Dose-escalated Radiation Therapy With and Without Short-course Androgen Deprivation for Intermediate-risk Prostate Cancer

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Abstract. *Aim: To investigate outcomes in intermediate-risk (IR) prostate cancer patients receiving dose-escalated external beam radiation therapy (RT) with or without short-course androgen deprivation (ADT). Patients and Methods: This study comprised of 203 patients with IR prostate cancer who were treated at a single institution to a dose of 7,560 cGy or more between 2003-2010. Of these, 62 (30.5%) patients received ADT. Biochemical recurrence, distant metastatic-free survival, prostate cancer-specific survival, and overall survival were analyzed using the Kaplan-Meier method. Results: The median follow-up was 62 months and the median duration of ADT was 6 months. The 6-year biochemical control was 89.2% for those receiving RT plus ADT versus 76.7% in those receiving RT alone (p=0.02). There were no differences between the two groups regarding distant metastatic-free survival, prostate cancer-specific survival, and overall survival (respective p-values of 0.91, 0.50, 0.67). Conclusion: Dose-escalated RT and short-course ADT results in improved biochemical outcomes for IR prostate cancer.*

While the benefit of dose-escalated radiation therapy has been shown in several large randomized studies (1-3), its role in conjunction with androgen deprivation (ADT) is less clear. Two randomized studies have in fact reported an improvement in overall survival with the addition of short-course ADT (4, 5). However, both of these studies used radiation doses of 6,660-7,000 cGy. In light of the prior studies providing evidence for dose escalation, this does call into question whether increasing the radiation dose would obviate the need for ADT in intermediate-risk disease.

There are two major trials attempting to address this question. The Groupe d'Etude des Tumeurs Uro-Genitales 14 (GETUG-14) study is comparing 80 Gy with and without ADT and have preliminarily reported no difference in biochemical or clinical control between the two arms at three years follow–up (6). The Radiation Therapy Oncology Group (RTOG) are currently accruing patients to RTOG 0815 in a similar study in order to further answer this question.

Until the long-term results from the randomized studies are reported, we are left primarily with retrospective and institutional reports to provide further guidance. These have also been unclear, as several studies have in fact shown no benefit of ADT with dose-escalated radiation (7-8), while one large series has reported a benefit (9). Therefore, we analyzed our cohort of patients at the NY Harbor Veterans Hospital who had intermediate-risk prostate cancer and were treated to a dose of 7,560 cGy or higher with our without ADT.

Patients and Methods

After approval by our Institutional Review Board, IRB 01211, we reviewed the charts of 483 patients who were diagnosed with prostate cancer and were treated with external-beam radiation to a dose of 7,560 cGy or higher from 2003-2010. Only patients who were categorized as having intermediate-risk disease by the National Comprehensive Cancer Network (NCCN) standards (www.nccn.org) were included. This left 203 patients who were included in the current study.

The radiation techniques evolved over time from three-dimensional conformal radiation therapy (3DCRT) in 2003-2006 to intensity-modulated radiation therapy (IMRT) from 2006-2010. Starting in 2010, all patients treated with IMRT were also treated using image-guided radiation therapy (IGRT), consisting of daily megavoltage cone beam CT scans matched either to the bony anatomy or to gold fiducial markers. Generally, patients who received ADT were treated neoadjuvantly for 1-2 months, followed

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by concurrent ADT with radiation, followed by further adjuvant ADT at the discretion of the treating physician. The treatment fields generally included the pelvis when 3D-CRT was used from 2003-2006 and generally included just the prostate or prostate and seminal vesicles when IMRT was used in subsequent years.

Upon completion of treatment, patients were generally followed every 3-6 months for five years, and were then followed yearly. If they were lost to follow-up at our clinic, the medical records of other clinics, as well as other Veterans facilities, were also reviewed in order to abstract information regarding toxicity or biochemical outcomes. Biochemical failure was defined using the Phoenix definition of prostate specific antigen (PSA) nadir + 2 ng/ml, or the initiation of any salvage therapy (such as ADT). Distant metastatic disease was defined as prostate cancer recurring outside of the pelvis. Death from prostate cancer was determined from the medical records or from our cancer registry records. If a patient died from undetermined cause and was known to have hormone-refractory prostate cancer then this was considered a prostate cancer death. Patients who were lost to follow-up, or those who were being followed-up in a different Veterans facility but without a recent PSA determination, were censored at their most recent follow-up with a measured PSA value.

Chi-square analysis was used to compare the characteristics of the two groups. PSA-relapse distant metastatic-free survival, prostate cancer-specific survival, and overall survival endpoints were determined from the date of completion of radiation treatments. They were analyzed using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate Cox regression modeling was performed to calculate the hazard risk (HR) and 95% confidence intervals (CI) of the impact of covariates on biochemical outcome. Statistical analysis was performed using SPSS version 20.0 (IBM, Armonk, NY, USA) and statistical significance was achieved with a p-value ≤0.05.

Results

This study included 203 patients, of whom 62 (30.5%) underwent ADT. The median radiation dose was 7560 cGy (range=7560-8100 cGy) The median follow-up was 62 (range=15-115) months and 96.6% of all patients were followed-up for a minimum of two years after completion of their radiation therapy. For those who received ADT, the median duration was six months. Thirty-one patients received ADT for six months or less, ten received ADT for 7-12 months, and the remaining patients received ADT for longer than one year.

The median age was 70 (range=49-85) years and the median PSA value was 7.3 ng/ml (range=0.5-19.9 ng/ml). Patients with a PSA above 10 ng/ml were more likely to receive ADT than those with PSA values of 10 ng/ml or less (p<0.001). There was a trend towards reduced ADT usage for those who were younger than 70 years compared to those who were older (p=0.10), as well as for those who were treated with further dose escalation above 7,560 cGy (p=0.06). There were no differences in ADT use based on the race or the Gleason score of the biopsy. Further patient characteristics and comparisons between the two groups are available in Table I.

Table I. *Patients' characteristics*.

	RT-alone (n=141)	RT + ADT (n=62)	p-Value
Age			0.10
≤70 years	77 (75%)	26 (25%)	
>70 years	64 (64%)	36 (36%)	
Race			0.97
Black	94 (69%)	42 (31%)	
Hispanic	8 (73%)	3 (27%)	
White	39(70%)	17 (30%)	
Gleason score			0.92
≤3+4	106 (69%)	47 (31%)	
4+3	35 (70%)	15 (30%)	
PSA			<0.001
≤10 ng/ml	106 (79%)	29 (22%)	
>10 ng/ml	35 (52%)	33 (49%)	
Radiation dose			0.06
7560 cGy	109 (67%)	55 (33%)	
7740-8100 cGy	32 (82%)	7 (18%)	
Perineural invasion			0.81
Yes	27 (71%)	11 (29%)	
No	114 (69%)	51 (31%)	

PSA: Prostate-specific antigen; ADT: androgen deprivation.

There were a total of 33 biochemical failures (16.3%) and the median time-to-biochemical failure was 42 months (range=4-98 months). Biochemical failure occurred in four patients out of the 62 who were treated with radiation and ADT (6.5%) but in 29 patients out of the 141 who were treated with radiotherapy-alone (20.6%). The 6-year biochemical control rates were 89.2% for those who received radiotherapy with ADT and 76.7% for those who received radiotherapy-alone, p=0.02 (Figure 1). For those who did not receive ADT, the median nadir PSA was 0.4 ng/ml and the median time-to-nadir was 24 months.

There were three distant failures, two in patients who received radiotherapy-alone and one in patient who received radiotherapy with ADT. The time to distant failure was 22 and 47 months for the patients who received radiotherapy alone and was 109 months for the patient who received radiotherapy with ADT. The 6-year distant metastatic-free survival, prostate cancer-specific survival, and overall survival were 98.2%, 99.0% and 82.3% for those receiving radiotherapy alone and was 100%,100%, and 72.3% for those receiving radiotherapy with ADT respectively (respective p-values of 0.91, 0.50, 0.67).

On univariate and multivariate analysis, androgen deprivation use was associated with improved biochemical outcome with an HR of 0.31 (95% CI=0.11-0.87; p=0.03) on univarate analysis and 0.24 (95% CI=0.08-0.70; p=0.01) on multivariate analysis. Perineural invasion was associated with worse biochemical control with an HR of 2.93, (95% CI=1.38-6.24; p=0.01), on univariate analysis and an HR of 2.94 (95%

Table II. *Univariate and multivariate analysis*.

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
Age				
≤70 years	1		1	
>70 years	1.28 (0.65-2.55)	0.48	1.23 (0.59-2.54)	0.58
PSA				
≤10 ng/ml	1		1	
>10 ng/ml	1.38 (0.69-2.79)	0.36	2.00 (0.97-4.30)	0.06
Gleason				
≤3+4	1		1	
4+3	1.34 (0.65-2.76)	0.44	1.05 (0.48-2.27)	0.91
ADT				
No	1		1	
Yes	0.32 (0.11-0.90)	0.03	0.24 (0.08-0.70)	0.01
Race*				
Black	1		1	
White	1.12 (0.53-2.36)	0.76	1.11 (0.52-2.34)	0.79
Perineural invasion				
No	1		1	
Yes	2.99 (1.41-6.35)	0.01	2.94 (1.36-6.34)	0.01

*There were no failures in Hispanic patients. CI: Confidence interval; PSA: prostate-specific antigen; ADT: androgen deprivation therapy.

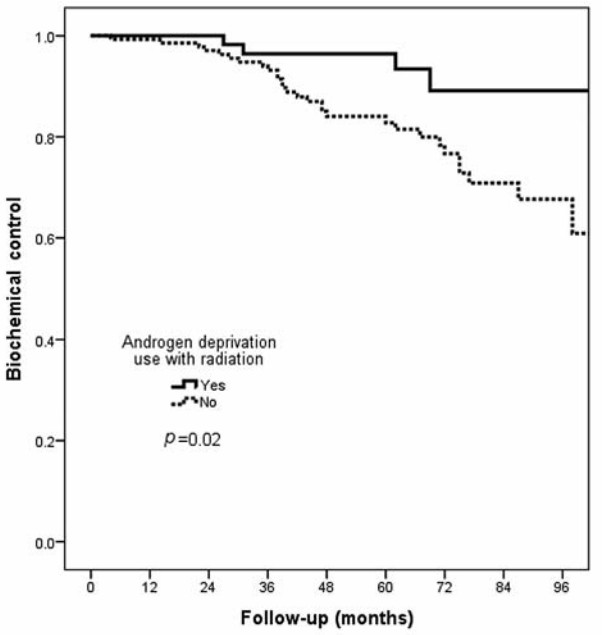

Figure 1. *This figure depicts the biochemical control rates for patients treated with dose-escalated radiation therapy with and without short-course androgen deprivation. As can be seen, there is improved biochemical control for those who received androgen deprivation (p=0.02).*

CI=1.36-6.34; p=0.01) on multivariate analysis. There was a trend towards worse biochemical control on multivariate analysis for those with PSA levels above 10 ng/ml, with an HR of 2.04 (95% CI=0.97-4.30; p=0.06). The other measured covariates did not have a significant impact on biochemical control. Table II presents further details.

Discussion

In this study of 203 patients with a median 5-year follow-up, there is an absolute improvement of 12.5% in biochemical control at 6 years with the addition of ADT to dose-escalated radiation therapy. These data suggest that dose-escalated radiotherapy does not necessarily obviate the need for short-course androgen deprivation for intermediate-risk prostate cancer. Longer term follow-up is needed in order to ascertain whether this improvement in biochemical control translates to a reduction in distant metastatic disease or prostate cancer-specific death.

There are currently only two randomized studies that are available to potentially answer the unresolved issue of whether androgen deprivation is beneficial along with dose-escalated radiation therapy. The first, GETUG-14, randomized patients to 80 Gy alone or 80 Gy along with four months of ADT (6). This study was closed after enrolling 377 patients due to poor accrual. Their initial results, with a median follow-up of three years, revealed that there was an improvement in biochemical control from 91% to 97% (p=0.04). However, the statistical end-point chosen for this study was biochemical and clinical control, and for this end-point there was only a trend towards improvement from 86% to 92%, p=0.09. The RTOG is conducting their own study, RTOG 0815, and are currently enrolling patients into one of two arms. The first will be treated to a dose of 7,920 cGy or will receive 4,500 cGy followed by a brachytherapy boost. The second will receive the same treatment with the addition of six months of androgen deprivation. This study is currently still enrolling patients and there are no results available for analysis.

As a consequence of the lack of prospective studies, we are left with retrospective studies to provide the next best level of evidence as to the potential benefit of ADT with dose escalation. The largest study of this type was reported by Zumsteg *et al*. from the Memorial Sloan Kettering experience (9). They treated 710 patients to a dose of 8100-8640 cGy with and without androgen deprivation and had a median follow-up of just under eight years. As in our study, the median duration of ADT was six months. They reported a 10-year biochemical control rate of 80% in the ADT group and 67% in the group treated with radiotherapy-alone and

this difference was statistically significant (p=0.003). The absolute 13% difference in biochemical control in their study mirrors our findings. Furthermore, they reported a novel finding in the setting of dose escalation in that there was also a reduction in distant metastatic disease from 12.3% to 6.5%, as well as a reduction in prostate cancer-specific deaths from 5% to 2.4% at 10 years with the addition of ADT.

In contrast to the Memorial Sloan Kettering report, as well as the current one supporting short course ADT with dose-escalated radiotherapy, others have also reviewed their experiences and have in fact found no benefit in biochemical control. The RTOG analyzed patients from the RTOG 94-06 dose-escalation study and identified 291 patients who received a median radiation dose of 7,740-7,900 cGy with 6.5- to 7-year follow-up. They found that the biochemical control rates at 5 years were 77% and 82% for the radiation alone and radiation plus ADT arms respectively. However, on Cox regression analysis this was not statistically significant (7). Similarly, Krauss *et al*. reported their experience, particularly analyzing 365 patients who received a median dose of 7560 cGy with or without ADT (8). They also found no difference in biochemical control at five years, with the control rates being 84.8% and 81.2% for the radiation alone and radiation plus ADT arms respectively.

Given the variation in patient selection, duration of ADT use, radiation dose and radiation techniques, it is likely that some interplay of these factors, yet to be determined, can account for these incongruent findings. Certainly it does further emphasize the importance of the current RTOG 0815 study that is looking to answer this question in a prospective fashion. To date, there has been one such prospective study, by D'Amico *et al*., which compared intermediate-/high-risk patients who received 70 Gy alone or along with six months of ADT (4). In that study, the addition of ADT resulted not only in improved biochemical control, but also in an improvement in the 8-year overall survival from 61 to 74% with the addition of ADT. The androgen deprivation in the current study best mirrors that of the study by D'Amico *et al*. in that the ADT was given two months neoadjuvantly, two months concurrently, and two months adjuvantly. In contrast, the other three studies were either restricted to neoadjuvant and concurrent ADT for the Memorial Sloan Kettering and RTOG studies, or it was mixed in the study by Krauss *et al*. However, there is no supportive evidence suggesting this ADT regimen is a key factor that improves biochemical control.

One particularly interesting finding in this study is the impact of perineural invasion on biochemical control. While perineural invasion on biopsy has been associated with more aggressive extent of disease after surgery (10-11), its role as a negative prognostic factor with lower doses of radiation has been unclear due to mixed findings (12-14). Feng *et al*. recently reported their findings on 651 men treated with dose-escalated radiation therapy of at least 75 Gy and found that perineural invasion was strongly predictive for biochemical and distant metastatic control, suggesting that perineural invasion is an important prognostic factor in the dose-escalation era (15). In the current study, on multivariate analysis, perineural invasion had a highly significant association with worse biochemical outcomes (HR=2.94, 95% CI=1.36-6.34, p=0.01), further supporting the suggestion by Feng *et al*. that this may in fact be an important prognostic factor with dose escalation.

There are several limitations to this study, primarily related to its retrospective nature. While the median duration of ADT was six months, some patients received longer term ADT. Previous studies in the more advanced setting have shown that longer ADT duration is superior to shorter course ADT(16) and therefore it is possible that this may have introduced bias in favor of the ADT arm. Furthermore, since these patients were non-randomized, it is unclear whether other unmeasured factors may have impacted the decision whether or not to offer ADT, or which patients were preferred candidates for ADT. Finally, although the median follow-up is currently five years, we still need longer term follow-up of these patients. It is possible that rather than actually curing more patients of their disease, ADT may just delay the onset of biochemical failure by a few years and upon longer follow-up, there may no longer be a difference between the two groups.

In conclusion, this study of 203 patients with intermediate-risk prostate cancer treated with dose-escalated radiation with or without ADT revealed an improvement in biochemical control at six years with the addition of ADT, and showed that the presence of perineural invasion is an important prognostic factor for biochemical control with dose-escalated radiation. These findings suggest that dose escalation does not obviate the need for ADT. However, we await the results of the prospective studies to better-clarify the role of ADT in conjunction with dose escalation.

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