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External beam radiotherapy (EBRT) and high-dose rate (HDR) brachytherapy for intermediate and high-risk prostate cancer: the impact of EBRT volume

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Declaration of Conflict of Interest

The authors declare no personal conflict of interest

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Abstract

Background: Whole pelvis radiotherapy (WPRT) may improve clinical outcomes over prostate-only radiotherapy (PORT)in high-risk prostate cancer patients by sterilization of micrometastatic nodal disease provided there is optimal control of the primary site.

Methods: A prospective multicentre cohort study of eligible patients (stage ≥T2c, Gleason score ≥7 or presenting prostate-specific antigen (pPSA) ≥10) treated between 2009 and 2013 in a UK national protocol with EBRT and HDR BT. Centres elected to deliver WPRT, 46Gy in 23 fractions or PORT 37.5Gy in 15 fractions. 15Gy single dose was delivered to all using HDR BT. The primary endpoint was biochemical progression-free survival (bPFS). Secondary endpoints were overall survival (OS) and acute and late genitourinary and gastrointestinal toxicity.

Results: 812 patients were entered; 401 received WPRT and 411 received PORT. With a median follow- up of 4.7 years, five-year bPFS rates for WPRT versus PORT arms were 89% vs 81% ($p = 0.007$) for all patients and 84% vs 77% ($p = 0.001$) for high-risk patients. Differences in bPFS remained significant after accounting for Gleason score, pPSA, T stage and androgen deprivation therapy duration as co-variates. There was no difference in OS. WPRT increased acute genitourinary toxicity ($p = 0.03$) with a smaller non-significant increase in acute gastrointestinal toxicity ($p = 0.06$). No difference in late radiation toxicity was observed.

Conclusion: A significant improvement in 5-year bPFS was seen in intermediate and high-risk prostate cancer treated with WPRT compared to PORT in a combined EBRT and BT schedule with no increase in late radiation toxicity.

Introduction

High-risk localised prostate cancer may be associated with a risk of occult pelvic lymph node metastases as high as 40%[1]. The use of whole pelvis radiotherapy (WPRT) as opposed to prostate-only radiotherapy (PORT) may improve outcomes in the high-risk population by sterilization of micrometastatic pelvic nodal disease. However, both prospective randomized trials comparing WPRT and PORT conducted in the modern PSA era were negative[2,3]. A limitation of both studies was the cumulative doses of 66-70Gy to the prostate which are sub-optimal in the context of modern dose-escalation series[4-6]. Inadequate treatment of the primary tumour and poor local control, may negate any potential benefit of regional nodal irradiation. With optimisation of dose intensity to the prostate, the true value of concurrent pelvic treatment may become apparent.

Interstitial brachytherapy is an effective means of intensifying dose to the prostate. The sharp fall-off in dose combined with the dose heterogeneity across the brachytherapy volume can result in dose escalation in some areas of the gland to greater than 140Gy (EQD2). Furthermore, the low α/β ratio of prostate cancer makes the extreme hypofractionation of high-dose rate (HDR) brachytherapy radiobiologically more efficient compared to fractionated external beam therapy. A prospective randomized trial[7] and several retrospective series comparing external beam radiotherapy (EBRT) alone with EBRT combined with a HDR brachytherapy boost in localized prostate disease have shown combined modality treatment to significantly improve biochemical control across all risk groups[8-13] . Two randomised trials have shown this to be the case also with a LDR iridium [14,15] or iodine-125 boost [16]. The beneficial impact of a brachytherapy boost has been

confirmed in a recent meta-analysis [17] Using brachytherapy in combination with EBRT to optimize local control may enable the benefit of prophylactic pelvic nodal irradiation to emerge.

Compared to PORT, WPRT has been associated with an increase in adverse effects. Higher rates of both genitourinary (GU) and gastrointestinal (GI) toxicity have been reported[18,198,2], although this is not consistent [20,3]. However these studies used 3D conformal techniques and with intensity modulated radiotherapy (IMRT) irradiating smaller bowel volumes, pelvic treatment is better tolerated.[21,22] and high-dose nodal irradiation is now feasible[23].

A prospective national database evaluating a standard protocol arising from following a national consensus meeting delivering external beam radiotherapy (EBRT) with single dose 15Gy HDR brachytherapy was used for this study. Two external beam schedules were permitted: 46Gy in 23 fractions WPRT or 37.5Gy in 15 fractions PORT preselected by each centre. The impact of EBRT volume (WPRT vs PORT) on biochemical progression-free survival (bPFS) was the primary end point; urinary and bowel toxicity has also been compared in intermediate and high-risk prostate cancer patients.

Methods and materials

Eligibility

Patients with histologically confirmed adenocarcinoma of the prostate and intermediate or high-risk features (T stage ≥ T2c and/or Gleason score (GS) ≥ 7 and/or presenting prostate-specific antigen (pPSA) ≥ 10μg/L), no evidence of nodal or other metastatic disease, suitable for radical radiotherapy, fit for general anaesthesia and able to give informed consent were eligible. On entry patients underwent clinical history, physical assessment including digital

rectal examination (DRE), serum PSA, transrectal ultrasound-guided biopsy of the prostate, pelvic magnetic resonance (MR) imaging and isotope bone scan. Additional computed tomography (CT) of the chest/abdomen/pelvis and positron emission tomography (PET) were performed at the clinician's discretion. Exclusion criteria were radiological evidence of metastatic disease, recent transurethral resection of the prostate (TURP), and medical co-morbidities precluding general anaesthesia. All patients provided written informed consent. Between 2010 and 2013, a total of 812 patients were recruited from nine centres across the UK.

Treatment protocol

All patients received EBRT with either 3D conformal (3D-CRT) or intensity-modulated radiotherapy (IMRT) using 6-18 megavoltage photons. EBRT was delivered to either the prostate only or to the whole pelvis according to institutional policy. Patients treated with PORT received 37.5Gy in 15 daily fractions. The clinical target volume (CTV) included prostate and seminal vesicles with a 5mm margin expanded by a further 5mm constrained posteriorly to the anterior rectal wall to define the PTV for external beam planning. Where WPRT was given then nodal regions were outlined based on a published atlas [24] to include internal iliac, external iliac, obturator and pre-sacral regions expanded by 5mm to define the PTV for the nodal fields. Patients treated with WPRT received 46Gy in 23 daily fractions.

All patients received high-dose rate brachytherapy (HDRBT). The CTV was defined as the prostate capsule plus any macroscopic extracapsular extension or seminal vesicle involvement expanded by 3mm (constrained posteriorly by the rectal contour). No additional expansion was used to form the PTV. A minimum peripheral dose of 15Gy was prescribed. Cumulative biologic equivalent prostate doses summing EBRT and BT were

107Gy and 100Gy for patients receiving WPRT and PORT respectively if α/β = 1.5 but could be as low as 96Gy and 91.4Gy respectively if the α/β = 3.5). The dose constraints to the rectum D_{2cc} were <12Gy with a maximum of <15Gy and to the urethra D10 <17.5Gy and D30 <16.5Gy with no area receiving ≥22.5Gy. All patients were treated with a single implant.

Neoadjuvant androgen deprivation therapy (ADT) commenced 1-3 months prior to radiotherapy was administered in 96.3% of patients. The duration of ADT ranged from 1 to 36 months with a median of 24 months. The protocol recommendation was for 6 months in intermediate risk disease and 24-36 months in high risk disease.

Patients were seen at 1, 3 and 6 months after treatment, 6 monthly intervals thereafter to five years and then annually. Each visit included a serum PSA, the International Prostate Symptom Score (IPSS) score and toxicity based on the Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0) Acute toxicity was defined as occurring within 90 days following completion of radiotherapy; all reported toxicity thereafter was classified as late toxicity. Data from each collaborating centre was collected centrally into a designated data base held at Mount Vernon Cancer Centre.

Statistical analysis

Pre-treatment patient characteristics were compared using an independent *t* test and chi-squared analysis for continuous and categorical variables respectively. The primary endpoint of the study was biochemical progression-free survival. Secondary endpoints were overall survival (OS), acute and late genitourinary and gastrointestinal toxicities. Biochemical failure was defined according to Phoenix criteria as an absolute rise of ≥2ng/ml above the nadir PSA value[25]. Patients free of biochemical recurrence were censored at the date of the

last PSA reading. OS was taken as the time to death from any cause; live patients were censored at the time of their last follow-up. Time zero was defined as the date of completion of all radiotherapy; bPFS and OS rates were calculated using the Kaplan-Meier method and the resulting survival curves compared using the Mantel-Cox log-rank test. A subgroup analysis was performed grouping patients according to risk category with high-risk defined as any one of the following parameters: T stage ≥ T3, Gleason score 8-10 or pPSA > 20. For evaluation of toxicity, patients were analysed according to EBRT treatment volume. The prevalence of GU and GI toxicity of grade 2 or greater was compared at each follow-up point using a contingency platform and a chi-square analysis to test for significance between treatment arms.

For bPFS analysis, the patient subgroups (EBRT volume, risk category, Gleason score, T stage, pPSA and duration of ADT) were classified. Univariate Cox regression analysis was performed to determine if any of the clinical variables predicted for bPFS. All the variables with a p value of <0.10 were entered into a multivariate, forward conditional Cox regression. For all tests, a p value of ≤0.05 was considered statistically significant.

For all tests, a *p* value of ≤0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 22.0 (IBM Corp., Armonk, NY).

Results

812 patients were included in this analysis. Baseline clinical and treatment-related parameters for the entire cohort are summarized in table 1. 401 received WPRT and 411 were treated with PORT; patient accrual by centre and external beam volume are shown in table 2. Adherence to the planning dose objectives was good as shown in table 3.

The median follow-up time for all patients was 4.7 years. The 5-year bPFS rate for all patients was 81% in the PORT arm and 89% in the WPRT arm (p = 0.007) (Figure 1). On subset analysis, the benefit of WPRT was maintained in the high-risk group (84% vs 77%, p = 0.001), but not in those with intermediate-risk disease (91% vs 90%, NS). When comparing favourable and unfavourable intermediate risk groups no benefit of WPRT was seen (favourable 96% vs 100%; unfavourable 89% vs 89%). Cox univariate and multivariate analyses of the whole study cohort are listed in Table 4. After adjustment, the use of WPRT, pre-treatment PSA, Gleason score, T stage and ADT duration were all found to independently predict for biochemical recurrence. Table 5 shows the sites of recurrence for all patients presenting with biochemical relapse. Five patients in the WPRT arm had radiologically confirmed pelvic nodal disease on relapse compared to 13 patients in the PORT arm. Isolated pelvic node relapse was seen in 1 (WPRT) and 4 (PORT) patients respectively. These differences are not statistically significantly different (p = 0.28). No statistically significant difference in 5-year overall survival rates between the WPRT and PORT arms was observed (94% vs 93%, p = 0.74).

Across the entire study population, treatment-related toxicity was mild with the prevalence of any ≥ grade 3 toxicity no higher than 1.5% at any follow-up time point. The prevalence of acute and late genitourinary and gastrointestinal toxicities ≥ grade 2 stratified according to EBRT volume are shown in Figure 2. WPRT resulted in a significant increase in acute genitourinary toxicity of grade 2 or greater (p = 0.03). A higher proportion of WPRT patients experienced acute gastrointestinal toxicity of ≥ grade 2 although this did not reach statistical significance (p = 0.06). No significant difference in late GU or GI radiation toxicity was observed between the two cohorts. Detailed toxicity scores are included in supplementary table 1.

Discussion

The benefits of dose-escalation and hormonal therapy have both been demonstrated in high-risk prostate cancer in terms of biochemical control but only ADT in combination with radiotherapy has been shown to confer an overall survival advantage. The efficacy of dose-escalation to the prostate may be limited by the presence of subclinical disease in the pelvic lymph nodes outside the radiation field so that even with optimal control of the primary site relapse occurs regionally. The use of WPRT to sterilize nodal micrometastases resulting in improved outcomes in patients at high risk of nodal micrometastases is therefore rational. Current evidence for this remains controversial and neither of the two prospective randomized trials comparing WPRT with PORT conducted in the modern PSA era have shown any clinical advantage to irradiating the pelvic lymph nodes[2,3].

The first of these trials was RTOG 94-13 where patients were assigned to one of four arms: WPRT with neoadjuvant ADT (NHT), WPRT with adjuvant ADT (AHT), PORT with NHT, and PORT with AHT. At primary analysis, WPRT significantly improved PFS compared to PORT (54% vs 48%) but this effect was lost at 7-year follow-up when unexpected sequence dependent interactions between EBRT volume and the timing of ADT were also reported[2]. These interactions left the study underpowered to compare each of the four treatment arms against each other. The second, smaller randomized study comparing WPRT and PORT, GETUG-01, also proved negative[3]. The majority of patients in this trial had a risk of subclinical pelvic nodal disease of <15% and therefore were less likely to benefit from prophylactic irradiation. Moreover, the upper border of the whole pelvis fields were at the level of S1/S2. Large-scale mapping studies evaluating the patterns of first lymph node failure following PORT have shown that with a superior WPRT field border placed as low as

S1/S2, only 33% of patients with pelvic lymph node failure would have had complete coverage of all recurrences[26].

In both of these randomized trials, the cumulative doses of 66Gy-70Gy delivered to the prostate would be regarded as sub-optimal in the modern dose-escalation era. It is difficult to evaluate pelvic nodal irradiation in the context of potentially inadequate local tumour control. In this study, the impact of WPRT in high-risk patients has been evaluated in the context of dose-escalation using HDR brachytherapy to the prostate optimising chances of local control. Dosimetric data has been collected on all patients to confirm uniform implant quality; constraints as defined in the protocol were adhered to in over 90% of patients.

WPRT significantly improved 5-year biochemical progression-free survival compared to PORT. There were imblances between the two cohorts for various factors which might affect outcome; the WPRT had a higher proportion of patients with poor prognostic parameters (stage T3, Gleason score and PSA) with 88% in the high risk category compared to 69% in the PORT cohort. Consistent with this there was more prolonged use of ADT in the WPRT group with 71% >18 months compared to 47% in the PORT group. However when baseline tumour parameters and duration of ADT as co-variates were explored in a multivariable model treatment volume remained an independent outcome predictor. (Table 3). On subgroup analysis this effect was clearly maintained in the high-risk population but no longer significant in intermediate-risk, even considering unfavourable intermediate risk patients, although the numbers with intermediate-risk disease treated with WPRT were limited (n = 47).

The results presented here support the hypothesis that those with more aggressive disease and a greater risk of pelvic nodal involvement are more likely to derive benefit from WPRT. However this should be interpreted with caution; this is a prospective protocol treated population but the selection for external beam volume is not randomised and hence there may be systematic bias. In fact, patients receiving WPRT had significantly worse prognostic features at presentation suggesting that any bias in population characteristics was in favour of the PORT group.

The doses delivered to the prostate are different with the WPRT group receiving a dose which is between 4.6 and 7 Gy greater than the PORT group based on a simple EQD formula using an α/β value of 1.5 to 3.5. The total EQD2 dose was in both cases ≥100Gy, well beyond the range for dose response observed in external beam trials. Also, the PORT group received a negligible dose to the lymph nodes and it is notable that a greater number of patients with biochemical relapse in the PORT arm had radiologically evident pelvic nodal disease compared to those treated with WPRT, suggesting the benefit may arise from eradication of micrometastatic disease in the pelvic nodes. Again however a cautionary note is needed as there was no systematic scanning protocol at relapse.

The use of ADT is a confounding feature in studies such as this, particularly when the durations vary, following evidence based recommendations based on risk group[27]. Inevitably, as in this cohort, higher risk patients receive more prolonged ADT. Whilst we have included ADT duration as a parameter in the multivariable model despite which radiotherapy volume was an independent predictor of bRFS an effect cannot be entirely excluded. With a median follow-up of over 4.5 years, we might expect recovery of androgen production in most patients but unfortunately testosterone levels following ADT to document recovery were not undertaken.

A further argument against the benefit of WPRT comes from the albeit immature results of HDR used as sole therapy for intermediate and high risk patients in which bRFS of 93 -95% in intermediate and high risk patients are reported[28], however comparison across series compared to this contemporary planned cohort study is even more fraught with potential bias.

The benefit in bPFS seen in this series with WPRT was associated with an increase in acute genitourinary toxicity consistent with other published acute toxicity data[17,18]. However, there was no statistically significant difference in acute GI adverse effects or late radiation sequelae between the two arms and overall morbidity rates across both cohorts were considered acceptable.

The results of this study have shown that in patients with high-risk prostate cancer treated with a combination of EBRT and HDR brachytherapy, whole pelvis EBRT significantly improves bPFS compared to prostate-only EBRT without any increase in late radiation toxicity. With optimization of dose escalation to the prostate, prophylactic pelvic nodal irradiation in appropriately selected patients may be of clinical benefit. The results of the UK PIVOTAL boost study and RTOG 0924 which are assessing this in prospective randomized trials are awaited.

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