The need for androgen deprivation therapy in patients with intermediate-risk prostate cancer treated with dose-escalated external beam radiation therapy

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Introduction: *To evaluate if androgen deprivation therapy (ADT) improves outcomes for patients with localized, intermediate-risk prostate cancer treated with definitive external beam radiation therapy (EBRT) in the dose-escalated era.*

Materials and methods: *This is a retrospective study using a single institutional database. We included patients with localized, intermediate-risk prostate cancer treated with dose-escalated radiation therapy (RT) with 3D conformal radiotherapy or intensity-modulated radiotherapy (74-80 Gy in daily fraction of 1.8 Gy-2.0 Gy, or 70.2 Gy in daily fraction of 2.7 Gy) from 1992 to 2013. To further risk stratify the patients, PSA 10 ng/mL-20 ng/mL, Gleason 3+4, and T2b-T2c were assigned risk score (RS) of 1, while Gleason 4+3 was assigned RS of 2. Patients with prior treatment for prostate cancer, those on long term ADT (≥ 23 months), or those with follow up < 1 year were excluded. We defined initial ADT as initiation within 9 months prior to the start of RT, during RT, or within 2 months after the completion of RT. Outcomes for patients who received initial ADT were compared to men treated with RT alone. Covariates included number of intermediate risk factors, age, and baseline comorbidities. Kaplan Meier estimates were compared using log rank tests. Competing risk regression and Cox proportional hazards regression were used to estimate hazard ratios adjusted for covariates.*

Results: *Of 1,134 patients included in this study, 155 received initial ADT with median duration of 4.0 months (m) (range 0.5 m-22.0 m). The median follow up was 56.4 m (range 12.3 m-200.7 m). Patients on ADT had higher RS compared to those with radiation alone (RS 1: 48% versus 58%; RS 2: 35% versus 32%; RS 3: 14% versus 9%; RS 4: 3% versus 1%; p=0.01). When patients with ADT were compared to those treated with radiation alone, there were no significant differences in freedom from biochemical failure (FFBF) (84.0% versus 87.3%, p = 0.83), freedom from distant metastasis (FFDM) (94.4% versus 96.9%, p = 0.41), or overall survival (OS) (92.3% versus 90.7%, p = 0.48) at 5 years. Among patients with RS ≥ 2, there were still no significant differences in FFBF, FFDM, or OS when patients treated with ADT were compared to those treated with radiation alone. In multivariable analyses adjusting for RS and age, the adjusted hazard ratio for ADT use was sHR = 0.89 (95% CI = 0.64-1.66, p = 0.64) for BCF; sHR = 1.13 (95% CI = 0.48-2.65, p = 0.77) for DM. For overall mortality, adjusted HR = 1.23 (95% CI = 0.76-2.01, p = 0.40) where comorbidities (including diabetes, cardiac disease, and hypertension) were also included as covariates.*

Conclusion: *Our study suggested that treatment of intermediate-risk prostate cancer with definitive dose-escalated EBRT alone resulted in acceptable outcomes, and it failed to show improved outcomes in patients who received short term ADT.*

Key Words: intermediate-risk prostate cancer, dose-escalated EBRT, ADT

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Introduction

Definitive radiation therapy (RT) and prostatectomy are two mainstays of treatment for localized prostate cancer. While RT offers good outcomes for patients with localized disease, a proportion of patients still experience treatment failure.[1] Multiple randomized trials have explored the role of neoadjuvant or adjuvant androgen deprivation therapy (ADT) combined with external beam radiation therapy (EBRT) for patients with intermediate-risk and high-risk disease.[2–7] Most of these trials demonstrated a benefit of ADT with significantly improved biochemical control, overall survival, and cancer specific survival, including a few trials with short term ADT ranging from 3 months to 10 months.[2,4,6,7] Currently, there are two common regimens for ADT: a short-course (around 6 months) for intermediate-risk patients,[8] and a long course (2-3 years) for high-risk patients.[9,10] The aforementioned trials established the role of ADT in an era where radiation dose for prostate cancer was typically ≤ 70 Gy (non dose-escalated). Studies have demonstrated that escalated dose of RT improves outcomes such as biochemical recurrence and overall survival,[1,5,11,12] but the benefit of ADT at higher doses is unclear. The question was raised whether a short-course of ADT still improves outcomes for patients with localized intermediate-risk prostate cancer who received definitive RT in the dose-escalated era.

Materials and methods

We reviewed our institutional review board-approved, prospectively collected prostate cancer database for those with clinical localized intermediate-risk prostate cancer treated with dose-escalated EBRT between 1992 and 2013. Intermediate-risk prostate cancer is defined according to NCCN risk-stratification group,[13] which include at least one of the following: PSA 10 ng/mL-20 ng/mL, Gleason score 7, or T2b-T2c. To further risk stratify patients, we calculated an intermediate-risk score (RS). We assigned 1 risk point each for PSA 10 ng/mL-20 ng/mL and T2b-T2c. As studies have shown that patients with Gleason 4+3 disease have significantly worse prognosis than those with Gleason 3+4[14,15] and are more likely to harbor Gleason 9 or 10 disease,[16] we assigned 1 risk point for Gleason 3+4, while Gleason 4+3 was assigned 2 points. RS was the sum of these risk points, with possible scores of 1 to 4. Patients with prior treatment for prostate cancer, those on long term ADT (≥ 23 months), or those with follow up < 1 year were excluded. We defined initial ADT as initiation within 9 months prior to the start of RT, during RT, or within 2 months after the completion of RT.

Outcomes for patients who received initial ADT were compared to men treated with RT alone. Patient characteristics at baseline were compared by initial ADT status using Chi-square tests. Kaplan Meier estimates of freedom from biochemical failure (FFBF), freedom from distant metastasis (FFDM), and overall survival (OS) by initial ADT use and higher RS were compared using log rank tests. Biochemical failure was defined according to the Phoenix definition of biochemical failure, which is a rise at least 2 ng/mL above the nadir PSA following radiation;[17] patients without 2 post-RT PSA measurements were excluded from the biochemical failure analyses (n = 37). Competing risk regression,[18] adjusting for the competing risk of death from any cause, was used to estimate the subdistribution hazard ratio (sHR) for RT+ADT verus RT only for the biochemical failure and distant metastasis outcomes, while Cox proportional hazards regression was used for overall mortality. Age at start of RT and risk score were included as covariates in adjusted models; comorbidity status at baseline for diabetes, hypertension and cardiac disease were also included for the overall mortality outcome.

All men were treated with either 3-dimensional conformal radiation therapy (3DCRT) or intensity modulated RT (IMRT), with escalated dose of 74 Gy-80 Gy in daily fraction of 1.8 Gy-2.0 Gy, or 70.2 Gy in daily fraction of 2.7 Gy. Details of our 3DCRT and IMRT treatment planning technique have been previously described.[19–21] The vast majority of patients had radiation delivered using 10-MV photons and prescribed to 95% of the planning target volume. In general, the radiation filed incudes prostate plus all seminal vesicles for intermediate-risk (with the distal seminal vesicles receiving a reduced dose which was typically 56 Gy in daily fraction of 1.8 Gy-2.0 Gy).

Results

Of 1,134 patients included in this study, 155 received initial ADT with median duration of 4.0 months (range 0.5 m-22.0 m). The median follow up was 56.4 months (range 12.3 m-200.7 m). Patient characteristics for RT alone and RT plus ADT patients are compared in Table 1.

Patients on ADT had higher RS compared to those with radiation alone (RS 1: 48% versus 58%; RS 2: 35% versus 32%; RS 3: 14% versus 9%; RS 4: 3% versus 1%; p = 0.01). When patients with ADT were compared to those treated with RT alone, there were no significant differences in FFBF (log rank test p = 0.83, 5 year

TABLE 1. **Baseline patient characteristics by initial androgen deprivation therapy (ADT) use**

	All n (%)	RT alone n (%)	RT +ADT n (%)	p value
Age (years)				0.38
≤ 65	381 (33.6)	322 (32.8)	59 (38.1)	
66-75	575 (50.7)	497 (50.8)	78 (50.3)	
76-88	178 (15.7)	160 (16.3)	18 (11.6)	
Risk score				0.01
1	641 (56.5)	567 (57.9)	74 (47.7)	
2	364 (32.1)	310 (31.7)	54 (34.8)	
3	114 (10.1)	92 (9.4)	22 (19.3)	
4	15 (1.3)	10 (1.0)	5 (3.2)	
Gleason score				0.30
2-6	340 (30.0)	299 (30.5)	41 (26.5)	
3+4	509 (44.9)	443 (45.3)	66 (42.6)	
4+3	285 (25.1)	237 (24.2)	48 (31.0)	
T stage				0.04
T1, T2a	871 (76.8)	762 (77.8)	109 (70.3)	
T2b, T2c	263 (23.2)	217 (22.2)	46 (29.7)	
PSA (ng/mL)				0.81
< 10	705 (62.2)	610 (62.3)	95 (61.3)	
10-20	429 (37.8)	369 (37.7)	60 (38.7)	
Diabetes				0.72
No	947 (83.5)	816 (83.4)	131 (84.5)	
Yes	187 (16.5)	163 (16.6)	24 (15.5)	
Hypertension				0.22
No	498 (43.9)	437 (44.6)	61 (39.4)	
Yes	636 (56.1)	542 (55.4)	94 (60.6)	
Cardiovascular disease				0.81
No	881 (77.7)	759 (77.5)	122 (78.7)	
Yes	253 (22.3)	220 (22.5)	33 (21.3)	

estimates 84.0% versus 87.3%), FFDM (p = 0.41, 5 yr 94.4% versus 96.9%), or OS p = 0.48, 5 yr 92.3% versus 90.7%) as shown in Figures 1-3.

The effect of ADT was further analyzed by risk stratification with RS, with the hypothesis that patients with higher RS are more likely to benefit from ADT. Among patients with RS ≥ 2, there was no significant difference in FFBF (Figure 4, p = 0.96), FFDM (p = 0.49), or OS (p = 0.21) when patients treated with ADT were compared to those treated with radiation alone.

In multivariable analyses adjusting for number of RS and age, the adjusted hazard ratio for ADT use was sHR = 0.89 (95% CI = 0.64-1.66, p = 0.64) for BCF; sHR = 1.13 (95% CI = 0.48-2.65, p = 0.77) for DM. For overall mortality, adjusted HR = 1.23 (95% CI = 0.76-2.01, p = 0.40) where comorbidities (including diabetes, cardiac disease, and hypertension) were also included as covariates.

Discussion

Escalated dose is now the standard for definitive RT for prostate cancer. It is unclear whether patients with intermediate-risk prostate cancer still benefit from a short term ADT in the setting of dose-escalated radiation. This single-institution retrospective study suggested that definitive dose-escalated EBRT alone resulted in acceptable outcomes for intermediate-risk prostate cancer, and it did not show improved outcomes from short term ADT.

A randomized trial by Groupe d'Etudes des Tumeurs Uro-Génitales named GETUG14 attempted to evaluate the benefit of short term ADT among patients with intermediate-risk prostate cancer treated with high dose RT. However, it closed early due to poor accrual. Preliminary results of GETUG14 were presented

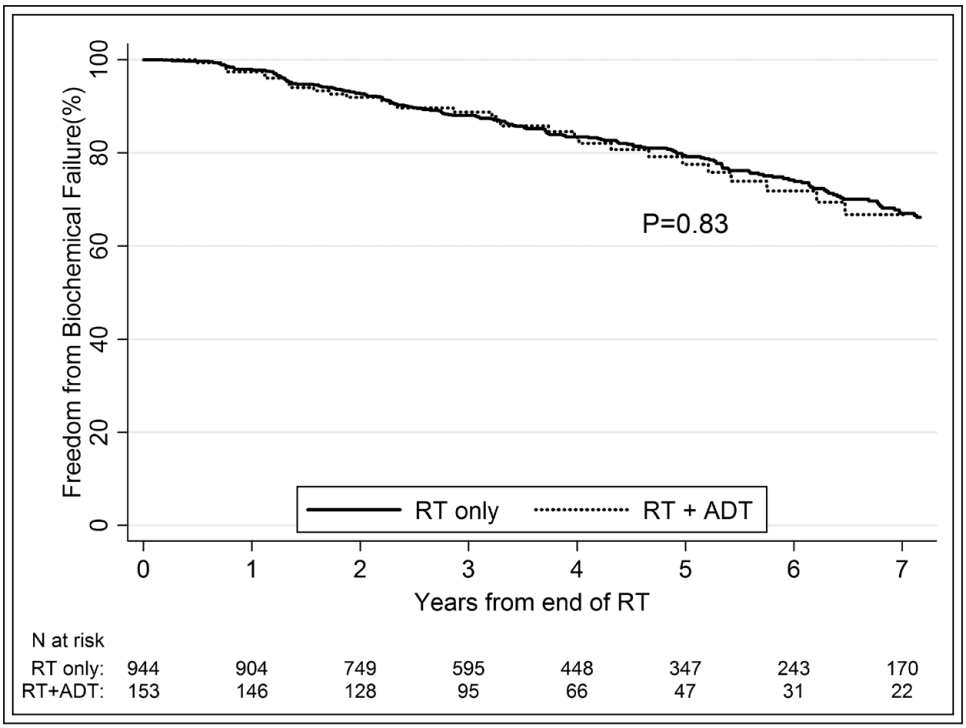

Figure 1. Freedom from biochemical failure for patients treated with radiation alone versus radiation plus androgen deprivation therapy (ADT).

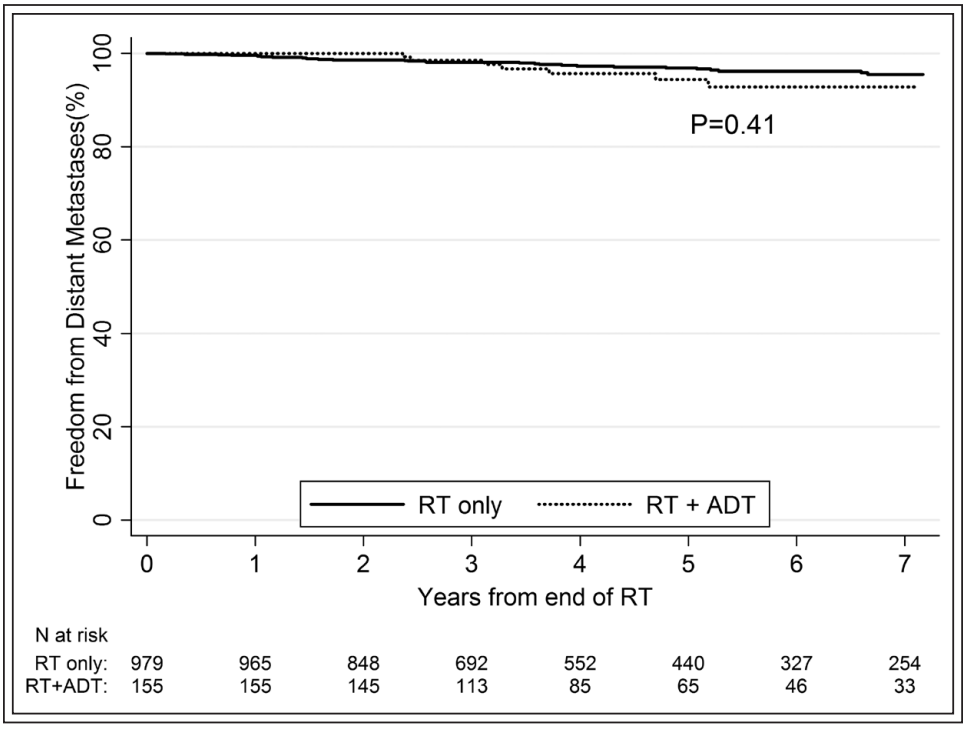

Figure 2. Freedom from distant metastasis for patients treated with radiation alone versus radiation plus androgen deprivation therapy (ADT).

at the American Society of Clinical Oncology (ASCO) 2011 conference, where 366 patients with intermediate-risk prostate cancer had undergone EBRT (80 Gy) with or without 4 month ADT.[22] There was a significant improvement in the 3 year biochemical failure free survival (BFFS) (97% versus 91%, p = 0.04), but the primary end-point (combined biochemical and local tumor control) was not significantly different (92% versus 86%, p = 0.09),[22] although it might not be powered to detect the difference in the primary end-point due to its early closure.

Another randomized phase III Canadian trial with a three-arm design (radiation of 70 Gy plus 6 month ADT versus radiation of 76 Gy plus 6 month ADT versus radiation of 76 Gy alone) was most recently presented at the American Society for Radiation Oncology (ASTRO) 2015 conference.[23] This Canadian trial showed adding short term ADT to radiation (either 70 Gy or 76 Gy) improved biochemical failure (BF) rate and disease-free survival (DFS) at 5 years and 10 years compared to radiation of 76 Gy alone, but there was no difference in OS among three arms, and the cancer specific mortality was only 1.3% among the entire cohort. The recently published EORTC 22991 trial also reported improved BF

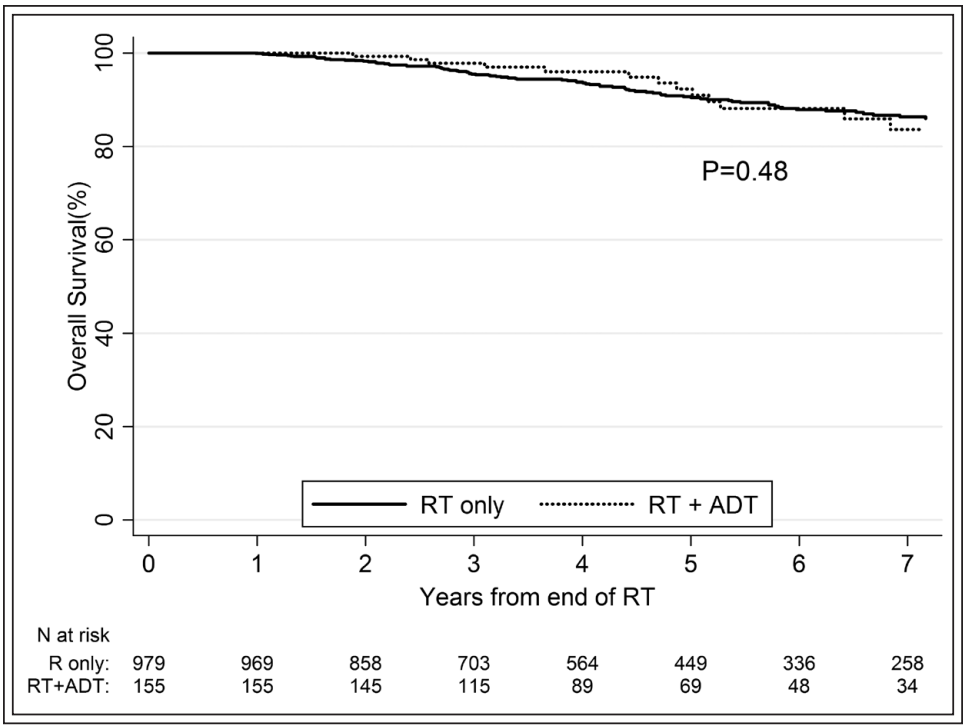

Figure 3. Overall survival for patients treated with radiation alone versus radiation plus androgen deprivation therapy (ADT).

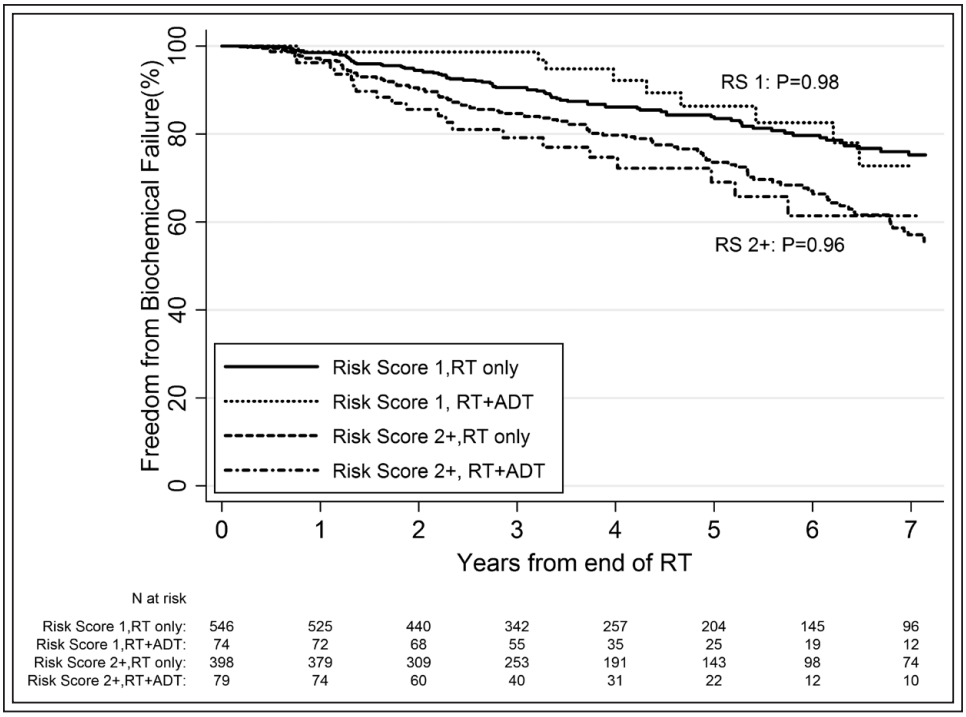

Figure 4. Freedom from biochemical failure for patients treated with radiation alone versus radiation plus androgen deprivation therapy (ADT) for risk score of 1 and 2+ respectively.

and DFS with 6 months of ADT in patients with intermediate and high-risk localized prostate cancer treated with dose of 70 Gy, 74 Gy, or 78 Gy at median follow up of 7.2 years.[24] The ongoing Radiation Therapy Oncology Group (RTOG) 0815 trial randomized patients with intermediate-risk patients to dose-escalated RT with or without ADT of 6 months. However, the results of RTOG 0815 would not be available for several years.

Many retrospective studies were also performed to evaluate the benefit of ADT in patients with intermediate-risk prostate cancer treated with dose-escalated radiation therapy with mixed results. Some showed no benefit of short term ADT in biochemical failure free survival (BFFS), distant metastasis free survival (DMFS), or OS,[25–27] while a few showed some benefit of ADT.[12,28,29] The retrospective study by Zelefsky showed that with median radiation dose of 81 Gy (range 64.8 Gy-86.4 Gy), ADT of median duration of 5 months improved the BFFS.[12] Another retrospective study including intermediate-risk men treated with dose-escalated radiation showed significant better freedom from failure with the addition of short term ADT in the unfavorable subset of patients (GS 4+3 or T2c

disease), but no difference for those with favorable disease.[28] A more recent retrospective study using the database from the same institution[28] showed significant reduction in BF and DM among men with intermediate-risk disease treated with high-dose EBRT, and ADT duration beyond 6 months did not further reduce the risk of biochemical failure.[29]

The discrepancies among the results of these studies are at least partially due to selection bias and the substantial heterogeneity of intermediate-risk prostate cancer. Men with more risk factors are more likely to benefit ADT than those with just one risk factor. Because the heterogeneity of this group of patients, additional clinical factors have been proposed to be incorporated into methods to evaluate the risk, including pre-treatment PSA velocity,[30] primary Gleason pattern,[31] perineural invasion,[32] and percentage of positive biopsy cores.[33] However, the best way to implement these clinical factors to better predict the risk for worse outcomes is still unclear.

The preliminary results of the Canadian trial did not specify the percentage of patients having one or two or three NCCN risk factors,[23] nor did the EORTC 22991 trial.[24] In this current study, we further risk-stratified the patients by assigning 1 risk point to each of the NCCN intermediate-risk factor with an extra point for Gleason 4+3 to account that Gleason 4+3 is typically considered more unfavorable disease compared to Gleason 3+4.[14,15,31] Within our definition of favorable intermediate-risk disease (RS of 1) and unfavorable intermediate-risk disease (RS of 2-4), there was still no observed benefit of ADT in the unfavorable group. It would be ideal if the number of positive cores could also be taken into account in risk-stratification.[33] However, we were unable to record the percentage of positive cores in our database.

On the other hand, the discrepancies in the results of these studies may also imply that even if a short term ADT offers statistically significant better outcomes, the added benefit may not be substantial. Physicians and patients need to weigh the risks and benefits of ADT. Even short term ADT can have significant toxicities. The Canadian trial reported a median of 21.6 months to recover to a normal testosterone level. Hot flashes were prevalent in 75% and 31% of patients at 6 and 18 months, and gynecomastia was present in 20% and 14% of patients at 6 and 18 months, respectively. Erectile dysfunction increased from 50% at presentation to 90% after short term ADT and to 71% after RT alone at 10 months ($p < 0.001$).[23]

Our retrospective study suggested no benefit of ADT for patients with intermediate-risk prostate cancer treated with escalated-dose EBRT. This study has limitations due to the inherited nature of retrospective studies, including the inhomogeneity of ADT duration and initiation time, and patient selection bias as those receiving ADT had significantly higher T stage and risk score. Although we included risk score in the multivariable analysis for the adjusted hazard ratio for ADT and did the subgroup comparison among patients with risk score ≥ 2, it may not fully account for the confounding effect of selection bias. The bias in giving ADT in patients with higher risk disease may have obscured the added benefit of ADT. Another limitation of this study is the relatively small percentage of patients who received ADT. The results of ongoing RTOG 0815 will further elucidate the role of ADT among men with intermediate-risk prostate cancer.

Conclusion

Our study suggested that treatment of intermediate-risk prostate cancer with definitive dose-escalated EBRT alone resulted in acceptable outcomes, and it failed to show improved outcomes in patients who received short term ADT.

Disclosure

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