered nodes in total shown in Figure 16. The blue lines on the figure mark the superior and inferior boundaries of the radiation field. 24/28 (86%) of the uncovered nodes (in red) were outside of the pelvic radiation field and the standard nodal areas that the contouring guidelines aim to cover.

The nodes that were not covered by the PIVOTAL contours were in the common iliac (19 nodes), pre-sacral (4 nodes), peri-rectal (3 nodes), inguinal (1 node) and external iliac regions (1 node).

Figure 16. Demonstrates the distribution of positive pelvic lymph nodes not covered by the radiation contours.

The CI=common iliac, PR=peri-rectal, PS=Pre-sacral and RI=Right inguinal lay outside the radiation field in areas that the contours do not aim to cover. The remaining CI, PS and EI=external iliac nodes lay inside the radiation field in areas the contours aim to cover.



A single inguinal node and three peri-rectal nodes were mapped that lay outside of the radiation field. These nodal groups are not traditionally included in the pelvic nodal target volume; inguinal nodes are not the local draining nodes for prostate cancer and peri-rectal nodes are less commonly involved.

The single node in the left external iliac region that was not covered lay just below the top of the femoral heads. This is the landmark at which the contour stops and it usually marks the transition from external iliac to deep inguinal node territory. The node in question was reviewed by the radiologists involved to double check it had been allocated to the correct territory.

Of the 9 pre-sacral nodes mapped, 4 were not covered by the PIVOTAL contours. Two were missed as they lay anterior to the CTV and PTV and the remaining 2 were lower than the S3/4 junction which is the bottom of the pre-sacral CTV.

21 common iliac nodes were mapped in 11 patients. Only two nodes were covered by the PIVOTAL contours. Of the 19 nodes that were not covered, one node was at the level of L5/S1 and was poorly covered as it lay anterior to the vascular margin used to create the CTV. The remaining 18 common iliac nodes were above the lower border of L5 and therefore were above the top border of the CTV.

In summary, 86% (24/28) uncovered nodes lay in areas that are not included in the PIVOTAL contours. These were 18 common iliac nodes above the top border, 2 low pre-sacral nodes, 3 peri-rectal nodes and 1 inguinal node. 71% (59/83) of the nodes identified lay within the pelvic areas that are targeted by the PIVOTAL contours and 93% (55/59) were adequately covered by the contours. The remaining 4 uncovered nodes were marginal misses in the common iliac (1), external iliac (1) and pre-sacral areas (2). Importantly, none of these nodes were uncovered because the CTV had been edited off bowel or the BEV.

3.5 Considering modifications to the contouring guidelines.

The results showed that the two lymph node groups where the PIVOTAL contours most poorly covered nodes were (a) the common iliacs (18 uncovered) and (b) the pre-sacral nodes (4 uncovered). Therefore, both these areas were examined in detail to consider if any modifications of the guidelines would have led to improved coverage.

3.5.1 Pre-Sacral LN coverage Modifications

The pre sacral PLN CTV contours are created by applying a 12mm wide strip along the bony sacrum. This is edited off any muscle and the BEV. A further 5mm expansion creates the PTV.

3.5.2 Widening the pre-sacral strip CTV

We first considered the 2 cases where nodes lay anterior to the sacral CTV and PTV. In both cases the combined CTV+PTV contour of 17mm was unedited as bowel was not in close proximity. However, both nodes still lay anterior to the PTV. The original RMH contouring guidelines had a 15mm strip along the sacrum

and one obvious modification may be to increase the sacral strip width again. These two nodes would not have been encompassed by either a 15mm (CTV) or 20mm (PTV) strip. The other issue to consider is whether a larger sacral strip can even be applied if there is nearby bowel. I reviewed the 32 cases planned in this study; In 18 cases, the bowel itself was encroaching on the 12mm CTV strip at least in one location, resulting in the strip being edited back. In a further 4 cases the BEV was encroaching on the strip, also reducing the size of the CTV. Therefore 22/32 (69%) cases did not have a full 12mm strip CTV all the way along the sacrum. This suggests that even if the pre-sacral strip was widened, this would not result in a uniformly larger volume along the sacrum.

It is not known what effect the proximity of bowel has on the location of sacral nodes. Several studies have shown that bowel moves considerably throughout the course of radiotherapy, and only 20% of bowel occupies the same position throughout a course of radiotherapy (21, 22). One assumption is that bowel pushes nodal tissue posteriorly towards the bony sacrum. Therefore, a narrower CTV strip should still encompass any potential pre-sacral nodes. However, it is not known whether the anatomical position of nodal tissue is affected by the movement of bowel away from the bony pelvis. For example, if bowel anterior to the sacrum were to move away, would this result in the pre-sacral nodal tissue expanding into the unoccupied space? If this were the case, a narrow CTV might not cover the nodal disease. In the 4 patients that had positive pre-sacral nodes in this study, there were no particular discrepancies between the pre-sacral bowel pattern in the Ch-PET CT scan and planning scan.

Our results are similar to those of previous imaging studies where a wider strip was needed to cover the pre-sacral nodes than in other parts of the pelvis. For example, Vilarino-Varela et al (23) found that a 15mm margin around vessels failed to encompass more than 3 of the 7 sacral nodes seen in her study. Overall, the number of sacral nodes identified in all studies (7, 8, 24, 25) (including ours) tends to be low compared to at other sites. This makes drawing any conclusions about coverage difficult, however it may be that along the sacrum, nodes are spread over a wider distance, making uniform coverage difficult with a standard strip size. As this is a less commonly involved pelvic nodal site, poorer coverage may have a smaller clinical impact. Certainly, there were very few pre-sacral

lymph node recurrences seen in the pelvic IMRT trial cohort reported in chapter 2.

3.5.3 Extending the pre-sacral CTV caudally.

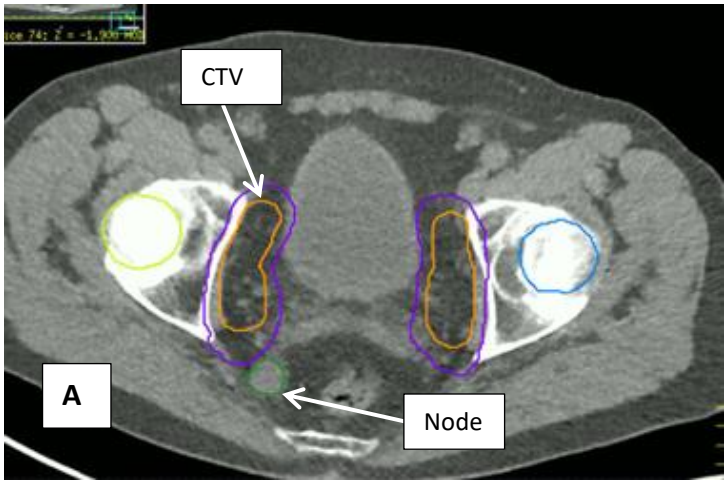
The remaining two pre-sacral nodes that were not covered by the pivotal CTV were below it at the level of S4 and S5. The main disadvantage of extending the pre-sacral strip inferiorly to cover beyond the S3/4 junction is the impact this would have on rectal dose. Isolated coverage of any nodes detected below S3/S4 would require a small CTV modification and therefore only impact on rectal dose over a small volume. An example is shown in figure 18 where a pre-sacral node at the level of S4 lies outside the standard CTV and PTV shown in Panel A. If a prophylactic volume was applied to the area in order to cover any potential low pre-sacral nodes, this would surround the rectum by more than 180 degrees – this potential CTV is shown on Panel B of Figure 17. It shows the rectum in very close proximity and even adjacent to the CTV. Given the established relationship between the volume and distribution of rectum treated and resulting GI toxicity (26), this modification of the standard pelvic radiation field would be likely to increase the risk of rectal toxicity for the additional coverage of a small number of extra nodes. Panel C shows a CTV modified over a small area in order to cover the identified node. This would also impact on the rectal dose, but over much smaller volume.

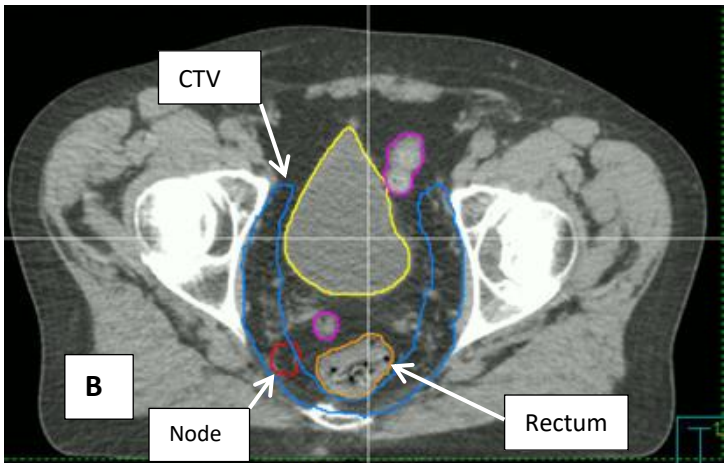
In summary, given the low number of pre-sacral nodes identified, expanding the target volumes anteriorly or inferiorly would at best have only a small benefit in overall pelvic nodal disease control. This benefit would also be at the expense of a potentially clinically significant increase in rectal and bowel radiation dose.

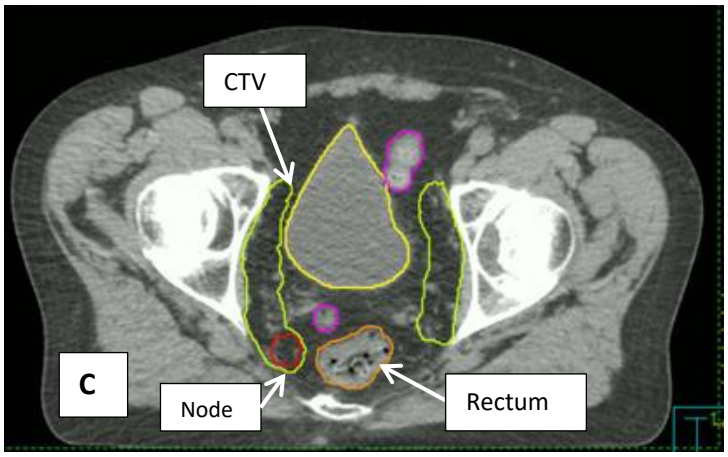
Figure 17. Potential methods for covering low sacral nodes.

Picture A shows the pre hormone therapy Choline PET CT for a patient with a pre-sacral node that lies outside the CTV and PTV. Picture B shows the corresponding planning CT scan after hormone therapy, with a modified CTV that extends posteriorly to cover the whole pre-sacral

space. Picture C shows the planning CT scan with the CTV modified posteriorly only to cover the pre-sacral node.







3.5.4 Common iliac LN Coverage Modifications

The common iliac (CI) lymph nodes accounted for 26% (24/92) of the nodes identified on Ch-PET. These nodes are located below the bifurcation of the aorta into the left and right common iliac arteries. The aortic bifurcation does not occur at a set anatomical landmark; in a third of the population it occurs at the level of the L5 vertebra and in the remaining two thirds, it occurs at the level of the L4 vertebra.

Our study found the coverage of these nodes to be poor, with 90% (19/21) of nodes in this area lying outside the PTV. Therefore, any modifications to improve nodal coverage of this area would potentially have a significant impact on the efficacy of PLN IMRT. The majority of uncovered CI nodes lay above the top border of the PIVOTAL contour which is at the L5-S1 vertebral level. The most reliable method of capturing all the nodes in this group would be to commence the CTV at the aortic bifurcation rather than L5-S1. This would mean the bifurcation itself would have to be identified on the planning CT scan rather than a bony landmark. The PLN IMRT guidelines for cervical cancer by Taylor et al recommend this approach to covering the CI nodes and in a validation study of the guidelines, the method resulted in coverage of 99% of the pelvic nodes seen using MRL (23).

Alternatively, the top border could be raised to a new vertebral level. In our study, 11 nodes were anterior to the L5 vertebral body, 5 were anterior to L4 and the last 2 were at anterior to the L5-L4 interspace. Therefore raising the superior border to the top of the L4/5 space would have covered an additional 13/19 common iliac nodes, improving the overall nodal coverage of the contours to 84% (70/83).

3.5.5 Impact of extending the radiation field on organs at risk

Raising the top border of the pelvic CTV would be likely to result in an increase in the volume of bowel irradiated. The bladder and rectum are largely below the sacral promontory and therefore are less likely to be affected.

Eight of the 9 patients with common iliac nodes had received radiotherapy with modified pelvic fields to cover the Ch-PET positive nodes that lay above L5/S1. For each of the 8 patients I created new PLN contours based on the PIVOTAL contours. These were compared to the extended field plans in order to quantify the additional impact on bowel for each patient. Bowel was outlined up to 2cm above the extended PLN CTV and a separate bowel contour was created which ended 2cm above the top of the PIVOTAL PTV. The top of the extended CTV reached the top of L4 for 5 patients and the top of L5 for 4 patients. All patients were treated with IMRT and received 74Gy in 37# over 7.5 weeks to the prostate and seminal vesicles. Patient 22 also received a simultaneous integrated boost to the dominant intra-prostatic lesion of 82Gy in 37#. The radiation dose to the pelvic lymph nodes was at the discretion of the clinician; 6 patients were treated with 55Gy in 37# and the remaining two were treated with 60Gy in 37#. All patients received an additional simultaneous integrated dose boost of 5Gy to the choline pet positive nodes. The pinnacle planning software was used to provide dose volume information for both the extended and standard plans. This is displayed in Table 18 The volume of bowel receiving 40-65Gy is reported in 5Gy intervals and any volumes breaching the mandatory constraints are recorded in red. No mandatory constraints are used below 45Gy and the volume of bowel receiving 10-40Gy in 10Gy intervals has been reported. At each dose level the difference in bowel volume between the PIVOTAL and extended pelvic field plan is recorded.

Table 18. Bowel volumes and treatment doses for all 8 patients who underwent extended pelvic field radiotherapy to cover common iliac lymphadenopathy above L5/S1

	Patient 16			Patient 9			Patient 23		
Top of extended CTV	L4			L4			L4		
PLN dose	55Gy/37#			55Gy/37#			55Gy/37#		
PLN Boost	60Gy/37#			60Gy/37#			60Gy/37#		
Pelvic CTV	Extended	Pivotal	Difference in bowel volume	Extended	Pivotal	Difference in bowel volume	Extended	Pivotal	Difference in bowel volume
Bowel volume (cc)	1427	458.9	968.1	870.8	448.7	422.1	1041.7	604.2	437.5
V65	0	0	0	0	0	0	0	0	0
V60	0	0	0	2.2	2.2	0	0.6	0.6	0
V55	11.7	6.5	5.2	11.3	11.3	0	23.7	19.1	4.6
V50	57.2	41.5	15.7	42	38.7	3.3	83.8	72.9	10.9
V45	94.5	66.9	27.6	81.4	69.2	12.2	144.8	124.4	20.4
V40	124.4	83	41.4	131.9	108.7	23.2	220.5	188.9	31.6
V30	283.1	141.9	141.2	253.7	200.7	53	464.6	407.5	57.1
V20	638.2	289	349.2	536.6	400.2	136.4	694	565.9	128.1
V10	998.3	413.2	585.1	637.9	425.3	212.6	799.2	585.5	213.7
	Patient 14			Patient 21			Patient 22		
Top of extended CTV	L4			L4			L5		
PLN dose	55Gy/37#			55Gy/37#			60Gy/37#		
PLN Boost	60Gy/37#			60Gy/37#			65Gy/37#		
Pelvic CTV	Extended	Pivotal	Difference in bowel volume	Extended	Pivotal	Difference in bowel volume	Extended	Pivotal	Difference in bowel volume
Bowel volume (cc)	1906.3	954.8	951.5	653.5	336.5	317	708.4	186.5	521.9
V65	0	0	0	0	0	0	0	0	0
V60	0	0	0	0	0	0	0.7	0.1	0.6
V55	16.9	15.9	1	4.9	4.8	0.1	10.5	7	3.5
V50	85	79.4	5.6	73.7	62.6	11.1	28.7	20.3	8.4
V45	131.1	123	8.1	146.6	123	23.6	56.1	38.1	18
V40	221.9	205.6	16.3	195	163.3	31.7	83.5	49.6	33.9
V30	535	417.3	117.7	300.7	236.7	64	231.6	134.8	96.8
V20	996.7	723.2	273.5	391	270.4	120.6	318.1	163.9	154.2
V10	1165	795.9	369.1	495.6	300.2	195.4	427.6	175.3	252.3

	Patient 18			Patient 29		
Top of extended CTV	L5			L5		
PLN dose	55Gy/37#			50Gy/37#		
PLN Boost	60Gy/37#			65Gy/37#		
Pelvic CTV	Extended	Pivotal	Difference in bowel volume	Extended	Pivotal	Difference in bowel volume
Bowel volume (cc)	687.1	557	130.1	792	638.8	153.2
V65	0	0	0	0	0	0
V60	0	0	0	0.3	0.3	0
V55	5.5	5.5	0	14.6	13.9	0.7
V50	67.1	66.8	0.3	95	90.3	4.7
V45	116.2	115.1	1.1	158	151.5	6.5
V40	231.6	229.4	2.2	279.2	273.1	6.1
V30	393.9	389.9	4	609.8	586	23.8
V20	481.5	474.5	7	691.2	638.7	52.5
V10	557.8	518	39.8	746.8	638	108.8

Patients 16, 9, 23, 14 and 21 had the field extended to the top of L4. Patients 22, 18 and 29 had the field extended to the top of L5. Values in red breached the optimal bowel constraints. The total bowel volume for each plan was defined as the volume of bowel present between the bottom of the pelvis and 2cm above the top of the PTV.

Table 19. Optimal and mandatory dose constraints for bowel

Bowel Volume	Optimal constraint	Mandatory constraint	No of cases breaching mandatory constraints	Extended plans that breached optimal constraints	Pivotal plans that breached optimal constraints
V65	0cc	0cc	0/8	0/8	0/8
V60	0.5cc	6cc	0/8	3/8	2/8
V55	14cc	28cc	0/8	3/8	3/8
V50	17cc	110cc	0/8	8/8	8/8
V45	78cc	158cc	0/8	7/8	5/8

The mandatory constraints were achieved in all 8 cases for both the extended and standard Pivotal contours. However, in clinical practice, if the mandatory constraints had not been achieved the prescribed dose to the PLN would be

decreased from 60Gy to 55Gy or treatment to the PLN would be abandoned for safety reasons. The optimal constraints were breached for several dose volumes as described in table 19.

Table 20 summarises the increase in bowel treated at each dose level between the two plans for each of the 8 patients. Five plans were extended up to the L4 vertebral level. The resulting mean increase in total bowel volume irradiated was 619.24cc and the median was 437.5cc (ranging from 130 to 521cc). The 3 volumes extended to L5 also resulted in a greater volume of bowel being treated compared to the standard plans, with a mean increase in bowel of 268.4cc. The median increase was 153.2cc (range 130.1 to 521.9cc).

The volume of bowel that received between 65 and 45Gy was similar for both plans, with less than 10cc difference. However, below 40Gy the difference in bowel volume between the two plans increased as the dose decreased.

Table 20. Displays the increase in bowel treated at each dose level, in total and the mean increase for all 8 patients with extended pelvic radiotherapy plans compared to standard pelvic radiotherapy plans

Increase in bowel volume treated between extended and pivotal contour	Patients treated up to L4					Mean change in dose volume (cc)
	Patient 9	Patient 14	Patient 16	Patient 21	Patient 23	
V65	0	0	0	0	0	0
V60	0	0	0	0	0	0
V55	0	1	5.2	0.1	4.6	2.18
V50	3.3	5.6	15.7	11.1	10.9	9.32
V45	12.2	8.1	27.6	23.6	20.4	18.38
V40	23.2	16.3	41.4	31.7	31.6	28.84
V30	53	117.7	141.2	64	57.1	86.6
V20	136.4	273.5	349.2	120.6	128.1	201.56
V10	212.6	369.1	585.1	195.4	213.7	315.18
Total increase in bowel volume outlined (cc)	422.1	951.5	968.1	317	437.5	619.24

Increase in bowel volume treated between extended and pivotal contour	Patients treated up to L5			Mean change in dose volume (cc)
	Patient 18	Patient 22	Patient 29	
V65	0	0	0	0
V60	0	0.6	0	0.2
V55	0	3.5	0.7	1.4
V50	0.3	8.4	4.7	4.47
V45	1.1	18	6.5	8.53
V40	2.2	33.9	6.1	14.07
V30	4	96.8	23.8	41.53
V20	7	154.2	52.5	71.23
V10	39.8	252.3	108.8	133.63
Total increase in bowel volume outlined (cc)	130.1	521.9	153.2	268.4

Overall, there are two clear findings from these results. Firstly, the results suggest that the main dosimetric effect of extending the CTV upwards to cover the higher common iliac nodes will be an increase in the overall volume of bowel being treated at lower doses (<40Gy) of radiation. This is likely to be a consequence of the change in the CTV contour. Low down in the pelvis the CTV surrounds the pelvis contents in a “C” shape and the bowel volume lies in the centre and anterior to it. Therefore, the bowel is in much closer proximity to the CTV and this is reflected in the higher V45-V60. Above the sacral promontory the PLN CTV reduces in size and lies directly in front of the vertebral column. The bowel tends to lie more anterior and lateral to the CTV. This change in CTV shape and the increased distance between the CTV and bowel means that less bowel is exposed to the higher doses of radiation.

The second interesting finding is that there was no predictable relationship between the volume of bowel in the pelvis and how much extra bowel was irradiated by extending the volume. In some cases only around 150cc of extra bowel was treated, and in others was up to 1000cc. This reflects the differences in bowel distribution that are naturally found between patients.

3.6 Discussion

The success of elective pelvic nodal irradiation depends upon accurate target definition to cover all areas at high risk of harbouring microscopic nodal disease. Maximising coverage needs to be balanced with dose to organs at risk and potential toxicity.

In this study I aimed to assess the PLN coverage provided by PIVOTAL based contouring guidelines using Choline-PET CT scans to identify small volume PLN metastases in patients with untreated high risk prostate cancer. I identified 92 involved pelvic lymph nodes in 32 patients. 85% of the nodes were between 5 -10mm in size and the most commonly involved lymph node groups were the obturator (53% of patients), common iliac (34%), internal iliacs (25%) and external iliacs (34%). Less commonly involved areas were the peri-rectal, pre-sacral and inguinal regions. These findings are in keeping with those seen in previous imaging studies (2, 3, 8, 24).

83 of these Choline PET positive lymph nodes were mapped out of in relation to PIVOTAL based PLN radiotherapy contours to assess coverage. We had estimated that 70% of the nodes would adequately covered by the contours. Our findings were that 66% of the nodes were covered by the contours.

3.6.1.1 Considering areas of poor coverage

3.6.1.2 Within the radiation field

When examining the areas of poor coverage, we found that only 14% (4/28) of these nodes were in groups that the contours aim to cover. Further examination revealed unique reasons for each of the nodes to lie outside the PTV. Crucially, the BEV technique did not appear to have a negative impact on PLN coverage. The low number of nodes identified, coupled with the unpredictable nature of their location in the field meant that no uniform modification would improve coverage. Ideally the CTV would only be modified if and when these unusually located nodes were felt to be

involved. Therefore, in high risk patients in whom elective PLN RT is being planned, accurate nodal staging with novel imaging modalities is crucial.

3.6.1.3 Outside the radiation field

The majority (86%, 24/28) of the uncovered nodes lay in nodal groups that the PIVOTAL guidelines do not aim to cover. The common iliac nodes above the L5/S1 border accounted for 64% (18/28) of uncovered nodes and the remaining were in the low pre-sacral, peri-rectal and inguinal groups.

When examining the common iliac nodes, 11 lay anterior to the L5 vertebral body, 2 anterior to the L4/L5 junction and 5 lay anterior to L4. Modifications to increase the top border to the L4/L5 junction would have covered an additional 13/18 common iliac nodes. However, raising the border to the bifurcation would have covered 100% of the nodes identified. One option would be to raise the upper border of the PIVOTAL CTV to the aortic bifurcation in order to encompass these nodes. Several other recent publications have also suggested this modification as a result of evaluating pelvic nodal relapses. In a study by Lepinoy et al 83 patients with biochemical failure post RT underwent choline pet scans. 42 Ch-PET positive nodes were identified in 33 patients. 20 (47%) of nodes were outside the RTOG PLN CTV (6 PCI, 2 peri-rectal, 2 peri-vesical, 2 inguinal, 6PA, 2 mediastinal). They recommended extending the upper border of the CTV to L2/L3 as this would have cover 95% of the occult nodal relapses (25). In another retrospective analysis of 2694 patients treated with prostate and SV RT alone, 60 patients had PLN relapse alone diagnosed on imaging. 33(55%) of these patients had PLN relapse involving the common iliacs. This included 6 (10%) of patients who had isolated common iliac failures. The authors recommended extending the superior coverage to L4/5 in order to capture these nodes. The current RTOG 0924 trial is evaluating the benefit of PLN RT with extended superior coverage to L4/5 and will provide important information about the clinical impact of this modification (27).

3.6.2 Do all patients need the same pelvic field?

In this study, 24 common iliac nodes were identified on ch-PET in 11 patients. Of these 11 patients, only 2 had isolated common iliac nodes without lower pelvic nodes identified on choline PET. This raises the question of whether it would be reasonable to only extend the field upwards in cases where lower pelvic nodes were identified as the likelihood of common iliac disease in the absence of lower pelvic nodes in our study is low. The common iliac nodes are not part of the primary drainage sites for the prostate which includes the internal and external iliac, the obturator and pre-sacral nodes (28, 29). This supports the hypothesis that nodal involvement at a secondary drainage site such as the common iliacs may be less likely without primary areas being involved. One surgical series has shown that in the absence of common iliac involvement on ePLND, retroperitoneal nodes were not found on RPLND (30). They also found that all the patients with retroperitoneal nodes also had positive lower pelvic nodes suggesting that skip lesions are uncommon and there is a clear path of spread from the pelvis up to the retroperitoneum in a sequential fashion.

To test this theory, I further examined the lower pelvic nodes in the 9/11 patients with common iliac nodes above L5/S1. Of these 9 patients, 4 had lower pelvic nodes that were categorised as 4B (11-≤20mm) or 4C (≥21mm) and therefore would have been picked up on CT or MRI imaging based on size criteria. In the remaining 5 patients, one had common iliac disease alone and the other 4 had lower pelvic nodes that were all classed as 4A (5-≤10mm) and would have not been found positive on CT or MRI. Therefore in our study only 4/9 patients had lower pelvic nodes that would have been detectable on CT/MRI and a policy of only extending the pelvic field in these patients would have missed upper common iliac lymph node involvement in 5/9 (56%) of the patients with this pattern of disease. To my knowledge there is no other information in the literature which has assessed the implication of PET CT scans and upper common iliac involvement in the absence of lower pelvic lymph node disease.

3.6.3 Impact of extended field PLN RT

It is well established in the context of conventional field and 3D-conformal RT that radiation toxicity is directly related to the volume of bowel treated (31). While there

have been no published randomised controlled trials, there have been several small studies comparing the toxicity between standard and extended pelvic radiation fields. These studies have reported an increase in GI toxicity with an increase in field length. Mak et al (32) published a study of 224 rectal cancer patients treated with 54Gy in 1.8-2Gy per fraction to a standard rectal field (up to the sacral promontory) or an extended field up to L1-2 using conventional fields. The rate of small bowel obstruction was 30% vs 9% ($p<0.008$) in patients with extended fields and standard fields respectively. However there was also a positive correlation between the risk of obstruction and post-surgical adhesions pre-radiotherapy ($p<0.05$). In a study by Lerschert et al (33), 111 post-operative rectal carcinoma patients received treatment with pelvic or pelvic and para-aortic field radiation at a dose 45-50Gy over 5 weeks. Patients were treated with a combination of ant-post or three radiation fields. They reported that the incidence of late GI toxicity was related to the volume of bowel within the treatment field. The lowest risk group (three-field pelvic RT, estimated 165 cc of small bowel) had a 6% incidence of severe late GI toxicity, whereas the highest risk group (opposed anterior and posterior treatment fields, estimated 790 cc) had a 37% risk ($p<0.05$).

However, these studies have been conducted in patients who have had surgery and received chemotherapy, both of which can increase pelvic radiation related toxicity. The treatment has also been delivered with four fields or 3D conformal RT which would have resulted in significantly more bowel receiving high doses than could be achieved with IMRT (34, 35) Therefore in the high risk prostate cancer patient cohort treated with IMRT, the expected increment in toxicity would be smaller.

The published data describing the toxicity from extended pelvic IMRT is even further limited to small retrospective case series. Lee et al (36) published a retrospective study of 76 cervical patients using extended field using IMRT to the renal vessels. The dose to the pelvis was 50.4Gy in 28 fractions, with a boost to positive nodes of 59.4Gy. All patients received weekly cisplatin and intra-cavitary brachytherapy. The CTCAE version 3.0 acute grade 3 and 4 GI toxicity was 2.6% and 0% respectively. The late grade 3 and 4 GI toxicities were 4% and 0% respectively. Another retrospective study by Ouyang et al (37) in 107 patients with cervical cancer treated with chemo-radiation using IMRT and HDR BT in a single centre. The pelvis was treated to a dose of 45Gy in 1.8Gy per fraction and intra-cavitary brachytherapy at a dose of 35Gy in 6 fractions

to the periphery of the high risk CTV. In the 55 patients with para-aortic nodal involvement, the pelvic volume was extended up to the superior border of L1 and all positive nodes were treated with a concomitant boost of 60Gy in 2.4Gy per fraction. There were no RTOG grade 4 toxicities in either group. The rate of grade 3 upper and lower GI toxicity was 3.6 and 5.5% in the extended field group and 0% and 3.8% in the standard pelvic field. Although there was a significant increase in the overall acute toxicity in the extended field cohort, the greatest difference was an increase in the haematological toxicity, presumably due to the increase in bone marrow irradiation. Ultimately, prospectively gathered toxicity data is needed to understand the long term impact of irradiating an extended field in this patient group.

3.6.3.1 Recommendations

There are two potential changes that could be made to the standard pelvic radiation field.

The first option would be to continue using conventional imaging to stage the pelvic nodes and extend the standard pelvic field upwards to the aortic bifurcation in order to better cover the common iliac nodes in all patients who are having PLN IMRT. This blanket modification would undoubtedly expose a larger volume of bowel to radiation doses of under 40Gy and the volume would vary from patient to patient. Until the benefit of pelvic radiotherapy is proven and safety data is available to support this extension of the pelvic field it would be important to consider methods for keeping the risk of toxicity as low as possible. For example treating to a lower radiation dose that 60Gy in 37 fractions (EQD2 of 53.5-55.5Gy if α/β for prostate is 1.5-3Gy). The alternatives could be 55Gy in 37 fractions (EQD2 of 47-49.5Gy if α/β for prostate is 1.5-3Gy). Existing dose constraints should be strictly adhered to and dose constraints to the lower dose levels below 40Gy could also be considered.

Alternatively, if Choline PET CT or a more sensitive imaging technique such as PMSA PET were used to stage all patients, a standard pelvic volume could be used. Unless pelvic lymph nodes were identified in which case bespoke modifications could be made to the CTV where required and dose boosts to the positive nodes considered. There would be several advantages to this approach. Firstly patients would be spared

the potential increase in toxicity that any CTV modifications might result in unless they had nodal disease that required treating. Secondly, a more sensitive nodal staging technique ought to improve the efficacy of pelvic radiotherapy in controlling disease by identifying nodes outside the standard pelvic field that might otherwise be missed.

3.6.4 Limitations of this work

The main limitation of this work is that the nodal detection was based on choline PET CT results. It may be that with more sensitive imaging techniques such as PMSA PET or MRL, more nodal disease would have been detected. However, there is no evidence to suggest that the overall distribution of positive nodes would change. The process of fusion between the Ch-PET scan and the planning scan fusion introduces a margin of error which may affect the accuracy of the results but every effort was made to refine the fusion at the site of evaluation and exclude poorly fused cases.

3.6.5 Future directions

At present the role of elective pelvic radiation in high risk node negative patients remains unproven. While there is safety data available for the use of pelvic IMRT, the ideal dose and pelvic field to use also remain uncertain. Therefore, I think the development of a validated highly sensitive and specific imaging technique to identify nodal disease in patients will be the most key step in the advancement of pelvic radiation. The accurate detection of nodal disease will allow for the appropriate adaptation of target volumes and reduce any geographical miss of nodes in unusual locations. Dose boost to positive nodes can then also be explored. As standard pelvic volumes will only be adapted if the need arises, patients will be spared any potential increase in toxicity unless there is a clear advantage in disease control.

3.7

3.8 Conclusions

In conclusion we have found that the PIVOTAL PLN contours adequately covered 66% of Choline PET CT identified pelvic lymph nodes. Common iliac nodes lying above the L5-S1 junction accounted for 64% of the uncovered nodes and the BEV technique did not account for any of the geographical misses. Increasing the top border of the standard pelvic field would improve coverage of the common iliac nodes but potentially increase bowel toxicity. As the use of pelvic radiotherapy is controversial and remains of unproven benefit, at present there is a strong rationale for recommending that instead only bespoke modifications to the CTV are made, based on nodal disease identified on sensitive imaging. This might identify which patients would clearly benefit from a larger pelvic field and justify any potential additional toxicity. Further work is needed to improve the accuracy of nodal detection on imaging and to understand the implications of increased low dose irradiation to large volumes of bowel in extended pelvic IMRT.

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Chapter 4 Investigating the bowel dose volume relationship in patients treated within the PIVOTAL trial

The PIVOTAL trial was designed, recruited and analysed by the ICR Clinical Trials and Statistics Unit (CTSU) with Prof. Dearnaley the Chief Investigator. Any toxicity data used in this chapter is reproduced with permission. All radiation dose volume interpretation was my own work with methodology support from Sarah Gulliford, staff scientist ICR. Douglas Brand – clinical fellow, ICR provided assistance with AUC calculation.

4.1 Introduction

Pelvic radiation is used for the treatment of rectal, anal canal, cervical, endometrial, bladder and prostate cancers. Therefore, the available data on pelvic radiation toxicity comes from a diverse patient population who have been treated with differing dose fractionation schedules, treatment volumes and with or without the addition of chemotherapy or prior surgery. These treatment differences can complicate the interpretation of any published toxicity data as several other factors can contribute to toxicity beyond the radiation treatment.

4.1.1 Risk factors for pelvic radiation toxicity

Concurrent chemotherapy with pelvic radiation is the standard of care in rectal, cervical and anal cancer and in several studies has been identified as a risk factor for increasing toxicity (1, 2). Pelvic surgery has also been identified as a key risk factor for pelvic radiation related toxicity. Gallagher et al (3) first described increased rates of bowel obstruction in patients who had had pelvic surgery, in particular a low abdomino-perineal resection. This resulted in an increased volume of bowel in the pelvic field and also less bowel motility – presumably due to post-surgical adhesions. There are also a host of patient related factors such as obesity, Diabetes Mellitus, cardiovascular disease, inflammatory bowel disease, smoking, medications, age over 75, abdomino-pelvic surgery and genetic predispositions to radiation sensitivity that have been identified as risk factors for increased toxicity from pelvic radiation (40).

4.1.2 Radiation Dose Volume relationship with bowel toxicity

Gallagher et al (3) first described the relationship between radiation and bowel toxicity in 150 patients undergoing pelvic radiotherapy for a variety of different cancers including rectal, colon, endometrial, cervical, ovarian and prostate cancer. Treatment was delivered to a wide range of field sizes and doses but only patients treated with a daily fraction size of 2Gy or less were included in the toxicity analysis. 50% of the patients had had prior surgery and in particular 25% had undergone an abdominoperineal resection. The severity of acute gastrointestinal side effects correlated with the volume of irradiated small bowel. They also found that late GI toxicity correlated with the volume of bowel receiving more than 45Gy and the total radiation dose. As mentioned above, one of the key risk factors for severe late toxicity was prior surgery, after which there was both increased bowel in the pelvis and decreased bowel mobility. The study also demonstrated that bladder distention and lower abdominal compression in the prone position could reduce the amount of bowel in the radiation field. This study formed the basis of the recommendations by Emami in 1991 (4). The estimated TD5/5 (total dose resulting in 5% risk of toxicity at 5 years) for 1/3 of small bowel irradiation at conventional fractionation was reported as 50Gy, and the TD5/5 and 50/5 (50% risk at 5 years) were 40Gy and 55Gy respectively.

The QUANTEC overview published in 2010 (5) recommended the absolute volume of small bowel receiving ≥15Gy be held to < 120cc to minimise the risk of acute small bowel toxicity if defining individual bowel loops. If delineating the intestinal cavity, they recommended restricting the volume receiving more than 45Gy to 195cc. However, the literature available to correlate small bowel toxicity with radiation dose was sparse compared with other organs. Only 6 studies with quantitative dose volume information on small bowel were found. These included studies on rectal cancer (1, 6-8) and cervix cancer (9, 10) – therefore the participants had received concurrent chemotherapy. The patients also varied in terms of operative status and irradiated doses and volumes. The authors admitted that the heterogeneity in patient, tumour and treatment factors confounded attempts to quantify a dose-volume relationship for the small bowel and provide generalisable dose constraints. Additionally, the studies were largely conducted with conventional field radiotherapy which exposes a larger proportion

of the bowel in field to high doses of radiation compared with 3D-CRT and IMRT (11, 12).

IMRT has resulted in an improvement in the incidence and severity of acute bowel toxicity (13-16) but there has been little further refinement of the constraints derived and the accepted dose tolerance of the small bowel to radiation is still debated in the literature (17).

4.1.3 Complications in reporting radiation toxicity assessment

There are a number of factors that complicate the reporting of bowel toxicity. Firstly, a key source of variability is the lack of a standardised method for contouring and reporting dose to the small bowel. The earliest studies used plain orthogonal films with contrast to identify small bowel in a 2-dimensional manner. With the advent of CT planning, individual bowel loops were outlined with or without contrast. More recently, another method has been developed which is to outline the peritoneal cavity or "bowel bag". One advantage of this technique is that it is faster to contour than individual bowel loops, particularly when there is a lack of contrast or when small bowel is closely interspersed with large bowel and pelvic vessels. Another potential advantage is that it can account for the internal motion of bowel by encompassing any potential region that a small bowel loop may occupy during the course of radiation treatment. A major disadvantage is that bowel bag and treated bowel volumes are not clearly associated. The Radiation Therapy Oncology Group (RTOG) published a consensus statement for the contouring of normal pelvic structures and a consensus was reached among the panellists about contouring definitions for all structures except the bowel. Some participants favoured individual loops and others preferred the "bowel bag" technique (18).

4.1.4 Toxicity Assessment

The second factor complicating the reporting of bowel toxicity are the tools used for reporting symptoms. The most commonly used tools to report acute and late radiation toxicity are the RTOG and CTCAE scores. While these scores are simple to use, they are criticised for under-reporting the range of symptoms that can occur. They also do not discriminate well between patients with subtle,

minimal toxicity and more severe symptoms. Lastly, they do not report on the impact that symptoms may have on quality of life (19,21,23, 50).

Patient reported outcomes are more likely to detect a wider range of symptom and also address their impact on daily living. One example of such a tool is the Inflammatory Bowel Disease Questionnaire (IBDQ) which has been used as a measure of disease activity in patients and also captures aspects of a patient's functional, social and emotional well-being (19). Another is the Vaizey incontinence questionnaire also provides a more effective measure of the severity of faecal incontinence than other questionnaires (20). Both tools have been used in clinical practice and found to be reliable and more sensitive in determining the range of gastrointestinal symptoms in patients undergoing radiotherapy than RTOG grading (21). While using these new endpoints and patient reported outcomes make it difficult to compare with the reported toxicities in older studies, they are a vital step forward in understanding the more subtle long-term impact of pelvic radiation.

4.1.5 Late toxicity and Quality of life

The priority of early work addressing radiation toxicity was to minimise the risk of severe acute and late toxicity such as bowel perforation or obstruction. However, consideration also needs to be given to the more subtle long-term sequelae of treatment and the impact they may have on patient quality of life. It is estimated that 90,000 cancer survivors have some form of pelvic radiation disease and many of these will have chronic GI symptoms that impact on their daily lives (22, 23). There are a number of new interventions improving the survival of high risk prostate cancer patients, so while the benefit of elective pelvic radiation is still uncertain, it is vital that work continues to minimise the risk of long term toxicity from this treatment and any potential impact on quality of life (24).

4.2 PIVOTAL trial

The PIVOTAL trial (ISRCTN 48709247,CRUK/10/022) was a randomised non-comparative multicentre phase II trial of prostate alone (PO) versus prostate and pelvic LN (P&P) IMRT for patients with locally advanced node negative prostate cancer. Following on from the IMRT trial, PIVOTAL was designed to establish the

acute and late toxicity profile associated with high dose pelvic lymph node IMRT using patient and clinician reported scores. Additionally, the trial aimed to assess whether this treatment was safely and consistently deliverable at multiple radiotherapy centres using the developed planning protocol. The primary endpoint of the trial was acute lower GI RTOG toxicity at week 18 and the aim was to exclude a grade 2 or greater toxicity free rate of 80% or lower in the prostate and pelvis group.

The pelvic lymph node dose was approximately 7-10Gy higher than that used in the RTOG-9413 (25) and GETUG-01 (26) studies. Assuming an α/β ratio of 3Gy for prostate (1.5Gy, 5.0Gy), the trial patients received an equivalent dose at 2Gy per fraction (EQD2) of 55.4Gy (53.5Gy, 56.7Gy) to the pelvic nodal regions, compared to 48.4Gy (47.5Gy, 49Gy) and 46Gy (46Gy, 46Gy) in the RTOG-9413 and GETUG-01 studies respectively. For both arms the prostate dose was 74Gy in 37 fractions. The phase I/II IMRT trial reported the toxicity associated with this pelvic lymph dose schedule (27) but the dosimetric analysis relied upon contemporaneously recorded volumes used for the purposes of ensuring the dose-volume constraints were met. Unlike the IMRT trial, detailed dose cube data was gathered prospectively for all the PIVOTAL trial patients. Alongside the traditional clinician reported toxicity tools of the CTCAE and RTOG, patient reported outcomes were a key secondary endpoint, with a focus on GI symptoms. This made the trial data ideal for further examining the relationship between radiation dose volume and bowel toxicity. Details of the trial design and results were published in 2019 (43).

4.3 Hypothesis and aims

The focus of this chapter was to further examine the relationship between bowel dose and patient and clinician reported late GI toxicity in patients undergoing pelvic IMRT for prostate cancer within the PIVOTAL trial.

Hypothesis; Bowel dose volume information and late toxicity results will further refine the currently used bowel dose constraints

Aims;

1) To establish the distribution and volume of bowel components (small bowel, sigmoid bowel, other large bowel and rectum) within the pelvic radiation field
2) Detect any significant correlation between the dose to various bowel components and late toxicity

4.4 Methods

4.4.1 Radiotherapy treatment planning

Patients recruited to the trial were treated with IMRT and received 74Gy in 37 fractions to the prostate. Patients randomised to receive PLN IMRT also received a dose of 60Gy in 37 fractions to the PLN. Pelvic LN outlining was performed according to guidelines developed for the study (49). The IMRT was conducted in accordance with the local centre's standard technique and Image-guided radiotherapy (IGRT) was permitted. The minimum treatment verification required was appropriate on/offline imaging 3 times in the first week of treatment and thereafter at least weekly using on/offline corrections. The use of fiducial markers was permitted, but the margins applied to create PTVs were not permitted to be altered as a result. The trial radiotherapy planning guidelines are contained in appendix 5.

Table 21 shows the radiotherapy planning dose constraints used in the trial. If individual plans failed to meet the optimal constraints, the target volumes and dose distributions were reviewed locally to produce a clinically acceptable solution. If the mandatory bowel dose constraints were not achieved the dose to the pelvic nodes was dropped to 55Gy in 37 fractions.

A pre-trial quality assurance program accredited sites for treatment within PIVOTAL and the volumes and plans for the first three prostate and PLN participants per site were centrally reviewed by the Chief Investigator or an accredited reviewer. Centres followed local practice for bladder and bowel preparation prior to treatment.

Table 21. Organ at risk dose constraints for bowel and rectum

Organ at risk	Dose-volume constraints		
Bowel	V45	78cc	158cc
	V50	17cc	110cc
	V55	14cc	28cc
	V60	0.5cc	6cc
	V65	0cc	0cc
Rectum	V30	80%	-
	V40	65%	-
	V50	50%	60%
	V60	35%	50%
	V65	30%	30%
	V70	15%	15%
	V75	3%	5%

4.4.2 Radiotherapy planning and treatment data

The dose cube data and structure sets were exported from each treating centre to the ICR CTSU in Digital Imaging and Communications in Medicine (DICOM) format. I imported the DICOM file for each patient into a dedicated analysis software programme; Visualisation and Organisation of Data for Cancer Analysis (VODCA, version 5.4.1.0, Medical software solutions). Within the VODCA programme the DICOM data for each patient could be viewed and I was able to review the planning CT scan, volumed structure sets, radiotherapy plan and dose information. For each patient I then additionally volumed the anal canal, rectum, sigmoid colon, small bowel and large bowel up to the top of L5, or the top CT slice if this was below L5. All the OARS were outlined in circumference. Figure 19 shows an example of a patient planning CT scan viewed in VODCA with the relevant organs at risk defined.

4.4.3 Organ at risk definition

In order to ensure accuracy in outlining the separate structures of the bowel, in particular differentiating small from large bowel, the first twenty patient datasets outlined were checked by a Consultant Radiologist (Dr Aslam Sohaib). Thereafter, his opinion was sought in cases where differentiation of the relevant structures was difficult.

4.4.3.1 Rectum and anal canal

The rectal volume was defined from the bottom of the anal sphincter up to the recto-sigmoid junction where there is an anterior inflection of the bowel. This was often best appreciated on the sagittal view of the planning scan. The anus was defined as per the trial contouring instructions to include the distal 3cm of rectum.

4.4.3.2 Sigmoid Bowel

The sigmoid bowel was outlined from the top of the rectum where it starts to bend anteriorly, usually at the level of the sacral promontory. Its course was followed to the point where it reached the left iliac fossa began to move vertically and posteriorly into the ascending colon.

4.4.3.3 Small bowel

In some patients the administration of oral contrast helped to identify the small bowel. Other features that differentiated it from the large bowel included its circular folds - the valvulae circulares, central location in the abdomen, narrower lumen and compact folds.

4.4.3.4 Large bowel

In contrast to small bowel, the ascending, descending colon and sigmoid colon had a “bubbly” appearance due to the presence of faeces, with fat filled tags “epiploicae” and haustra scattered along the length of the bowel. The loops were larger in size and more peripheral in the abdomen. The ascending and

descending colon were outlined as separate structures to the sigmoid and labelled as “large bowel”.

4.4.3.5 Total bowel

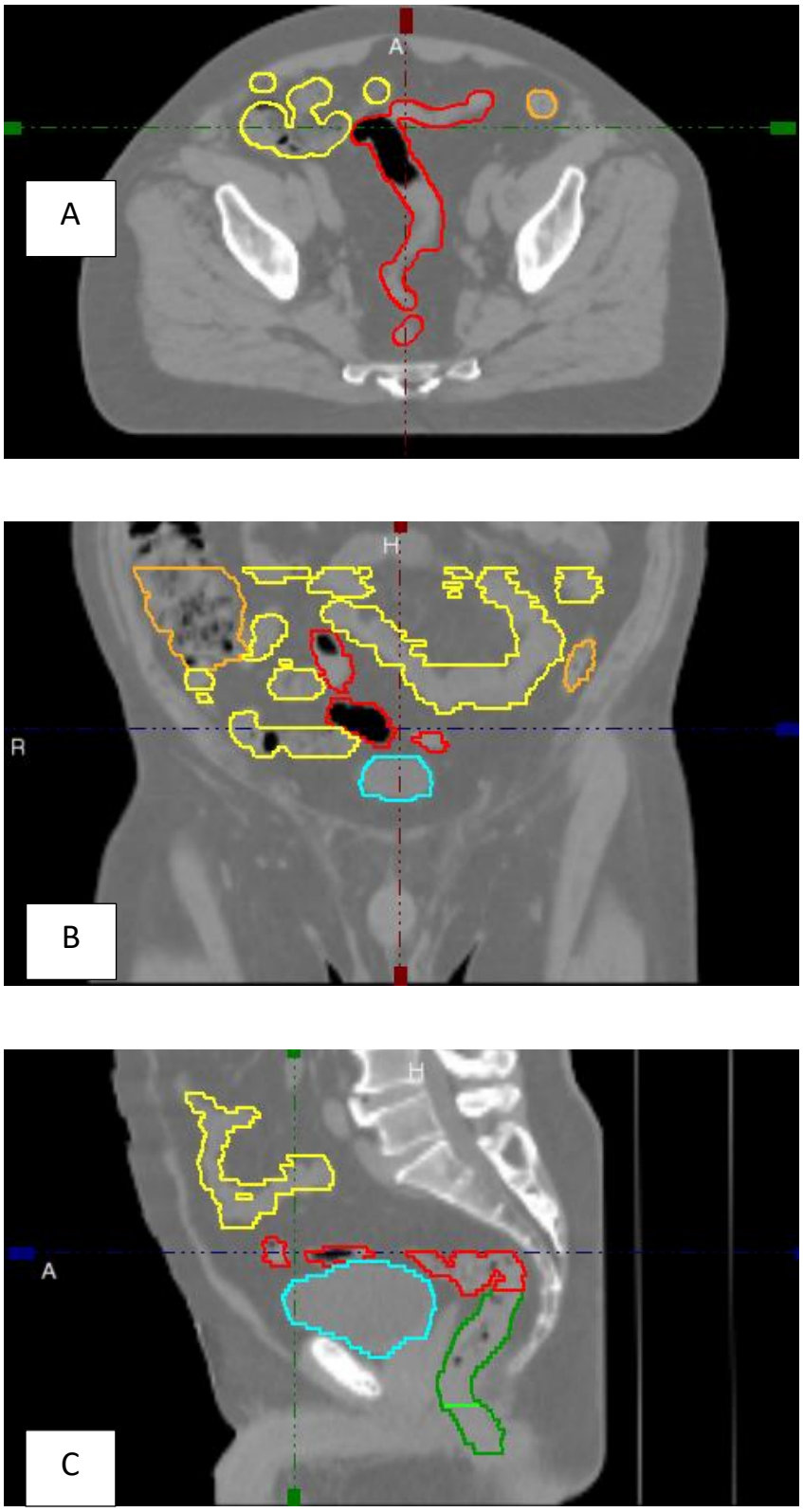
The sigmoid, small bowel and large bowel volumes were summed using the VODCA software and labelled “Total bowel”.

Dose volume histograms (cumulative, absolute) were then extracted in VODCA for each of the structures. This DVH data was exported into excel and then into SPSS (version 25, IBM) for analysis.

4.4.4 Statistical Analysis

The Mann-Whitney U test was used to compare treatment groups in terms of the peak late bowel toxicity experienced by 24 months and the absolute volume of bowel at 0Gy, 10Gy, 20Gy, 30Gy, 40Gy, 50Gy, 60Gy and 70Gy for the total bowel, sigmoid, small bowel, large bowel and rectum.

Figure 18. Panel A=axial section through planning CT scan in VODCA software, Panel B=coronal slice, Panel=C sagittal slice. Sigmoid bowel outlined red, small bowel outlined yellow, large bowel outlined orange, rectum outlined green and bladder outlined blue.



4.4.5 Toxicity Assessment and Follow up

Baseline pre radiotherapy, CTCAE GI and GU toxicity scores were recorded along with the Gulliford rectal scores. Additionally, the patient reported Inflammatory Bowel Disease Questionnaire (IBDQ) score, Vaizey incontinence and International prostate symptom score (IPSS) were recorded at baseline. During radiotherapy the clinical reported toxicity scores were recorded at week 2, week 4 and week 6 and week 8. Following completion of radiotherapy, the clinician and patient reported scores were recorded at week 10 and 18 and then at 6 months, 12 months, 18 months and 24 months.

4.5 PIVOTAL Trial Results

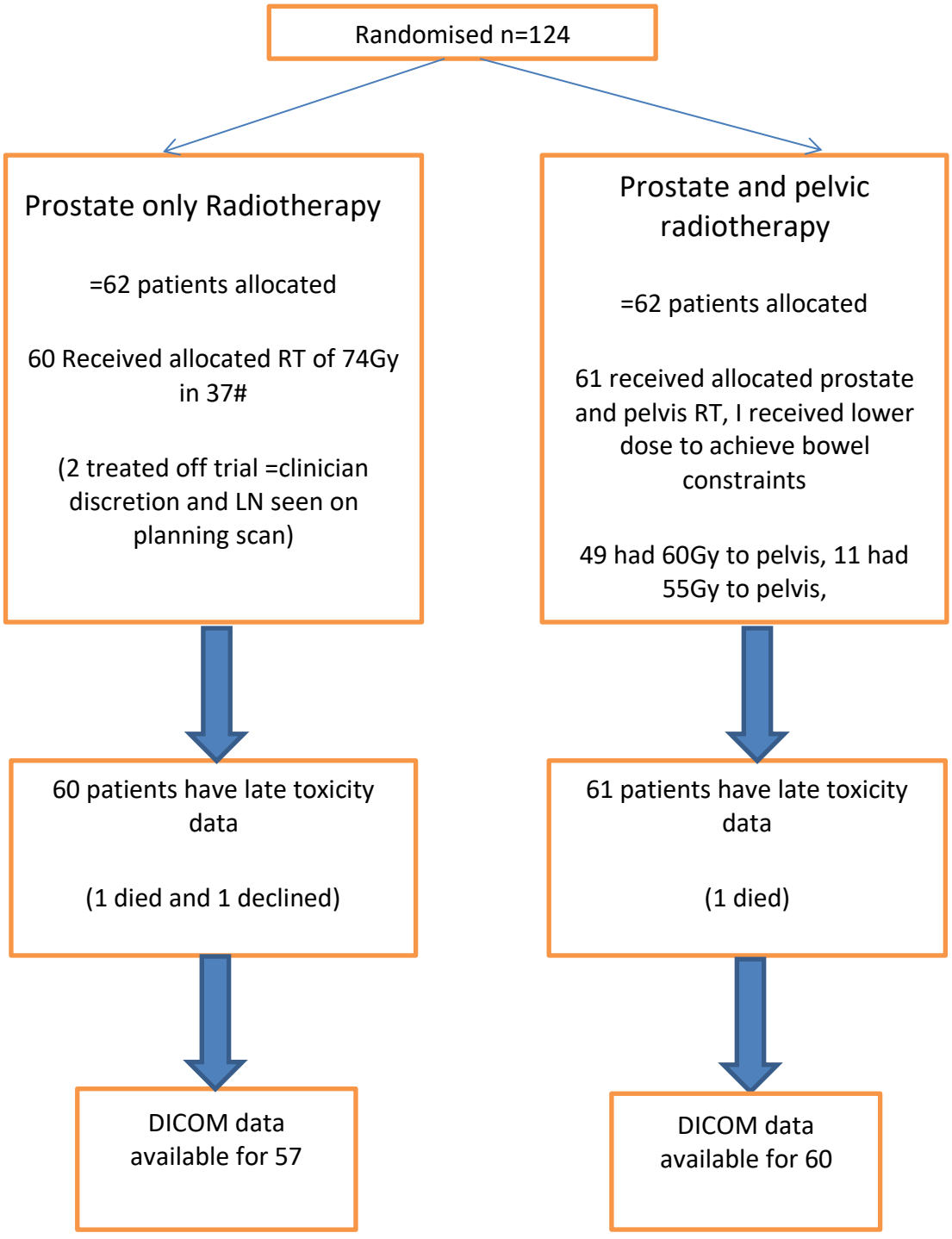
The results of the PIVOTAL trial have been reported by the Trial Management Group and the ICR CTSU (43) and are summarised below. Between May 2011 and March 2013 124 participants were randomised into the trial from nine UK radiotherapy centres. Sixty-two patients were randomised to receive prostate only radiotherapy (PO) and 62 to prostate and pelvis radiotherapy (P&P). Three patients were found to be ineligible after randomisation: one patient had an involved peri-rectal LN discovered on planning CT scan; one had a white blood cell count of $3.3x10^9$/l prior to randomisation; and one had testosterone >20ng/dL prior to randomisation. The randomised groups were well balanced for baseline characteristics, shown in table 23. The median age of patients was 69 years. In terms of prostate cancer high risk features; 78% of patients had T3 disease, 74% Gleason scores ≥8 and the median PSA was 22ng/ml. 59 patients (48%) had 2 high risk features and 60 (48%) had 3 high risk features.

The median duration of hormone therapy prior to RT was 6.8 months in both groups. In the PO group 57 patients (92%) received LHRH + short term anti-androgens, 4 (6%) maximum androgen blockade and one monotherapy bicalutamide. All the P&P patients received LHRHa + short term anti-androgens. The baseline CTCAE bowel symptom and Gulliford rectal scores of overall bowel habit were well balanced between the groups. At the time of the data snapshot (14/04/2016) the median follow-up was 37.6 (IQR 35.4-38.9) months.

Table 22. Baseline patient and disease characteristics

Baseline characteristics	Prostate only n=62, n (%)	Prostate and Pelvis n=62, n (%)	Total n=122
Age median, IQR)	68 (65-74)	70 (65-74)	69 (65-74)
Radiological T stage			
T1c/T2	15 (25)	17 (30)	32 (26)
T3a	20 (35)	22 (35)	42 (34)
T3b	25 (42)	21 (35)	46 (38)
T4	0	0	0
u/k	2	2	4
Gleason score			
7	18 (29)	14 (23)	32 (26)
8	12 (20)	17 (27)	29 (23)
9	31 (50)	30 (50)	61 (49)
10	1 (2)	1 (2)	2 (2)
Index PSA (median, IQR)	21 (9-34)	22 (13-38)	22 (12-35)
CTCAE (GI) score	n=60	n=60	n=120
0	47 (78)	46 (78)	93
1	12 (20)	11 (18)	23
2	1 (2)	3 (5)	4
3/4/5	0	0	0
Gulliford rectal score (overall bowel habit)	n=58	n=59	n=117
No problem	50 (88)	53 (90)	103
Very small problem	4 (7)	4 (7)	8
Small problem	3 (5)	1 (2)	4
Moderate problem	0	1 (2)	1

Figure 19. Consort Diagram; Recruited patients who received allocated trial treatment and subsequently had toxicity and radiotherapy data available for analysis



4.5.1 Acute GI toxicity

The acute toxicity results were reported from the start of radiotherapy to week 18 post radiotherapy for both groups. Overall the patients with P&P treatment experienced more acute GI toxicity than the PO group. This difference was largest in the reported Grade 2 RTOG toxicity which peaked at week 6 and was 4/61 (7%) and 15/61 (25%) in the PO and P&P patients respectively. However, toxicity levels then fell and by week 18 were very similar in both groups. The primary endpoint of the trial was acute lower GI RTOG toxicity at week 18, aiming to exclude a grade 2 or greater toxicity free rate of 80% or lower in the P&P group. Patients were included in the analysis if they had received at least one fraction of radiotherapy and had completed the 18-week toxicity assessment. The proportion of patients that were toxicity (RTOG) free by week 18 was 96.7% (95% CI; 90.0-99.4%) in the PO group and 95.2% (95% CI; 88.0-98.7%) in the P&P group. There was very little G3 toxicity; only one P&P patient had RTOG G3 proctitis, diarrhoea and rectal bleeding at 6 and 8 weeks. No RTOG G4 lower GI acute toxicity events were reported.

The Gulliford scores are summarised in table 26. At baseline pre radiotherapy 50 (88%) and 53 (90%) of patients in the PO and P&P groups had no problems with their overall bowel habit. The scores at week 18 showed some deterioration with 50 (82%) and 45 (75%) in the PO and P&P groups respectively reporting no problems with overall bowel habit. However individual symptoms were recorded more frequently in the P&P compared with P group at 18 weeks, with rectal bleeding occurring in 7 (11%) vs 1(2%) and an approximate doubling of stool frequency ≥mild 21 (34%) vs 13 (21%), sphincter control ≥mild 6 (10%) vs 3 (5%), loose/liquid stool ≥mild 10 (17%) vs 4 (6%) and rectal urgency ≥mild 13 (21%) vs 7 (11%). Symptom levels and possible differences remained fairly constant by 6 months with the exception that rectal bleeding reduced to a single patient (2%) in the P&P group.

Both the IBDQ and Vaizey questionnaires (table 27) showed similar results for both treatment groups. The 10-week time point showed the worst symptoms in all questionnaires; similar to the clinician reported data showing the worst symptoms at 8 weeks. Week 10 had the highest proportion of patients with a

clinically significant deterioration in IBDQ-bowel score compared to the pre-RT score median scores deteriorating from 69 to 65 in both treatment groups. By week 18 median IBDQ score had recovered to 68 in the P group but remained lower with median score of 66 in the P&P group mirroring the changes seen in Gulliford symptom scores at week 18. However, no differences were apparent after 6 months.

4.5.2 Late toxicity

The PIVOTAL study was not designed to directly compare the rates of late toxicity between the two treatment groups. However, reviewing the data there does not seem to be a clear trend of increased late toxicity in the P&P group compared to the PO group using either the clinician or patient reported scores. Secondly, overall late toxicity rates are consistently low using all clinician and patient reported scores (low rates of change in bowel habit from baseline for all patients).

4.5.2.1 Clinician reported outcomes

The cumulative incidence and prevalence of late GI toxicity assessed with the RTOG scoring systems was similar in the two randomised groups. The RTOG proctitis and diarrhoea late toxicity scores are shown in tables 23 and 24. The cumulative incidence of RTOG G2+ toxicity at 2 years was 16.9% (95% CI 8.9-30.9) and 24.0% (95% CI 8.4-57.9) in the PO and P&P groups respectively. There was no recorded RTOG G3 toxicity. Two patients had G4 RTOG bowel toxicity, one P&P patient at 6 months (bowel obstruction) and one PO patient at 18 months (bowel obstruction). The majority of patients, 96/121 (79.3%) had no reported proctitis (grade 0) at any time point, and a small number of patients reported grade 1 (21/121,17.4%) or grade 2 (6/121, 5.0%) proctitis by 24 months. Similarly, for RTOG diarrhoea, the majority (85/121, 70.2%) had reported no diarrhoea at any late time point and by 24 months a small minority had grade 1 (10/121, 8.3%) or Grade 2 (5/121, 4.1%) diarrhoea.

The Gulliford scoring system indicated that at 24 months the majority of patients experienced no problem with their overall bowel habits (94/119, 79.0%) with 8% (10/119, 8.4%) reporting a moderate/severe problem. Overall ≥ mild symptoms

were reported in 11 (18%) of the PO group and 14 (24%) of the P&P group with ≥ mild urgency in 5 (8%) vs 11 (18%) and ≥mild sphincter control in 2(3%) vs 11(18%) of the PO and P&P groups respectively. The results are summarised in table 25.

4.5.2.2 Patient reported outcomes

The IBDQ-Bowel scores and Vaizey incontinence scores from baseline to 24 months are summarised in table 26. Following the deterioration in IBDQ-Bowel scores at week 10, the majority of patients have little change to their bowel function from week 18 to month 24 in comparison with function pre-radiotherapy. There is very little difference between the two treatment groups at each time point and overall the results at 24 months were very close to the baseline scores pre radiotherapy. The Vaizey incontinence scores remained similar over time for both treatment groups and like the IBDQ scores were similar to baseline scores at 24 months.

Table 23. RTOG proctitis at months 6, 12, 18 and 24 and maximum reported grade of proctitis by 24 months

RTOG Proctitis	6 months		12 months		18 months		24 months		Maximum reported grade of toxicity by 24 months	
	PO n=60	P&P n=61	PO n=59	P&P n=60	PO n=58	P&P n=60	PO n=60	P&P n=61	PO n=60	P&P n=61
Grade 0	56(93%)	56(92%)	57(97%)	57(95%)	53(91%)	56(93%)	52(87%)	54(88%)	46(77%)	50(83%)
Grade 1	4(7%)	4(7%)	2(3%)	3(5%)	5(9%)	2(3%)	7(12%)	5(8%)	13(22%)	6(10%)
Grade 2	0	1(2%)	0	0	0	2(3%)	1(1%)	2(4%)	1(2%)	5(8%)

Table 24. RTOG diarrhoea at months 6, 12, 18 and 24 and maximum reported grade of diarrhoea by 24 months

RTOG Diarrhoea	6 months		12 months		18 months		24 months		Maximum reported grade of toxicity by 24 months	
	PO n=60 (%)	P&P n=61	PO n=59	P&P n=60	PO n=58	P&P n=60	PO n=60	P&P n=61	PO n=60	P&P n=61
Grade 0	53(88%)	51(84%)	55(93%)	54(90%)	50(86%)	53(88%)	52(87%)	54(88%)	43(72%)	42(69%)
Grade 1	5(8%)	8(13%)	2(3%)	6(10%)	4(7%)	5(8%)	5(8%)	5(8%)	10(17%)	14(23%)
Grade 2	2(3%)	2(3%)	2(3%)	0	4(7%)	2(3%)	3(5%)	2(3%)	7(12%)	5(8%)

Table 25. Gulliford Rectal scoring criteria categorised as none, mild or moderate/severe at baseline, week 18, month 6, 12 and 24

	Pre-RT		Week 18		Month 6		Month 12		Month 24	
	P0 N=60	P&P N=59	PO N=61	P&P N=62	PO N=61	P&P N=61	PO N=60	P&P N=60	PO N=60	P&P N=61
Rectal bleeding										
None	53 (88)	57 (97)	60 (98)	55 (89)	58 (95)	60 (98)	56 (93)	54 (90)	49 (82)	53 (87)
Mild	5 (8)	2 (3)	1 (2)	6 (10)	2 (3)	1 (2)	4 (7)	6 (10)	10 (17)	7 (12)
Moderate / Severe	2 (3)	0	0	1 (2)	1 (2)	0	0	0	1 (2)	1 (2)
Proctitis[1]										
None	-	-	57 (93)	57 (92)	56 (93)	55 (90)	55 (92)	53 (88)	52 (87)	54 (89)
Mild	-	-	4 (7)	5 (8)	4 (7)	6 (10)	5 (8)	7 (12)	7 (12)	6 (10)
Moderate/Severe	-	-	0	0	0	0	0	0	1 (2)	1 (2)
Stool frequency										
None	50 (83)	50 (86)	48 (79)	40 (66)	47 (78)	38 (63)	45 (76)	44 (73)	45 (75)	45 (76)
Mild	10 (17)	8 (14)	13 (21)	19 (31)	13 (22)	21 (35)	13 (22)	15 (25)	14 (23)	14 (24)
Moderate / Severe	0	0	0	2 (3)	0	1 (2)	1 (2)	1 (2)	1 (2)	0
Difficulty with sphincter control										
None	57 (97)	57 (97)	58 (95)	56 (90)	57 (97)	52 (87)	58 (97)	56 (95)	58 (97)	52 (85)
Mild	2 (3)	2 (3)	3 (5)	5 (8)	2 (3)	8 (13)	1 (2)	3 (5)	2 (3)	8 (13)
Moderate / Severe	0	0	0	1 (2)	0	0	1 (2)	0	0	1 (2)
Loose/liquid stool frequency										
None	60 (100)	54 (92)	57 (93)	50 (83)	54 (92)	52 (88)	55 (92)	57 (97)	54 (92)	56 (93)
Mild	0	2 (3)	2 (3)	6 (10)	3 (5)	6 (10)	2 (3)	1 (2)	4 (7)	2 (3)
Moderate / Severe	0	3 (5)	2 (3)	4 (7)	2 (3)	1 (2)	3 (5)	1 (2)	1 (2)	2 (3)
Rectal urgency frequency										
None	56 (93)	57 (97)	54 (89)	48 (79)	52 (87)	49 (82)	51 (85)	54 (92)	54 (92)	49 (82)
Mild	3 (5)	1 (2)	5 (8)	7 (11)	5 (8)	9 (15)	4 (7)	4 (7)	3 (5)	8 (13)
Moderate / Severe	1 (2)	1 (2)	2 (3)	6 (10)	3 (5)	2 (3)	5 (8)	1 (2)	2 (3)	3 (5)
Overall bowel habit problem										
None	52 (88)	53 (90)	50 (82)	45 (75)	46 (78)	46 (75)	46 (77)	48 (81)	49 (82)	45 (76)
Mild	7 (12)	5 (9)	7 (11)	13 (22)	11 (19)	12 (20)	10 (17)	10 (17)	6 (10)	9 (15)
Moderate / Severe	0	1 (2)	4 (7)	2 (3)	2 (3)	3 (5)	4 (7)	1 (2)	5 (8)	5 (9)

Table 26. Patient reported bowel symptom scores of the IBDQ and Vaizey incontinence scores

	Pre-RT		Week 10		Week 18		Month 6		Month 12		Month24	
	PO n (%)	**P&P n (%)**	**PO n (%)**	**P&P n (%)**	**PO n (%)**	**P&P n (%)**	**PO n (%)**	**P&P n (%)**	**PO n (%)**	**P&P n (%)**	**PO n (%)**	**P&P n (%)**
IBDQ bowel Total score[1]												
N	55	55	49	46	47	49	46	51	49	45	47	48
Median (IQR) Range	69 (67-70) 28-70	69 (67-70) 60-70	65 (61-69) 20-70	65 (61-68) 34-70	68 (65-70) 48-70	66 (62-69) 45-70	68 (66-69) 52-70	68 (62-69) 49-70	68 (65-69) 37-70	68 (64-70) 51-70	67 (65-69) 28-70	68 (67-70) 44-70
Vaizey Total score[2]												
N	54	54	50	49	47	52	49	51	49	49	45	49
Median (IQR) Range	4 (4-7) 0-13	4 (4-6) 0-11	6 (4-8) 0-18	5 (4-7) 0-14	5 (4-8) 0-13	5 (4-8) 0-18	5 (4-7) 0-20	5 (4-7) 0-16	6 (4-8) 0-13	5 (4-7) 0-15	5 (4-8) 0-17	5 (4-7) 0-13

1. IBDQ bowel domain total score ranges from 0 (most severe symptoms) to 70 (asymptomatic)

2. Vaizey total scores ranges from 0 (asymptomatic) to 24 (most severe symptoms)

4.6 Radiation dose analysis

The dose volume analysis was performed using the reported late RTOG diarrhoea and proctitis scores. Both the reported toxicity at 24 months and the maximum reported grade of toxicity between 6 and 24 months were used. Figures 20-24 demonstrate the volume distribution of bowel volumes for the two trial cohorts. None of the component bowel volumes were normally distributed and therefore a non-parametric test was picked as most appropriate for analysing toxicity differences between the two groups.

Figure 20. Distribution of total bowel volume in trial patients treated with prostate only (PO) and prostate and pelvic (PP) radiation

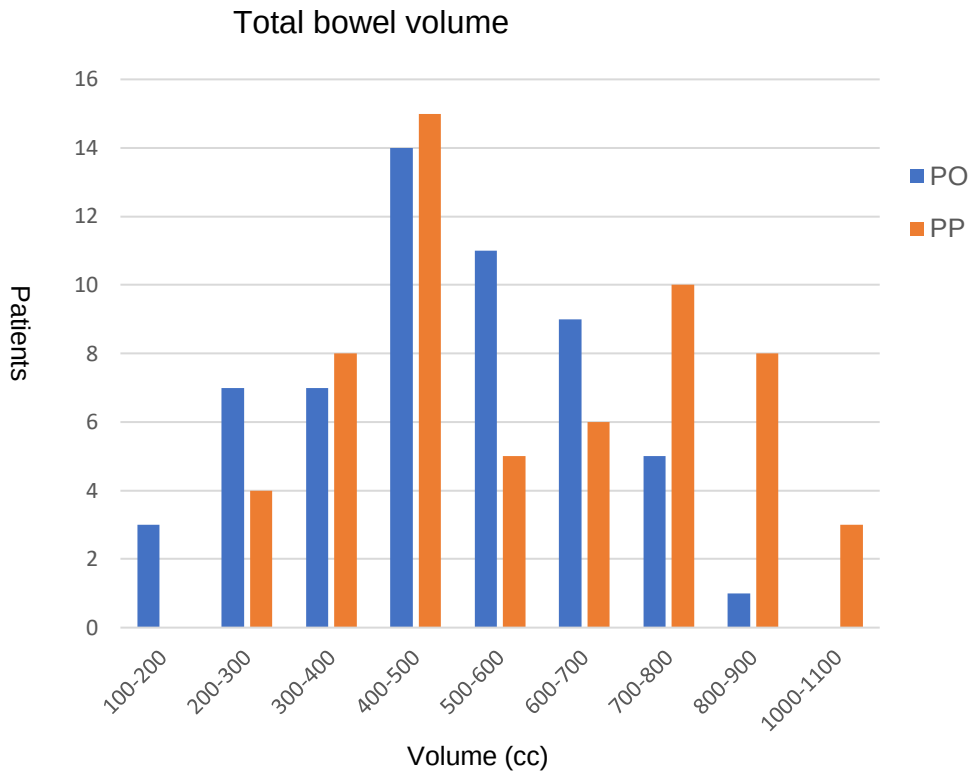


Figure 21 - Distribution of small bowel volume in trial patients treated with prostate only (PO) and prostate and pelvic (PP) radiation

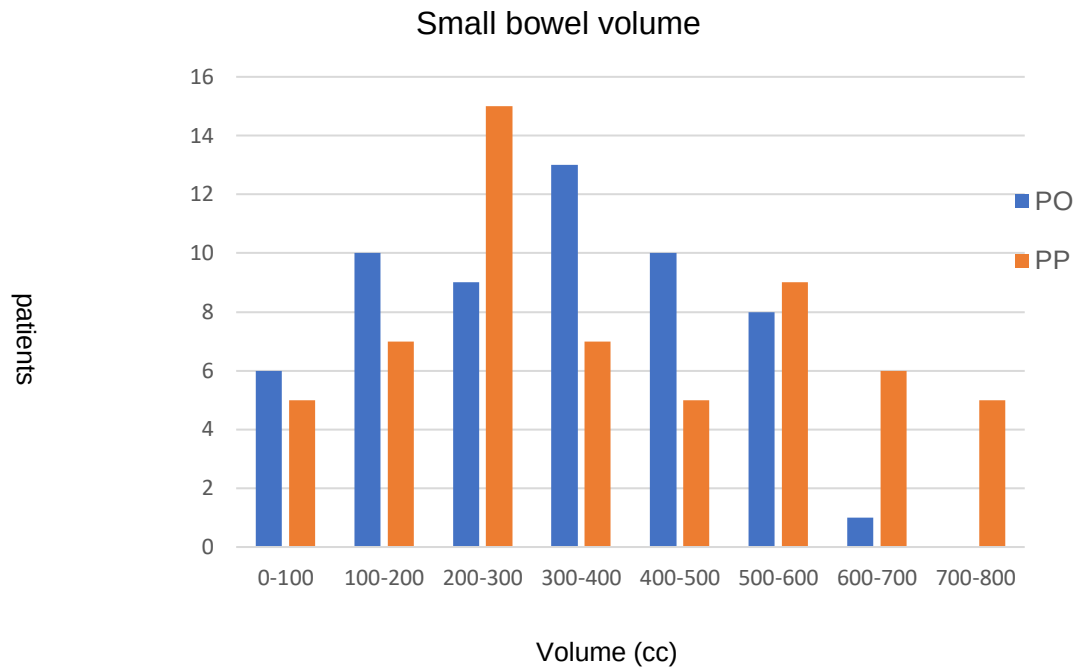


Figure 22. Distribution of total bowel volume in trial patients treated with prostate only (PO) and prostate and pelvic (PP) radiation

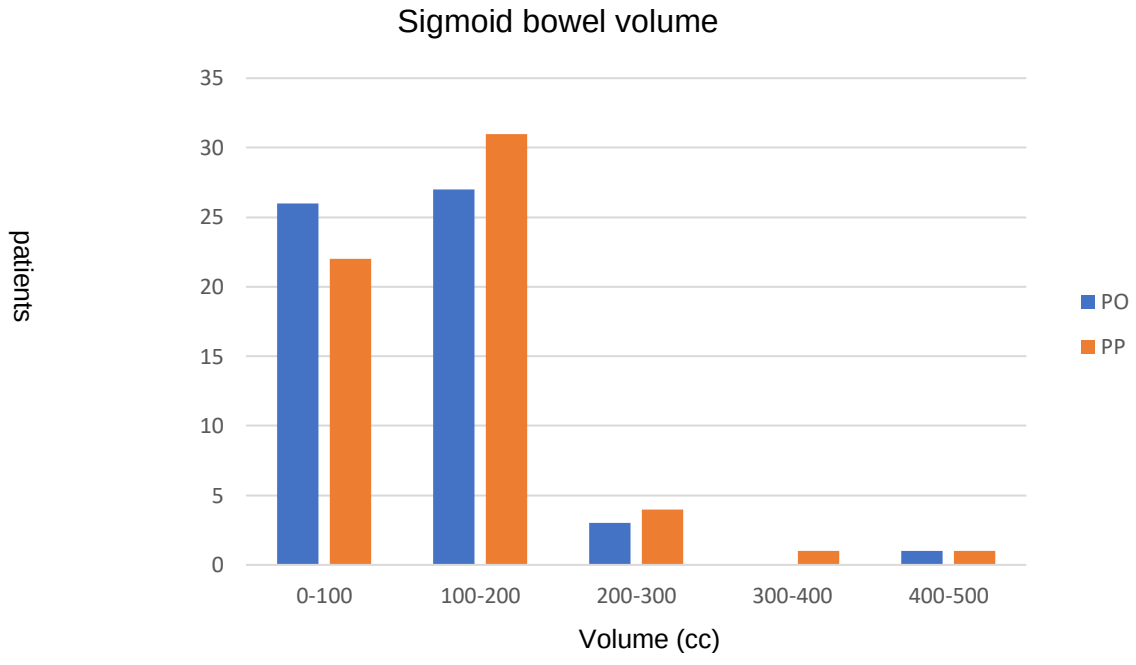


Figure 23- Distribution of Large bowel volume in trial patients treated with prostate only (PO) and prostate and pelvic (PP) radiation

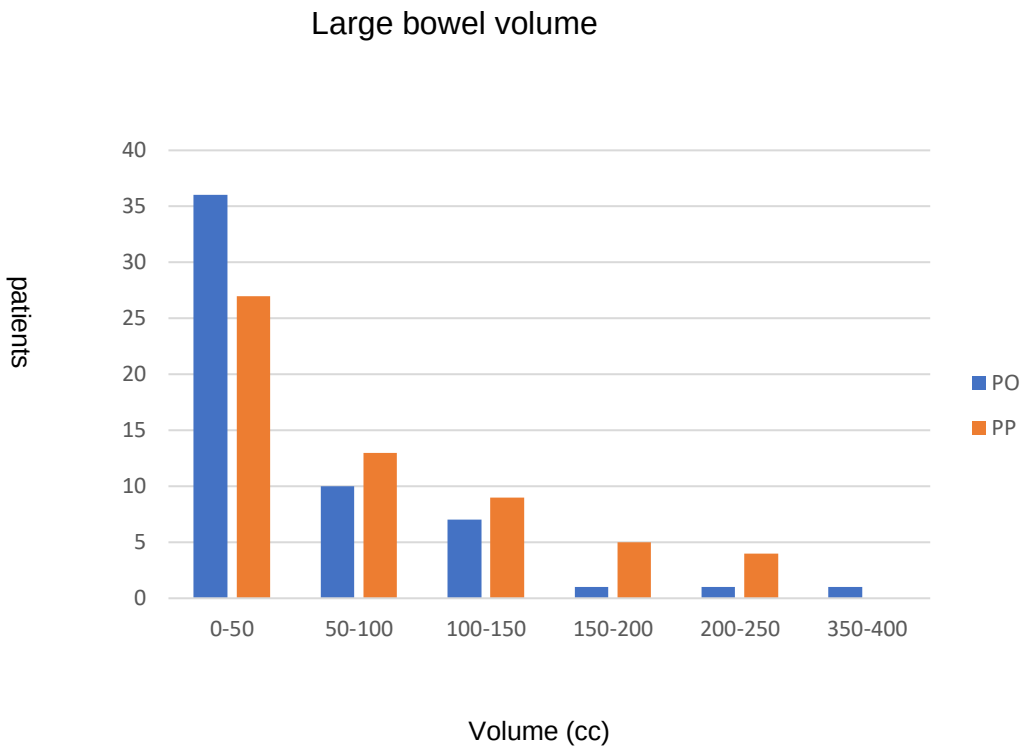
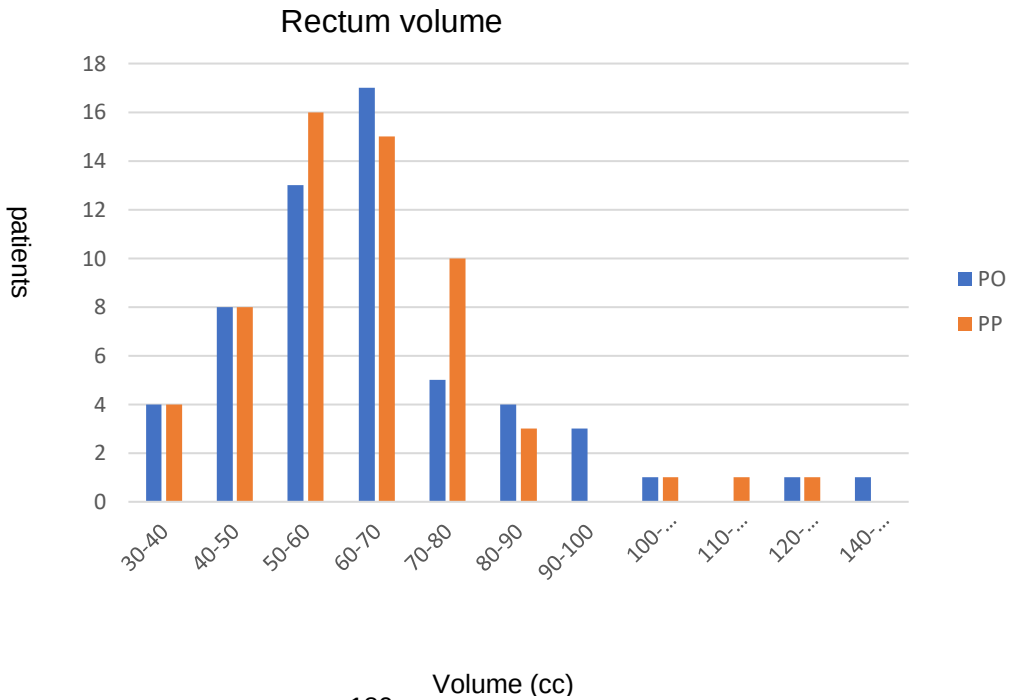


Figure 24- Distribution of rectum volume in trial patients treated with prostate only (PO) and prostate and pelvic (PP) radiation



4.6.1 ***Total bowel***

The total bowel volume included the small bowel, large bowel and sigmoid up to the top of the L5 vertebra and is represented by the V0 volume reported in the results. There was a significant difference between the mean volume of pelvic bowel (V0) in patients with grade 0-1 proctitis vs grade 2+ proctitis. This volume difference was significantly different (tables 27,28 figure 25) in the maximum reported proctitis results (533.5cc vs 698.2cc, p=0.038) and the 24 month proctitis results (535.0cc vs 808.1cc, p=0.013).

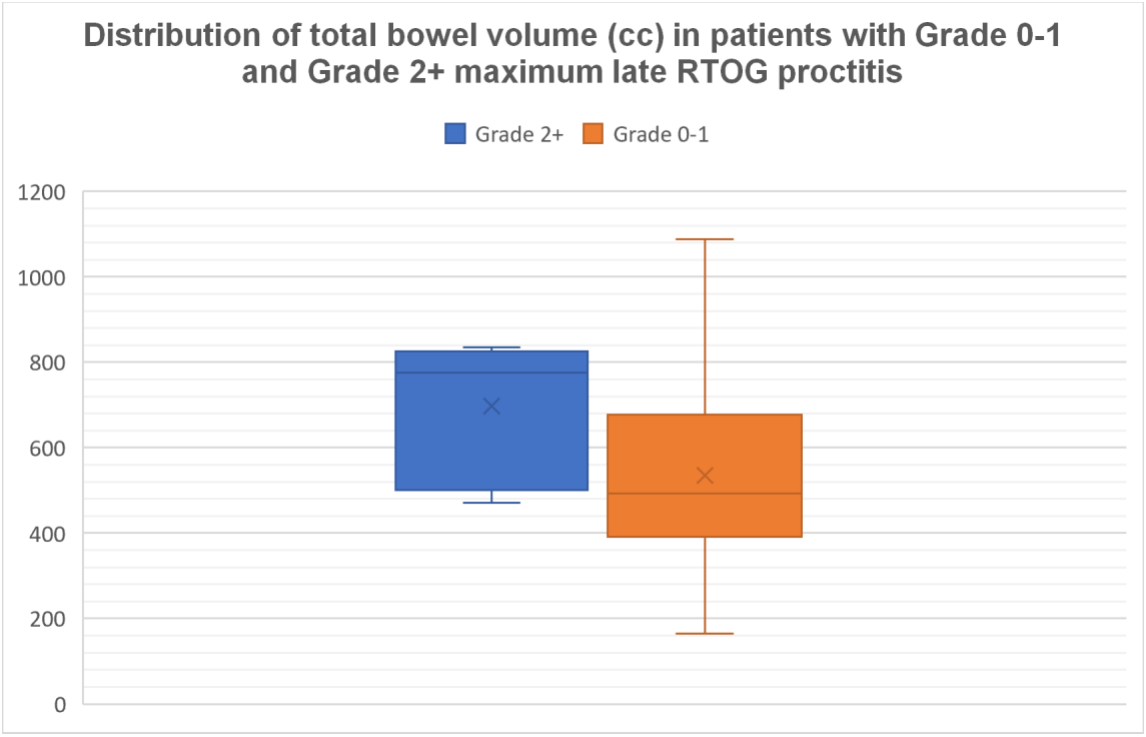


Figure 25– Box plot illustrating the difference in total bowel volume between pts with maximum Grade 0-1 and Grade 2+ RTOG proctitis. The X marks the mean, straight line marks the median, edges of the coloured box mark the upper and lower quartiles, the ends of the whiskers mark the range.

Table 27. Mann-Whitney U test to compare the mean volume of total bowel receiving 0-70Gy in patients with maximum reported late RTOG Grade 2+ and Grade 0-1 proctitis

	Maximum late RTOG proctitis	Mean volume (cc)	SD (cc)	*P* value
Total bowel (V0)	Grade 0-1 n=115 (95%)	533.5	202.4	**0.038**
	Grade 2+ n=6 (5%)	698.2	163.3	
V10	Grade 0-1	203.3	232.3	0.127
	Grade 2+	353.9	269.6	
V20	Grade 0-1	161.0	192.8	0.130
	Grade 2+	279.5	217.3	
V30	Grade 0-1	107.5	132.4	0.139
	Grade 2+	192.5	166.8	
V40	Grade 0-1	57.7	69.5	0.222
	Grade 2+	107.4	104.3	
V50	Grade 0-1	22.7	26.8	0.149
	Grade 2+	40.9	31.3	
V60	Grade 0-1	1.0	1.8	0.587
	Grade 2+	1.0	1.2	
V70	Grade 0-1	0.0	0.2	0.526
	Grade 2+	0.0	0.0	

Table 28. Mann-Whitney U test to compare the mean volume of total bowel receiving 0-70Gy in patients with RTOG Grade 2+ and Grade 0-1 proctitis at 24 months

	RTOG proctitis at 24 months	Mean volume (cc)	SD (cc)	*P* value
Total bowel volume	Grade 0-1 n=118 (98%)	535.0	201.1	**0.013**
	Grade 2+ n=3 (2%)	808.1	36.5	
V10	Grade 0-1	206.3	232.2	0.288
	Grade 2+	394.0	338.9	
V20	Grade 0-1	163.3	192.6	0.304
	Grade 2+	311.4	273.1	
V30	Grade 0-1	108.8	131.9	0.329
	Grade 2+	231.4	222.5	
V40	Grade 0-1	58.3	69.1	0.453
	Grade 2+	136.9	143.0	
V50	Grade 0-1	23.2	27.0	0.453
	Grade 2+	41.8	36.6	
V60	Grade 0-1	1.0	1.8	0.517
	Grade 2+	1.4	1.6	
V70	Grade 0-1	0.0	0.2	0.870
	Grade 2+	0.0	0.0	

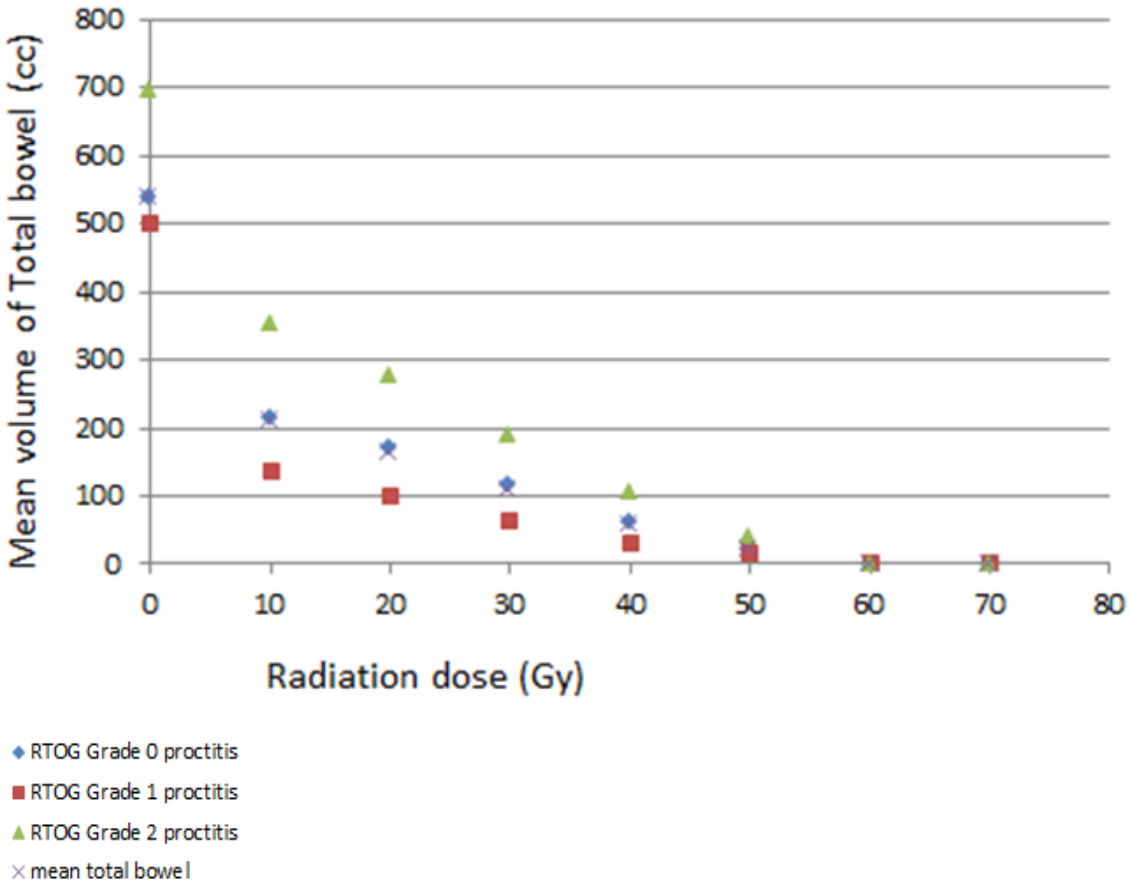


Figure 26. Mean bowel volumes receiving between 0 and 70Gy in the whole trial cohort and maximum reported grade of proctitis RTOG Grade 0 (n=96), Grade 1 (n=21) and Grade 2 (n=6)

For the dose volume endpoints between V10 and V70 no significant correlation was seen between the mean bowel volume and the maximum reported RTOG grade of proctitis or the RTOG proctitis reported at 24 months (tables 27 and 28 above and appendix 6).

Figure 26 shows the mean bowel volumes at each dose level for patients with maximum RTOG grade 0, 1 and 2 proctitis. The graph demonstrates that patients with RTOG grade 2+ proctitis had higher volumes of bowel treated at each dose level from 0-50Gy, whereas dose distributions for the Grade 0 and Grade 1 groups were similar. Mean total bowel volumes were approximately doubled for doses in the range 10Gy - 50Gy in the patients with ≤Grade 1 RTOG proctitis scores compared with the patients with Grade 2 scores.

Receiver operator curves were calculated using excel for the V0Gy of total bowel and grade 2+ proctitis. The V0 for total bowel has an AUC of 0.75, 95% CI 0.59-0.9. All other examined dose volume points had 95% confidence intervals crossing AUC 0.5 and showed no effect (figure 27). For total bowel volume ≥766cc there was a very high risk of Grade≥2 side effects (67% sensitivity/85% specificity) and for volumes ≥510cc (83% sensitivity /53% specificity) but for volumes less than 470cc no Grade ≥2 side effects were apparent.

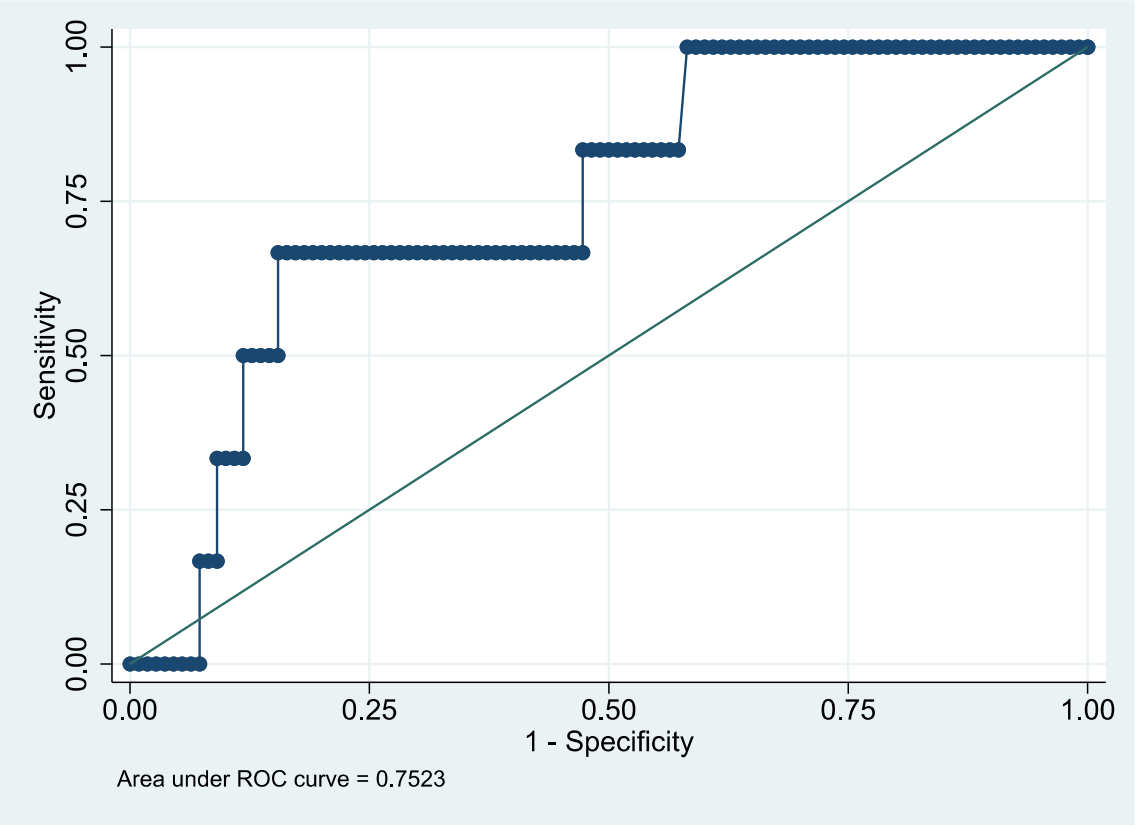


Figure 27– The ROC curve analysis for total bowel volume as predictor for maximum RTOG Grade 2+ proctitis. The data points correspond to sensitivity /specificities for bowel volumes of 470cc, 100% sensitivity /42% specificity; 510cc, 83% sensitivity /53% specificity; 766cc,67% sensitivity /85% specificity; 784cc 50% sensitivity /88% specificity; 823cc, 33% sensitivity and 91% specificity; 1088cc, 0% sensitivity /100% specificity.

4.6.1.1 Total bowel – RTOG Diarrhoea

No statistically significant difference was detected in the volume of bowel irradiated at doses between 0-70Gy for patients experiencing grade 0 or grade 1+ RTOG diarrhoea or grade 0-1 and grade 2+ diarrhoea at 24 months for maximum toxicity by or at 2 years (tables in appendix 6).

4.6.2 Small bowel

4.6.2.1 Proctitis

There was a significant difference in the mean volume of small bowel in the pelvis between patients who experienced grade 0-1 and grade 2+ proctitis (Figure 28) This difference was significant in the 24 month toxicity results (348.5cc vs 566.9cc, p=0.028, table 29) as well as for the maximum reported results (346.7cc vs 489.7cc, p=0.044, table 30). However, there was no statistically significant difference seen in the mean volume of small bowel exposed to radiation doses between 10-60Gy in patients who experienced proctitis grade 0 vs grade 1+ or grade 0-1 vs grade 2+. Nevertheless, the small bowel volume treated in the dose range 10-50Gy was approximately doubled in those patients (6/121) with maximum Grade 2 toxicity (table 30 and Figure 29). The remaining results are in appendix 6.

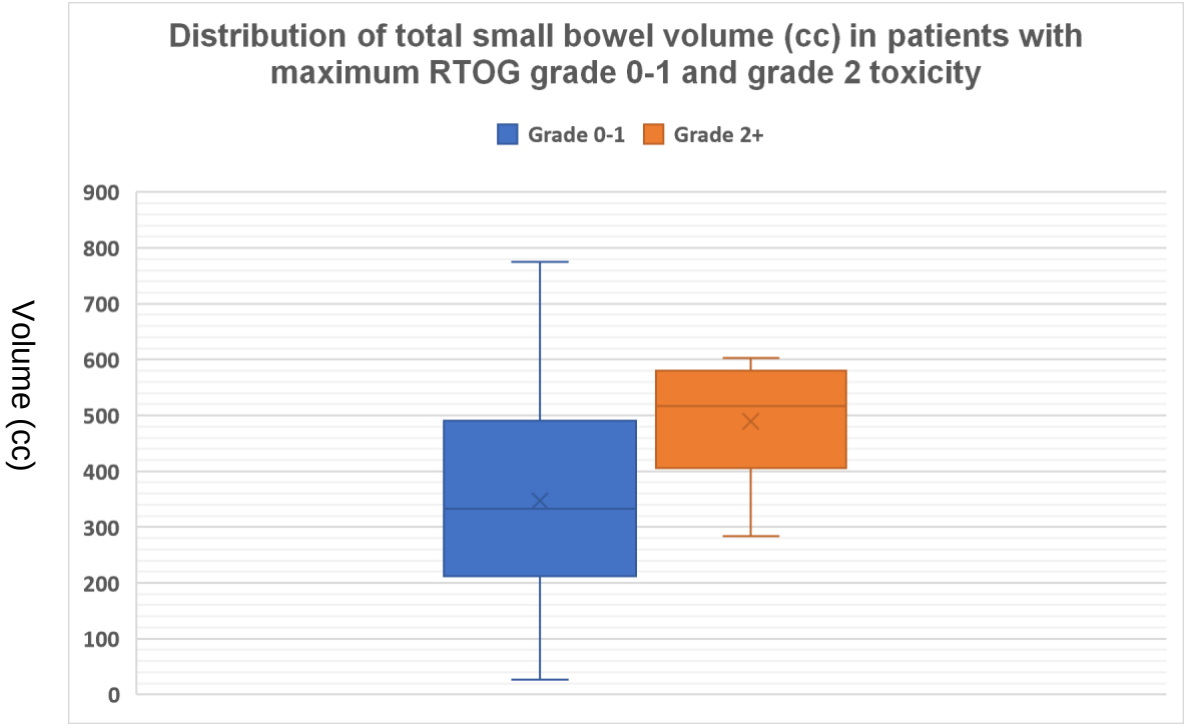


Figure 28– Box plot of total small bowel distribution in patients with maximum grade 0-1 and 2 proctitis. The X marks the mean, straight line marks the median, edges of the coloured box mark the upper and lower quartiles, the ends of the whiskers mark the range.

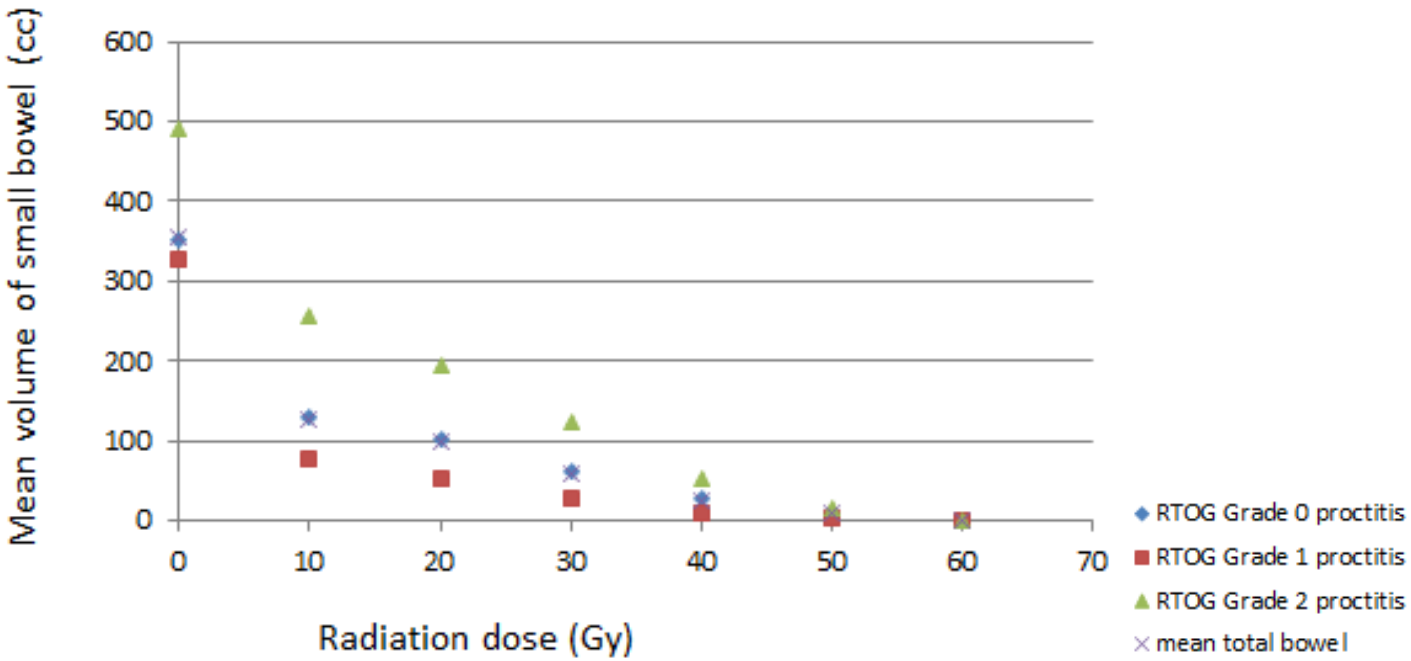
Table 29. Mann-Whitney U test to compare the mean volume of small bowel receiving 0-60Gy in patients with RTOG Grade 2+ and Grade 0-1 proctitis at 24 months

	RTOG proctitis at 24 months	Mean volume (cc)	SD (cc)	*P* value
Total small bowel	Grade 0-1 n=118 (98%)	348.5	181.0	**0.028**
	Grade 2+ n=3 (2%)	566.9	348.5	
V10	Grade 0-1	122.5	165.4	0.106
	Grade 2+	302.2	252.3	
V20	Grade 0-1	94.2	134.4	0.102
	Grade 2+	233.3	196.6	
V30	Grade 0-1	55.6	85.3	0.102
	Grade 2+	163.2	143.1	
V40	Grade 0-1	23.4	38.5	0.216
	Grade 2+	79.8	70.9	
V50	Grade 0-1	7.8	14.7	0.257
	Grade 2+	22.6	23.2	
V60	Grade 0-1	0.2	1.9	0.168
	Grade 2+	1.1	1.7	

Table 30. Mann-Whitney U test to compare the mean volume of small bowel receiving 0-60Gy in patients with maximum reported late RTOG Grade 2+ and Grade 0-1 proctitis

	Maximum late RTOG proctitis	Mean volume (cc)	SD (cc)	*P* value
Total Small bowel	Grade 0-1 n=115 (95%)	346.7	182.4	**0.044**
	Grade 2+ n=6 (5%)	489.7	114.6	
V10	Grade 0-1	120.1	165.0	0.092
	Grade 2+	255.7	206.5	
V20	Grade 0-1	92.6	134.5	0.086
	Grade 2+	193.8	158.6	
V30	Grade 0-1	54.9	85.8	0.090
	Grade 2+	122.1	111.3	
V40	Grade 0-1	23.4	38.9	0.192
	Grade 2+	52.3	55.7	
V50	Grade 0-1	7.8	14.9	0.171
	Grade 2+	15.7	17.2	
V60	Grade 0-1	1.0	0.2	0.114
	Grade 2+	1.2	0.6	

Figure 29. Mean small bowel volumes receiving between 0 and 70Gy in the whole trial cohort and maximum reported RTOG proctitis. Grade 0 (n=96), Grade 1 (n=21) and Grade 2 (n=6)



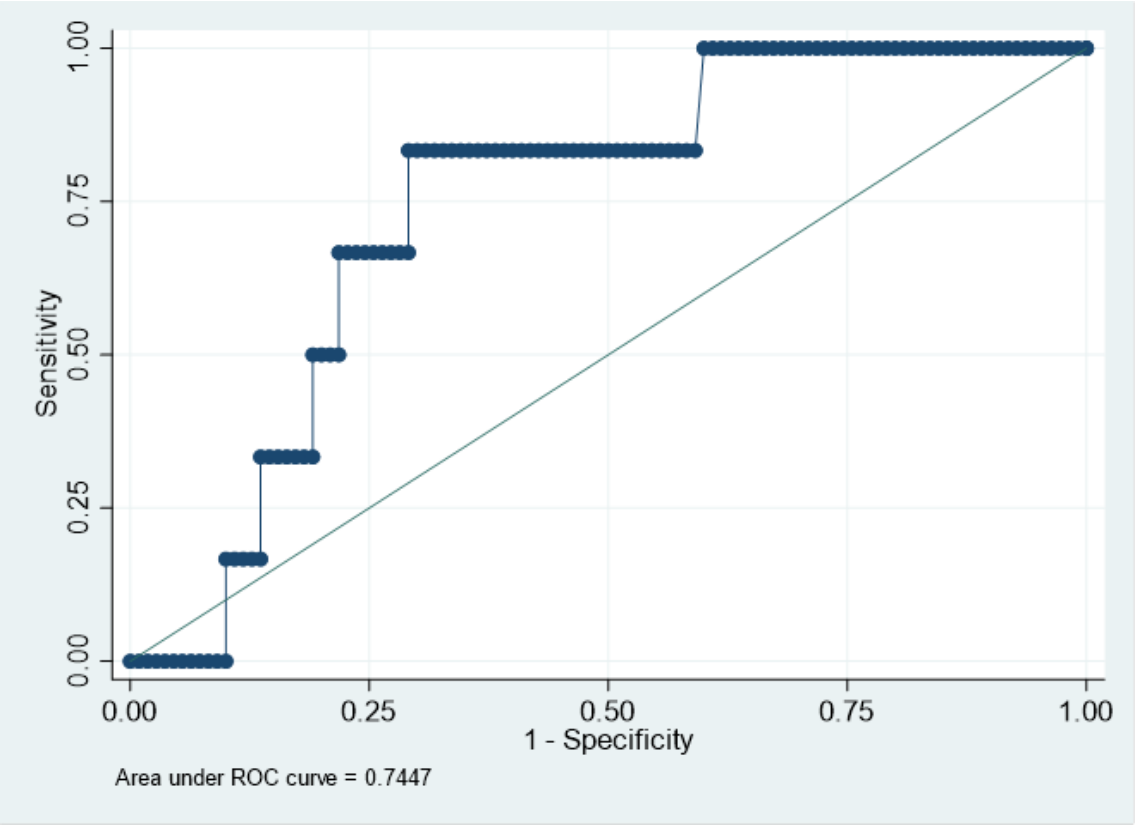


Figure 30. The ROC curve analysis for total small bowel volume and maximum RTOG Grade 2+ proctitis. The data points correspond to sensitivity/specificities of total small bowel volumes of 284cc, 100% sensitivity /40% specificity; 446cc 83% sensitivity /71% specificity; 507cc 67% sensitivity/78% specificity;525cc 50% sensitivity/81% specificity; 572cc 33% sensitivity/86% specificity; 774cc 0% sensitivity/100% specificity.

Receiver operator curves were calculated using excel for the V0Gy of small bowel and grade 2+ proctitis (Fig 30). The V0 for small bowel has an AUC of 0.74, (95% CI 0.59-0.90). All other examined dose volume points had 95% confidence intervals crossing AUC 0.5 and showed no effect For small bowel volume ≥ both 507cc and 446cc there was a high risk of Grade ≥2 side effects (67% sensitivity/78% and 83% sensitivity /71% specificity respectively) but for volumes less than 284cc no Grade ≥2 side effects were apparent.

Diarrhoea

There was no significant difference between the mean small bowel volumes receiving between 0-60Gy in patients experiencing RTOG grade 0 vs 1+ or grade 0-1 vs grade 2+ diarrhoea. The results are in tables 31 and 32 below and appendix 6.

Table 31. Mann-Whitney U test to compare the mean volume of small bowel receiving 0-60Gy in patients with RTOG Grade 2+ and Grade 0-1 diarrhoea at 24 months

	RTOG diarrhoea at 24 months	Mean volume (cc)	SD (cc)	*P* value
Total small bowel	Grade 0-1 n=116 (96%)	357.4	179.2	0.345
	Grade 2+ n=5 (4%)	282.0	251.1	
V10	Grade 0-1	126.4	167.9	0.677
	Grade 2+	143.1	213.9	
V20	Grade 0-1	97.5	136.8	0.726
	Grade 2+	104.9	156.9	
V30	Grade 0-1	57.5	86.9	0.870
	Grade 2+	77.3	119.7	
V40	Grade 0-1	24.2	39.2	0.926
	Grade 2+	40.9	60.8	
V50	Grade 0-1	8.2	15.1	0.930
	Grade 2+	9.6	13.3	
V60	Grade 0-1	0.2	1.0	0.537
	Grade 2+	0.1	0.2	

Table 32. Mann-Whitney U test to compare the mean volume of small bowel receiving 0-60Gy in patients with maximum reported late RTOG Grade 2+ and Grade 0-1 diarrhoea

	Maximum late RTOG diarrhoea	Mean volume (cc)	SD (cc)	*P* value
Total Small bowel	Grade 0-1 n=109 (90%)	353.7	182.1	0.971
	Grade 2+ n=12 (10%)	343.8	190.1	
V10	Grade 0-1	126.6	170.8	0.833
	Grade 2+	111.9	151.7	
V20	Grade 0-1	98.4	139.8	0.936
	Grade 2+	81.4	112.2	
V30	Grade 0-1	57.7	88.9	0.924
	Grade 2+	55.7	82.5	
V40	Grade 0-1	24.0	40.0	0.794
	Grade 2+	28.3	42.1	
V50	Grade 0-1	8.2	15.6	0.686
	Grade 2+	7.6	9.5	
V60	Grade 0-1	0.2	1.1	0.192
	Grade 2+	0.3	0.5	

4.6.3 Sigmoid Colon

No significant difference was seen in the mean sigmoid bowel volume of patients experiencing any grade of RTOG proctitis or diarrhoea. The results are displayed below in tables 33-35 below and appendix 6.

Table 33. Mann-Whitney U test to compare the mean volume of sigmoid bowel receiving 0-70Gy in patients with maximum late RTOG Grade 1+ and Grade 0 proctitis

	Maximum late RTOG proctitis	Mean volume (cc)	SD (cc)	*P* value
Total sigmoid	Grade 0 n=96 (79%)	119.7	66.0	0.843
	Grade 1+ n=25 (21%)	119.1	57.7	
V10	Grade 0	63.8	65.4	0.392
	Grade 1+	52.5	61.8	
V20	Grade 0	56.5	61.1	0.335
	Grade 1+	45.6	59.0	
V30	Grade 0	48.3	54.5	0.429
	Grade 1+	40.1	54.7	
V40	Grade 0	34.1	38.9	0.519
	Grade 1+	29.1	38.8	
V50	Grade 0	17.0	14.8	0.649
	Grade 1+	14.7	18.5	
V60	Grade 0	1.4	0.8	0.772
	Grade 1+	0.8	1.6	
V70	Grade 0	0.0	0.2	0.155
	Grade 1+	0.0	0.0	

Table 34. Mann-Whitney U test to compare the mean volume of sigmoid bowel receiving 0-70Gy in patients with maximum reported late RTOG Grade 2+ and Grade 0-1 proctitis

	Maximum late RTOG proctitis	Mean volume (cc)	SD (cc)	*P* value
Total sigmoid	Grade 0-1 n=115 (95%)	119.2	64.7	0.497
	Grade 2+ n=6 (5%)	127.3	53.7	
V10	Grade 0-1	61.0	65.0	0.613
	Grade 2+	67.6	61.2	
V20	Grade 0-1	53.5	60.7	0.537
	Grade 2+	65.0	62.8	
V30	Grade 0-1	45.7	54.0	0.427
	Grade 2+	62.1	64.2	
V40	Grade 0-1	32.0	37.6	0.356
	Grade 2+	52.5	56.9	
V50	Grade 0-1	14.3	16.9	0.226
	Grade 2+	24.7	22.9	
V60	Grade 0-1	0.8	1.5	0.788
	Grade 2+	0.4	0.4	
V70	Grade 0-1	0.0	0.2	0.526
	Grade 2+	0.0	0.0	

Table 35. Mann-Whitney U test to compare the mean volume of sigmoid bowel receiving 0-70Gy in patients with maximum late RTOG Grade 2+ and Grade 0-1 diarrhoea

	Maximum late RTOG Diarrhoea	Mean volume (cc)	SD (cc)	*P* value
Total Sigmoid bowel	Grade 0-1 n=109 (90%)	118.9	63.3	0.812
	Grade 2+ n=12 (10%)	109.7	49.2	
V10	Grade 0-1	59.7	62.3	0.985
	Grade 2+	57.4	56.7	
V20	Grade 0-1	53.2	60.1	0.905
	Grade 2+	50.6	55.1	
V30	Grade 0-1	45.8	54.1	0.826
	Grade 2+	45.2	55.2	
V40	Grade 0-1	32.0	37.4	0.854
	Grade 2+	35.2	47.1	
V50	Grade 0-1	13.9	15.8	0.864
	Grade 2+	16.7	21.1	
V60	Grade 0-1	0.8	1.5	0.729
	Grade 2+	1.0	1.6	
V70	Grade 0-1	0.0	0.2	0.354
	Grade 2+	0.0	0.0	

4.6.4 Large bowel

There was no significant difference seen in the mean volume of large bowel of patients experiencing different grades of RTOG proctitis or diarrhoea. The results are shown in tables 36 and 37 below in appendix 6.

Table 36. Mann-Whitney U test to compare the mean volume of large bowel receiving 0-50Gy in patients with maximum reported late RTOG Grade 2+ and Grade 0-1 proctitis

	Maximum late RTOG Proctitis	Mean volume (cc)	SD (cc)	*P* value
Large bowel	Grade 0-1 n=115 (95%)	61.8	62.7	0.547
	Grade 2+ n=6 (5%)	73.8	67.7	
V10	Grade 0-1	20.3	44.0	0.196
	Grade 2+	30.3	40.4	
V20	Grade 0-1	13.4	30.7	0.179
	Grade 2+	20.7	34.3	
V30	Grade 0-1	6.1	16.2	0.209
	Grade 2+	8.2	15.7	
V40	Grade 0-1	2.0	5.9	0.623
	Grade 2+	2.4	4.5	
V50	Grade 0-1	0.6	1.8	0.969
	Grade 2+	0.5	1.3	

Table 37. Mann-Whitney U test to compare the mean volume of large bowel receiving 0-50Gy in patients with maximum reported late RTOG Grade 2+ and Grade 0-1 diarrhoea

	Maximum late RTOG Diarrhoea	Mean volume (cc)	SD (cc)	*P* value
Total Large bowel	Grade 0-1 n=109 (90%)	61.4	63.2	0.602
	Grade 2+ n=12 (10%)	70.7	62.9	
V10	Grade 0-1	21.4	44.8	0.576
	Grade 2+	17.9	36.9	
V20	Grade 0-1	14.3	31.5	0.652
	Grade 2+	11.3	25.9	
V30	Grade 0-1	6.4	16.7	0.914
	Grade 2+	5.1	11.4	
V40	Grade 0-1	1.9	6.1	0.598
	Grade 2+	1.7	3.5	
V50	Grade 0-1	0.6	1.9	0.989
	Grade 2+	0.5	1.1	

4.6.5 Rectum

There was no significant difference in the mean volume of rectum seen in patients experiencing different grades of RTOG proctitis and diarrhoea. The results are shown in table 38 below and in appendix 6. The mean rectal volume was 63.9cc with V10 of 92%, V20 of 85%, V30 of 74%, V40 of 56%, V50 of 37%, V60 of 20%, and V70 of 4% respectively. For comparison the optimal rectal dose target constraints were V40 65%, V50 50%, V60 35% and V70 15%. The recently published new rectal dose constraints calculated from CHHiP Trial data included V50 of 39.1% and V60 of 27.3% (44). Both the standard and more recent stricter constraints were readily met in the PIVOTAL patient cohort.

Table 38. Mann-Whitney U test to compare the mean volume of rectum receiving 0-70Gy in patients with maximum reported late RTOG Grade 2+ and Grade 0-1 diarrhoea

	Maximum late RTOG Diarrhoea	Mean volume (cc)	SD (cc)	*P* value
Total Rectum	Grade 0-1 n=109 (90%)	64.3	18.6	0.599
	Grade 2+ n=12 (10%)	60.4	12.9	
V10	Grade 0-1	58.8	18.5	0.751
	Grade 2+	55.9	12.6	
V20	Grade 0-1	54.1	18.6	0.978
	Grade 2+	52.6	11.4	
V30	Grade 0-1	47.2	16.7	0.697
	Grade 2+	47.2	10.2	
V40	Grade 0-1	36.0	13.2	0.520
	Grade 2+	36.1	10.2	
V50	Grade 0-1	23.8	9.5	0.779
	Grade 2+	24.1	8.1	
V60	Grade 0-1	11.3	4.8	0.631
	Grade 2+	5.1	12.5	
V70	Grade 0-1	2.7	1.5	0.717
	Grade 2+	2.8	1.1	

4.7 Discussion

The PIVOTAL study was designed to explore the safety of delivering dose escalated pelvic radiotherapy in a multicentre setting and build upon the safety record established in the Phase I/II pelvic IMRT trial. The established dose constraints and newly developed PIVOTAL contouring methodology outlined in chapter 3 rely upon individual bowel loop outlines. The overall late GI toxicity levels for the whole trial cohort were low and the patient reported late IBDQ scores and Vaizey incontinence scores were very similar to pre-treatments values. Furthermore, the late toxicity results did not indicate a substantial increased late GI toxicity in the patients receiving pelvic IMRT compared to those receiving prostate only IMRT. At 24 months RTOG Grade 2+ proctitis was reported in 1 patient (1%) of the PORT group and 2 patients (4%) of the WPRT group. RTOG Grade 2+ diarrhoea was reported in 3 patients (5%) of the PORT group and 2 patients (3%) of the WPRT group. The similarity in outcomes between the two trial groups was consistent using both clinician and patient reported outcome measures. These results reflect the findings of some other retrospective studies where patients were treated with lower doses of PLN radiation. An increase in late GI toxicity was not seen in patients who had PLN IMRT compared to patients who received prostate only or prostate bed only IMRT (29, 30).

My work aimed to investigate if these dose constraints could be further refined using the dose–cube data derived from individual patient treatment plans in correlation with the toxicity they experienced. In particular, if anything further could be learnt about the dose volume relationship by segmenting the total bowel volume into component parts and analysing the sigmoid and small bowel separately. I used the late toxicity results as a surrogate for the more long-term impact of pelvic RT which can affect quality of life.

4.7.1 Dose /volume relationships in the PIVOTAL trial

For all trial patients, the total volume of bowel and separate components of small bowel, sigmoid bowel and other large bowel were examined for a relationship with RTOG late toxicity.

The mean volume of total bowel in the pelvis (represented by V0) was significantly larger in patients experiencing late grade 2+ proctitis compared to those experiencing grade 0-1 proctitis. This difference was apparent in the toxicity results at 24 months as well as the maximum experienced late toxicity results (total bowel volume 698cc Grade 2+ vs 534cc Grade 0-1, p=0.04). When the anatomical components of bowel were analysed separately, the mean volume of small bowel in the pelvis was also significantly higher in patients experiencing grade 2+ proctitis compared to grade 0-1+ proctitis (small bowel volume 490cc Grade 2+ vs 347cc Grade 0-1, p=0.04). The difference between total and small bowel volumes in patients with or without Grade 2 proctitis was similar at 164cc and 153cc respectively. The volumes of sigmoid colon and other large bowel did not appear to relate to proctitis.

The total bowel had an average volume of about 540cc and small bowel made up the largest component of this with an average volume of 350cc. The next largest component of pelvic bowel was the sigmoid which had a volume of around 120cc followed by other large bowel at 64cc.

While the volume of total and small bowel at other dose points were not significantly related to Grade ≥2 RTOG proctitis, it is noteworthy that the volumes of both total and small bowel in the range of 10-50Gy were approximately doubled in the small group of patients with RTOG grade 2 toxicity (Table 29,31,37,39 fig 27,30). For example, at 50Gy, for maximum Grade 2 proctitis, mean total and small bowel volumes were 22.7cc vs 40.9cc and 7.8cc vs 15.7cc respectively for patients with or without Grade 2 side effects.

ROC analysis showed AUC values of 0.75 and 0.74 respectively for total and small bowel which is in the range of values 0.7 to 0.8 considered acceptable. The “cut-off” values for discriminating between patient populations with low/high risk of developing toxicity depend on trade-offs between sensitivity and specificity. For sensitivities of 67% /83% total bowel and small bowel volumes were 766cc/510cc and 507cc/446cc respectively with specificities of 85%/53% and 78%/71% respectively.

The upper quartile for mean total or small bowel volumes were 675cc and 500cc in the PIVOTAL trial. These fall between the potential cut-off values described in the ROC curves above. I would suggest that a pragmatic approach would be to carefully review radiotherapy planning in these higher risk patients with a view to modification of prescribed dose or treated volume.

The mandatory and optimal total bowel volume dose constraints in the trial for V50 were set at 110cc and 17cc respectively. In a recent separate analysis of the Pelvic IMRT study (which used the same dose constraints) it was suggested that the previous "optimal" dose constraints should now be the target doses for IMRT/VMAT planning and that the optimal bV50 constraint should be updated to 24 cm^3 instead of 17 cm^3 as results showed this level to be more appropriate for predicting gastrointestinal side-effects (45). My present analysis lends support to this suggestion demonstrating that this new constraint was met in the majority of PIVOTAL patients and that the "mandatory" constraints may be more liberal than desirable.

It is interesting that bowel volume was related to proctitis but not diarrhoea. Grade 2 diarrhoea was very uncommon with only 5 patients (4%) with symptoms at 2 years and 12 patients (10%) at any time. Small numbers may have obscured any dose volume effects and this was probably because of the strict and successful application of dose constraints. Diarrhoea is characterised by loose and frequent stool. Proctitis is a misnomer for late reactions as it is not an inflammatory process. A better term is "radiation proctopathy" which in the chronic setting is characterised by the pathological changes of ischemia and fibrosis (46). Symptoms that may manifest include diarrhoea, rectal bleeding, painful defecation, incontinence, and excess flatulence. Symptomatically "proctitis" is therefore a term which may well capture the impact of radiation on the bowel more generally rather than being confined to rectal pathophysiology and this may explain the perhaps counter-intuitive findings in this analysis. Another surprising finding in the PIVOTAL cohort was that there was no relationship shown between rectal dose/volume parameters and "proctitis". This may relate to radiation to other parts of the bowel contributing to proctitis. At 24 months only 2% of patients had Grade 2 rectal bleeding (table 26) which is well known to relate to high rectal dose (47) but rectal urgency was present in 4% (table 26) which

is not necessarily due to rectal irradiation. Additionally, rectal doses were modest with mean dose/volume parameters not only meeting the optimal constraints used in the trial but also the new constraints derived from the recent CHHiP data analysis (44)***.***

Given the very small numbers of patients experiencing grade 2+ toxicity, the association of total and small bowel volume in the pelvis and side effects need to be regarded as exploratory and interpreted with caution. Other larger studies including the PIVOTAL boost UK national trial (ISRCTN80146950) are ideally needed to validate findings in larger cohorts of patients.

4.7.2 Dose /volume relationships in other studies

To my knowledge there are two published studies that have investigated the relationship between individual bowel components and toxicity. The first study by Fonteyne et al (31) described patients that were treated with primary prostate IMRT to 74-80Gy (n=360) or post-operative IMRT to the prostate bed at 74Gy (n=209). The sigmoid and small-bowel in the field were outlined. For planning the same constraints were applied to the sigmoid as the rectum and the only objective for small bowel was the maximum dose of 70Gy. They reported the maximum sigmoid dose was a predictor for late GI toxicity on univariate analysis and that the sigmoid irradiated to intermediate doses (S_{40}-S_{65}) predicted for a series of GI symptoms including grade 1 diarrhoea.

The group advocated applying the same volume parameters for sigmoid colon as for rectum. However, the constraints used for the rectum were more relaxed than those used in current practice. For example, for a patient treated with primary prostate IMRT to a dose of 74Gy, the constraints were V50 <100%, V60 <60%, V70<20%, whereas our rectal constraints were V50 ≤60%, V60≤50%, V70 <15%. Furthermore, in the PIVOTAL trial, the sigmoid colon was treated to the same constraints as the rest of the bowel which was much more conservative (V50 ≤110cc, V60≤6cc, V65≤0cc, see table 1). No predictive volume parameters were found for small bowel, but the radiation field only included low volumes of small bowel and fewer than 20% of the patients had parts of the small bowel irradiated up to 50-60Gy.

A more contemporary study by Sini et al (32) used the patient reported tool IBDQ to record acute toxicity from whole pelvic IMRT in 206 patients. Of these, 159 patients were having post-operative radiotherapy. The median dose to the pelvis nodes was 51.8Gy (range 50.4–54.4, 1.7–2Gy/#), the prostatic bed was 71.4Gy (66.6-78Gy) and prostate was 77Gy (70-80Gy). The sigmoid bowel was outlined separately from the rest of the bowel. With respect to IMRT planning optimization, no specific constraints were specified, and the radiation oncologists of each Institute were permitted to follow their own internal guidelines. The only requests concerning bowel dose reduction were: a) bowel loops and sigmoid should be considered as OARs during optimisation and the volume receiving more than 40-50Gy should be reduced as much as possible without reducing the coverage of PTVs; b) hot spots in these structures (defined as >60Gy) should be avoided; c) for the small bowel loops or sigmoid adjacent to the high-dose PTVs, the dose to the overlap between these structures and high-dose PTV should be kept below 56Gy whenever possible. The median baseline IBDQ score was 66 and this deteriorated to 61 at the mid-point and end of radiotherapy. The study did not report any correlation between dose to the sigmoid and the IBDQ clinical endpoints. However, with the small bowel, they found that a single IBDQ question regarding loose stools (IBDQ5) was associated with dose/volume parameters. The absolute mean DVH's in the range of 5-50Gy for patients who had less than -2 deterioration (IBDQ5 <-2, n=43) were significantly lower than those of patients who had a deterioration of more than -2 (IBDQ5 ≥-2, n=148). Three parameters representing "low" (V20), "intermediate" (V30) and high (V42) dose values were considered with the aim of characterising the whole DVH. The best cut-off points (assessed by ROC curves) discriminating between patients with and without loose stools were V20≤470cc, V30≤245cc and V42≤110cc. Patients with all three constraints breached were considered high risk and the study found that these patients had a higher density of bowel loops in the intestinal cavity. Of note, all of the above listed dose volume constraints are significantly higher than those permitted in the IMRT and PIVOTAL studies.

4.7.3 Limitations

4.7.3.1 Accounting for bowel motion

One of the main limitations in the methodology was using a single planning scan to estimate pelvic bowel dose as it only provides a snapshot in time of the anatomical distribution of bowel. Small bowel is known to be mobile during a course of radiation and studies have reported that only about 20% of the bowel is occupying the same position in the intestinal cavity during a course of treatment (33-35). When pelvic radiation was being delivered using conventional fields, large volumes of bowel were exposed to high doses, which may have meant that the movement of bowel during treatment would not have necessarily resulted in a significant difference to the dose that bowel received. However, the sharper dose fall-off with IMRT may mean that bowel is moving in and out of high dose regions throughout treatment and the planning scan may give a poor estimate of the delivered bowel dose.

In a planning study Hysing et al (33) found that a margin of 3cm around bowel loops was required to account for all intestinal motion in 90% of patients. But if only taking into account the volume that contained bowel for at least 50% of the treatment time, a 1cm margin would cover 90% of the volume in 90% of the patients. The intestinal cavity definition accounts for the varying positions of bowel during treatment. Additionally, planning is faster than outlining individual bowel loops. However, no information is gained about the volume of bowel loops contained within the cavity. There have also been multiple small pelvic radiotherapy studies investigating the use of the intestinal cavity definition as a surrogate for individual bowel loops (34, 36-39) in a variety of cancer types However to my knowledge there has been no comprehensive assessment of the bowel-bag as a useful parameter to determine robust dose volume constraints. One study by Sanguinetti (34) was performed in 9 patients with prostate cancer treated with prostate and pelvic IMRT. The pelvic nodal dose was 55Gy in 1.8Gy per fraction. Patients were planned using the bowel loop definition, but additional structures of bowel with a 1cm margin (BS+1cm) and intestinal cavity (IC) were also created for each plan. Weekly cone beam CT scans were used to investigate the position of bowel in the radiation field. Over the course of treatment ~280cc of bowel fell out of the bowel loops volume, compared with ~75cc of

IC ($p<0.001$) and ~30cc of BS+1cm ($p<0.001$) regardless of the treatment week. Three IMRT plans were created for each of the 9 patients using the three different bowel definitions. The PTV coverage and bowel DVH was similar for all three definitions, but over the course of treatment, the bowel V45 was significantly higher in patients planned using the bowel loop definition compared to BS+1 ($p=0.008$) or IC ($p=0.03$). The authors concluded that the bowel loop definition might underestimate the V45 during treatment in the order of 10% and recommended using the IC definition of bowel due to its ease of use and similar results to BS+1cm. However, there was no attempt to correlate the methods with clinical outcomes

Bowel loop definition only gives a snap shot of the position of bowel at the time of planning, which may therefore underestimate the bowel in the high dose volume or radiation field throughout treatment. But the advantage of this definition is that it at least provides a reasonable estimate of the total volume of bowel in the radiation field. Secondly and most importantly it is the method used to establish the dose volume constraints most commonly used for bowel and validated in this study and others. Application of these constraints has been associated with low levels of side effects. In comparison there is currently a lack of prospectively gathered toxicity data to validate any suggested intestinal cavity constraints at present.

4.7.3.2 Patient factors

Patients related factors may influence the development of radiation toxicity even if dose volume tolerances are respected. Multiple patient related factors have been shown to influence toxicity – such as age >75, Diabetes, cardiovascular disease, smoking status and arthritis and abdomino-pelvic surgery. Genetic factors are also likely to influence individual patient risk of radiation toxicity; Radiogenomics describes an emerging field which is investigating how individual genetic variation is associated with the development of early and late radiation toxicity (51). Variations in the genes associated with repair pathways, cell cycle arrest and immune response may increase the radio-sensitivity of tissues and relate to radiation side effects (40). There is also interest in the gut microbiota which may play a role in the individual immune response and development of late radiation damage (41). In the future there may be several

patient related factors that predict for the risk of toxicity and need to be considered when picking the appropriate patients for pelvic irradiation.

4.7.3.3 Radiation toxicity assessment

There are also issues with the definition of late GI toxicity. Patients may present with a range of symptoms which may relate to toxicity, or be caused by a number of other conditions which can co-exist with toxicity (42). The future development of objective endpoints for toxicity would therefore be useful in future studies investigating the radiation dose- toxicity relationship.

4.7.4 Conclusions

The dose and volume relationships for bowel toxicity are debated in the literature and the majority of the data informing current constraints is based on outdated radiation techniques in diverse patient populations. However, in the PIVOTAL trial, the dose constraints used in combination with the target volumes and planning techniques in this patient cohort have resulted in low levels of late toxicity using both clinical and patient reported toxicity scores. Both higher total bowel volume and small bowel volume outlined in the pelvis were associated with Grade 2 toxicity demonstrated with ROC analysis AUCs of 0.75 and 0.74 respectively. This data suggests that patients with total or small bowel volumes > 675cc and >500cc respectively (corresponding to the upper quartiles) might be reviewed with regard to dose reduction or LN target volume modification. However, small patient numbers mean that these finding would need to be interpreted with caution and validated. In the dose range 10Gy-50Gy about twice the volume of both total and small bowel was treated in patients with Grade 2 side-effects, although this was not statistically significant perhaps due to the overall low number of patients with side effects. Nevertheless, the bowel volumes treated in patients with ≤ grade 1 toxicity are supportive of the optimal dose/volume constraints used in both the PIVOTAL and pelvic IMRT trial, including the recent modification suggested by Ferreira and colleagues (45).

I did not find that segmenting the bowel into its different components to be of advantage which is in accord with the present RTOG guidance (48).

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Chapter 5 Discussion

Patients with high risk localised prostate cancer carry a significant risk of local recurrence, distant metastases and dying from prostate cancer, even If they are diagnosed with non-metastatic disease and receive appropriate treatment in accordance with current guidelines (1).

There is good evidence from extended pelvic lymph node dissections that these patients carry a significant risk of occult pelvic nodal disease (2) and it would stand to reason that left untreated, this will have a negative impact on overall disease control.

Historically patients with clinically node positive prostate cancer were treated with ADT alone. However, newer evidence suggests they will benefit from the addition of local treatment to the prostate and pelvic nodes (3, 4). In contrast to this, the role of elective pelvic nodal treatment remains unproven in patients with high risk node negative disease. There have been multiple retrospective studies investigating the role of WPRT with mixed results (5-10) and three randomised controlled trials (11-13) that have been negative. However, limitations in the trial methodologies and radiation delivery may account for the negative results, leaving the role of pelvic lymph node thus far unanswered.

The development of intensity modulated radiotherapy has improved the toxicity profile for whole pelvic radiotherapy (14). It has also created the opportunity for dose escalation, which has already been established as key in improving disease control in the context of prostate radiation (15-17). Both of these features may improve the therapeutic ratio for WPRT. The aim of my thesis was to explore methods of refining pelvic lymph node IMRT in order to improve target coverage while maintaining acceptable toxicity.

5.1 Chapter 2. Outcomes and patterns of recurrence in advanced localised prostate cancer using prostate and pelvic IMRT and long course ADT

The IMRT Trial (18) was a single-centre phase I/II study explore dose escalated and hypofractionated IMRT to the prostate and pelvic lymph nodes (PLN) in patients with

advanced localized prostate cancer. 426 patients were sequentially treated 5 cohorts. Cohorts 1, 2 and 3 received 70-74Gy in 35-37 fractions to the prostate and 50Gy (cohort 1), 55Gy (cohort 2) or 60Gy (cohort 3) to the PLN. Two additional hypofractionated cohorts were treated with 60Gy in 30 fractions to the prostate and 47Gy to the PLN in either 5 days/week (cohort 4) or 4 days/week (cohort 5). All patients were treated with long course hormone therapy. My hypothesis was that dose escalated pelvic IMRT achieves a low rate of pelvic lymph node relapse, with relapses occurring outside the target volume

Aims;

1. To establish the anatomical pattern of disease relapse in all trial patients

2. To correlate pelvic lymph node relapses with respect to the planned radiation treatment volume in order to establish if a dose response effect is evident.

For the whole trial cohort, the most common site of relapse was distant metastatic disease, affecting 23% of patients. The next most common site of relapse was in the prostate, affecting 10% of the cohort and the least common site of failure was the pelvic nodes, affecting only 6% of the cohort. Overall this anatomical pattern of disease relapse was very similar for patients treated in all five cohorts.

In the 26 patients with pelvic nodal relapse, the most common site of recurrence was at the proximal common iliac nodes that lie just above the radiation field and was involved in 77% (20/26) of patients. This work confirmed that pelvic IMRT is effective at controlling pelvic nodal disease, with very few pelvic nodal relapses in the radiation field. There was no clear dose gradient for pelvic nodal control apparent from the data. The trial results suggest that metastatic disease and local relapse are the most significant risks to this patient population and may play a greater overall role in the outcomes of high risk patients than pelvic nodal control. Treatment intensification should therefore first focus on reducing these risks in order to have the greatest impact on overall disease control.

5.2 Chapter 3. Evaluating pelvic lymph node target contouring guidelines using Choline PET CT

The aim of IMRT is to cover the target as closely as possible whilst minimising the radiation dose to adjacent normal tissues. In order to achieve this without geographically missing the target, accurate target definition is crucial. The advent of 3D-CRT and IMRT lead to the development of pelvic lymph node target volumes using data from vascular mapping studies. These studies assessed the spatial distribution of lymph nodes around the pelvic vessels and the information was used to develop the RMH pelvic contouring guidelines used in the IMRT trial. Following this, a phase II trial (PIVOTAL) was planned and the original pelvic lymph node contouring methods were adjusted for multicentre use. Choline-PET CT scans were used in clinical practice at the RMH from 2012 to stage high risk prostate cancer patients and identify occult nodal and metastatic disease.

My hypothesis was that 75% of the pelvic nodes identified would be covered by the pelvic nodal contours

The following objectives test the hypothesis;

1) identify a group of prostate cancer patients with pelvic node positive disease identified on Choline-PET CT who had undergone prostate and PLN RT.

2) Establish the proportion of cases where a CTV (and PTV) based on the PIVOTAL contouring guidelines cover the Ch-PET identified PLN disease.

2) Consider any modifications to the CTV (and PTV) which might consistently improve PLN coverage and how they impact organs at risk.

Of the 83 Choline-PET CT identified nodes mapped out, 55 (66%) were adequately covered by the radiotherapy contours. The majority of nodes that were poorly covered fell just outside the contours, predominantly in the proximal common iliac and pre-sacral regions. Modifications to the CTV were considered. Extending the contours caudally and anteriorly to improve pre-sacral node coverage would increase the

volume of rectum and bowel being irradiated and a substantial part would receive close to the pelvic nodal prescription dose.

Extending the contours cranially to improve coverage of the common iliac nodes would result in larger volumes of bowel being exposed to doses of radiation under 30Gy. Most of the data available on the dose volume relationship between radiation and bowel suggests that doses upwards of 40Gy (19) have a more significant impact on toxicity. However, the QUANTEC report also reported that the volume of bowel receiving 15Gy is also a key predictor of toxicity (20). While there is no data reporting the GI toxicity of an extended field of radiation at this dose fractionation schedule and patient population, data from cervical cancer patients treated with chemo-radiation suggests extending the field would result in increased acute and late toxicity (21, 22).

In summary, due to the potential risk of in increased GI toxicity, no blanket modifications to the contours were suggested. Instead, an approach of using the standard CTV, unless pelvic nodes were identified on sensitive imaging (for example PSMA-PET, Choline PET, or MR using USPIO contrast) that required bespoke modifications in order to be covered. The development of more sensitive well validated imaging techniques to identify pelvic nodal involvement will further support this approach in the future.

5.3 Chapter 4. Investigating the bowel dose volume relationship in patients treated within the PIVOTAL trial

The phase 1/2 IMRT trial reported toxicity using clinical reported toxicity assessments and the dosimetric analysis relied upon contemporaneously recorded volumes used for the purposes of ensuring the dose-volume constraints were met. Detailed dose-cube data was not available. For the PIVOTAL trial the full DVH information and prospectively gathered patient reported as well clinician reported outcomes are available. Therefore, I used this data with the aim of assessing the bowel dose volume relationship for reported late GI toxicity. My aim was to identify any further refinements that can be made to the currently used bowel dose constraints in order to improve the toxicity profile of pelvic IMRT.

My hypothesis was that late toxicity results and bowel dose information could be used to refine the current bowel dose constraints.

Aim;

3. To Establish any significant correlation between the volume of bowel treated to 0-70Gy and development of late toxicity.

4. To Identify if radiation dose to any anatomical subtype of bowel is particularly associated with the development of late toxicity

Using the most common late toxicity scores of RTOG diarrhoea and proctitis, no significant correlation was found between radiation dose to the sigmoid, large bowel, rectum and toxicity was seen. No relationship between the volume of small bowel or total bowel exposed to radiation doses of 10-70Gy was seen and no refinements to the dose constraints are suggested.

Patients in the trial experiencing late RTOG grade 2+ proctitis had significantly increased total bowel and small bowel in the pelvis compared to those patients who experienced only grade 0-1 proctitis. The difference was significant in the 24 month toxicity results and maximum experienced late toxicity results. These results are interpreted with caution given the small numbers of patients experiencing grade 2+ toxicity and ideally should be validated in larger cohort of patients. Nevertheless, the ROC analysis with AUC of 0.75 and 0.74 suggested that patients with greater total and small bowel volumes should have dose prescription or planning modifications considered. I suggest that making modifications for patients with total bowel volumes ≥675cc or small bowel volumes ≥500cc which correspond to the upper quartiles observed in the PIVOTAL trial would be reasonable.

Overall it would appear that the total bowel volume rather than a particular dose/volume response relationship is important in identifying patients at high risk of late bowel side-effects provided the dose constraints in the trial have been respected. This could relate to bowel mobility and the imprecision of prediction of dose to particular bowel loops adjacent to the pelvic LN target volume based on the single

snap-shot of a planning CT scan. One strategy might be to decrease the prescribed dose. Dose reduction is reasonable as the PIVOTAL trial dose of 60 Gy in 37 fractions is considerably higher (EQD2 of about 54Gy and 56Gy for alpha/beta ratio of 2Gy or 3Gy respectively) than a typical pelvic LN dose of 46 Gy in 23 fractions. The alternative solution of target volume restriction reduces common iliac or pre-sacral LN coverage and would increase risk of geographic miss. Such a decision can usefully be made after target and normal tissue outlining but before dosimetry planning so as to avoid time-consuming re-planning.

Overall, this work demonstrates that the currently used dose constraints for pelvic IMRT result in a favourable toxicity profile for PORT and WPRT.

5.4 Future Directions

Since I have embarked on this work, new data has emerged to support the early use of systemic treatments such as Docetaxel chemotherapy (23) and Abiraterone (24) in patients with hormone sensitive high risk localised prostate cancer. For high risk patients, both Docetaxel and abiraterone have been shown to improve disease free survival thus far (23,24) and both agents improve both cause specific and overall survival in metastatic disease (25) although this has not yet translated to a survival advantage in localised disease. Further follow-up will determine if these agents in addition to long course androgen deprivation will impact on the risk of developing and dying from metastatic disease in patients with high risk localised disease. The question arises of how these developments impact upon the role of elective PLN radiotherapy. If intensifying systemic treatment can eradicate micro-metastatic disease at distant sites, can it also treat microscopic nodal disease, obviating the need for radiotherapy to the PLN?

5.4.1 Trials

Some current research may help to answer these questions; The PEACE 2 trial (26) is currently recruiting in the US and investigating both pelvic IMRT and upfront systemic therapy with Cabazitaxel chemotherapy. It is a randomised controlled trial in high risk node negative patients with four arms. The standard arm will be treated

with 3 years of ADT and radiotherapy to the prostate using IMRT/IGRT at a dose of 74-78Gy. There are three experimental arms which include 1) The addition of pelvic IMRT/IGRT at a dose of 46-50Gy alongside prostate RT and 3 years of ADT, 2) 4 cycles of Cabazitaxel chemotherapy with prostate RT and 3 years of ADT and 3) 4 cycles of Cabazitaxel chemotherapy with prostate and pelvic RT and 3 years of ADT. Patients will be randomised in a 1:1:1:1 fashion. The primary endpoint is progression free survival and the secondary outcomes include biochemical progression and metastatic free survival, overall survival and acute and long-term toxicity.

The current PIVOTAL Boost trial (27) in the UK is also evaluating the role of pelvic radiotherapy in the context of dose escalation to the prostate. It is a phase III, multicentre, randomised controlled trial of prostate and pelvic radiotherapy versus prostate alone with or without a prostate boost. The four treatment arms are; A. prostate IMRT alone, B. prostate and pelvic IMRT, C. prostate IMRT and prostate boost, D. prostate and pelvic IMRT with prostate boost. The boost can be delivered with either IMRT or HDR brachytherapy and depends on a suitable boost volume being identified on MRI and the available services at the participating centres. The primary objective of the trial is to assess whether PLN radiotherapy with or without dose escalation to the prostate with HDR brachytherapy to the whole gland, HDR incorporating a focal boost, or focal boost IMRT can lead to improved biochemical control with similar levels genitourinary and bowel side effects experienced by patients. The primary endpoint is failure free survival and the secondary endpoints include disease specific endpoints, acute toxicity, late toxicity, quality of life and health economic endpoints.

The current RTOG 0924 phase III randomised controlled trial (28) is also investigating the role of WPRT in patients with unfavourable, intermediate risk or favourable high risk prostate cancer. In the standard arm patients will undergo high-dose radiotherapy to the prostate and seminal vesicles using intensity-modulated radiotherapy (IMRT) or 3D-conformal radiation therapy (3D-CRT) once daily, 5 days a week, for approximately 9 weeks with long or short course ADT. Patients may also undergo permanent prostate implant (PPI) brachytherapy or high-dose rate brachytherapy (I 125 or Pd 103 may be used as the radioisotope). In the experimental arm, patients WPRT using 3D-CRT or IMRT once daily, 5 days a week, for approximately 9 weeks. Patients may also

undergo brachytherapy as in the standard arm. The PLN RT has extended superior coverage to L4/5 and will provide important information about the clinical impact of this modification. The primary endpoint is overall survival and the secondary endpoints include biochemical relapse free survival, disease specific survival and acute and late toxicity.

5.4.2 Patient selection for WPRT

In the event that this emerging trial data does not demonstrate a clear benefit for the use of elective WPRT, identifying a sub-population of high risk patients to treat may be another future direction. Patient selection for treatment intensification may be guided by genomic information. Molecular biomarker tests (such as Decipher, Oncotype DX Prostate, Prolaris or Promark) have further refined risk stratification algorithms. While most of these tissue based tests for prostate cancer risk stratification and prognosis were developed for use in early stage disease (29), they are now being adapted and developed for more higher risk groups (29). No randomised trials have tested the utility of using molecular biomarkers so far. In the UK, tissue biopsy banks have been established from the CHHiP and STAMPEDE trials as well as the ICR/RMH pelvic IMRT trial and ongoing work will compare biomarker patterns with outcome.

Predictive biomarkers to improve the prediction of microscopic lymph node involvement and/or determine which patients may benefit most from WPRT are ideally needed. While there are no such biomarkers in clinical practice, several candidates are in development. Proteomic analysis has been used to identify proteins that might act as potential biomarkers for the early detection of lymph node metastases. Protein samples from patients with localised node negative prostate cancer, node positive prostate cancer and patients with benign prostatic hypertrophy were used. Six proteins were identified that are functionally relevant to cancer metastases and differentially expressed in node negative and node positive patients. Expression of these proteins was further validated in tissue samples of the same cohort and a larger independent cohort. The lymph node positive patients had increased expression of e-FABP5, MCCC2, PPA2, Ezrin, and SLP2 and decreased expression of SM22. All of which have the potential to be developed as potential diagnostic markers for the

presence of lymph node metastases (30). Microarray and next generation sequencing technologies have been used to identify hub genes for the development of lymph node metastases in prostate cancer using the cancer genome atlas database. The hub genes were identified as having significantly different levels of expression in patients with and without lymph node metastases, as well as an overall survival difference between those with low and high expression levels. Several targets were identified as potential biomarkers including the ARPC1A, CDCA8, CKAP2L and ERCC6L (31). Another group of novel serum biomarkers include circulating nucleic acids (miRNAs and DNA). Several independent studies have found raised serum levels of miR-141 and miR-375 in correlation with metastatic prostate cancer, higher Gleason score and positive lymph node status (32).

5.4.3 Moving away from elective WPRT

Since I embarked on this MD more is understood about the diverse nature of high risk prostate cancer which may mean that the concept of prophylactic WPRT for these patients should be reconsidered altogether. The perceived wisdom is that as in other epithelial cancers, lymph node metastases play an essential role in the development of distant metastatic disease. Studies looking at the evolution of prostate cancer and various sub-populations of cancer suggest that lymph node metastases could be a distinct biological and clinical entity rather than a precursor for more distant visceral or bony metastases (34). A small study looking at tumour phylogenesis revealed that lymph node metastases arise exclusively from cell clones in the region of extra prostatic spread and never from clones that are directly within the centre of the gland (35). There is also clinical data to suggest that lymph node disease at presentation or recurrence post treatment has a better prognosis than that of bony and visceral disease (36,37). Therefore, if patients are identified as having a high risk of metastatic bony or visceral metastases, this may suggest that systemic treatment needs to be prioritised over WPRT regardless of the risk of lymph node involvement. Additionally, with more sensitive and frequent imaging being used both pre and post treatment, the detection of pelvic nodal recurrences may be dealt with as and when needed without detriment to survival (33).

5.5 Conclusions

The work in this thesis supports the safety of elective pelvic lymph node IMRT and suggests it is effective in controlling pelvic lymph node disease. However, the exact pelvic nodes to cover, dose to deliver and patients to treat remains debated. The planning techniques and dose constraints used to deliver pelvic IMRT in the PIVOTAL trial are associated with a favourable toxicity profile for WPRT and no further refinements are recommended on the basis of my work except to modify treatment if extensive volumes of bowel are present in the pelvis.

Ultimately though, the role of elective PLN radiotherapy in improving the outcomes for patients with high risk prostate cancer remains uncertain. Biomarkers in development may lead to more personalised treatment plans for patients with high risk disease in the future and aid selection of patients who have the most to gain from PLN treatment. More sensitive imaging techniques detecting lymph node metastases may obviate the need for prophylactic treatment altogether. New developments in systemic therapy and dose escalation to the prostate may play a greater role in the overall management of these patients and even supersede the need for pelvic radiotherapy. The clinical trials and developments discussed above may help to clarify the role of pelvic radiotherapy in the context of these other forms of treatment intensification.

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Appendices

Appendix 1. IMRT Trial Protocol

FULL TITLE OF PROJECT

A Phase 1 dose escalation study of the use of intensity modulated radiotherapy (IMRT) to treat the prostate and pelvic nodes in patients with prostate cancer

SHORT TITLE: Pelvic IMRT for prostate cancer

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1) SUMMARY OF PROJECT

Intensity Modulated Radiotherapy (IMRT) is a new development of conformal radiotherapy. It allows the irradiation of concave tumours, and reduces the radiation dose to radiosensitive normal tissues close to or even surrounded by a tumour.
In the treatment of the pelvis with current radiation techniques, patients commonly experience side effects due to irradiation of small bowel, colon, bladder and rectum. In around 5% of patients these side effects can be serious enough to require surgical correction, and in addition this risk of side effects limits the dose that can safely be prescribed.

We have performed radiotherapy planning studies of pelvic irradiation, which suggest that IMRT reduces the volume of small bowel treated to radiation tolerance from 20% to 4-6%. Five fold reductions in the dose to rectum and bladders were also measured. We have delivered these treatments to phantoms showing a delivery accuracy of $\leq$2%. This project is to test the feasibility of delivering this novel radiotherapy technique to patients, and to perform a dose escalation study of pelvic node irradiation in men with prostate cancer to ascertain the optimal dose level for future studies.

2) BACKGROUND

Current techniques for pelvic radiotherapy are associated with considerable morbidity. This limits the dose of radiation that can be prescribed to 45-50 Gy using conventional 1.8-2.0 Gy daily fractions if significant quantities of bowel lie in the field. IMRT reduces the dose to bowel, and is likely to reduce treatment-related complications, and should allow dose escalation. If clinically proven, this would have a major impact on the treatment of prostate cancer on a National and International level. Additionally, the technique would have application to other pelvic tumours such as rectal cancer, anal cancer, and gynaecological tumours in the pelvis.

Results using pelvic lymph node irradiation in prostate cancer

Two large phase III trials evaluating the role of whole pelvic radiotherapy in patients with intermediate and high risk prostate cancer have been recently published(1, 2). Initial results of the 1,323 patient Radiation Therapy Oncology Group (RTOG) 94-13 trial(3), suggested pelvic radiotherapy (dose to whole pelvis 50.4 Gy in 1.8 Gy fractions) improved progression-free survival compared with prostate only radiotherapy (dose received 70.2 Gy in 1.8Gy fractions) among patients with a greater than 15% chance of pelvic lymph node involvement (as per the Roach formula)(4). With five year median follow-up, pelvic radiotherapy was associated with a 4 year progression-free survival rate of 54% (95% CI: 50-59) compared with 47% (42-52) in patients treated with prostate only (p=0.02). This study changed clinical practice for high risk patients in North America such that intermediate and high risk patients now receive whole pelvic radiotherapy. However, interpretation of this trial's results are complicated by the finding of a significant interaction between field size and timing of hormonal therapy (the trial also randomised patients, in a 2x2 factorial design, to neoadjuvant versus adjuvant hormone therapy, but was not powered to compare the four treatment arms one against the other). Recently updated results are less convincing, with no statistically significant difference seen between the two radiotherapy treatment groups: 5 year biochemical progression free survival was just under 50% in both groups (p=0.72; p=0.07 in favour of pelvic radiotherapy for patients receiving neo-adjuvant hormone therapy, p=0.06 in favour of prostate only

radiotherapy in patients receiving adjuvant hormone therapy (2). A detailed analysis of the toxicity of pelvic radiotherapy in this trial is not yet available.
GETUG-01, a smaller phase III trial of 444 patients conducted by the French FNLCC group, failed to show any difference between whole pelvic and prostate only radiotherapy: after a median follow-up of 42 months, five year progression-free survival was 63% (95% CI: 54-73) and 60% (51-69) in the high risk prostate alone and pelvis and prostate groups respectively (p=0.20) (1). The dose to the whole pelvis was 46Gy in 2Gy fractions and in both treatment groups the dose to the prostate was 66-70Gy in 2 Gy fractions. The GETUG group used a lower radiotherapy dose than RTOG, with a significant cohort being treated to 66Gy; median dose to the prostate was 68Gy. The superior border of the pelvic field was approximately 2cm lower (S1/S2 interspace) than in the RTOG trial. The GETUG trial included patients with high and low risk of lymph node involvement (<15/≥15% as per Roach formula) : >50% of patients had <15% risk - this may have contributed to the lack of an observed effect. The French study, by treating the prostate to a low dose by contemporary standards, may have a higher local failure rate diluting any possible benefit on regional control.
In general, the use of lymph node irradiation is limited to between 44 and 50Gy to avoid side effects which is probably a sub-optimal dose to destroy all micro metastases. Pre-clinical studies have shown that IMRT techniques can substantially reduce the bowel and bladder volume irradiated during pelvic radiotherapy. Bowel and colon irradiated to the 90% isodose level is reduced from 24% using conventional radiotherapy to 18% using conformal techniques but only 5% reaches this dose level using IMRT (5). Initial acute and late toxicity results are now available for the first two cohorts treated in this current study of IMRT. Low levels of both acute and late toxicity with target lymph node doses of 50 and 55 Gy (6) have been observed.

Treatment of lymph node positive patients

Despite the inevitable stage migration associated with PSA testing for asymptomatic patients, there is a sub-population of patients, who present with locally advanced node positive (N1) disease, whose optimal management remains uncertain. Various management approaches have been put forward in the literature; from not treating the primary tumour definitively and comparing timings of the initiation of hormonal deprivation therapy (7, 8) to aggressive surgical approaches (9, 10). Surgically treating patients has been shown to demonstrate a survival advantage for patients who have had a radical prostatectomy (RP) and a pelvic lymph node dissection (PLND) compared with a similar cohort whose pathologically positive nodes were not removed at the time of surgery(9).

There is limited evidence describing the use of radiotherapy and hormonal suppression in patients with locally advanced node positive prostate cancer. Non-randomised series (11, 12) have described overall and actuarial prostate cancer specific survival at 8 years of 72% and 87%. 50.4Gy in 1.8Gy fractions was delivered to the pelvic lymph node regions. These series compare more favourably to RTOG data on a separate group of patients who received radiotherapy as monotherapy with a similar dose delivered to the pelvic nodal regions (13), however, direct comparisons cannot be made. RTOG 85-31(14) evaluated the use of radiotherapy +/- hormonal therapy in patients with locally advanced prostate cancer; a subset analysis on patients who were node positive, with a median follow-up of 6.5 years for all patients and 9.5 years for living patients, estimated progression-free survival with prostate-specific antigen (PSA) level less than 1.5 ng/mL at 5 and 9 years was 54% and 33%, respectively, for patients who received immediate LHRH agonist versus 10% [corrected] and 4% for patients who received radiation alone with hormonal

manipulation instituted at time of relapse (P < .0001) (15). In the absence of results from randomised trials it appears appropriate to treat patients with locally advanced node positive disease with external beam radiotherapy and hormonal suppression.

Recently, Da Pozzo and colleagues (16) reported a retrospective study including 250 consecutive patients with pathologic lymph node invasion. All patients underwent RP and PLND plus adjuvant hormones &/or radiotherapy. After a mean follow-up of 95.9 months, the 51.6% (129) patients who received hormones and radiotherapy had a prostate cancer specific survival of 80% at 10 years compared to 53% in the cohort who received hormones alone.

The impressive long-term survival data from the Italian group (16) further supports the role for treating patients with node positive prostate cancer aggressively. It has been demonstrated that dose escalation in radical radiotherapy for localised prostate cancer results in an increase in biochemical disease control (17-19)

In the pelvic node positive cohort, the pelvic lymph node regions will receive 60Gy in 37 fractions over 7.5 weeks to the lymph node regions; pathologically enlarged nodes will receive 65Gy as an integrated boost. The prostate and involved seminal vesicles will be treated to 74Gy, which is current standard care in the UK[25].

3) PART 1 - FEASIBILITY STUDY

Initially a feasibility study will be undertaken. Men with localised prostate cancer stage T3a/b or T2 with PSA >20ng/ml or Gleeson score $\geq$8 will be recruited. Planning CT scan will be performed, and the clinicians will segment the images for treatment planning. The anatomical location of the planning target volume will be based on published atlases of pelvic nodal anatomy, supplemented with our own experience and that of radiologist colleagues. Inverse treatment planning will be undertaken using the CORVUS Planning System (NOMOS Corporation, Pittsburgh, USA) to deliver 70Gy to the prostate, 64Gy to the seminal vesicles, and 50Gy to the pelvic lymph nodes. Intensity maps will be produced for delivery with the dynamic MLC (Elekta Oncology Systems, Crawley, UK). For the first 5-10 patients, the treatment plan will be delivered to a phantom, and dosimetry verified using radiographic film in 2 and 3 dimensions. Thereafter, the phantom studies will be continued on patients where there is any concern regarding the delivery of the planned dose distribution. In addition, for all patients, portal images of each treatment field will be taken using radiographic film to verify the correct dose intensity map is delivered from each beam direction, and exit portal images will be used to check that the patient is correctly positioned. Current levels of treatment set-up accuracy and protocols for patient movement will be applied. i.e. If a field set-up error of greater than 3mm is detected on three consecutive days, then the patients position will be adjusted accordingly. Acute and late radiotherapy toxicity data will be collected using the EORTC/RTOG LENT/SOM and RTOG standard toxicity survey systems. Data collected from this cohort of men will act as a base-line for the dose escalation protocol.

4) PART 2 - DOSE ESCALATION TRIAL

A. DESIGN

Once feasibility of treatment delivery has been established, a cohort dose escalation study will be performed. Dose to the pelvic nodes will be escalated in 5Gy increments from 50Gy to, 55Gy, and subsequently 60Gy. In patients thought to have radiologically suspicious lymph nodes, IMRT would allow the delivery of an additional

5Gy boost to these nodes. The 60Gy cohort will be expanded provided there is no evidence of dose limiting toxicity in the first 30 patients (see below).

5) PART 3 – HYPOFRACTIONATED COHORT

Following completion of recruitment to the 60Gy cohort, an hypofractionated 4 week schedule will be studied, using the same initial and then expanded patient groups provided no significant toxicity is observed in the first 30 patients. This hypofractionated schedule was modified after an interim analysis demonstrated an increase in acute toxicity. This hypofractionated schedule was modified to a five weeks schedule.

6) Part 4 – PELVIC NODE POSITIVE COHORT

Parts 1-3 of the study have demonstrated the feasibility of delivering escalated doses of radiotherapy using IMRT to the pelvic lymph node regions. Patients with radiologically node positive disease have also been treated within each cohort; however, a separate toxicity analysis was not planned for this sub-set of patients. Radiotherapy will be delivered using a simultaneous integrated boost technique; 74Gy in 37 fractions to the prostate and pathologically involved seminal vesicles, 60Gy in 37 fractions to lymph node regions and uninvolved seminal vesicles and 65Gy in 37 fractions to the radiologically pathological nodes.

Reported Toxicity to date

Successive cohorts of patients with locally advanced prostate cancer have been treated with radiotherapy receiving 70Gy in 35 fractions to the prostate and seminal vesicles and 50Gy (n=25), 55Gy (n=55) or 60Gy (n=135) to the pelvic lymph node region. Acute and late toxicity rates were low in the 50Gy and 55Gy groups (20, 21). In the 60Gy group, acute (RTOG ≥2) bladder and bowel toxicity peaked at 40% and 38% respectively at week 6/7 of follow-up. The 2-year actuarial rate of late bladder and bowel toxicity (RTOG ≥2) was favourable at 2.5% (95% CI: 0.8% - 7.6%) and 12.5% (7.7% - 20%) respectively(22).

B. ELIGIBILITY CRITERIA

1 Cohorts 1 – 4

i. **Men with prostate cancer** with either:

1. Radiological or pathological pelvic nodal metastases or T3b/T4 disease **or**
2. Localized prostate cancer (pT2-T4) with a >30% estimated risk of pelvic nodal metastases* **or**
3. National Collaborative Cancer Network (NCCN) High Risk (Gleason score ≥8 or ≥2 risk factors) or Very High Risk Disease (23) (Appendix 1)
4. Post-prostatectomy patients (T2-T3a, N0) with extensive high grade disease (Gleason score ≥8) or seminal vesicle involvement or lymph node involvement.

*Risk of pelvic nodal metastases = (Gleason score – 6) x 10 + 2/3 PSA

2 Cohort 5 (NODE POSITIVE COHORT)

i. **Men with prostate cancer** with either:

1. Radiological or pathological proven pelvic nodal metastases

2. Post-prostatectomy patients with residual nodal disease on post-operative Imaging

ii. **Informed consent**

iii. **Exclusion criteria**:

Patients unsuitable for radical radiotherapy
Previous pelvic radiotherapy or surgery (excluding prostatectomy)
Inflammatory bowel disease or other small bowel disease

C. MEASUREMENT OF RADIATION TOXICITY

Acute side effects will be documented weekly using the RTOG scoring system.
Late side effects will be monitored by RTOG, LENT SOM and Quality of Life assessments using the FACT-P and UCLA prostate instruments. Late side effects will be monitored 6, 12, 18 and 24 months after treatment, and annually thereafter.

D. TUMOUR CONTROL

Tumour control will be monitored clinically and by PSA estimation taken 6 months after treatment and at six monthly intervals for 5 years and thereafter annually.

E. END POINTS

i. **Primary endpoint**:

Late RTOG radiotherapy toxicity.

ii. **Secondary endpoints**:

Overall survival
Local control
PSA control
Acute side effects
Quality of Life
Patterns of recurrence

F. PATIENT NUMBERS AND STATISTICS

i. Cohorts 1 – 4

At each dose/volume level a total of 15 men will be treated and followed up for at least 1 year, to exclude a ≥20% Grade ≥3 late toxicity rate. If 0/15 men have Grade ≥3 RTOG complications then a ≥20% Grade≥3 toxicity rate is excluded with 95% power.

In order to speed up the recruitment process, patients in the low small bowel volume group in the feasibility study will be able to be recruited to the next dose level once at least 7 men have had ≥12 months follow-up, and 0/7 grade≥3 complications have been recorded (excludes ≥20% Grade≥3 toxicity rate with 80% power). If 1/7 Grade≥3 complications is seen, dose escalation will not be attempted, and a total of 15 men will be recruited into that group.

Cohort 3 (60Gy to pelvic nodes) will be expanded (see below) provided 0/15 men have Grade ≥3 bowel complications after ≥1 year's follow up.

Cohort 4 (hypofractionated schedule 47Gy to pelvic lymph nodes) will recruit at least 15 men at each volume level and be expanded (see below) provided 0/15 men have Grade ≥3 bowel after ≥1 year's follow up. In this cohort, a 4Gy boost will be given to patients with radiologically involved lymph nodes.

We expect a late toxicity rate of ≥ grade 2 RTOG toxicity rate at 2 years would be around 15% (p1 = 85%) and that a rate in excess of 25% would be unacceptable (p0 = 75%). Then with 80% power and a 1 sided alpha of 0.05 we would require that at least 85 patients or more, out of a total of 103 eligible patients, are free from toxicity. This would ensure that the 95% Confidence interval of the grade 2 or more RTOG toxicity rate will be less than and exclude 25%. Approximately 20% of patients may

not be assessable at 2 years for all trial end points (personal communication from MRC RT01 Trial) so 123 men will be recruited to cohorts 3 and 4.

ii. Cohort 5 (node positive cohort)

We expect ≥ grade 2 RTOG late toxicity rate at 2 years to be around 15% (p1 = 85%) and that a rate in excess of 30% would be unacceptable (p0 = 70%). Then with 80% power and a 1 sided alpha of 0.05 we would require that at least 35 patients or more, out of a total of 49 eligible patients, are free from toxicity. This would ensure that the 95% confidence interval of the grade 2 or more RTOG toxicity rate will be less than and exclude 30%. Approximately 20% of patients may not be assessable at 2 years for all trial end points (personal communication from MRC RT01 Trial) so 58 men will be recruited to cohorts 5. 23 patients in cohort 3 had radiologically positive nodes; 14 of whom received a boosted dose to the pathological node of 5Gy. These 14 patients will be analysed as part of the node positive cohort for the purposes of the primary endpoint, ie late RTOG grade II toxicity.

G. RADIOTHERAPY PLANNING

i. Scanning and Outlining

Patients have a planning CT scan in the treatment position. The following structures are outlined on the planning computer:

Targets: CTV_1 = Prostate and any involved seminal vesicle
CTV_2 = Uninvolved seminal vesicle and pelvic lymph nodes
CTV_3 = Radiologically or pathologically involved lymph nodes.

The pelvic lymph node target volume (CTV_2) will be outlined as described in Staffurth et al 2005 (24)

Normal Tissue: Rectum
Bladder
Bowel (small bowel to sigmoid colon)
Femoral heads

ii. Margins

CTV_1 is grown by 8 mm posteriorly and 10 mm in all directions to create PTV_1.
CTV_2 is grown by 5 mm uniformly to create PTV_2.
CTV_3 is grown by 5 mm uniformly to create PTV_3.

iii. Inverse Planning

Patients will be inverse planned to deliver the following **median** target doses. For dose escalation protocol see below.

	PTV_1	PTV_2	PTV_3
Cohort 1	70 Gy 35F	50 Gy	55 Gy
Cohort 2	70 Gy 35F	55 Gy	60 Gy
Cohort 3	70 Gy 35F	60 Gy	65 Gy
Cohort 4	60 Gy 20F	47 Gy	51 Gy
Cohort 5	74Gy 37F	60Gy	65Gy

For post-prostatectomy patients in cohorts 1-2, the prostate bed dose will be 64Gy in 32 fractions. In cohort 3, the dose is 65Gy in 35 fractions and in cohort 4, the prostate bed will receive 55Gy in 20 fractions.
The post-prostatectomy dose in cohort 5 will be 64Gy in 32 fractions

H. TREATMENT PLANNING AND DELIVERY

Treatment planning and delivery will be performed with the systems currently available and most suitable for purpose at the Sutton and Chelsea branches of the RMH. At Sutton, the NOMOS Corvus system was initially used to plan dynamic IMRT delivery; subsequently Helax-TMS and Pinnacle planning systems will be used to deliver "step and shoot" IMRT. Treatment delivery is given with ELEKTA linear accelerators. At Chelsea, initially the CADPLAN and subsequently ECLIPSE and HELIOS planning systems were used. Dynamic treatment delivery on a VARIAN 2100CD linear accelerator. All of the planning methods use a simultaneous boost technique treating the prostate and pelvis together. 5 coplanar beams are used delivering treatment from posterior, 2 anterior oblique and 2 posterior oblique fields.

I. TREATMENT VERIFICATION

i. **Pre-treatment**

For the first 5-10 patients, the treatment plan will be delivered to a phantom, and dosimetry verified using radiographic film in 2 and 3 dimensions. Thereafter, the phantom studies will be continued on patients where there is any concern regarding the delivery of the planned dose distribution.

ii. **On-treatment**

For all patients, portal images of each treatment field will be taken using radiographic film to verify the correct dose intensity map is delivered from each beam direction, and exit portal images will be used to check that the patient is correctly positioned. Current levels of treatment set-up accuracy and protocols for patient movement will be applied. i.e. If a field set-up error of greater than 3mm is detected on three consecutive days, then the patients position will be adjusted accordingly.

iii. Verification techniques will be developed and adopted during the trials progress to take advantage of new technological developments in IMRT planning and dosimetry.

J. SYSTEMIC MANAGEMENT

All patients will be advised to receive a minimum of six months of hormonal therapy prior to definitive radiotherapy . Additional adjuvant therapy for a total of 3 years will be considered for patients particularly those with high grade (Gleason score ≥8) or NCCN very high risk disease.

L. ADVERSE EVENTS (AE) / SERIOUS ADVERSE EVENTS (SAE)

Definition of an Adverse Event

An 'adverse event' is any untoward medical occurrence in a patient administered a research procedure; where the events do not necessarily have a causal relationship with the procedure.

For the purpose of this trial, any detrimental change in the patient's condition subsequent to the start of the trial (i.e. registration) and during the follow-up period, which is not unequivocally due to progression of disease (prostate cancer), should be considered as an AE.

Whenever one or more signs and/or symptoms correspond to a disease or well-defined syndrome only the main disease/syndrome should be reported. For each sign/symptom the highest grade observed since the last visit should be reported.

Definition of Serious Adverse Events
A serious adverse event is any untoward occurrence, that:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity or
- consists of a congenital anomaly or birth defect
- additionally RTOG Grade≥4 acute or late radiation side effects i.e. related to study treatment, will be regarded as an SAE

A related adverse event is one for which the Principal Investigator and/or Chief Investigator (or nominated representative), assesses as resulting from administration of any of the research procedures.

An unexpected adverse event is any type of event not listed in the protocol as an expected occurrence.

Reporting of Adverse Events
Adverse events will be collected from the time of randomisation to the end of the follow-up period. Adverse events should be recorded in the appropriate section of the CRF.

Due acknowledgement has to be given to likely co-morbidity and co-morbid events in an elderly and ageing male population, many of whom will die from diseases unrelated to prostate cancer and its treatment.

The following are possible anticipated treatment related SAEs (i.e. expected occurrences) which are not subject to expedited reporting but should be reported in the appropriate section of the CRF.

Bone fractures
Bowel strictures
Second Malignancies
Ureteric obstruction

Expedited reporting of SAEs

All SAEs occurring within 30 days of study treatment (i.e. intensity modulated radiotherapy) being administered and not listed above, are subject to expedited reporting. In addition RTOG grades ≥4 acute or late radiation side effects occurring within 5 years of radiotherapy treatment are subject to expedited reporting.

All SAEs must be reported within 24 hours using the SAE form. The form must be sent by FAX to the Bob Champion Unit on **020 8643 1725**. It must be completed, signed and dated by the Principal Investigator or nominated representative.

The Bob Champion Unit (BCU) will send the SAE to the Chief Investigator (or nominated representative) for review of causality and expectedness.

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Appendix 2. IMRT Abstract

ICR The Institute of Cancer Research

Clinical efficacy of dose escalated and hypofractionated pelvic IMRT in prostate cancer

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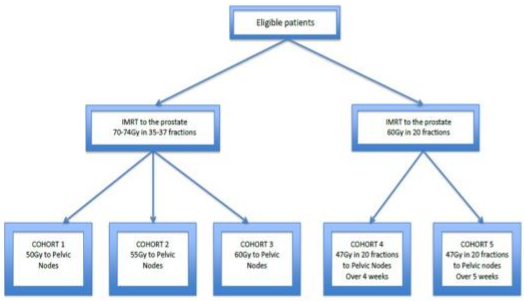
Introduction

The role of pelvic lymph node (PLN) radiotherapy in advanced localised prostate cancer remains controversial (1). In past studies the dose to PLN has been limited in order to minimise bowel toxicity. Intensity modulated radiotherapy (IMRT) has been shown to spare the bowel (2) and introduced the potential for dose-escalation and hypofractionation. The IMRT trial was a phase I/II trial conducted in 426 patients at a single centre. It was designed to explore dose- escalated and hypofractionated regimes of PLN IMRT. We report the long term clinical outcomes of this trial cohort.

Methods

Eligible patients had high risk (≥T3a, Gleason ≥8 or PSA ≥20) disease with an estimated risk of lymph node involvement of ≥30%, or lymph node positive disease. IMRT was inverse planned to give 70-74Gy in 35-37 fractions to the prostate and sequential patient cohorts received 50Gy (n=25), 55Gy (n=70) and 60Gy (n=138) to the pelvis in 35-37 fractions using a simultaneous integrated boost technique. Positive lymph nodes received an additional 5Gy boost. The remaining patients were recruited into two hypofractionated cohorts. They received 60Gy in 20 fractions to the prostate and 47Gy in 20 fractions over 4 weeks (n=64) or 47Gy in 20 fractions over 5 weeks (n=129) with an additional 4Gy boost to positive lymph nodes.

All patients received long course androgen deprivation therapy, commencing at least 6 months before radiotherapy. Biochemical failure was defined according to the Phoenix criteria of the nadir +2ng/ml. Local recurrence was confirmed with MRI and/or histological confirmation. Distant staging with CT, MRI, nuclear medicine bone scan or choline-PET CT was performed in patients with biochemical relapse to establish all sites of relapse.



Results

Between 09/08/2000 and 09/06/2010 426 patients were recruited and treated. Median age at treatment was 65 years (IQR 60-70 years) and median presenting PSA was 21.4 ng/ml (IQR10.2-42.8 ng/ml).

The median follow up for the whole cohort at the time of analysis was 7.6 years The total number of failure events was 169. Freedom from biochemical /clinical failure at 5 years was 71% (95% CI 66%-75%). The 5 year prostate cancer specific survival was 92% (95% CI 89%-94%) and overall survival was 87% (95% CI 84%-90%). Pelvic lymph node control was 94% for the whole cohort.

Site of relapse	50Gy/35# to PLN n=25	55Gy/35# to PLN n=70	60Gy/35# to PLN n=138	47Gy/20# in 4 weeks to PLN n=64	47Gy/20 # in 5 weeks to PLN n=129	Total n=426
Local	6 (24%)	11 (16%)	12 (9%)	3 (5%)	9 (7%)	41(10%)
Pelvic LN	3 (12%)	5 (7%)	9 (6%)	3 (5%)	6 (5%)	26(6%)
Non-pelvic LN	3 (12%)	12 (17%)	12 (9%)	5 (8%)	7 (5%)	29 (9%)
Other distant sites	13 (52%)	25 (36%)	34 (25%)	9 (14%)	18 (14%)	99 (23%)
Median Follow up (years)	13.9	11.2	9.0	7.1	5.7	7.6

Conclusion

Pelvic IMRT with dose escalation and hypofractionation is associated with a low rate of pelvic recurrence. Freedom from biochemical/clinical failure, cancer specific survival and overall survival appear favourable, but high dose pelvic IMRT requires testing in a phase 3 trial

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Appendix 3. IMRT publication

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Phase 1/2 Dose-Escalation Study of the Use of Intensity Modulated Radiation Therapy to Treat the Prostate and Pelvic Nodes in Patients With Prostate Cancer

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Summary

Elective pelvic lymph node (PLN) radiation therapy and hypofractionation for advanced localized prostate cancer remains controversial. We report a single-center sequential cohort study using intensity modulated radiation therapy (IMRT) to deliver conventionally fractionated

Purpose: To investigate the feasibility of dose escalation and hypofractionation of pelvic lymph node intensity modulated radiation therapy (PLN-IMRT) in prostate cancer (PCa). **Methods and Materials:** In a phase 1/2 study, patients with advanced localized PCa were sequentially treated with 70 to 74 Gy to the prostate and dose-escalating PLN-IMRT at doses of 50 Gy (cohort 1), 55 Gy (cohort 2), and 60 Gy (cohort 3) in 35 to 37 fractions. Two hypofractionated cohorts received 60 Gy to the prostate and 47 Gy to PLN in 20 fractions over 4 weeks (cohort 4) and 5 weeks (cohort 5). All patients received long-course androgen deprivation therapy. Primary outcome was late Radiation Therapy Oncology Group toxicity at 2 years after radiation therapy for all cohorts. Secondary outcomes were acute and late toxicity using other clinician/patient-reported instruments and treatment efficacy.

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M.R.F. and A.K. contributed equally to this work.

Conflict of interest: none.

Supplementary material for this article can be found at www.redjournal.org.

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50 Gy, 55 Gy, and 60 Gy to the PLN and 70 to 74 Gy (2 Gy per fraction) to the prostate. Additionally, we studied modest hypofractionation delivering 60 Gy (3 Gy per fraction) to the prostate with 47 Gy to the PLN over 4 to 5 weeks. Our findings highlight the safety of dose escalation and hypofractionation in PLN-IMRT.

Results: Between August 9, 2000, and June 9, 2010, 447 patients were enrolled. Median follow-up was 90 months. The 2-year rates of grade 2+ bowel/bladder toxicity were as follows: cohort 1, 8.3%/4.2% (95% confidence interval 2.2%-29.4%/0.6%-26.1%); cohort 2, 8.9%/5.9% (4.1%-18.7%/2.3%-15.0%); cohort 3, 13.2%/2.9% (8.6%-20.2%/1.1%-7.7%); cohort 4, 16.4%/4.8% (9.2%-28.4%/1.6%-14.3%); cohort 5, 12.2%/7.3% (7.6%-19.5%/3.9%-13.6%). Prevalence of bowel and bladder toxicity seemed to be stable over time. Other scales mirrored these results. The biochemical/clinical failure–free rate was 71% (66%-75%) at 5 years for the whole group, with pelvic lymph node control in 94% of patients. **Conclusions:** This study shows the safety and tolerability of PLN-IMRT. Ongoing and planned phase 3 studies will need to demonstrate an increase in efficacy using PLN-IMRT to offset the small increase in bowel side effects compared with prostate-only IMRT. © 2017 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Prostate cancer is the most common cancer in men, accounting for 27% of new cancer cases in 2014, and more than 307,000 men died from prostate cancer in 2012 worldwide (1, 2). In the United Kingdom, 46,690 new cases were diagnosed in 2014 (2). Most men are now diagnosed with localized disease, but high-risk prostate cancer remains life-threatening. Treatment with external beam radiation therapy, androgen deprivation therapy (ADT), and in selected cases, high-dose-rate brachytherapy has been used in this patient group (3). Approximately 15,800 men receive radical prostate radiation therapy every year in the United Kingdom (4). However, the merit of elective pelvic lymph node radiation therapy (PLNRT) compared with treatment of prostate and seminal vesicles alone remains controversial, and present guidelines suggest that PLNRT should be considered but not mandated for high-risk disease (1, 5). This uncertainty may relate to the modest doses of radiation therapy that are usually given with PLNRT so as to avoid bowel toxicity.

Intensity modulated radiation therapy (IMRT) makes it possible to increase bowel sparing, which is the dose-limiting normal tissue when treating the pelvis (6, 7). Intensity modulated radiation therapy brings the opportunity to dose escalate, which has been linked with increased disease control in prostate cancer (8-11). The low α/β ratio of prostate cancer makes hypofractionation an attractive option for treatment, with recent data demonstrating equivalent outcomes to standard dose schedules treating the prostate alone (4). Dose escalation and hypofractionation have not been adequately evaluated for pelvic LNRT, with limited data available from small case series (8-10, 12).

The aim of this study was to test the feasibility of using IMRT to deliver LNRT to patients with high-risk prostate cancer, using dose-escalated conventional and hypofractionated schedules.

Methods and Materials

Study design and participants

We performed a single-center, phase 1/2 study of IMRT to irradiate the prostate and PLN in patients with advanced localized prostate cancer. Eligible patients had prostate cancer with very high risk (T3b/T4) or node-positive disease, high-risk disease with Gleason score $\geq$8 or $\geq$2 risk factors, or an estimated risk of nodal metastases of >30% based on the Roach formula (1, 13). Postprostatectomy patients (T2-T3a, N0) with extensive Gleason score $\geq$8 disease and seminal vesicle or lymph node involvement were also eligible. Patients unsuitable for radical radiation therapy or with a history of pelvic surgery or inflammatory bowel disease were excluded.

Patients were sequentially assigned to receive 3 different dose schedules to the PLN of 50, 55, or 60 Gy (cohorts 1, 2, and 3, respectively) giving 70 to 74 Gy in 2-Gy fractions over 7 weeks to the prostate. An integrated boost of 5 Gy was given to radiologically suspicious PLN. Two hypofractionated cohorts (cohorts 4 and 5) were then studied, based on equivalent doses to the conventional schedule calculated assuming an α/β ratio of 2.5 Gy. They received 60 Gy to the prostate in 3-Gy fractions over 4 to 5 weeks and 47 Gy to the PLN. An integrated boost of 4 Gy was given to radiologically suspicious PLN. Patients were initially treated on a 4-week schedule (cohort 4), which was later modified to a 5-week schedule (cohort 5) because of acute gastrointestinal (GI) toxicity. Patients irradiated after prostatectomy received 64 Gy in 32 fractions in cohorts 1 and 2, 65 Gy in 35 fractions in cohort 3, or 55 Gy in 20 fractions in cohorts 4 and 5 (Table E1; available online at www.redjournal.org).

Procedures

Patients received long-course (2-3 years) ADT with at least 6 months' treatment before radiation therapy commenced.

Patients underwent planning computed tomography (CT) scans with a comfortably full bladder and empty rectum. From 2011, sodium citrate enemas were used for patients with rectal dilatation. Inverse radiation therapy planning was performed for all patients, using mandatory normal tissue dose constraints (Table E2; available online at www.redjournal.org) as previously described (14, 15). Clinical target volume-1 included the prostate and any radiologically involved seminal vesicle, with a margin of 8 mm posteriorly and 10 mm in all other directions to create planning target volume-1. Clinical target volume-2 included PLN and uninvolved seminal vesicles (Text E2; available online at www.redjournal.org). A uniform margin of 5 mm was applied to create planning target volume-2. Clinical target volume-3 included any radiologically involved lymph nodes, and a uniform margin of 5 mm was applied to create planning target volume-3. All organs at risk were contoured as solid organs, by defining the outer wall of rectum, bowel, and bladder. The rectum was contoured from the anus (usually at the level of the ischial tuberosities or 1 cm below the lower margin of the planning target volume, whichever was more inferior) to the recto-sigmoid junction. Bowel was outlined separately, excluding rectum and extending 2 cm above the superior extent of planning target volume-2. The bladder was outlined from base to dome. Treatment verification was performed offline using bony anatomy for registration (Text E1; available online at www.redjournal.org).

Staging investigations included prostate-specific antigen (PSA) measurement, histologic diagnosis, radiologic or surgical lymph node assessment, and staging magnetic resonance imaging (MRI), CT, or bone scan.

Acute side effects were recorded weekly using the Radiation Therapy Oncology Group (RTOG) scoring system up to 18 weeks after initiating radiation therapy. Late toxicity was scored according to the European Organization for Research and Treatment of Cancer/RTOG and Late Effects Normal Tissue—Subjective, Objective, Management, Analytic (LENT-SOMA) late toxicity scales, and University of California, Los Angeles Prostate Cancer Index (UCLA-PCI) patient-reported outcomes (16-18). Data were collected at baseline, every 6 months up to 5 years after radiation therapy, and yearly thereafter.

Prostate-specific antigen was measured every 6 months for 8 years after the start of ADT and annually thereafter. The nadir PSA level was the lowest level recorded after radiation therapy. Biochemical failure was defined according to the Phoenix consensus guidelines as a PSA value greater than the nadir plus 2 ng/mL. Local recurrence was confirmed on MRI of the pelvis or biopsy, and post-prostatectomy patients (n = 34) were excluded from this endpoint. Distant relapse was confirmed on MRI, CT scan, bone scan, or choline positron emission tomography—CT scan.

Statistical considerations

The primary endpoint was late RTOG toxicity assessed 2 years after radiation therapy. Secondary endpoints included assessment of all toxicity scales during follow-up and disease recurrence. Patients were stratified by total bowel volume outlined (<450 cm^3 vs ≥ 450 cm^3). For each dose level stratified by bowel volume, at least 15 men were treated and followed up for at least 1 year. If 0 of 15 men had a grade 3 or higher (grade 3+) RTOG complication, then a 20% grade 3+ toxicity rate was excluded with 1-sided significance level of .05. Because the dose to the initial cohort was modest, patients in the low bowel volume group were recruited to the second dose level after 7 men had $\geq$12 months of follow-up, provided none of these had recorded a grade $\geq$3 complication. For other cohorts and bowel volume groups, recruitment continued at that level until such time as 15 men had been treated and followed up for at least 1 year. This strategy ensured that the low bowel volume group moved to the higher dose cohorts in advance of the high bowel volume group. Because recruitment continued in each cohort and bowel volume group until such time as the required total of men had reached $\geq$12 months of follow-up, in all cases the eventual sample size in each group exceeded the required total to an extent that varied according to the recruitment rate over time.

In cohorts 3 and 4, a further dose expansion phase was planned, with a target sample size of 103 patients (of any bowel volume) evaluable at 2 years, to rule out a late grade 2 or higher (grade 2+) bowel toxicity rate of $\geq$25%, using a 1-sided alpha 0.05 and power of 80% with an assumed true rate of toxicity not more than 15%. The sample size was expanded to a total of 123 in each of cohort 3 and 4 to allow for an expected dropout rate of 16% by 2 years. However, because of high levels of acute bowel toxicity observed in cohort 4 (4-weekly schedule), the treatment schedule was amended to 5 weeks (cohort 5) with a target of 123 patients.

Late toxicity rates were calculated using Kaplan-Meier methods, with time measured from start of radiation therapy. Rates by 1 and 2 years were calculated with 95% confidence intervals (CIs). One-sided 95% CIs were constructed for rate of RTOG grade 3+ bowel toxicity at 1 year (cohorts 1 and 2) and for rate of RTOG grade 2+ bowel toxicity at 2 years (cohorts 3 and 4), to assess safety of the primary endpoint. In addition, the number of men experiencing defined toxicity grades at each time point was reported as a percentage of all men assessed. Efficacy was assessed using Kaplan-Meier methods to calculate duration of disease control (defined as a composite endpoint of biochemical progression, local or lymph node/pelvic recurrence, or distant metastasis, or recommencement of ADT), duration of local disease control, duration of distant disease control, and disease-specific and overall survival from start of radiation therapy. For disease-specific and overall survival, patients were censored at the date they were last known to be alive. Rates at 2 and 5 years were

calculated with 95% CIs. Data were extracted in September 2015 and analyzed using STATA version 13.1 (StataCorp, College Station, TX).

Univariable Cox regression on duration of disease control was performed using factors of dose cohort, N stage (N0 vs N1-3), baseline PSA level (log transformed), clinical T stage (grouped as T1/T2; T3a; T3b+), and Gleason score (grouped as $\leq$6; 7; $\geq$8). Forward and backward stepwise selection methods were used to combine significant factors ($P<.05$ on univariable analysis) into a multivariable model and produce adjusted hazard ratios with 95% CIs.

Trial setup

Institutional clinical research and ethics committees approved the study, which was included in the National Cancer Research Network portfolio in December 2003. The trial was performed in accordance with the principles of good clinical practice and overseen by a trial management group. All patients provided written informed consent.

Results

Between August 9, 2000, and June 9, 2010, 447 male patients were recruited to cohorts 1 to 5; 426 were treated according to protocol, and 421 were available for late toxicity assessment (Fig. 1). Median age was 65 years (interquartile range, 60-70 years), with median presenting PSA level of 21.4 ng/mL (10.2-42.8 ng/mL). Forty-six percent of patients had clinical T3/T4 disease, 54% had Gleason $\geq$8 scores, and 17% PLN involvement. Cohort 1 had a higher proportion of patients with adverse features than cohorts 2 to 5. Median duration of adjuvant hormone therapy was 35 months (33-37 months), and median follow-up was 90 months (Table 1), with 398 patients out of 426 followed up for toxicity for at least 2 years and 327 followed up for at least 5 years. Thirty-four patients (8%) were treated adjuvantly after undergoing a radical prostatectomy before entering the trial (Table E6; available online at www.redjournal.org).

Acute bowel toxicity peaked at 6 to 8 weeks in the conventionally fractionated (CFRT) cohorts 1 to 3, compared with 4 to 5 and 5 to 6 weeks in the hypofractionated (HFRT) cohorts 4 and 5, respectively. Peak grade 2+ toxicity was recorded in 40%, 56%, and 54% of cohorts 1 to 3 respectively. Patients in cohort 4 developed the highest acute bowel toxicity rates, with 66% reporting grade 2+ bowel toxicity, compared with 48% in cohort 5. However, by 18 weeks after treatment the incidence of grade 2+ RTOG bowel toxicity was similar in all cohorts (Fig. 2 and Table E3 [available online at www.redjournal.org]). Acute grade 3+ peak

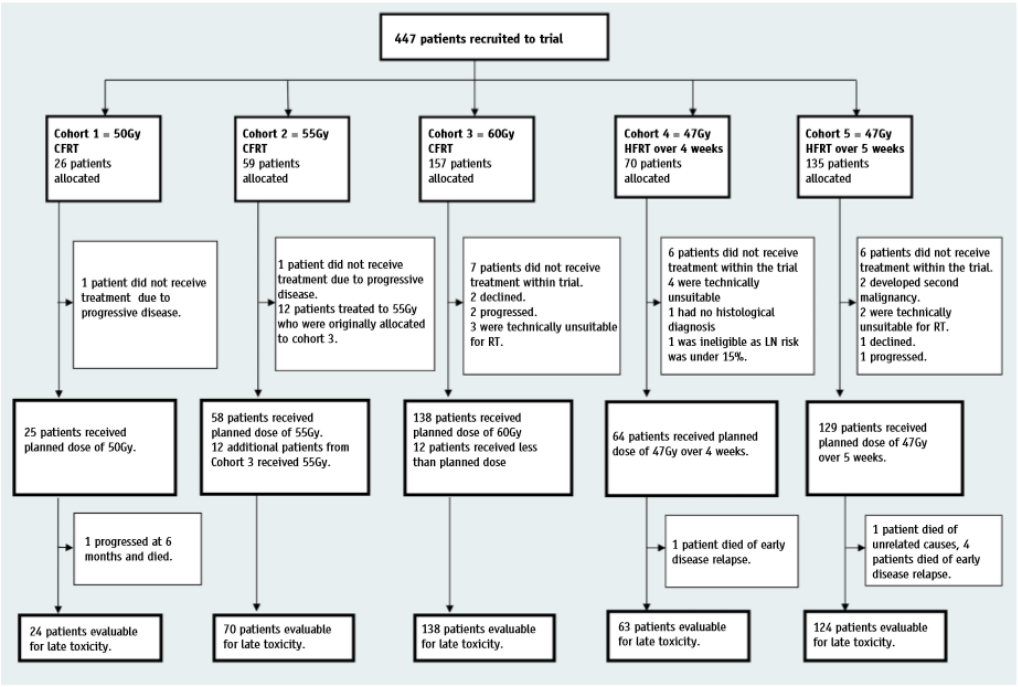

Fig. 1. Trial profile. *Abbreviations:* CFRT = conventionally fractionated radiation therapy; HFRT = hypofractionated radiation therapy; LN = lymph node; RT = radiation therapy.

Table 1 Patient demographics

Variable	Cohort 1, 50 Gy (n=25)	Cohort 2, 55 Gy (n=70)	Cohort 3, 60 Gy (n=138)	Cohort 4, 47 Gy/4 wk (n=64)	Cohort 5 47 Gy/5 wk (n=129)	Cohorts 1-5 (n=426)
Age at diagnosis (y)	63 (56-67)	62 (57-67)	65 (59-69)	66 (62-72)	67 (62-71)	65 (60-70)
PSA at diagnosis (ng/mL)	39.1 (24.7-78.0)	25.4 (12.4-44.7)	24.5 (10.2-47.1)	15.4 (8.5-31.4)	18 (8.1-37.9)	21.4 (10.2-42.8)
Gleason score						
≤7	13 (52)	34 (48)	60 (43)	22 (35)	56 (44)	185 (44)
8	4 (16)	17 (24)	29 (21)	13 (20)	11 (9)	74 (17)
≥9	6 (24)	16 (22)	48 (35)	28 (44)	60 (47)	158 (37)
Unknown	2 (8)	3 (4)	1 (1)	1 (2)	2 (2)	9 (2)
CT/MR N stage						
N0	16 (64)	49 (70)	115 (83)	51 (80)	110 (85)	341 (80)
N1	9 (36)	14 (20)	22 (16)	11 (17)	18 (14)	74 (17)
Unknown	0 (0)	7 (10)	1 (1)	2 (3)	1 (1)	11 (3)
Clinical T stage						
cT1/T2	18 (32)	23 (33)	60 (43)	6 (9)	42 (32)	156 (37)
cT3	17 (68)	34 (49)	57 (41)	17 (27)	56 (43)	192 (45)
cT4	0 (0)	2 (3)	3 (2)	28 (44)	1 (1)	6 (1)
Unknown	0 (0)	11 (16)	18 (13)	13 (20)	30 (23)	72 (17)
Duration of ADT (mo)	36 (32-36)	35 (33-37)	36 (33-40)	34 (33-36)	35 (34-37)	35 (33-37)
Median follow-up (y)	13.9	11.2	9.0	7.1	5.7	7.6

Abbreviations: ADT = androgen deprivation therapy; CT = computed tomography; MR = magnetic resonance; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen.
Data are n (%) or median (interquartile range) unless otherwise stated.

toxicity occurred in 0 (0%), 1 (1%), 5 (4%), 3 (5%), and 9 (7%) patients in cohorts 1 to 5, respectively. One patient in each of cohorts 4 and 5 developed grade 4 acute toxicity, and there was 1 death (recorded as grade 5 toxicity), determined at autopsy to have resulted from perforation of an undiagnosed caecal carcinoma.

Acute bladder toxicity was related to dose in the CFRT cohorts, with peak grade 2+ toxicity recorded in 28%, 44%, and 53% of patients in cohorts 1 to 3, respectively. Patients in cohort 4 experienced higher rates of bladder toxicity of grade 2+ (61%) than patients in cohort 5 (53%). However, rates of grade 2+ bladder toxicity at 18 weeks were low and similar in all cohorts (Fig. 2).

The 2-year cumulative rate of RTOG grade 2+/grade 3+ bowel toxicity was 8.3% (95% CI 2.7%-24.3%)/0%, 8.9% (4.1%-18.7%)/1.5% (0.2%-10.4%), and 13.2% (8.6%-20.2%)/2.2% (0.7%-6.7%) in cohorts 1 to 3 (CFRT), respectively. In the HFRT cohorts 4 and 5, the 2-year rate of grade 2+/grade 3+ bowel toxicity was 16.4% (9.2%-28.4%)/6.6% (2.5%-16.7%) and 12.2% (7.6%-19.5%)/0.8% (0.1%-5.7%), respectively (Fig. 3 and Tables E4 and E5 [available online at www.redjournal.org]). A comparable 12.2% (4.7%-29.3%) of postprostatectomy patients experienced grade 2+ bowel toxicity, with no clear difference between the cohorts in view of the small numbers included (Table E6; available online at www.redjournal.org).

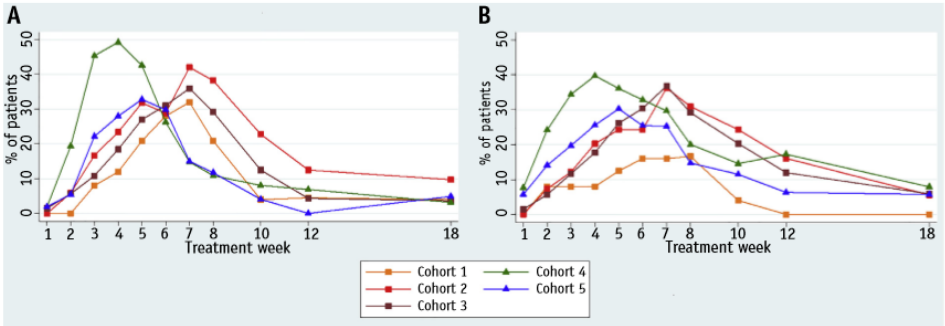

Fig. 2. Acute Radiation Therapy Oncology Group (RTOG) grade 2 or worse toxicity by time point and treatment group. Prevalence of (A) acute RTOG grade 2+ bowel toxicity and (B) acute RTOG grade 2+ bladder toxicity.

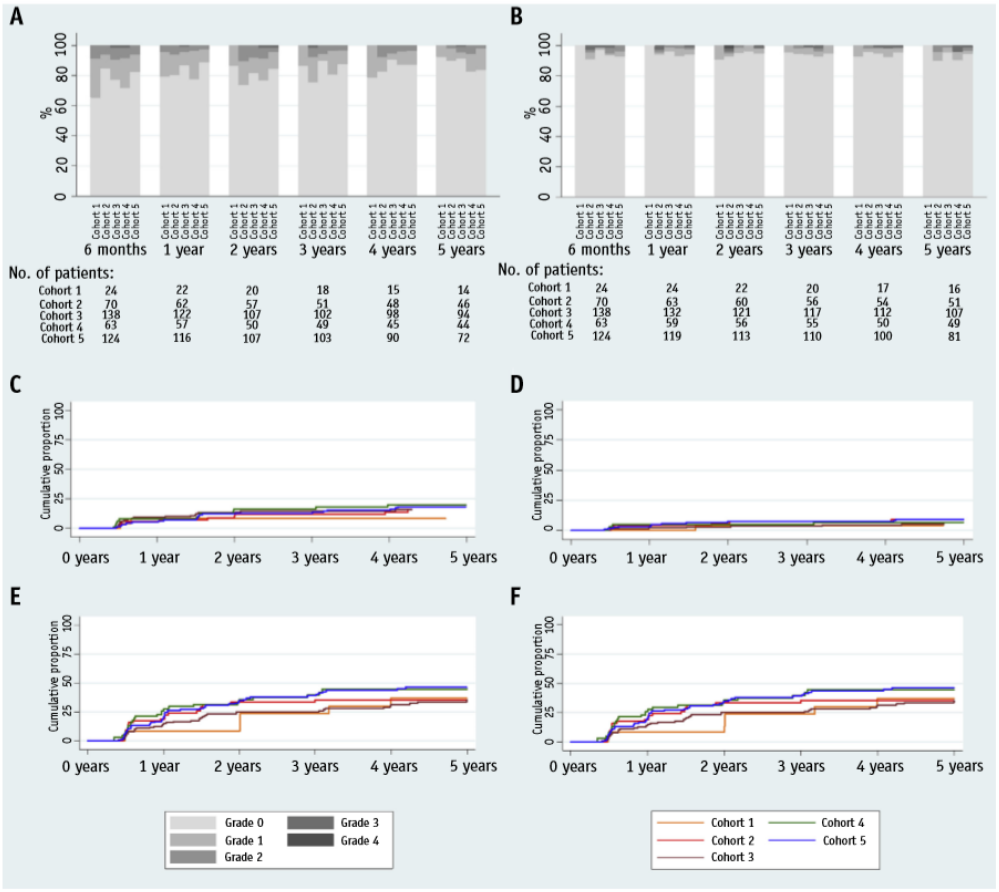

Fig. 3. Late bowel and bladder toxicity by time point, assessment, and treatment group. Grade distribution of (A) bowel adverse events and (B) bladder adverse events measured with Radiation Therapy Oncology Group (RTOG) scale. Cumulative incidence of (C) grade 2 or worse bowel adverse events measured with RTOG scale and (E) small or worse bowel symptom scores measured with University of California, Los Angeles Prostate Cancer Index (UCLA-PCI). Cumulative incidence of (D) grade 2+ bladder adverse events measured with RTOG scale and (F) small or worse bladder symptom scores measured with UCLA-PCI.

The 2-year cumulative rates of grade 2+/grade 3+ bladder toxicity were 4.2% (0.6%-26.1%)/4.2% (0.6%-26.1%), 5.9% (2.3%-15.0%)/2.9% (0.7%-11.3%), and 2.9% (1.1%-7.7%)/2.2% (0.7%-6.8%) in cohorts 1 to 3 (CFRT), respectively. In cohorts 4 and 5 (HFRT), rates were 4.8% (1.6%-14.3%)/1.6% (0.2%-10.9%), and 7.3% (3.9%-13.6%)/1.2% (0.4%-6.4%), respectively (Fig. 3 and Tables E4-E6 [available online at www.redjournal.org]). Post-prostatectomy patients had a higher rate of urinary symptoms at 9.0%, albeit with a large CI (3.0%-25.4%), with no clear differences between cohorts (Table E6; available online at www.redjournal.org).

The prevalence of bowel and bladder toxicity seemed to be stable over time (Fig. 3 and Tables E4 and E5 [available online at www.redjournal.org]). At 5 years' follow-up, 0/0 (0%/0%), 1/0 (2%/0%), 5/1 (5%/1%), 3/0 (6%/0%), and 2/0 (2%/0%) men had grade 2+/3+ RTOG bowel toxicity in cohorts 1 to 5, respectively. The 5-year prevalence of grade 2+ bladder toxicity was 0/0 (0%/0%), 2/0 (4%/0%), 1/0 (1%/0%), 2/2 (4%/4%), and 3/1 (3%/1%) in cohorts 1 to 5, respectively.

All estimates of late toxicity met predefined safety criteria. Results using the Royal Marsden Hospital (RMH) and LENT-SOMA assessments are given in Tables E4 and

E5 (available online at www.redjournal.org). Table E6 (available online at www.redjournal.org) details rates of late symptoms in patients treated after prostatectomy.

Patient-reported outcomes (PRO) were obtained with the UCLA-PCI instrument (Tables E4 and E5; available online at www.redjournal.org). The cumulative 5-year rate of small or worse bowel/bladder bother was 26% (95% CI 13%-50%)/37% (19%-63%), 49% (37%-63%)/35% (24%-49%), 38% (30%-48%)/35% (27%-45%), 56% (43%-69%)/45% (32%-59%), and 54% (44%-64%)/46% (37%-57%) in cohorts 1 to 5, respectively. Prevalence of moderate/severe bowel problems at 2 years was 1 of 22 patients (5%), 4 of 47 (9%), 6 of 84 (7%), 4 of 45 (9%), and 10 of 85 (12%) in cohorts 1 to 5, respectively. Moderate/severe urinary problems at 2 years were reported by 1 of 22 patients (5%), 5 of 47 (10%), 6 of 85 (7%), 6 of 47 (13%), and 10 of 85 (12%) in cohorts 1 to 5, respectively. At 5 years, prevalence rates for moderate/severe bowel problems were 0 of 12 patients (0%), 1 of 42 (2%), 1 of 76 (1%), 2 of 35 (6%), and 2 of 54 (4%) in cohorts 1 to 5, respectively. No severe bowel problems were reported at 5 years. Prevalence of moderate/severe urinary problems at 5 years was 0 of 12 patients (0%), 2 of 42 (4%), 6 of 78 (7%), 2 of 35 (6%), and 3 of 57 (5%) in cohorts 1 to 5, respectively. No men in the HFRT cohorts had severe urinary problems at 5 years.

Biochemical or clinical progression occurred in 169 of 426 patients (39.7%). At first relapse, biochemical failure alone occurred in 141 of 169 patients (59%), local recurrence in 11 of 169 patients (7%), distant metastases in 7 of 169 patients (4%), and 3 of 169 patients (2%) commenced salvage hormone therapy in the absence of radiologic confirmation of sites of disease. On subsequent follow-up there were 41 of 426 patients (10%) with confirmed relapses within the prostate, 26 of 426 (6%) with PLN recurrences, 39 of 426 (9%) with relapses in distant nodal groups, and 99 of 426 (23%) with relapses at other metastatic sites. The biochemical/clinical failure–free rate was 71% (95% CI 66%-75%) at 5 years for the whole group, with 38%, 61%, 70%, 80%, and 78% remaining recurrence free in cohorts 1 to 5, respectively.

Disease-specific survival at 5 years was 92% (95% CI 89%-94%) for the whole cohort and 79%, 88%, 92%, 97%, and 95% in cohorts 1 to 5, respectively. The 5-year overall survival was 87% (95% CI 84%-90%) and 76%, 87%, 86%, 89%, and 91% in cohorts 1 to 5, respectively (Fig. 4).

Multivariate analysis identified pretreatment PSA level ($P=.004$), PLN involvement ($P=.02$), T stage ($P=.05$), and dose cohort ($P=.05$) as factors associated with duration of disease control. Patients treated in cohorts 4 and 5 had similar outcomes (Table 2).

Discussion

We found acceptable acute and late GI/genitourinary (GU) toxicity measured using both clinician-reported outcomes (CRO) and PRO in all patient cohorts. To assess the impact of

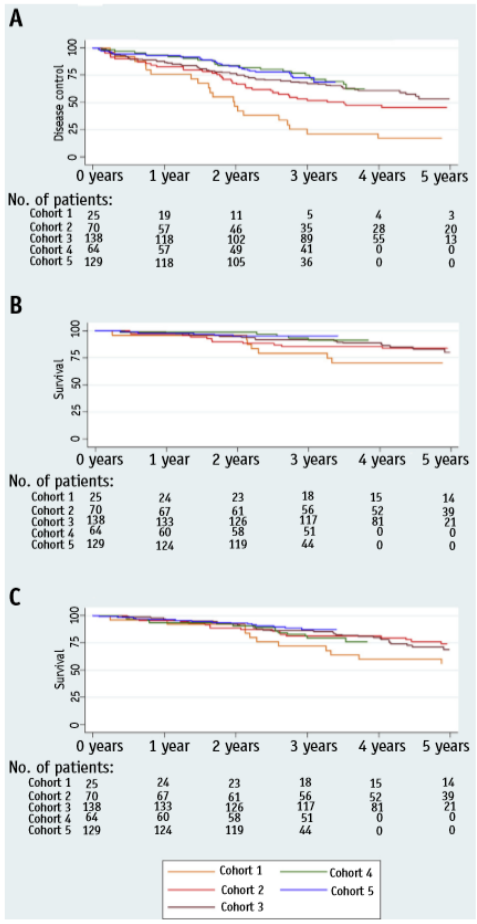

Fig. 4. Biochemical failure–free survival (A), disease-specific survival (B), and overall survival (C).

PLNRT, we compared these results with a large contemporaneous group of patients treated in the CHHiP phase 3 trial, which used IMRT to treat the prostate alone using similar CFRT/HFRT schedules and scored side effects with the same compendium of CRO and PRO (4). We also used comparable data reported in a recent systematic review by Holch et al (19), which included no studies with PLNRT. We found that acute grade 2+ GI toxicity occurred in 40% to 56% of CFRT patients in cohorts 1 to 3, compared with 25% in CHHiP and 21% to 60% in Holch et al, with a rate of 66% in cohort 4 (4-week HFRT), compared with 30% in the CHHiP HFRT group and 36% in Holch et al. Increasing the overall treatment time to 5 weeks reduced the rate to 48% in cohort 5. However, these side effects settled rapidly in all groups. There were no differences in grade 2+ toxicity by 18 weeks, although some

Table 2 Multivariate Cox regression analysis, for duration of disease control (n=326)

Factor	Hazard ratio (95% CI)	*P*
Dose cohort		.05
Cohort 1, 50 Gy	1 (NA)	
Cohort 2, 55 Gy	0.71 (0.40-1.26)	
Cohort 3, 60 Gy	0.45 (0.26-0.80)	
Cohort 4, HFRT 4 wk	0.50 (0.25-1.01)	
Cohort 5, HFRT 5 wk	0.45 (0.24-0.84)	
Log max pretreatment PSA		<.01
Continuous, ng/mL	1.30 (1.08-1.57)	
Clinical T stage		.05
T1/T2	1 (NA)	
T3a	1.22 (0.78-1.91)	
T3b+	1.70 (1.11-2.60)	
Radiologic N stage		.02
N0	1 (NA)	
N+	1.65 (1.09-2.48)	

Abbreviations: CI = confidence interval; HFRT = hypofractionated; NA = not available.

increase in mild grade 1+ side-effect rates persisted with PLNRT (25%-36%, compared with 21% in CHHiP). There were no clear differences between grade 2+ peak/week-18 or grade 1+ week-18 GU toxicities among cohorts 1 to 5 or when comparing with the CHHiP or Holch et al GU toxicity rates (Table E3; available online at www.redjournal.org).

Late GI side effects seemed highest in cohort 4 using CRO scales, both 2 and 5 years after treatment. For example, 2-year estimated cumulative proportions with grade 2+ (CRO) or small or worse bowel problems (PRO) were 16%, 16%, 34%, and 53% using the RTOG, RMH, LENT-SOMA, and UCLA-PCI scales, respectively, compared with 8% to 13%, 8% to 15%, 13% to 25%, and 21% to 43% for the other cohorts. The rates for the comparator CHHiP group were 8% to 9%, 10% to 11%, 16% to 18%, and 25% to 27%, respectively. Applicable results in the Holch et al systematic review (19) were similar to those in CHHiP. The increased acute and late GI toxicity seen in cohort 4 would be consistent with a consequential late side effect (20, 21). Extending treatment duration to 5 weeks by treating 4 times per week seems to reduce any impact of hypofractionation (Tables E4 and E5; available online at www.redjournal.org).

Late GU side effects, assessed using RTOG and RMH CRO scales, were similar among all groups, with no obvious impact from dose, fractionation schedule, or use of PLNRT. However, the cumulative proportion of patients with grade 2+ toxicity (LENT-SOMA, CRO) or small or worse bladder bother (UCLA-PCI, PRO) at 2 years was somewhat higher than in the CHHiP groups, suggesting these scales are more sensitive. Any differences had disappeared by 5 years, when the prevalence of small or worse bladder bother was 8% to 20% in cohorts 1 to 5 and 17% in the CHHiP comparator group (Tables E4 and E5; available online at www.redjournal.org).

Late bowel and bladder side effects did not show consistent differences when the subgroup of patients treated after prostatectomy was analyzed, either with CRO or PRO data (Table E6; available online at www.redjournal.org). However, these results should be interpreted with caution given that only 34 patients were treated adjuvantly in this trial, and limited conclusions can be drawn.

The low level of side effects seen in the present series probably relates to the use of a strict IMRT protocol and the mandating of dose constraints for both bowel and bladder. However, the doses delivered in cohorts 3 to 5 are at least 10% higher than used in past and contemporary practice (Fig. E1; available online at www.redjournal.org). Similar dose increments have been shown to improve disease outcome in trials treating the prostate alone (22, 23).

The 5-year overall survival in this series (87%; 95% CI 84%-90%) is at least comparable to a recent retrospective series from the National Cancer Database, in which 7606 patients were treated with PLNRT, with 5-year overall survival of 81.6% (24). In the group randomized to PLNRT in the RTOG 94-13 trial, a 4-year overall survival of 84% was reported. The 5-year biochemical/clinical failure–free rate of 71% for our entire series is similar to the control group treated with radiation therapy in the contemporaneous MRC STAMPEDE trial, which showed an estimated 75%/50% 5-year control in patients with N0/N1 disease, respectively (25).

The low PLN recurrence rate of 6% is reassuring, but further efforts to improve local control in the prostate for patients with aggressive bulky disease seem warranted (hazard ratio for local disease control in T3b+: 1.70, 95% CI 1.11-2.60; Table 2). Approaches using high-dose focal radiation therapy boosts, prostatectomy, or additional ablative focal therapies using, for example, high intensity focused ultrasound or cryotherapy can be considered (26). Avoidance of toxicity, however, is important, because a considerable majority of patients have disease controlled by IMRT and ADT or, alternatively, relapse with metastatic disease outside the pelvis, making additional measures to improve local control futile. The development of biomarkers to predict the response to radiation therapy and define patient groups destined to develop metastatic disease would therefore be invaluable in guiding treatment individualization (27). Treatment intensification with additional systemic treatments, such as docetaxel or the new generation of hormonal therapies, can be considered (28). Additionally, radiogenomic and dosimetric studies are aiming to refine estimates of an individual's risk of developing side effects (29, 30).

Conclusion

This study has provided the safety data to encourage further investigation of high-dose LNRT. The treatment techniques described have been generalized in a United Kingdom national phase 2 randomised pilot study, PIVOTAL

(ISRCTN48709247), which compares prostate and pelvis with prostate-alone IMRT. Hypofractionated radiation therapy will become the United Kingdom standard of care after the CHHiP trial (4). The safety data of hypofraction ated schedules in the present study is encouraging, and the use of HFRT in a new trial, PIVOTALboost, is planned. It will assess the value of pelvic IMRT as well as the effects of a focal high-dose intraprostatic boost to dominant lesions. These studies will complement other ongoing phase 3 studies, RTOG 09-24 (NCT01368588) and PEACE 2 (NCT01952223), which should finally determine the role of PLNRT in prostate cancer. An increase in efficacy will need to be demonstrated to offset the small but expected adverse effects of pelvic IMRT.

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Appendix 4. RMH Contouring instructions for pelvic lymph nodes.

Lymph nodes are not readily identifiable on the planning CT scans. The relationship between the nodes and the vasculature is therefore used to ensure that the nodes are included within the CTV_2. Before outlining it is advisable to identify the various structures – especially the vessels and bowel. This can be done with more confidence by following their course over several scans.
Three distinct sections of the outlining process for CTV_2 are identified. The outlining procedure starts cranially, and the outline is drawn separately on each subsequent scan.

a) Sacral promontory to bottom of anterior extent of S3/4 junction – pre-sacral and upper pelvic nodes.

During this section, there is a single outline.

- The outline starts at the sacral promontory, which is defined from the sagittal scout film as the most anterior point of S1. The outline starts at the anterior extent of iliac vessels. It follows the anterior wall of the vessels. The plane between the vessels and psoas muscle should be identified. The lateral extent of the outline follows this plane or the medial border of the psoas muscle if there is a distinct fat plane between the vessels and psoas. Posteriorly the outline extends onto the sacrum and stops at the anterior extent of the sacrum and crosses the midline.

- The contralateral outline is effectively a mirror. The outline continues to run laterally until it has reached a point equivalent to the lateral extent of the iliac vessels. At this point the outline runs anteriorly and again runs along the tissue plane between the vessels and the psoas. The outline then follows the anterior curvature of the vessels and then runs posteriorly along the medial edge of the vessels.

- To cross the midline anteriorly, three situations occur. Firstly, if there is a vessel crossing the midline, the outline should follow the anterior extent of this vessel and continue anterior to the wall of the vessel until it joins the starting point. Secondly, if there is no vessel crossing the midline, the anterior extent of the outline crossing the midline should be 15mm anterior to the sacrum. This will include the pre-sacral nodes. Thirdly, if there is bowel in this pre-sacral space it should be specifically excluded from the wall of the bowel. The first outline should now be complete.

- The outline on subsequent scans follows the same path until it reaches the anterior aspect of the S3/4 junction apart from one point. As the sacral promontory becomes less prominent, the anterior extent of the sacrum becomes almost horizontal. At this point the lateral extent of the sacrum is defined by the sacro-iliac joints and usually corresponds to the point where the psoas muscle meets the pelvic bone. A corner is created. This corner marks the postero-lateral extent of the outline. The lateral outline, running between the iliac vessels and the psoas should follow the medial border of psoas posteriorly onto the bone, and the outline should then continue medially.

- Proceeding caudally, the sacrum has hollows, which correspond to the exit foramina of the sacral nerves. These hollows are included within the volume, i.e. the outline continues to follow the anterior extent of the bone. The pyriformis muscle lies

anterior to the sacrum and becomes bulkier caudally. Its anterior border becomes the posterior border of the outline, i.e. it is excluded from the volume.

- During this section the common iliac vessels bifurcate. The external iliac vessels become more anterior on caudal slices. The anterior extent of the outline should follow anterior wall of the external iliac vessel.

- The bottom of this section corresponds to the anterior extent of the S3/4 junction, which is identified from the sagittal scout film and approximates to the bottom of the sacro-iliac joints.

b) <u>S3/4 junction to the tips of the seminal vesicles – mid pelvic nodes</u>

- At the anterior extent of S3/4 junction (defined form lateral scout view) the outline now excludes the remaining inferior extent of the pre-sacral space. This point approximates to the bottom of the sacro-iliac joints and the top of the sciatic notches. This results in two disconnected outlines. The outlining procedure for each side is identical, although the volumes are usually not mirror images.

- The outline starts at the anterior extent of the external iliac vessels. Laterally it follows initially the medial edge of the psoas muscle, and then the medial wall of the pelvis. The posterior edge of the ilium marks the anterior portion of the sciatic notch. The pre-sciatic nodes (also known as the internal pudendal nodes) accompanying vessels (continuation of the internal iliac vessels) and the sciatic nerve lie in this area. The outline extends down from the bony pelvis and passes lateral to these structures (i.e. they are included). The outline runs along the visible musculature (obturator externus), which forms the postero-lateral border of the volume. The posterior extent of the outline runs along the most posterior of the previously mentioned structures. This usually involves outlining as much as 2/3rds of the sciatic foramen. The outline then runs up the medial border of the internal iliac vessels.

- The next part of the medial outline is variable. The outline eventually follows the medial border of the external iliac vessels. The outline between the internal and external iliac vessels is drawn to include branches of the internal iliac vessels but excludes bowel.

- During this section, the external iliac arteries become gradually more anterior. The anterior extent of the outline continues to be the anterior wall of the vessels, but it should not extend more than about 2cm anterior to the most anterior point of the bony pelvis. It should include both artery and vein. Eventually both vessels are anterior and lateral to the pelvic brim, as they descend into the groin. At this point, the anterior extent of the outline corresponds to the antero-medial point of the bony pelvis and usually approximates to the level of the acetabulum.

- Caudally, the tips of the seminal vesicles or small vascular structures may become visible medially. At this point the medial edge of the outline follows the medial edge of the vessels/seminal vesicles. The outlines may stay separate. If the vessels/seminal vesicles meet in the midline, the outlines join to form a single volume. This outlining process for this volume is described in the next section.

c) Tips of seminal vesicles to prostate GTV_1 - lower pelvic nodes and uninvolved seminal vesicle.

- Caudally, the tips of the seminal vesicles or small vascular structures may become visible in the midline. At this point the two separate volumes join medially into a single outline.

- The anterior extent of the outline follows the medial edge of the obturator internus muscle and posteriorly the bony pelvis. When the structures in the pre-sciatic notch become invisible, the posterior extent of the outline becomes the posterior point of the ilium. The medial outline follows the medial border of the small vessels and curves into the midline. As much distance as possible is kept between the outline and rectum at this point. The outline is drawn across midline and the process is repeated on the other side.

- Contralaterally, the anterior extent is again the antero-medial bony pelvis. the antero-medial outline is drawn to cover the medial aspect of the small vessels. The outline is drawn as far away from the bladder as possible. The outline crosses the midline, becomes more anterior again, as it follows the small vessels, and joins the starting point.

- As the superior pubic ramus starts to appear, the nodal volume reduces further in size. The anterior extent of the nodal volume becomes the anterior extent of the vessels on the pelvic sidewalls, and the posterior extent becomes the posterior extent of the vessels. The lateral border remains the musculature and bony pelvis. The outline stops extending to the pelvic side walls 0.5-1cm above the top of the acetabulum.

Throughout this stage of the outlining process, all of the seminal vesicles should be included in CTV_2 unless they are included in GTV_1. As GTV_1 may include the central portion (base) of the seminal vesicles, any remaining seminal vesicles should be outlined as CTV_2.

Appendix 5. PIVOTAL Trial Radiotherapy planning document.

A RANDOMISED PHASE II TRIAL OF PROSTATE AND PELVIS VERSUS PROSTATE ALONE TREATMENT FOR LOCALLY ADVANCED PROSTATE CANCER

RADIOTHERAPY PLANNING DOCUMENT

Version 3.3
29 July 2011

Please refer to current version of protocol for full PIVOTAL trial design, eligibility details and treatment information, available from PIVOTAL trials office

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WITHOUT WRITTEN PERMISSION OF THE ICR-CTSU

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CONTENTS

1. TARGET VOLUMES, MARGINS AND DOSES

1.1. VOLUME DEFINITION

Volumes will be defined according to the International Commission on Radiation Units and Measurements (ICRU) report 50, supplement report ICRU 62: Prescribing, Recording and Reporting Photon Beam Therapy[55, 56] and ICRU 83: Prescribing, Recording and Reporting Photon-Beam Intensity Modulated radiotherapy (IMRT)[57]. Outlining should be carried out with the aid of all diagnostic MRI and CT scans.

Three tumour and clinical target volumes will be defined. These are:

- Prostate and seminal vesicles - Tpsv;
- Prostate alone (plus any involved seminal vesicles) - Tp
- Pelvic lymph nodes - CTVn

Planning target volumes are defined by addition of appropriate margins (see later) to the previously defined tumour volume (T) and clinical target volume (CTV). Patients in both prostate/seminal vesicle alone and prostate/seminal vesicle/lymph node randomised groups will have similar planning target volume and dose levels applied to the prostate and seminal vesicles.

PTVpsv_6000: The prostate and seminal vesicles will be outlined with a 10mm margin in all directions to form PTVpsv_6000. The median dose to uninvolved seminal vesicles will be 60Gy (81% isodose) with a minimum dose of at least 57Gy (77% isodose).

PTVp_7100 and PTVp_7400: Two planning target volumes will be used to define the prostate and any involved seminal vesicle.

PTVp_7100 is created by outlining the prostate and any involved seminal vesicle. A 10mm margin is applied in all directions except posteriorly where the margin will be 5mm. In practice a 5mm margin should be added to PTVp_7400 in all directions to include the additional rectal sparing offered by the exclusion of the rectum from PTVp_7400. The dose to PTVp_7100 will be 71Gy (minimum dose 67.3Gy (91%)).

PTVp_7400 is created by outlining the prostate and any involved seminal vesicle. A 5mm margin is applied in all directions except posteriorly where the margin will be 0mm. The aim is to exclude rectum from PTVp_7400. The dose to PTVp_7400 will be 74Gy (100% ± 1%) with a minimum dose of 70.3Gy (95%).

PTVn_6000: The pelvic lymph node volume CTVn will be outlined as per section 3 of this document. A 5mm margin is applied in all directions. PTVpsv_6000 should be excluded from PTVn_6000. The dose to PTVn_6000 will be 60Gy (81% isodose) with a minimum dose of 57Gy (77% isodose).

The prescribed doses will be defined as the median doses.

Note: the prostate and seminal vesicle target volumes and dose levels are the same as in the CHHiP trial except that the target dose to uninvolved seminal vesicle is 60Gy (81% isodose) rather than 59.2Gy (80% isodose).

In-keeping with ICRU-83, we will be recording near-minimum (D98) and near-maximum (D2) doses to allow standardization of reporting. However, the mandatory minimum doses for the PTVs have been defined in the following table using D99 (prostate) and D95 (node) values for consistency with previous trial data on which these dose constraints are based.

Tumour and Clinical Target Volumes	Planning Target Volumes	Doses to Planning Target Volumes
Prostate and seminal vesicles Tpsv	**PTVpsv_6000** Outline: prostate and seminal vesicles Add: 10mm margin in all directions	**RING_PTVpsv** **(PTVpsv_6000 – PTVp_7100)** ≥60Gy (81%) median ≥57Gy (77%) to ≥ 99% of the volume (MANDATORY)
Prostate (+ any involved seminal vesicle) Tp	**PTVp_7100** Outline: prostate and any involved seminal vesicle Add:5mm to PTVp_7400 (unless rectal distension, see section 1.2)	**RING_PTVp** **(PTVp_7100 – PTVp_7400)** ≥71Gy (96%) median ≥67.3Gy (91%) to ≥ 99% of the volume (MANDATORY)
	PTVp_7400 Outline: prostate and any involved seminal vesicle Add: 5mm except 0mm posteriorly and exclude rectum (unless rectal distension, see section 1.2)	**PTVp_7400** 74Gy (100% ± 1%) median ≥70.3Gy (95%) to ≥ 99% of the volume (MANDATORY) 77.7Gy (105%) maximum to ≤2% of the volume
Pelvic lymph nodes CTVn	**PTVn_6000** Outline: pelvic lymph nodes Add: 5mm margin in all directions and exclude PTVpsv_6000	**PTVn_6000** ≥60Gy (81%) median ≥54Gy (73%) to ≥ 99% of the volume (MANDATORY) ≥57Gy (77%) to ≥ 95% of the volume (MANDATORY) *≥57Gy (77%) to≥ 98% of the volume (OPTIMAL)*

1.2. RECTAL DISTENSION

Prior to planning CT scan, diagnostic imaging should be assessed for the presence of rectal distension. Any patients with rectal distension should be commenced on glycerine suppositories or micro-enemas (see section 6.1).

If there is significant rectal distension the posterior margins of PTVp_7100 and PTVp_7400 may be increased to a maximum of 10mm and 3mm respectively (see section 6.1 for management of rectal distensions). If the posterior margins are increased, the larger margins should only be used for the CT slices on which the rectum is distended (i.e. ***not*** the entire rectum).

Factors which will influence whether the rectal distension is considered 'significant':

- Presence of rectal distension on diagnostic scans
- Impact of distension on prostatic contour (e.g. flattened or concave)
- Is the distension at the level of the prostate or seminal vesicles (in patients where the seminal vesicles are uninvolved, these act as a 'spacer' between prostate and rectum, however if the seminal vesicles are involved, potential toxicity should be considered)

2. OUTLINING PROTOCOL FOR PROSTATE AND SEMINAL VESICLES: PROSTATE, BASE OF SEMINAL VESICLE AND ANY INVOLVED SEMINAL VESICLE.

The outlining of the prostate and the involved seminal vesicles should be carried out with the initial diagnostic MRI scans, which will aid identification of the prostate apex (using coronal and T2 weighted images), areas of potential extra-capsular extension and seminal vesicle involvement. In order to identify the prostate apex, the planning CT scans should be reviewed in a caudal to cranial direction to identify as accurately as possible the urethral bulb, pelvic floor musculature, membranous urethra and finally the prostate apex.

The position of the apex should then be confirmed with the diagnostic MRI scans by reference to bony landmarks, e.g. the obturator fossa. The lowest outlined slice should include the membranous urethra to ensure geographical coverage of the apex due to the uncertainties in image interpretation in this region. Starting at the apex, the prostate outline continues cranially and includes the prostate and possible areas of extracapsular extension, taking care to avoid inclusion of the pelvic sling muscles. Often a fat plane exists between the prostate and these muscles. At the base of the prostate (superior aspect) any protrusion into the bladder base must be outlined.

The base of the seminal vesicles (central portion), arbitrarily defined as the proximal 5 mm, is included in the prostate outline as well as any MRI defined involved seminal vesicle.

3. OUTLINING PROTOCOL FOR PELVIC LYMPH NODES

The Royal Marsden Hospital phase I/II dose-escalation pelvic IMRT trial utilised a detailed in-house delineation guideline for pelvic lymph node delineation[36]. The RTOG[35] has also recently published a consensus document on guidelines for lymph node delineation. The PIVOTAL Trial Management Group has reached a consensus on the most appropriate delineation protocol to be employed which is based upon the RTOG guidelines with some additional modifications (referred to as 'ICR-modified RTOG guidelines').

Lymph nodes are not readily identifiable on the planning CT scans. The relationship between the nodes and the vasculature is therefore used to ensure that the nodes are included within the CTVn. Before outlining it is advisable to identify the various structures – especially the vessels and bowel. Identification of the pelvic vessels is made much easier by administering i.v. contrast. Bowel can be identified with more confidence by following the course over several scans.

N.B. Since the vessel expansion technique takes advantage of the ability of radiotherapy planning software to avoid organs at risk when expanding volumes, it is essential to firstly outline all organs at risk (see section 4) before expanding or editing the outlined pelvic blood vessels.

3.1. PLANNING CT SCAN & IV CONTRAST ADMINISTRATION

I.V. contrast is only required in patients who have been randomised to prostate and pelvic node radiotherapy. Oral contrast should preferably be used to aid delineation of small bowel, again only in those patients randomised to prostate and pelvic node radiotherapy.

At the time of planning CT scan, i.v contrast should be administered to patients who are able to receive it in order to better visualize pelvic blood vessels. One possible technique for achieving this uses 100 mls Omnipaque 300 / Visipaque contrast (following U&E assessment and confirmation of satisfactory renal function). Contrast is given at a flow rate of 1-3mls/sec (depending upon cannula gauge), with a minimum delay of 60secs from start of contrast administration to the start of scanning, assuming a flow rate of 2mls/sec. The delay time may need to be adjusted if the flow rate is 1ml/sec.

3.2. VESSEL CONTOURING AND EXPANSION

The vessels are outlined as structure 'vessels' on each axial CT slice in continuity. Outlining should begin superiorly at the mid-point of the most anterior part of the L5/SI vertebral interspace (identified on the sagittal view of the planning CT scan). The vessels should be readily identified due to the presence of i.v. contrast.

As contouring proceeds inferiorly, the external iliac vessels extend anteriorly; they should continue to be outlined until the level of the top of the femoral head is reached. At this point, the vessel contour will move inside the bony pelvis. The vessels are contoured as inferiorly as possible, however, it is difficult to see the obturator vessels, and this area is dealt with separately (see section 3.3.3). The lowest vessel contour stops 1cm superior to the pubic symphysis.

The vessel contours are then expanded using the radiotherapy planning software program to create a new structure CTVn. A margin of 7mm is applied in lateral and anterior-posterior directions only. (*NB Superior and inferior expansion is not performed)*. At the time of volume expansion, the bowel avoidance volume (obtained by adding a 3mm isotropic margin to the total bowel outline, see section 4.3), rectum and bladder should be excluded from the new contour CTVn.

3.3. EDITING OF CTVN VOLUME

3.3.1. Presacral region

The lymph node volume CTVn now requires editing. The pre-sacral lymph node area will need to be added to the volume, this extends from L5/S1 to the S3/4 junction, and is determined by the sagittal scan view. To do this a 12mm 'rollerball' is drawn along the anterior surface of the sacrum to connect the lateral parts of the volume. Care should be taken to exclude any bony protrusions (e.g. osteophytes) which are not part of the body of the sacrum, and the volume does not extend posteriorly to include the sacral exit foramina.

There may be a vessel crossing the midline, in which case the CTVn volume should be edited to connect the lateral volumes, incorporating this vessel, using a 12mm rollerball anterior to the bone surface. (i.e. not extending more than 12mm anterior to the bone)

If there is bowel in this pre-sacral space it should be specifically excluded from the volume. In this case the outline follows the posterior wall of the bowel avoidance volume.

3.3.2. Connecting internal and external iliac volumes

As the volume continues inferiorly on each side of the pelvis the external iliac vessels extend anteriorly and the internal iliac vessels extend posteriorly. On some of the more inferior slices on both sides of the pelvis, the CTVn contour will comprise 2 discrete areas (anterior and posterior). These should be joined to form one volume by connecting each volume (again taking care to exclude muscle and bone) using a 18mm rollerball along the medial surface of the bony pelvis, and ensuring that laterally the volume abuts muscle or bone. The 3mm bowel avoidance volume, rectum and bladder volumes should all be excluded.

3.3.3. Obturator region

Using a 18mm rollerball, a volume is created by drawing along the medial surface of the bony pelvis bilaterally. This creates 2 parallel volumes on the pelvic side walls which encompass the obturator lymph nodes. Manual editing should then be performed to exclude muscle/ bowel avoidance volume/ bladder/ rectum. This region starts at the level of the top of the femoral heads.

On all slices, any 'small white dots' in close proximity to blood vessels/ CTVn should be regarded as lymph nodes and therefore incorporated into the volume.

3.3.4. Muscle and bone

Muscle and bone should be manually edited from the CTVn on all axial CT slices.

3.4. LYMPH NODE PLANNING TARGET VOLUME PTVN_6000

In the RMH Pelvic IMRT phase I/II studies a uniform 5mm margin was added to CTVn to create the pelvic lymph node planning target volume PTVn. The RTOG guidelines do not suggest a CTVn to PTVn margin. A 5mm margin similar to the RMH algorithm will therefore be used to create PTVn_6000. It is important to note that the lymph node sites to be included in CTVn are the same in both RMH, RTOG, and ICR-modified RTOG methods. An important consideration is that the safety data from the RMH phase I/II study has enable safe dose escalation to pelvic lymph nodes of 60Gy in 35 fractions.

The prostate and seminal vesicles PTV (PTVpsv_6000) will be excluded from PTVn_6000 to avoid conflicts in plan optimization and reporting.

4 ORGANS AT RISK

Normal Structures to be outlined include:

- Bladder
- Rectum (and anal canal)
- *Small bowel
- *Large Bowel
- Right femoral head
- Left femoral head

* The large bowel (no contrast) and small bowel (contrast) should be outlined as separate structures where possible; however, a combined volume will be used for the Dose-Volume Constraints.

4.1. BLADDER

The outside of the bladder wall should be outlined. The entire bladder should be included.

4.2. RECTUM

A suggested bowel preparation protocol is given in section 6. The use of daily micro enemas may also be considered.

The circumference of the rectum should be outlined in its entirety. If the anterior-posterior diameter of the rectum is >4cm at any level adjacent to the prostate, the patient should be rescanned. Presently the rectum is outlined to include the rectal contents. Outlining should extend from the bottom of the ischial tuberosities to the rectosigmoid junction. At the rectosigmoid junction, the rectum and sigmoid will be outlined as different structures. The rectosigmoid junction will be defined as the level at which there is an anterior inflection of the bowel – this is usually best appreciated on sagittal reconstructions on the CT planning scan. When localising on the planning computer, the sagittal views are often helpful. The anus will be defined as the distal 3cm of rectum. The combined volume 'Rectum' (including anus) will be used for the 'Rectum' dose-volume constraint.

4.3. BOWEL

Small and large bowel (including sigmoid colon) should be outlined as separate structures when possible. The entire small and large bowel visible on relevant levels of the planning scan will be outlined as individual bowel loops. Oral contrast visible in the small bowel will aid the differentiation of small bowel from large bowel which usually does not contain contrast. The combined volume 'Bowel' (large bowel, including sigmoid, and small bowel) will be used for the 'Bowel' dose-volume constraint. The outlining will include the small bowel, the large bowel and the sigmoid colon, down to the level of the recto-sigmoid junction. The superior extent of outlining should be 2cm beyond the superior extent of CTVn. An avoidance margin of 3mm will be applied to the 'bowel' structure in 3 dimensions and will be excluded from the CTVn volume.

4.4. RIGHT AND LEFT FEMORAL HEADS

The femoral heads are outlined to the bottom of the curvature of their heads (femoral necks are not included).

5. IMRT PLANNING AND DOSE-VOLUME CONSTRAINTS

5.1. IMRT PLANNING

The prescribed doses will be defined as the median doses. Minimum doses will be defined as near-minimum D(98%) for reporting purposes and D(99%) for mandatory minimum dose constraints. Maximum doses will be defined as near maximum (D2%). Maximum dose to PTVp_7400 is105%.

IMRT will be performed using the local planning system using multiple beams to obtain a uniform coverage of the PTV and satisfy the dose constraints to the OARs.

- PTVp_7400 should receive 74 Gy, and at least 70.3Gy (95%) to 99% of its volume
- PTVp_7100: target dose to PTVp_7100 – PTVp_7400 (RING_PTVp) is 71Gy (96% isodose) and at least 67.3Gy (91% isodose) to 99% of PTVp_7100
- PTVpsv_6000: target dose to PTVpsv_6000 – PTVp_7100 (RING_PTVpsv) is 60Gy (81% isodose) and at least 57Gy (77% isodose) to 99% of PTV(psv)
- PTVn_6000 should receive 60 Gy (81% isodose), and at least 57Gy (77% isodose) to 95% of its volume (optimally to 98% of its volume), and at least 54Gy (73% isodose) to 99% of its volume

5.2. DOSE-VOLUME CONSTRAINTS

Dose volume constraints will be as shown in the table. Literature suggests that these will limit the incidence of late toxicity for conventional fractionation. In the event that the dose constraints cannot be achieved or the plan is unacceptable then the dose to the lymph node region should be decreased to 55Gy.

Organ at risk	**Dose-volume constraints**		
		Optimal	Mandatory
Rectum:[59-61]	V30	80%	-
	V40	65%	-
	V50	50%	60%
	V60	35%	50%
	V65	30%	30%
	V70	15%	15%
	V75	3%	5%
Bladder: [61,62]	V50	50%	
	V60	25%	-
	V65	-	50%
	V70	5%	35%
Sigmoid, Small & Large Bowel:[11, 63]	V45	78cc	158cc
	V50	17cc	110cc
	V55	14cc	28cc
	V60	0.5cc	6cc

	V65	0cc	0cc
Femoral heads:	50Gy	5%[64]*	25%

*52Gy to 100% gives an estimated 5% risk of necrosis within 5 years

5.3. STRUCTURE NAMING CONVENTIONS

Consistent naming of contoured structures used in radiotherapy treatment planning is essential to facilitate the comparison of dose-volume statistics across patients for quality assurance and outcomes analysis. Maintaining consistency in structure names is particularly important (and challenging) in multi-institutional clinical trials, in which treatment planning data are collected from many participating institutions. A scheme for uniform naming of contoured structures for PIVOTAL is provided in the following table. These names must be used for treatment planning of all trial patients.

Structure name	Description
Tumour and clinical target volumes – as defined in section 1.1	
Tp	Prostate and seminal vesicles
Tpsv	Prostate alone (plus any involved seminal vesicles)
CTVn	Pelvic lymph nodes
VESSELS	Pelvic vessels. Outlined and expanded to facilitate creation of CTVn.
Planning target volumes – as defined in section 1.1	
PTVp_7400	Prostate PTV. Tp + 5mm margin / 0mm posteriorly. Excludes RECTUM. Median dose 74Gy
PTVp_7100	Prostate PTV. PTVp_7400 + 5mm in all directions
PTVpsv_6000	Prostate + SVs PTV. Tpsv + 10mm margin in all directions
PTVn_6000	Pelvic lymph nodes PTV. CTVn + 5mm margin in all directions. Median dose 60Gy
RING_PTVp	Planning volume PTVp_7100 – PTVp_7400. Median dose 71Gy
RING_PTVpsv	Planning volume PTVpsv_6000 – PTVp_7100. Median dose 60Gy
Organs at risk – as defined in section 4	
BLADDER	
RECTUM	Entire rectum, including anal canal. Used for dose constraints
ANUS	Anal canal
RECTUM_A_ANUS	Rectum EXCLUDING anal canal
BOWEL	Combined volume large bowel, including sigmoid, and small bowel. Used for dose constraints

SM_BOWEL	Small bowel
LG_BOWEL	Large bowel, including sigmoid colon
FEMORAL_HEAD_L	Left femoral head
FEMORAL_HEAD_R	Right femoral head

Appendix 6. Additional results tables from Chapter 4

Table 39. Mann-Whitney U test to compare the mean volume of total bowel receiving 0-70Gy in patients with maximum reported late RTOG Grade 1+ and Grade 0 proctitis

	Maximum late RTOG proctitis	Mean volume (cc)	SD (cc)	*P* value
Total bowel (V0)	Grade 0 n=96 (79%)	540.7	207.0	0.670
	Grade 1+ n=25 (21%)	546.8	193.2	
V10	Grade 0	217.3	236.2	0.470
	Grade 1+	188.8	236.0	
V20	Grade 0	173.7	199.0	0.403
	Grade 1+	143.1	181.2	
V30	Grade 0	116.9	137.8	0.548
	Grade 1+	93.9	124.5	
V40	Grade 0	63.1	72.4	0.432
	Grade 1+	50.2	70.5	
V50	Grade 0	24.3	27.5	0.536
	Grade 1+	21.5	26.5	
V60	Grade 0	1.0	1.8	0.741
	Grade 1+	1.1	1.7	
V70	Grade 0	0.0	0.2	0.155
	Grade 1+	0.0	0.0	

Table 40. Mann-Whitney U test to compare the mean volume of total bowel receiving 0-70Gy in patients with RTOG Grade 1+ and Grade 0 proctitis at 24 months

	RTOG proctitis as 24 months	Mean volume (cc)	SD (cc)	*P* value
Total bowel volume	Grade 0 n=106 (88%)	545.4	201.1	0.730
	Grade 1+ n=15 (12%)	519.1	223.4	
V10	Grade 0	214.1	235.7	0.388
	Grade 1+	190.8	240.3	
V20	Grade 0	169.5	196.0	0.387
	Grade 1+	151.5	193.5	
V30	Grade 0	112.9	134.5	0.548
	Grade 1+	105.4	141.2	
V40	Grade 0	60.6	70.4	0.509
	Grade 1+	58.3	83.9	
V50	Grade 0	23.8	26.9	0.576
	Grade 1+	22.5	30.0	
V60	Grade 0	1.1	1.9	0.415
	Grade 1+	0.5	0.9	
V70	Grade 0	0.0	0.2	0.295
	Grade 1+	0.0	0.0	

Table 41. Mann-Whitney U test to compare the mean volume of total bowel receiving 0-70Gy in patients with maximum reported late RTOG Grade 1+ and Grade 0 diarrhoea

	Maximum late RTOG diarrhoea	Mean volume (cc)	SD (cc)	*P* value
Total bowel	Grade 0 n=85 (70%)	524.4	208.4	0.131
	Grade 1+ n=36 (30%)	573.7	182.0	
V10	Grade 0	199.3	234.3	0.366
	Grade 1+	226.7	232.0	
V20	Grade 0-	159.1	196.0	0.520
	Grade 1+	178.4	191.8	
V30	Grade 0	104.8	133.5	0.552
	Grade 1+	123.5	137.5	
V40	Grade 0	55.3	68.6	0.500
	Grade 1+	68.6	77.5	
V50	Grade 0	21.9	26.1	0.595
	Grade 1+	25.8	27.7	
V60	Grade 0	1.0	1.8	0.780
	Grade 1+	1.3	1.7	
V70	Grade 0	0.0	0.1	0.363
	Grade 1+	0.0	0.0	

Table 42. Mann-Whitney U test to compare the mean volume of total bowel receiving 0-70Gy in patients with maximum reported late RTOG Grade 2+ and Grade 0-1 diarrhoea

	Maximum late RTOG diarrhoea	Mean volume (cc)	SD (cc)	*P* value
Total bowel	Grade 0-1 n=109 (90%)	539.9	200.2	0.949
	Grade 2+ n=12 (10%)	530.7	221.1	
V10	Grade 0-1	209.6	235.5	0.869
	Grade 2+	188.3	218.0	
V20	Grade 0-1	167.3	196.8	0.876
	Grade 2+	143.3	176.5	
V30	Grade 0-1	110.9	134.5	0.938
	Grade 2+	106.0	139.3	
V40	Grade 0-1	58.5	69.5	0.934
	Grade 2+	65.3	88.2	
V50	Grade 0-1	22.8	26.2	0.978
	Grade 2+	24.9	30.1	
V60	Grade 0-1	1.9	1.8	0.529
	Grade 2+	1.3	1.7	
V70	Grade 0-1	0.0	0.2	0.354
	Grade 2+	0.0	0.0	

Table 43. Mann-Whitney U test to compare the mean volume of total bowel receiving 0-70Gy in patients with RTOG Grade 1+ and Grade 0 diarrhoea at 24 months

	RTOG Diarrhoea at 24 months	Mean volume (cc)	SD (cc)	*P* value
Total bowel	Grade 0 n=106 (88%)	543.7	201.3	0.899
	Grade 1+ n=15 (12%)	530.8	223.3	
V10	Grade 0	212.1	236.5	0.957
	Grade 1+	204.8	235.7	
V20	Grade 0	169.8	198.1	0.761
	Grade 1+	149.1	176.9	
V30	Grade 0	112.9	135.8	0.814
	Grade 1+	105.5	132.3	
V40	Grade 0	59.4	70.1	0.924
	Grade 1+	66.4	85.3	
V50	Grade 0	23.5	27.1	0.970
	Grade 1+	24.4	29.1	
V60	Grade 0	1.0	1.8	0.963
	Grade 1+	1.1	1.9	
***V70**	Grade 0	0.0	0.2	0.913
	Grade 1+	0.0	0.1	

Table 44. Mann-Whitney U test to compare the mean volume of total bowel receiving 0-70Gy in patients with RTOG Grade 2+ and Grade 0-1 diarrhoea at 24 months

	RTOG Diarrhoea at 24 months	Mean volume (cc)	SD (cc)	*P* value
Total bowel	Grade 0-1 n=116 (96%)	547.2	198.6	0.234
	Grade 2+ n=5 (4%)	427.6	293.6	
V10	Grade 0-1	211.4	234.1	0.620
	Grade 2+	205.1	293.3	
V20	Grade 0-1	167.4	194.2	0.760
	Grade 2+	162.3	235.3	
V30	Grade 0-1	111.1	132.7	0.849
	Grade 2+	130.8	195.1	
V40	Grade 0-1	59.1	69.2	0.940
	Grade 2+	86.0	126.1	
V50	Grade 0-1	23.4	26.9	0.962
	Grade 2+	28.6	37.4	
V60	Grade 0-1	1.1	1.8	0.944
	Grade 2+	0.6	0.6	
V70	Grade 0-1	0.0	0.2	0.564
	Grade 2+	0.0	0.0	

Table 45. Mann-Whitney U test to compare the mean volume of small bowel receiving 0-60Gy in patients with RTOG Grade 1+ and Grade 0 proctitis at 24 months

	RTOG proctitis at 24 months	Mean volume (cc)	SD (cc)	*P* value
Total small bowel	Grade 0 n=106 (88%)	356.9	183.3	0.663
	Grade 1+ n= 15 (12%)	335.3	177.9	
V10	Grade 0	127.7	168.7	0.437
	Grade 1+	123.0	177.3	
V20	Grade 0	98.6	137.9	0.555
	Grade 1+	92.7	135.0	
V30	Grade 0	58.5	88.0	0.621
	Grade 1+	57.4	90.7	
V40	Grade 0	24.8	39.8	0.517
	Grade 1+	25.5	43.9	
V50	Grade 0	8.3	15.2	0.503
	Grade 1+	8.0	13.9	
V60	Grade 0	0.2	1.0	0.847
	Grade 1+	0.3	0.8	

Table 46. Mann-Whitney U test to compare the mean volume of small bowel receiving 0-60Gy in patients with maximum reported late RTOG Grade 1+ and Grade 0 proctitis

	Maximum late RTOG proctitis	Mean volume (cc)	SD (cc)	*P* value
Small bowel	Grade 0 n=96 (79%)	350.9	188.1	0.617
	Grade 1+ n=25 (21%)	366.0	160.8	
V10	Grade 0	129.0	167.8	0.459
	Grade 1+	120.3	176.6	
V20	Grade 0	100.7	139.7	0.499
	Grade 1+	87.4	128.3	
V30	Grade 0	60.6	90.5	0.544
	Grade 1+	50.3	79.5	
V40	Grade 0	26.2	41.3	0.358
	Grade 1+	20.2	35.9	
V50	Grade 0	8.7	15.9	0.456
	Grade 1+	6.5	11.6	
V60	Grade 0	0.2	1.1	0.958
	Grade 1+	0.3	0.7	

Table 47. Mann-Whitney U test to compare the mean volume of small bowel receiving 0-60Gy in patients with RTOG Grade 1+ and Grade 0-1 diarrhoea at 24 months

	RTOG diarrhoea at 24 months	Mean volume (cc)	SD (cc)	*P* value
Total small bowel	Grade 0 n=106 (88%)	353.7	182.1	0.938
	Grade 1+ n=15 (12%)	357.3	187.5	
V10	Grade 0	126.7	170.1	0.926
	Grade 1+	130.3	167.0	
V20	Grade 0	99.1	140.4	0.949
	Grade 1+	89.3	114.9	
V30	Grade 0	58.6	89.8	0.921
	Grade 1+	56.3	77.5	
V40	Grade 0	24.2	40.1	0.686
	Grade 1+	29.2	41.2	
V50	Grade 0	8.2	15.6	0.601
	Grade 1+	8.1	10.2	
V60	Grade 0	0.2	1.1	0.438
	Grade 1+	0.2	0.5	

Table 48. Mann-Whitney U test to compare the mean volume of small bowel receiving 0-60Gy in patients with maximum reported late RTOG Grade 1+ and Grade 0 Diarrhoea

	Maximum late RTOG diarrhoea	Mean volume (cc)	SD (cc)	*P* value
Total small bowel	Grade 0 n=85 (70%)	335.9	185.5	0.100
	Grade 1+ n=36 (30%)	392.6	170.0	
V10	Grade 0	115.9	166.3	0.264
	Grade 1+	146.8	173.5	
V20	Grade 0	90.1	136.8	0.272
	Grade 1+	112.1	137.9	
V30	Grade 0	52.1	87.8	0.342
	Grade 1+	70.3	88.2	
V40	Grade 0	21.0	38.7	0.210
	Grade 1+	32.7	42.5	
V50	Grade 0	7.3	15.6	0.214
	Grade 1+	10.1	13.8	
V60	Grade 0	0.0	0.2	0.485
	Grade 1+	0.3	0.7	

Table 49. Mann-Whitney U test to compare the mean volume of sigmoid bowel receiving 0-70Gy in patients with RTOG Grade 1+ and Grade 0 proctitis at 24 months

	RTOG proctitis at 24 months	Mean volume (cc)	SD (cc)	*P* value
Total Sigmoid bowel	Grade 0 n=106 (88%)	118.3	63.8	0.627
	Grade 1+ n=15 (12%)	127.9	67.5	
V10	Grade 0	62.7	63.7	0.378
	Grade 1+	51.9	71.4	
V20	Grade 0	55.0	59.4	0.401
	Grade 1+	48.4	70.0	
V30	Grade 0	46.9	53.0	0.563
	Grade 1+	44.5	65.2	
V40	Grade 0	33.2	37.9	0.631
	Grade 1+	31.7	45.6	
V50	Grade 0	14.9	17.0	0.609
	Grade 1+	14.2	19.7	
V60	Grade 0	0.9	1.5	0.409
	Grade 1+	0.3	0.4	
V70	Grade 0	0.0	0.2	0.295
	Grade 1+	0.0	0.0	

Table 50. Mann-Whitney U test to compare the mean volume of sigmoid bowel receiving 0-70Gy in patients with RTOG Grade 2+ and Grade 0-1 proctitis at 24 months

	RTOG proctitis at 24 months	Mean volume (cc)	SD (cc)	*P* value
Total Sigmoid bowel	Grade 0-1 n=118 (98%)	118.8	64.3	0.257
	Grade 2+ n=3 (2%)	150.6	55.0	
V10	Grade 0-1	61.1	64.4	0.909
	Grade 2+	71.0	83.9	
V20	Grade 0-1	53.8	60.3	0.935
	Grade 2+	68.3	85.1	
V30	Grade 0-1	46.1	53.8	0.883
	Grade 2+	64.5	86.7	
V40	Grade 0-1	32.4	37.7	0.831
	Grade 2+	55.8	79.0	
V50	Grade 0-1	14.7	17.2	0.857
	Grade 2+	19.2	24.3	
V60	Grade 0-1	0.8	1.5	0.909
	Grade 2+	0.3	0.5	
V70	Grade 0-1	0.0	0.2	0.807
	Grade 2+	0.0	0.0	

Table 51. Mann-Whitney U test to compare the mean volume of sigmoid bowel receiving 0-70Gy in patients with RTOG Grade 1+ and Grade 0 diarrhoea at 24 months

	RTOG diarrhoea at 24 months	Mean volume (cc)	SD (cc)	*P* value
Total sigmoid bowel	Grade 0 n=106 (88%)	119.6	66.7	0.648
	Grade 1+ n=15 (12%)	119.3	43.3	
V10	Grade 0	61.6	66.1	0.840
	Grade 1+	59.8	54.9	
V20	Grade 0	54.6	61.8	0.964
	Grade 1+	50.8	53.3	
V30	Grade 0	46.8	55.0	0.898
	Grade 1+	45.1	52.1	
V40	Grade 0	32.6	38.1	0.964
	Grade 1+	35.8	44.7	
V50	Grade 0	14.6	17.0	0.960
	Grade 1+	16.1	19.7	
V60	Grade 0	0.8	1.5	0.969
	Grade 1+	0.9	1.6	
V70	Grade 0	0.0	0.2	0.913
	Grade 1+	0.0	0.1	

Table 52. Mann-Whitney U test to compare the mean volume of sigmoid bowel receiving 0-70Gy in patients with RTOG Grade 2+ and Grade 0-1 diarrhoea at 24 months

	RTOG diarrhoea At 24 months	Mean volume (cc)	SD (cc)	*P* value
Total sigmoid bowel	Grade 0-1 n=116 (96%)	119.3	43.4	0.812
	Grade 2+ n=5 (4%)	119.8	64.3	
V10	Grade 0-1	59.8	54.9	0.822
	Grade 2+	61.6	64.6	
V20	Grade 0-1	50.8	53.3	0.973
	Grade 2+	54.2	60.5	
V30	Grade 0-1	45.1	52.1	0.951
	Grade 2+	46.3	53.9	
V40	Grade 0-1	35.8	44.7	0.897
	Grade 2+	32.5	37.7	
V50	Grade 0-1	16.1	19.7	0.940
	Grade 2+	14.6	17.0	
V60	Grade 0-1	0.9	1.6	0.736
	Grade 2+	0.8	1.5	
V70	Grade 0-1	0.0	0.1	0.564
	Grade 2+	0.0	0.2	

Table 53. Mann-Whitney U test to compare the mean volume of sigmoid bowel receiving 0-70Gy in patients with maximum reported late RTOG Grade 1+ and Grade 0 diarrhoea

	Maximum late RTOG Diarrhoea	Mean volume (cc)	SD (cc)	*P* value
Total sigmoid bowel	Grade 0 n=85 (70%)	120.3	67.7	0.900
	Grade 1+ n=36 (30%)	112.2	45.2	
V10	Grade 0	58.8	63.6	0.780
	Grade 1+	61.0	57.2	
V20	Grade 0	52.4	61.3	0.910
	Grade 1+	54.1	55.5	
V30	Grade 0	45.4	55.5	0.958
	Grade 1+	46.6	50.7	
V40	Grade 0	31.9	38.8	0.899
	Grade 1+	33.3	37.4	
V50	Grade 0	13.9	16.1	0.980
	Grade 1+	15.1	16.9	
V60	Grade 0	0.8	1.4	0.961
	Grade 1+	0.9	1.6	
V70	Grade 0	0.0	0.2	0.363
	Grade 1+	0.0	0.0	

Table 54. Mann-Whitney U test to compare the mean volume of large bowel receiving 0-50Gy in patients with RTOG Grade 1+ and Grade 0 proctitis at 24 months

	RTOG proctitis at 24 months	Mean volume (cc)	SD (cc)	*P* value
Total large bowel	Grade 0 n=106 (88%)	64.2	64.3	0.316
	Grade 1+ n=15 (12%)	50.2	53.8	
V10	Grade 0	22.0	45.7	0.792
	Grade 1+	14.6	28.6	
V20	Grade 0	14.5	32.0	0.879
	Grade 1+	10.1	23.1	
V30	Grade 0	6.7	16.9	0.910
	Grade 1+	3.5	10.2	
V40	Grade 0	2.2	6.2	0.849
	Grade 1+	1.0	2.9	
V50	Grade 0	0.6	1.9	0.275
	Grade 1+	0.2	0.8	

Table 55. Mann-Whitney U test to compare the mean volume of large bowel receiving 0-50Gy in patients with RTOG Grade 2+ and Grade 0-1 proctitis at 24 months

	RTOG proctitis at 24 months	Mean volume (cc)	SD (cc)	*P* value
Total Large Bowel	Grade 0-1 n=118 (98%)	61.9	63.0	0.456
	Grade 2+ n=3 (2%)	80.9	69.8	
V10	Grade 0-1	21.0	44.3	0.500
	Grade 2+	20.1	20.2	
V20	Grade 0-1	14.1	31.3	0.534
	Grade 2+	9.2	8.9	
V30	Grade 0-1	6.3	16.4	0.546
	Grade 2+	3.3	5.6	
V40	Grade 0-1	2.1	6.0	0.873
	Grade 2+	1.1	2.0	
V50	Grade 0-1	0.6	1.8	0.629
	Grade 2+	0.0	0.0	

Table 56. Mann-Whitney U test to compare the mean volume of large bowel receiving 0-50Gy in patients with maximum reported late RTOG Grade 1+ and Grade 0 proctitis

	Maximum late RTOG Proctitis	Mean volume (cc)	SD (cc)	*P* value
Total Large bowel	Grade 0 n=96 (79%)	64.2	66.1	0.824
	Grade 1+ n=25 (21%)	55.9	49.2	
V10	Grade 0	22.5	47.1	0.531
	Grade 1+	15.0	28.1	
V20	Grade 0	14.9	32.6	0.571
	Grade 1+	10.0	23.0	
V30	Grade 0	7.0	17.4	0.391
	Grade 1+	3.5	10.3	
V40	Grade 0	2.3	6.4	0.362
	Grade 1+	1.0	2.9	
V50	Grade 0	0.6	2.0	0.204
	Grade 1+	0.3	0.9	

Table 57. Mann-Whitney U test to compare the mean volume of large bowel receiving 0-50Gy in patients with RTOG Grade 1+ and Grade 0 diarrhoea at 24 months

	RTOG diarrhoea at 24 months	Mean volume (cc)	SD (cc)	*P* value
Total large bowel	Grade 0 n=106 (88%)	64.3	65.3	0.660
	Grade 1+ n=15 (12%)	49.9	44.2	
V10	Grade 0	22.2	45.7	0.441
	Grade 1+	13.3	28.7	
V20	Grade 0	14.8	31.9	0.447
	Grade 1+	8.6	23.1	
V30	Grade 0	6.6	16.9	0.452
	Grade 1+	3.8	10.2	
V40	Grade 0	2.2	6.2	0.931
	Grade 1+	1.1	2.9	
V50	Grade 0	0.6	1.9	0.275
	Grade 1+	0.2	0.8	

Table 58. Mann-Whitney U test to compare the mean volume of sigmoid receiving 0-50Gy in patients with RTOG Grade 2+ and Grade 0-1 diarrhoea at 24 months

	RTOG Diarrhoea at 24 months	Mean volume (cc)	SD (cc)	*P* value
Total Large bowel	Grade 0-1 n=116 (96%)	64.1	63.7	0.099
	Grade 2+ 5 (4%)	25.7	26.4	
V10	Grade 0-1	21.7	44.7	0.631
	Grade 2+	5.2	8.6	
V20	Grade 0-1	14.4	31.5	0.766
	Grade 2+	4.4	7.7	
V30	Grade 0-1	6.4	16.5	0.981
	Grade 2+	2.2	4.2	
V40	Grade 0-1	2.1	6.0	0.640
	Grade 2+	0.7	1.5	
V50	Grade 0-1	0.6	1.8	0.309
	Grade 2+	0.0	0.0	

Table 59. Mann-Whitney U test to compare the mean volume of large bowel receiving 0-50Gy in patients with maximum reported late RTOG Grade 1+ and Grade 0 diarrhoea

	Maximum late RTOG Diarrhoea	Mean volume (cc)	SD (cc)	*P* value
Total Large bowel	Grade 0 n=85 (70%)	62.0	66.0	0.656
	Grade 1+ n=36 (30%)	63.3	55.7	
V10	Grade 0	22.7	48.4	0.922
	Grade 1+	16.9	30.4	
V20	Grade 0	15.2	33.5	0.989
	Grade 1+	10.9	23.4	
V30	Grade 0	6.5	17.3	0.956
	Grade 1+	5.6	13.4	
V40	Grade 0	2.0	5.6	0.632
	Grade 1+	2.1	6.6	
V50	Grade 0	0.6	1.9	0.447
	Grade 1+	0.5	1.6	

Table 60. Mann-Whitney U test to compare the mean volume of rectum receiving 0-70Gy in patients with RTOG Grade 1+ and Grade 0 proctitis at 24 months

	RTOG proctitis at 24 months	Mean volume (cc)	SD (cc)	*P* value
Total rectum	Grade 0 n=106 (88%)	63.4	17.8	0.157
	Grade 1+ n=15 (12%)	68.3	20.1	
V10	Grade 0	58.5	17.5	0.544
	Grade 1+	59.9	21.6	
V20	Grade 0	54.0	17.0	0.599
	Grade 1+	54.8	24.3	
V30	Grade 0	47.3	15.6	0.441
	Grade 1+	48.3	20.1	
V40	Grade 0	36.1	13.0	0.359
	Grade 1+	36.0	13.0	
V50	Grade 0	24.0	9.4	0.645
	Grade 1+	23.4	8.9	
V60	Grade 0	11.6	4.7	0.942
	Grade 1+	10.9	5.8	
V70	Grade 0	2.8	1.5	0.797
	Grade 1+	2.5	1.6	

Table 61. Mann-Whitney U test to compare the mean volume of rectum receiving 0-70Gy in patients with RTOG Grade 2+ and Grade 0-1 proctitis at 24 months

	RTOG proctitis at 24 months	Mean volume (cc)	SD (cc)	*P* value
Total rectum	Grade 0-1 n=118 (98%)	64.2	18.2	0.653
	Grade 2+ n=3 (2%)	57.5	15.2	
V10	Grade 0-1	58.8	18.1	0.560
	Grade 2+	51.8	12.2	
V20	Grade 0-1	54.2	18.1	0.571
	Grade 2+	48.3	11.1	
V30	Grade 0-1	47.5	16.3	0.839
	Grade 2+	44.3	10.2	
V40	Grade 0-1	36.1	13.0	0.606
	Grade 2+	38.4	7.2	
V50	Grade 0-1	23.8	9.4	0.483
	Grade 2+	26.4	4.3	
V60	Grade 0-1	11.5	4.9	0.702
	Grade 2+	12.1	2.0	
V70	Grade 0-1	2.8	1.5	0.955
	Grade 2+	2.7	0.8	

Table 62. Mann-Whitney U test to compare the mean volume of rectum receiving 0-70Gy in patients with maximum late RTOG Grade 1+ and Grade 0 proctitis

	Maximum late RTOG Proctitis	Mean volume (cc)	SD (cc)	*P* value
Total Rectum	Grade 0 n=96 (79%)	63.4	17.6	0.338
	Grade 1+ n=25 (21%)	66.3	20.1	
V10	Grade 0	58.5	17.3	0.740
	Grade 1+	59.1	20.7	
V20	Grade 0	54.0	17.0	0.710
	Grade 1+	54.3	21.4	
V30	Grade 0	47.3	16.0	0.452
	Grade 1+	47.8	17.0	
V40	Grade 0	36.1	13.4	0.332
	Grade 1+	36.3	11.2	
V50	Grade 0	24.0	9.6	0.651
	Grade 1+	23.6	8.2	
V60	Grade 0	11.6	4.7	0.928
	Grade 1+	11.2	5.3	
V70	Grade 0	2.8	1.5	0.623
	Grade 1+	2.5	1.4	

Table 63. Mann-Whitney U test to compare the mean volume of rectum receiving 0-70Gy in patients with RTOG Grade 2+ and Grade 0-1 proctitis

	Maximum late RTOG Proctitis	Mean volume (cc)	SD (cc)	*P* value
Total Rectum	Grade 0-1 n=115 (95%)	64.3	18.3	0.810
	Grade 2+ n=6 (5%)	59.0	15.7	
V10	Grade 0-1	58.9	18.2	0.706
	Grade 2+	53.5	13.9	
V20	Grade 0-1	54.3	18.2	0.625
	Grade 2+	49.8	12.5	
V30	Grade 0-1	47.5	16.4	0.936
	Grade 2+	46.3	12.0	
V40	Grade 0-1	36.0	13.1	0.541
	Grade 2+	37.6	9.8	
V50	Grade 0-1	23.8	9.5	0.477
	Grade 2+	25.3	5.2	
V60	Grade 0-1	11.5	5.0	0.557
	Grade 2+	12.0	1.5	
V70	Grade 0-1	2.7	1.6	0.397
	Grade 2+	3.0	0.9	

Table 64. Mann-Whitney U test to compare the mean volume of rectum receiving 0-70Gy in patients with RTOG Grade 1+ and Grade 0 diarrhoea at 24 months

	RTOG diarrhoea at 24 months	Mean volume (cc)	SD (cc)	*P* value
Total Rectum	Grade 0 n=106 (88%)	63.9	18.4	0.568
	Grade 1+ n=15 (12%)	64.9	16.6	
V10	Grade 0	58.9	17.9	0.948
	Grade 1+	57.0	18.7	
V20	Grade 0	54.4	17.6	0.877
	Grade 1+	52.2	20.8	
V30	Grade 0	47.5	16.0	0.514
	Grade 1+	46.7	17.6	
V40	Grade 0	36.3	12.8	0.819
	Grade 1+	34.9	14.4	
V50	Grade 0	24.0	9.3	0.967
	Grade 1+	23.3	10.0	
V60	Grade 0	11.5	4.7	0.741
	Grade 1+	11.7	5.6	
V70	Grade 0	2.8	1.5	0.328
	Grade 1+	2.3	1.3	

Table 65. Mann-Whitney U test to compare the mean volume of rectum receiving 0-70Gy in patients with RTOG Grade 2+ and Grade 0-1 diarrhoea at 24 months

	RTOG diarrhoea at 24 months	Mean volume (cc)	SD (cc)	*P* value
Total Rectum	Grade 0-1 n=116 (96%)	64.0	18.4	0.609
	Grade 2+ n=5 (4%)	65.6	10.4	
V10	Grade 0-1	58.6	18.3	0.590
	Grade 2+	59.9	10.1	
V20	Grade 0-1	54.0	18.3	0.492
	Grade 2+	56.4	8.7	
V30	Grade 0-1	47.2	16.4	0.230
	Grade 2+	51.9	5.6	
V40	Grade 0-1	36.0	13.1	0.200
	Grade 2+	39.6	8.1	
V50	Grade 0-1	23.8	9.4	0.544
	Grade 2+	25.5	7.6	
V60	Grade 0-1	11.5	4.8	0.736
	Grade 2+	11.6	5.8	
V70	Grade 0-1	2.8	1.5	0.637
	Grade 2+	2.4	1.4	

Table 66. Mann-Whitney U test to compare the mean volume of rectum receiving 0-70Gy in patients with maximum reported late RTOG Grade 1+ and Grade 0 diarrhoea

	Maximum late RTOG Diarrhoea	Mean volume (cc)	SD (cc)	*P* value
Total Rectum	Grade 0 n=85 (70%)	63.5	18.8	0.374
	Grade 1+ n=36 (30%)	64.9	16.5	
V10	Grade 0	58.4	18.3	0.643
	Grade 1+	58.6	17.2	
V20	Grade 0	54.0	17.9	0.718
	Grade 1+	53.9	18.4	
V30	Grade 0	47.1	15.7	0.621
	Grade 1+	47.6	17.2	
V40	Grade 0	35.8	11.7	0.736
	Grade 1+	36.5	15.7	
V50	Grade 0	23.4	8.1	0.638
	Grade 1+	24.8	11.9	
V60	Grade 0	11.3	4.6	0.794
	Grade 1+	11.8	5.3	
V70	Grade 0	1.5	2.9	0.094
	Grade 1+	2.3	1.2	

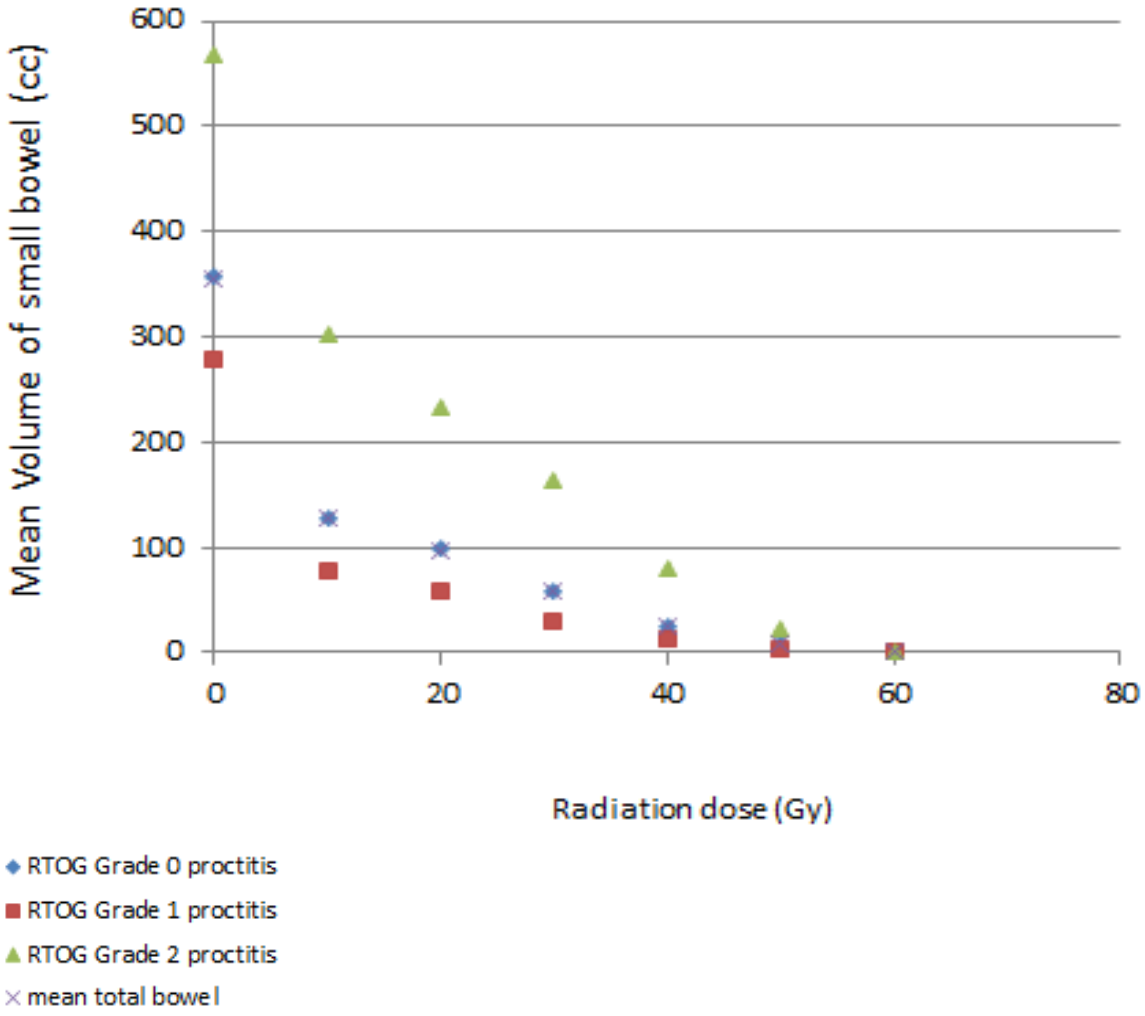

Figure 26. Mean small bowel volumes receiving between 0 and 70Gy in the whole trial cohort and RTOG proctitis reported at 24 months. RTOG Grade 0 (n=106), Grade 1 (n=12) and Grade 2 (n=3)

Total dose to pelvic LN (Gy)	No of Fractions	Dose per fraction (Gy)	EQD2	α/β =1.5	α/β =3.0	α/β =5.0	α/β =10
46	23	2	46	46	46	46	46
45	25	1.8	42.6	42.4	43.2	43.7	44.3
50	35	1.43	42.9	41.9	44.3	45.9	47.6
55	35	1.57	49.1	48.2	50.3	51.6	53.0
60	35	1.71	55.6	55.0	56.5	57.5	58.5
65	35	1.86	62.7	62.3	63.1	63.7	64.2
47	20	2.35	51.1	51.7	50.3	49.3	48.4
51	20	2.55	58.0	59.0	56.6	55.0	53.3

Table 67. Dose fractionation schedule for Phase I/II IMRT trial with boost doses compared to standard PLN dose fractionation schedules

Appendix 7.