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DOSE-ESCALATED RADIOTHERAPY FOR HIGH-RISK PROSTATE CANCER: OUTCOMES IN MODERN ERA WITH SHORT-TERM ANDROGEN DEPRIVATION THERAPY

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Abstract

Purpose—Randomized data have supported the use of long-term androgen deprivation therapy (ADT) combined with radiotherapy (RT) for men with high-risk prostate cancer. The present study reviewed the outcomes of intermediate- and high-risk men treated with RT and short-term ADT.

Materials and Methods—A total of 184 men with any single risk factor of prostate-specific antigen ≥10 ng/mL, clinical Stage T2b or greater, or Gleason score ≥7 were treated with primary external beam RT for nonmetastatic adenocarcinoma of the prostate. The median radiation dose was 74 Gy; 55% were treated with intensity-modulated RT. All patients received ADT for 1 to 6 months (median, 4), consisting of a gonadotropin-releasing hormone analog. Univariate and multivariable analyses were performed for risk factors, including T stage, Gleason score, radiation dose, and prostate-specific antigen level.

Results—With a median follow-up of 51 months, the 4-year freedom from biochemical failure (FFBF) using the nadir plus 2 ng/mL definition was 83% for all patients. Clinical Stage T3 disease was the only variable tested associated with FFBF on univariate (4-year FFBF rate, 46% vs. 87% for Stage T1-T2c disease; $p = .0303$) and multivariable analysis (hazard ratio, 3.9; $p = .0016$). On a subset analysis of high-risk patients (National Comprehensive Cancer Network criteria), those with clinical Stage T3 disease (4-year FFBF rate, 46% vs. 80%; $p = .0303$) and a radiation dose <74 Gy (4-year FFBF rate, 64% vs. 80%) had a poorer outcome on univariate analysis. However, clinical Stage T3 disease and radiation dose were not significant on multivariable analysis, although a statistical multivariable trend was seen for both ($p = .0650$ and $p = .0597$, respectively).

Conclusion—Short-term ADT and RT might be acceptable for men with intermediate- and high-risk prostate cancer, especially for clinically localized disease treated with doses of ≥74 Gy.

Keywords

Prostate cancer; radiotherapy; hormonal therapy

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INTRODUCTION

Although considerable debate is ongoing regarding whether immediate treatment is necessary for all men diagnosed with prostate cancer (PCa) (1), a reasonable consensus has been reached that men with higher risk features (2) (*i.e.*, prostate-specific antigen [PSA] ≥10 ng/mL, Gleason score ≥7, clinical Stage T2b or greater) can be expected to derive benefit from immediate treatment in the absence of any serious comorbidities or a limited life expectancy. External beam radiotherapy (RT) is an effective method of primary therapy for such men. Several randomized trials have established the role of androgen deprivation therapy (ADT) in combination with RT for PCa patients with higher risk features (3–6). Two randomized studies (7,8) have further indicated a survival benefit with the use of long-term (≥2 years) rather than short-term (≤6 months) ADT.

As a result of these randomized data, long-term ADT is commonly prescribed to high-risk PCa patients treated with RT. However, recent outcomes with dose escalation have indicated significant improvements (9–11) compared with the lower doses (≤70 Gy) of RT used in the major ADT trials. The benefit of dose escalation appears to span all risk categories and improves the biochemical control rates of even those men at the greatest risk of distant failure (12) because of improved local control. Furthermore, the high-risk PCa patient seen today might not have the same features as the high-risk patient for whom long-term ADT was clearly indicated by the randomized trials, which predominantly included those with locally advanced (Stage T2c-T4N0) disease (7,8). In the current era of PSA screening, men are less likely to present with such advanced disease, and the outcomes would likely be improved as a result of earlier detection and treatment. These improvements in disease presentation, coupled with improvements in RT delivery, make the benefit of long-term ADT less certain in the contemporary era. Considered in conjunction with the results of studies indicating the negative effects of short- or long-term ADT (13–15) on bone, muscle, and cardiovascular health, it is important to identify which men warrant the use of no, short-, or long-term ADT.

The purpose of the present study was to review the outcomes of higher risk PCa patients treated with RT and short-term (≤6 months) ADT at a single academic center. The primary goal was to identify the prognostic variables associated with the outcomes. Men with the best disease outcomes might be suitably treated with RT and short-term (or perhaps no) ADT, and men with the least favorable disease outcomes would be candidates for more aggressive therapies targeting systemic disease, including long-term ADT.

MATERIALS AND METHODS

The study cohort was identified from a clinical database of 707 patients with Stage T1-T3N0M0 PCa treated with primary external beam RT at the University of Chicago Pritzker School of Medicine between 1992 and 2006. No patient had previously undergone radical prostatectomy. Using the National Comprehensive Cancer Network criteria (16), 260 men with intermediate-risk (any single risk factor of PSA >10 ng/mL, clinical stage T2b-T2c, or Gleason score 7) and 182 men with high-risk (any single risk factor of PSA >20 ng/mL, clinical Stage T3–T4, or Gleason score ≥8) PCa were identified. Of these, 118 intermediate-risk patients (45%) and 125 high-risk patients (69%) received any amount of ADT, consisting of a gonadotropin-releasing hormone analog concurrently with RT. The duration of ADT was documented in 217 (89%) of 243 patients. Of these 217 men, 184 (85%) received 1–6 months of ADT. The patient data, including demographic, treatment, and follow-up information, were reviewed with approval from the hospital's institutional review board.

The patient and treatment characteristics of 105 intermediate-risk patients and 79 high-risk patients are listed in Table 1. The median age for the overall cohort was 69 years (range, 42–83), and the median pretreatment PSA level was 14.4 ng/mL (range, 2.2–225). Of the 184 patients, 138 (75%) had clinical Stage T1-T2a disease, 28 (15%) had clinical Stage T2b-T2c disease, and 18 (10%) had clinical Stage T3 disease. The Gleason score was centrally reviewed by a genitourinary pathologist and was ≤6 in 67 (36%), 7 in 90 (49%), and ≥8 in 27 (15%) patients. The median external beam RT dose was 74 Gy (range, 45–76.4); 7 patients (3%) received a ^{125}I brachytherapy boost of 110 Gy after 45 Gy. Overall, 110 patients (60%) received a dose of ≥74 Gy. All patients were treated using computed tomography planning. Intensity-modulated RT was used in 102 patients (55%). The dose was prescribed to the planning target volume, which was typically 6–10 mm beyond the prostate when only the prostate and/or seminal vesicles were treated. Only 13 patients (7%) were treated with initial whole pelvic fields to cover the lymph nodes at risk. The use of ADT was at the discretion of the treating physician during this period. All patients selected for the present study underwent ADT with a gonadotropin-releasing hormone analog, typically starting 2 months before RT. The length of administration was 1–2 months for 13 patients (8%), 3 months for 43 patients (23%), 4 months for 108 patients (59%), and 5–6 months for 20 patients (10%). An oral antiandrogen (bicalutamide or flutamide) was given 1–2 weeks before the initiation of the gonadotropin-releasing hormone analog and continued until RT completion in 122 (68%) of 180 patients for whom this information was available.

The median follow-up, defined as the interval from RT completion to the last PSA measurement, was 51 months (range, 1–204). The primary endpoint was freedom from biochemical failure (FFBF), which was defined according to the nadir plus 2 ng/mL definition (17). Deaths from any reason were censored if the primary endpoint was not met. Overall, 27 patients died, 16 in the absence of the primary endpoint. The differences between groups were tested with univariate analysis using chi-square analysis for nominal variables and the *t* test for continuous variables. Kaplan-Meier curves for FFBF were generated, and survival comparisons were made using with the log–rank test. Multivariable analysis was performed with proportional hazards analysis, using prespecified categorical explanatory variables (*i.e.*, clinical stage, Gleason score, PSA, and radiation dose) stratified by the median value. Subset analyses were repeated for the intermediate- and high-risk categories after analysis of the entire cohort.

RESULTS

Patient characteristics

The overall characteristics are listed in Table 1. No significant differences were found in the radiation dose, the use of intensity-modulated RT, duration of ADT, or median follow-up between the intermediate- and high-risk patients. The high-risk patients were younger and more likely to be treated with an initial whole pelvic field, although the proportion of patients (13%) even in the high-risk group was small.

Biochemical outcomes

For the overall group, the FFBF rate was 83% at 4 years, 83% at 5 years, and 77% at 6 years. The 4-year FFBF rate was significantly greater for patients with intermediate-risk disease than for patients with high-risk disease (92% vs. 73%, $p = .0039$; Fig. 1). Univariate analysis (Table 2) demonstrated that T stage was the only factor associated with the biochemical outcome. Men with stage T3 disease had a 4-year FFBF rate of 46% compared with 87% for those with Stage T1-2a disease and 89% for those with Stage T2b-T2c disease ($p = .0001$; Fig. 2). On multivariable analysis (Table 3), T stage was associated with the

biochemical outcome (risk ratio, 3.9; $p = .0016$), and the Gleason score, radiation dose, and pretreatment PSA level were not.

The univariate and multivariable analyses were repeated for the subsets of intermediate- and high-risk patients. For the intermediate-risk patients, no tested factors were associated with improved outcome on univariate analysis (Table 4), including T stage, Gleason score, radiation dose, PSA level, or percentage of cores positive. Multivariable analysis (Table 5) also did not indicate any association with T stage ($p = .6435$), Gleason score ($p = .4820$), radiation dose ($p = .8668$), or PSA level ($p = .3911$) with outcome. The analysis within this subset was limited by the small number of endpoints met; only 13 (12%) of 105 men had developed biochemical failure by the last follow-up examination.

For the high-risk patients, univariate analysis (Table 6) revealed that patients with Stage T3 disease had a poorer 4-year FFBF rate (46% vs. 80%, $p = .0303$), as did patients treated with radiation doses of ≤74 Gy (64% vs. 80%, $p = .0333$). No factors were associated with outcomes on multivariable analysis (Table 7), including Gleason score ($p = .6357$) or PSA level ($p = .3456$), although T stage ($p = .0650$) and radiation dose ($p = .0597$) were of borderline statistical significance.

DISCUSSION

The purpose of the present study was to review the disease outcomes for men with intermediate- or high-risk PCa treated with RT and short-term ADT. Although comparisons with historical controls are complicated by the stage and grade migration of more recent years (18,19), the data from the present study have not indicated any significant compromise for select men treated without long-term ADT.

Within the intermediate-risk category, no tested covariates were associated with a more favorable outcome. The pretest hypothesis was that we might be able to identify men with more favorable outcomes within this subset, for whom ADT could be unnecessary. However, our ability to detect such a difference was limited by the small number of patients with biochemical failure. The lack of prognostic factors found in the present study does not imply that no such means exist of improving the risk stratification within this category. An analysis of intermediate-risk men treated without ADT has shown that the percentage of positive biopsy cores could be one method to further stratify the risk and better select men for ADT when treating with dose-escalated RT (20,21). It is possible that a high ratio of positive biopsy cores is a surrogate for pathologic upstaging to high risk (pathologic Stage T3 or Gleason score 8) disease, a population for whom ADT might have more importance.

Within the high-risk category, the men with locally confined disease treated with dose-escalated RT had the most favorable outcomes. Men with Stage T1-T2c disease who received ≥74 Gy had a 4-year FFBF rate of 77%. However, patients with clinical Stage T3 disease and lower radiation doses had less favorable outcomes, indicating that short-term ADT and RT could be inadequate therapy for these men. These results are in agreement with those from the Radiation Therapy Oncology Group 9202 study (8), which indicated a benefit for long-term hormonal therapy for men treated with 70 Gy for locally advanced PCa (notably, 55% of the men in the Radiation Therapy Oncology Group 9202 study had clinical Stage T3–T4 disease). However, because the contemporary “high-risk” patient often has locally confined disease and is a candidate to receive dose-escalated RT, the recommendation for long-term ADT might no longer be prudent for all high-risk patients. The potential benefit in disease outcome with long-term ADT must be weighed against the adverse effects of testosterone suppression, including bone, muscle, and cardiovascular health (13–15). The results of the present study suggest that for select high-risk patients

treated with ≥74 Gy, short-term ADT is a reasonable consideration to help reduce the risks associated with long-term ADT.

Although the randomized data regarding the addition of ADT to RT in the setting of locally advanced PCa are unequivocal for improvement in disease control, the exact mechanism is still debated. ADT could affect the spread or growth of micrometastases in patients with high-risk disease, a mechanism that could be supported by the noted benefit of long- compared with short-term ADT. Although hormonal therapy has not been proven to have direct cytotoxic effects, men with node-positive PCa treated with indefinite ADT after prostatectomy have had significantly improved rates of distant control compared with men who underwent observation (22). Other data have strongly suggested that ADT is a potent radiosensitizer for PCa, which can improve local control when combined with external beam RT (23). Thus, the benefit of concurrent ADT might come more from improved local, rather than distant, control. The lack of benefit in disease outcome with ADT in the context of surgical therapy for node-negative PCa might further support this claim.

If the primary benefit of combining ADT with RT is to improve local control, short-term ADT (with testosterone suppression concurrent with RT) would contribute most of the overall effect. Additionally, for men with the most locally advanced disease treated with lower radiation doses, prolonged ADT might help further inhibit the regrowth of locally persistent disease and thereby improve local control. Distant control would then be improved as a result of the lower metastatic potential for spread from local recurrence. With greater radiation doses, local control rates improve (24), and the beneficial effect of long-term ADT could be expected to diminish. It is plausible to surmise that patients with the most bulky (*i.e.*, clinical Stage T3) disease would require the most aggressive methods of achieving local control, and that this group of patients would continue to benefit from prolonged ADT, primarily for the potential effect on local control. However, it might not be possible to discern the most favorable length of adjuvant ADT from the available data and apply that recommendation to all patients. The optimal course of ADT would ideally be individualized to the disease characteristics and patient comorbidities, and for certain patients could be somewhere between 4 or 28 months as tested in the Radiation Therapy Oncology Group 9202 study.

In the absence of prospective data on this subject, retrospective data can be an important source of information. However, the present study had several limitations inherent to a retrospective analysis. The patient and treatment characteristics during the study period were not homogeneous. Treatment was not defined upfront, but by physician preference, leading to uncontrolled bias in which patients were selected for short-term ADT. The numbers of patients, especially in each subset analysis, also limited the power to make conclusions. Although the length of potential follow-up was long (median potential follow-up, approximately 8 years), it was still not long enough to draw conclusions on endpoints such as PCa-specific or overall mortality, which typically require more than a decade of follow-up. The use of FFBF as our sole endpoint was valid, especially given that higher risk patients are more likely to die of PCa than low-risk patients (25), but competing risks of mortality in older men could cause one to question the use of a FFBF endpoint as a surrogate for a clinically meaningful outcome in all cases.

CONCLUSION

These results indicate acceptable outcomes for select intermediate- and high-risk patients treated with RT and short-term ADT. Greater radiation doses should be considered when the risk/benefit ratio allows. For men with clinical Stage T3 disease, additional measures are justified (*e.g.*, consideration of longer term ADT, whole pelvic RT, or the use of another

sensitizing agent). For the somewhat common clinical scenario of an older man diagnosed as a result of PSA screening with a PSA level of <10 ng/mL, clinically localized disease, but with a Gleason score 8, these data suggest that long-term ADT need not be a foregone conclusion in the setting of dose-escalated RT. Additional prospective studies are necessary to explore this hypothesis.

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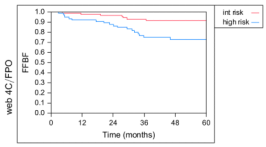

Fig. 1.

Freedom from biochemical failure (n = 184). Intermediate risk indicated by red and high risk by blue. Log–rank test, p = .0039.

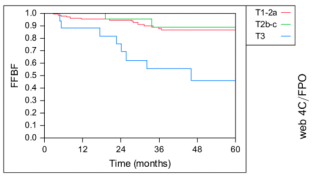

Fig. 2.

Freedom from biochemical failure, by T stage (n = 184), with Stage T1-T2a indicated by red, Stage T2b-T2c by green, Stage T3 by blue. Log–rank test, p = .0001.

Table 1

Patient and treatment characteristics (n = 184)

Characteristic	Intermediate risk (n = 105)	High risk (n = 79)	p
Age (y)			.0046
Median	70	67	
Range	53–83	42–83	
Race			.2354
White	44 (42)	25 (32)	
Black	56 (54)	48 (61)	
Other/unknown	5 (4)	6 (8)	
Pre-RT PSA level (ng/mL)			< .0001
Median	11.7	25.2	
Range	2.5–19.9	2.2–225	
PSA level (ng/mL)			< .0001
0–4	6 (6)	1 (1)	
4–10	32 (31)	8 (10)	
10–20	67 (64)	12 (15)	
>20	0 (0)	58 (73)	
Clinical T stage			< .0001
T1-T2a	90 (86)	48 (62)	
T2b-T2c	15 (14)	13 (17)	
T3	0 (0)	18 (22)	
T4	0 (0)	0 (0)	
Gleason score			< .0001
2–6	38 (36)	29 (37)	
7	67 (64)	23 (29)	
8–10	0 (0)	27 (34)	
Percentage of cores positive (n = 128)			.1403
0–33	35 (47)	16 (30)	
34–49	11 (15)	8 (15)	
50–100	29 (39)	29 (55)	
External beam radiation dose (Gy)			.8325
Median	74	74	
Range	45–76.4	45–76.4	
RT technique			
Intensity-modulated RT	61 (58)	41 (52)	.4027
Whole pelvis RT	3 (3)	10 (13)	.0096
ADT duration (mo)			.6653
Median	4	4	
Range	1–6	1–6	
Follow-up (mo)			.1286
Median	55	50	

Characteristic	Intermediate risk (*n* = 105)	High risk (*n* = 79)	*p*
Range	1–197	1–204	

Abbreviations: PSA = prostate-specific antigen; RT = radiotherapy; ADT = androgen deprivation therapy.

Table 2

Univariate analysis of biochemical failure for all patients (n = 184)

Variable	Biochemical control at 4 y (%)	*p*
T stage (T3 vs. T1-T2c)	46 vs. 87	< .0001
Gleason score (≤6 vs. ≥7)	83 vs. 83	.8337
Radiation dose (≥74 vs. <74 Gy)	87 vs. 78	.1840
PSA (≥14 vs. <14 ng/mL)	81 vs. 86	.2102
Whole pelvic RT (yes vs. no)	92 vs. 83	.4848
Percentage of cores positive (≥50% vs. <50%)	85 vs. 86	.2177

Abbreviations: PSA = prostate-specific antigen; RT = radiotherapy.

Table 3

Multivariable analysis of biochemical failure for all patients (n = 184)

Variable	Risk ratio (95% CI)	*P*
T stage (T3 vs. T1-T2c)	3.90 (1.73–8.17)	.0016
Gleason score (≥7 vs. ≤6)	1.09 (0.55–2.23)	.8115
Radiation dose (≥74 vs. <74 Gy)	0.66 (0.32–1.32)	.2422
PSA (≥14 vs. <14 ng/mL)	1.22 (0.60–2.62)	.5904

Abbreviations: CI = confidence interval; PSA = prostate-specific antigen.

Table 4

Univariate analysis of biochemical failure in intermediate-risk subset (n = 105)

Variable	Biochemical control at 4 y (%)	*p*
T stage (T2b-T2c vs. T1-T2a)	91 vs. 92	.5213
Gleason score (≤6 vs. ≥7)	93 vs. 91	.7444
Radiation dose (≥74 vs. <74 Gy)	93 vs. 91	.8302
PSA (≥12 ng/mL vs. <12 ng/mL)	90 vs. 94	.5536
Whole pelvic RT (yes vs. no)	100 vs. 91	.7043
Percentage of cores positive (≥50% vs. <50%)	94 vs. 92	.4762

Abbreviations as in Table 2.

Table 5

Multivariable analysis of biochemical failure in intermediate-risk subset (n = 105)

Variable	Risk ratio (95% CI)	*P*
T stage (T2b-T2c vs. T1-T2a)	1.48 (0.22–6.12)	.6435
Gleason score (≥7 vs. ≤6)	1.64 (0.41–6.71)	.4820
Radiation dose (≥74 vs. <74 Gy)	1.12 (0.30–4.27)	.8668
PSA (≥12 vs. <ng/mL)	1.80 (0.46–7.04)	.3911

Abbreviations as in Table 3.

Table 6

Univariate analysis of biochemical failure in high-risk subset (n = 79)

Variable	Biochemical control at 4 y (%)	*p*
T stage (T3 vs. T1-T2c)	46 vs. 80	.0303
Gleason score (≤6 vs. ≥7)	71 vs. 74	.3296
Radiation dose (≥74 vs. <74 Gy)	80 vs. 64	.0333
PSA (≥25 vs. <25 ng/mL)	71 vs. 75	.7239
Whole pelvic RT (yes vs. no)	89 vs. 71	.3253
Percentage of cores positive (≥50% vs. <50%)	76 vs. 74	.7470

Abbreviations as in Table 2.

Table 7

Multivariable analysis of biochemical failure in high-risk subset (n = 79)

Variable	Risk ratio (95% CI)	*P*
T stage (T3 vs. T1-T2c)	2.38 (0.94–5.74)	.0650
Gleason score (≥7 vs. ≤6)	0.80 (0.33–2.04)	.6357
Radiation dose (≥74 vs. <74 Gy)	0.42 (0.16–1.04)	.0597
PSA (≥25 vs. <25 ng/mL)	1.54 (0.63–3.89)	.3456

Abbreviations as in Table 3.