

Can we avoid dose escalation for intermediate-risk prostate cancer in the setting of short-course neoadjuvant androgen deprivation?

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Background: Both dose-escalated external beam radiotherapy (DE-EBRT) and androgen deprivation therapy (ADT) improve the outcomes in patients with intermediate-risk prostate cancer. Despite this, there are only few reports evaluating DE-EBRT for patients with intermediate-risk prostate cancer receiving neoadjuvant ADT, and virtually no studies investigating dose escalation >74 Gy in this setting. We aimed to determine whether DE-EBRT >74 Gy improved the outcomes for patients with intermediate-risk prostate cancer who received neoadjuvant ADT.

Findings: In our institution, patients with intermediate-risk prostate cancer were treated with neoadjuvant ADT and DE-EBRT, with doses sequentially increasing from 74 Gy to 76 Gy and then to 78 Gy between 2006 and 2012. We identified 435 patients treated with DE-EBRT and ADT, with a median follow-up of 70 months. For the 74 Gy, 76 Gy, and 78 Gy groups, five-year biochemical disease-free survival rates were 95.0%, 97.8%, and 95.3%, respectively; metastasis-free survival rates were 99.1%, 100.0%, and 98.6%, respectively; and prostate cancer-specific survival rate was 100% for all three dose levels. There was no significant benefit for dose escalation either on univariate or multivariate analysis for any outcome.

Conclusion: There was no benefit for DE-EBRT >74 Gy in our cohort of intermediate-risk prostate cancer patients treated with neoadjuvant ADT. Given the higher risks of toxicity associated with dose escalation, it may be feasible to omit dose escalation in this group of patients. Randomized studies evaluating dose de-escalation should be considered.

Keywords: radiotherapy, IMRT, dose, dose escalation, dose de-escalation, androgen deprivation therapy, prostate cancer

Introduction

Meta-analyses demonstrate that both dose-escalated external beam radiotherapy (DE-EBRT)¹ and androgen deprivation therapy (ADT) combined with radiotherapy² improve prostate cancer outcomes. However, it has been noted that there is little evidence supporting the use of dose escalation in patients also receiving ADT.³

Only two randomized trials have evaluated DE-EBRT in patients receiving ADT.^{4,5} Both studies compared 64 Gy EBRT with 74 Gy DE-EBRT, with all patients receiving neoadjuvant ADT. Neither study reported a significant benefit for dose escalation in the intermediate-risk group. It is thus not surprising that others have questioned the benefit of DE-EBRT for patients receiving ADT.^{3,6}

Several randomized trials show that in the absence of ADT, EBRT doses >70 Gy provide some benefits,^{7–10} with several national guidelines recommending doses up to 78–81 Gy for intermediate-risk patients.^{11–13} All these guidelines recommend consideration of neoadjuvant ADT with DE-EBRT. However, there is virtually no

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evidence for dose-escalating radiotherapy to these levels in the setting of ADT.

Given the lack of available evidence, we evaluated whether dose escalation up to 78 Gy had any advantage in terms of prostate-specific antigen (PSA) disease-free survival, metastasis-free survival (MFS), or prostate cancer-specific survival (PCaSS) outcomes in our cohort of intermediate-risk patients treated exclusively with neoadjuvant ADT and dose-escalated intensity-modulated radiotherapy (IMRT).

Methods

From 2006, the North Coast Cancer Institute implemented a dose-escalation program for patients with localized prostate cancer. Patients were initially treated with 74 Gy, which was escalated to 76 Gy in 2008, then 78 Gy from 2009 until 2012. All patients were treated with either three-dimensional EBRT or IMRT, as has been previously reported.^{14,15} In brief, after institutional ethics approval (North Coast New South Wales Human Research Ethics Committee, Reference Number QA 101), the electronic medical record of our institution (Mosaik; Elekta, Crawley, UK) was interrogated to identify all patients with National Comprehensive Cancer Network (NCCN)-defined intermediate-risk prostate cancer¹³ treated with our standard protocol of DE-EBRT and ADT. Exclusion criteria included patients postprostatectomy, NCCN low or high risk, node positive, metastatic, histology other than adenocarcinoma, did not receive ADT, or treated from 2013 onward.

All patients received ADT using leuporelin or goserelin acetate monotherapy (using 3- or 4-month depots), with 3–6 months of neoadjuvant/concurrent ADT. Over 90% of patients received ADT for 6 months. Patients underwent transrectal ultrasound-guided insertion of fiducial markers followed by magnetic resonance imaging/computed tomography (CT) fusion as previously reported,¹⁶ unless contraindicated. Patients were treated on our “Bowel and Bladder Protocol,” involving low-residue diet, aperients, and a pretreatment oral fluid regimen to achieve a comfortably full bladder and empty rectum. The planning CT (2 mm slices) was performed with patients supine and immobilized with ankle stocks. The prostate and proximal seminal vesicles measuring 4–8 mm were included in the clinical target volume. The clinical target volume to planning target volume expansion was 5 mm. Patients were treated using a 7- to 9-field IMRT technique with the angles optimized to achieve target coverage and organ at risk sparing. The planning target volume was treated with 73.8–78 Gy in 1.8–2.0 Gy fractions prescribed to the reference point. Image guidance used either daily online kV portal images (matched to fiducial markers) or daily cone beam CT. Patients without fiducial markers (<1% of all

patients) underwent daily cone beam CT matching to soft tissue and bone. Patients were followed up by the treating radiation oncologists, with data prospectively recorded in Mosaik. Biochemical failure was determined using the Phoenix definition (PSA nadir + 2 ng/mL). All patients with biochemical failure were restaged with CT and bone scans, and more recently prostate-specific membrane antigen (PSMA) positron emission tomography (PET).¹⁷ Salvage ADT was initiated when the PSA reached 10–20 ng/mL or with documented metastatic disease.

Data were analyzed using SPSS Version 19 (IBM Corporation, Armonk, NY, USA). Biochemical disease-free survival (bDFS), MFS, and PCaSS were calculated with Kaplan–Meier curves, and the log-rank (Mantel–Cox) test was used to compare survival between groups. Follow-up time was calculated from the date of commencement of ADT as recommended by Denham et al.¹⁸ Univariate analysis was done to assess the relationship between potential prognostic factors and bDFS, MFS, and PCaSS. The variables included were age (≤ 70 vs > 70), pretreatment PSA (< 10 ng/mL vs 10 ng/mL or higher), Gleason score (3+3=6/3+4=7 vs 4+3=7), use of IMRT (no vs yes), and radiation dose (73.8–74 Gy, 76 Gy, and 78 Gy). All hazard ratios were calculated with Cox proportional hazard models and expressed relative to the control group. *P*-values were two tailed and considered statistically significant if < 0.05 .

Results

In total, there were 435 intermediate-risk patients treated with DE-EBRT and ADT, with a median follow-up of 70 months. Patient demographics are shown in Table 1.

Table 1 Patient characteristics

Age (in years)	
Median	70
Range	50–85
Gleason score	
3+3=6	34 (7.8%)
3+4=7	226 (52.0%)
4+3=7	175 (40.2%)
IMRT	
No	5 (1.1%)
Yes	430 (98.9%)
Dose	
74 Gy	128 (29%)
76 Gy	47 (10.8%)
78 Gy	260 (59.8%)
PSA (ng/ml)	
Median	9.0
Range	0.8–20.0

Abbreviations: IMRT, intensity-modulated radiotherapy; PSA, prostate-specific antigen.

The 5-year bDFS for all 435 patients was 95.5%. The bDFS rates for 74 Gy, 76 Gy, and 78 Gy, respectively, were 95.0%, 97.8%, and 95.3% (Kaplan–Meier curves shown in Figure 1). These differences were not statistically significant ($P=0.2$).

On both univariate and multivariate analyses, only the PSA level was significant for bDFS (PSA >10 ng/ml doing worse, $P=0.01$, hazard ratio 2.9, 95% CI 1.3–6.5). Dose levels had no impact on bDFS. Further analyses comparing 74–76 Gy (grouped) vs 78 Gy and comparing 74 Gy vs 76–78 Gy (grouped) showed no impact of dose on bDFS, and PSA remained the only significant variable in the Cox regression analysis.

Five-year MFS was 98.9%. The MFS rates for 74 Gy, 76 Gy, and 78 Gy, respectively, were 99.1%, 100.0%, and 98.6%. Dose had no impact on MFS ($P=0.6$). Five-year PCaSS was 100.0% for all dose levels.

Discussion

Dose escalation improves bDFS for patients with localized prostate cancer,¹ whereas ADT not only improves bDFS but also PCaSS and overall survival (OS).^{2,19} This has led some to question the need for dose escalation in patients receiving ADT.^{3,6} Few studies have investigated this issue. Only two randomized studies have been reported,^{4,5} which are limited by the fact that doses were only escalated to 74 Gy. Creak et al⁵ found a nonstatistically significant trend for PSA control favoring dose escalation but did not analyze for intermediate-risk patients. Dearnaley et al⁴ did find a significant progression-free survival benefit for DE-EBRT

in the whole cohort of patients; however, the favorable trend was not statistically significant for the intermediate-risk subgroup.

The few other studies evaluating dose escalation in the setting of ADT do not analyze the results for intermediate-risk patients. For example, Denham et al²⁰ conducted a nonrandomized evaluation of EBRT dose levels up to 74 Gy and 46 Gy EBRT combined with high dose rate (HDR) brachytherapy. Higher dose reduced local progression, with no analysis of bDFS. There were 207 intermediate-risk patients (only 19 in the HDR group), however, the results were not analyzed for this risk group.

Stoyanova et al⁶ reviewed the relative benefits of ADT and DE-EBRT up to 80 Gy, but they did not report the results of the risk group. The results did enable a conclusion that the benefit of ADT far outweighed the benefit of dose escalation. These views have been echoed by Roach,³ who also attempted to address the issue of dose escalation vs ADT. With a paucity of high-quality studies, he concluded that the data supporting ADT were greater than the data for dose escalation.

We report one of the largest series of patients with intermediate-risk prostate cancer treated exclusively with a combination of neoadjuvant ADT and DE-EBRT. To our knowledge, this is the only study evaluating the potential benefit of dose escalation >74 Gy in the setting of neoadjuvant ADT and EBRT in the management of this risk group. With 70-month median follow-up, we failed to demonstrate any statistically or clinically significant benefit for dose escalation up to 78 Gy. This seems to be consistent with the previous reports comparing 64 Gy and 74 Gy.^{4,5}

If dose escalation has a questionable benefit in terms of cancer outcomes, it has well-documented adverse effects. The only meta-analysis of randomized trials of dose escalation with long-term follow-up showed that dose escalation increases both late genitourinary and gastrointestinal toxicity.¹ It is true that ADT has its own toxicities; however, many of these toxicities are reversible, particularly after cessation of short neoadjuvant courses.²¹ Indeed in some studies, ADT has been found to protect against both late radiotherapy-induced urinary and bowel toxicity,^{21,22} perhaps in part due to reduction in prostate size, reducing bladder and rectal dose.²³

If short-course ADT is more beneficial than dose escalation, it may be possible to limit dose escalation or even dose de-escalate (eg, 60–70 Gy). Similar concepts have been demonstrated in other cancer types, where systemic therapy has allowed radiotherapy doses to be reduced.^{24,25} We believe that further research should be directed to the relative benefits

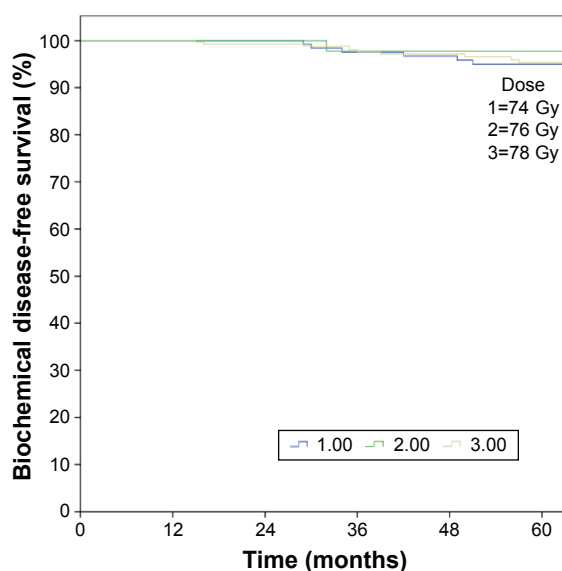


Figure 1 Biochemical disease-free survival for various dose levels.

of high radiotherapy doses in the setting of neoadjuvant ADT for intermediate-risk prostate cancer.

There are several limitations in our study. First, it is a retrospective review and thus should be regarded as hypothesis generating. We report with a median follow-up of 70 months, and it is possible that significant benefits of dose escalation might occur only with longer follow-up. We also do not report on doses >78 Gy, and it is possible that benefits may only be seen with much higher doses. We also note that PSMA PET imaging was only available for the most recent follow-up period¹⁷ and that may have unknown effects on the outcomes. Finally, we have not reported toxicity, with the unknown interactions between escalating doses and ADT, which requires further study.

Conclusion

In conclusion, for intermediate-risk prostate cancer patients receiving neoadjuvant ADT, we found no benefit for escalating doses up to 78 Gy. There is a lack of evidence for dose escalation in the setting of ADT, and it is apparent that further investigation is required. We hope that our results provide impetus for studies of dose escalation and dose de-escalation, in this group of patients.

Author contributions

TPS participated in the design of the study, data collection, performed the statistical analysis, and helped draft the manuscript. SWW and NJA participated in data collection and helped draft the manuscript. All authors read and approved the final manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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