What is the optimal duration of androgen deprivation therapy in prostate cancer patients presenting with prostate-specific antigen levels > 20 ng/ml?

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Purpose: *To evaluate the optimal duration of androgen deprivation therapy (ADT) in patients with prostate cancer treated with external beam radiotherapy (EBRT), who present with PSA levels > 20 ng/mL.*
Materials and methods: *A total of 307 patients presenting with a PSA > 20 ng/ml were treated with EBRT and ADT. The cohort was divided into four groups according to the duration of ADT: Group 1 received < 6 months (n = 71), group 2 received 6-12 months (n = 80), group 3 received 12-24 months (n = 72), and group 4 received > 24 months (n = 84) of ADT. The endpoints analyzed were biochemical control (bNED), overall survival (OS) and cause-specific survival (CSS). Statistical analysis was conducted using Kaplan-Meier estimates and Cox regression models.*
Results: *Compared to patients who received < 6 months of ADT, patients treated with 12-24 months or > 24 months of ADT experienced significantly improved bNED (p = 0.01 and p < 0.0001, respectively). Cause-specific survival with ADT durations 12-24 and > 24 months were significantly higher compared to < 6 months (p < 0.007 and 0.024, respectively). Overall survival with ADT durations > 24 months was also significantly higher compared to < 6 months (p = 0.0025).*
Conclusions: *The present analysis supports the hypothesis that longer durations of ADT improves bNED, CSS and OS in patients presenting with a PSA > 20 ng/ml.*

Key Words: prostate cancer, androgen deprivation therapy, prostate specific antigen, biochemical outcome, prostate radiotherapy

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Introduction

The addition of androgen deprivation therapy (ADT) to external beam radiotherapy (EBRT) has been demonstrated by randomized controlled trials to improve outcomes for patient with high-risk prostate cancer, particularly locally advanced disease and/or high Gleason scores.[1-12] The benefit of ADT relative to different prostate-specific antigen (PSA) levels at presentation is a subject of ongoing investigation. In a recent analysis, our group reported that for patients presenting with PSA levels ≥ 20 ng/ml, ADT durations of > 12 months improved biochemical control (no-evidence of disease) (bNED), cause-specific survival (CSS), and overall survival (OS) compared to shorter

durations.[10] In the present study, the objective was to carry out subgroup analyses to evaluate outcomes associated with different AD durations and to further characterize optimal ADT duration for patients presenting with PSA levels > 20 ng/ml undergoing EBRT.

Methods and materials

Patient population

The Prostate Cancer Outcome Initiative is a provincial database that prospectively records information on clinical outcomes in patients with prostate cancer treated with EBRT. Between 1994 and 2000, 2753 patients underwent EBRT at the British Columbia Cancer Agency, 1589 of whom were prospectively followed. Among these patients, 307 presented with PSA levels > 20 ng/ml, which constitutes one of the high-risk criteria in the Canadian Consensus.[12] These patients all received EBRT and ADT and formed the cohort for this analysis. After examination of interquartile ranges, patients were divided into 4 groups according to the duration of ADT: Group 1 received < 6 months (n = 71), group 2 received 6-12 months (n = 80), group 3 received 12-24 months (n = 72), and group 4 received > 24 months (n = 84) of ADT.

Treatment

All patients underwent EBRT using four-field beam arrangements, 10-18MV photons, to a total dose of 66-72 Gy in 2 Gy per fraction according to institutional policy.[10,13,14] Patients underwent CT planning and urethrograms. Pelvic field target delineation included the locoregional vasculature and lymphatics. Typical fields were 17 cm x 17 cm for the anterior–posterior fields and 13 cm x 17 cm for the lateral fields.[10]

ADT was usually delivered with luteinizing hormone-releasing hormone agonists with an oral antiandrogen given initially for the first 2-4 weeks to block the flare. Decisions in ADT duration in this cohort were made by the treating oncologist based on individualized assessment of the patient's disease stage, comorbidities, and PSA levels at presentation and on follow-up.

Patients were followed every 6 months for 3-5 years and yearly thereafter. At each follow-up visit, assessment consisted of history and physical examinations including digital rectal examination, and bloodwork including PSA and testosterone levels.

Endpoints

The endpoints analyzed were bNED, CSS, and OS. Time zero was set at the date of EBRT completion.[15] The Houston definition was used to assess biochemical relapse since it was considered to be the most appropriate in patients treated with AD.[16] Logistic and Cox regression models were used to conduct univariate and multivariate analyses. Survival endpoints were calculated using Kaplan-Meier and Cox multivariate analyses.

Results

Patient, tumor, and treatment characteristics of the entire cohort are presented in Table 1. The median durations of ADT in groups 1, 2, 3, and 4 were 4.2, 8.8, 16.0 and 38.1 months, respectively.

The distributions of patient age, Gleason score and T stage were similar in the 4 groups. Patients in Group 1 had higher proportions of pelvic EBRT use and purely neoadjuvant ADT.

1) Biochemical control

The results of univariate and multivariate analyses for biochemical control are presented in Table 2. Stage and Gleason score were significantly associated with bNED in both univariate and multivariate analyses. No statistically significant difference in bNED outcome was observed between the groups receiving < 6 months versus 6-12 months of ADT. However, compared to patients who received < 6 months of ADT, patients treated with 12-24 months or > 24 months of ADT experienced significantly improved bNED ($p = 0.01$ and $p < 0.0001$, respectively).

Kaplan-Meier curves for biochemical control are presented in Figure 1. At 5 years, the rates of bNED were 34%, 35%, 47% and 77% for groups 1-4 respectively.

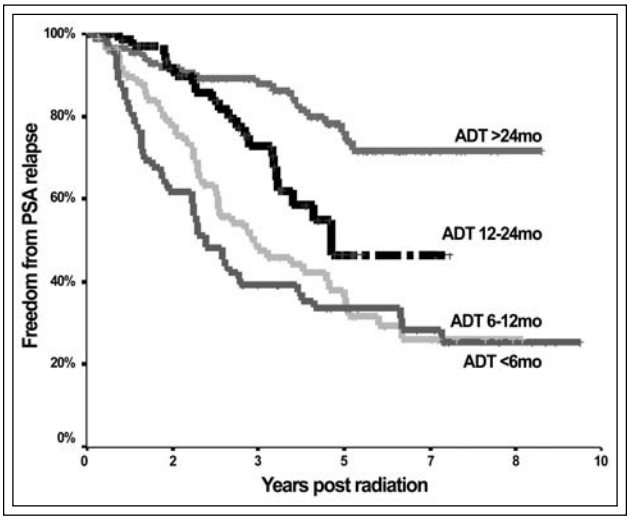

Figure 1. Kaplan-Meier biochemical control comparisons according to ADT duration.

TABLE 1. **Patient, tumor, and treatment characteristics**

ADT groups	**Group 1 (< 6 mos) N=71**	**Group 2 (6-12 mos) N=80**	**Group 3 (12-24 mos) N=72**	**Group 4 (> 24 mos) N=84**	**P**
Median follow-up time (months)	63	31	32	52	< 0.001
Median age (years)	69	69	69	69	0.43
Median PSA (ng/ml)	35	36	30	33	0.03
Gleason score (%)					0.14
≤ 6	38%	37%	42%	26%	
7	30%	39%	40%	38%	
≥ 8	32%	24%	18%	36%	
Stage (%)					0.07
T1	6	12	18	5	
T2	28	28	31	24	
T3	60	47	46	64	
T4	6	13	5	8	
Pelvic RT (%)					< 0.001
prostate only	91%	50%	56%	57%	
pelvic boost	9%	50%	44%	43%	
Timing of ADT (%)					< 0.001
NA	79%	41%	4%	0%	
NA-C	17%	28%	3%	2%	
NA-C-A	4%	31%	93%	98	

ADT = androgen deprivation therap
PSA = prostatic specific antigen
RT = radiotherapy
NA = neoadjuvant
C = concurrent
A = adjuvant

TABLE 2. **Univariate and multivariate analysis of factors for biochemical control**

Factor	**Univariate**	**Multivariate**	**Odds ratio (95% confidence interval)**
Stage	0.01	0.02	1.37 (1.1-1.8)
PSA (log)	0.0023	ns	-
Gleason score	0.035	0.0003	1.55 (1.2-2.0)
Age	ns	-	
Radiation dose	ns	-	-
Year of treatment	0.001		ns
ADT < 6 v 6-12 m	ns	ns	-
ADT < 6 v 12-24 m	0.002	0.004	0.46 (0.27-0.78)
ADT < 6 v > 24 m	< 0.0001	0.0003	0.14 (0.08-0.25)

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TABLE 3. **Univariate and multivariate analyses of factors for cause specific survival**

Factor	Univariate	Multivariate	Odds ratio (95% confidence interval)
Stage	0.013	0.02	1.9 (1.1-3.3)
PSA (log)	0.0001	ns	-
Gleason score	< 0.0001	0.0002	2.4 (1.5-3.7)
Age	0.029	ns	-
Radiation dose	0.046	0.014	0.92 (0.86-0.98) per Gy
Year of treatment	0.027	-	-
ADT < 6 v 6-12 m	ns	ns	-
ADT < 6 v 12-24 m	0.007	ns	-
ADT < 6 v > 24 m	0.0238	0.006	0.26 (0.1-0.7)

2) Cause-specific survival

Table 3 presents the univariate and multivariate analyses for CSS. Similar to the analysis of bNED outcomes, stage and Gleason score were significant tumor variables for CSS. EBRT dose was a treatment variable significantly associated with CSS.

Figure 2 depicts Kaplan-Meier CSS curves according to different ADT durations. At 5 years, the CSS rates were 82%, 82%, 97% and 92.5% for groups 1-4, respectively. Cause-specific survival estimates with ADT durations 12-24 and > 24 months were significantly higher compared to < 6 months ($p < 0.007$ and 0.024, respectively). The difference between group 3 and 4 was not statistically significant ($p = 0.16$).

3) Overall survival

The univariate and multivariate analyses for overall survival are presented in Table 4. Gleason score was the sole variable significantly associated with OS. A statistically significantly difference in OS was observed only in the comparison of cohorts receiving < 6 months versus > 24 months of ADT.

Kaplan-Meier OS curves are presented in Figure 3. The OS rates at 5 years were 74%, 77%, 83% and 92% for groups 1-4, respectively. Overall survival estimates with ADT durations > 24 months was significantly higher compared to < 6 months ($p = 0.0025$).

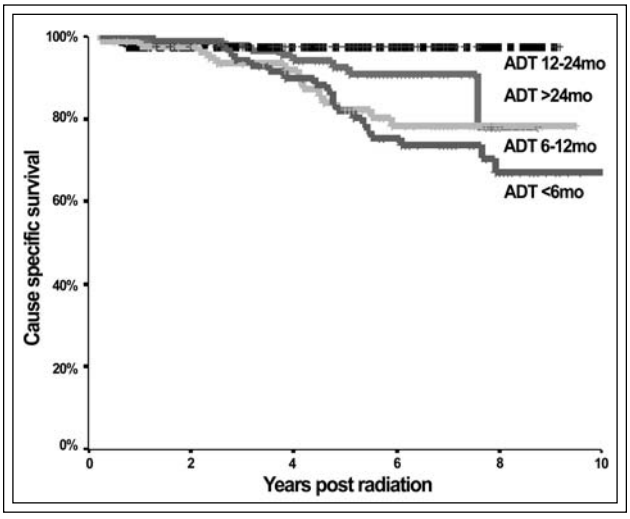

Figure 2. Kaplan-Meier cause-specifc survival comparisons according to ADT duration.

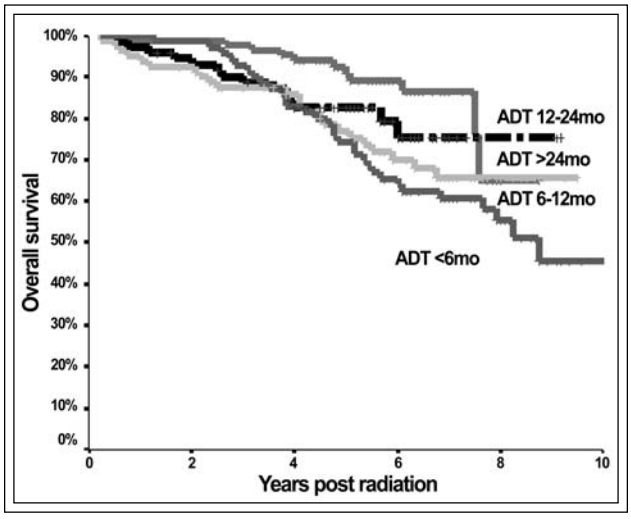

Figure 3. Kaplan-Meier overall survival comparisons according to ADT duration.

TABLE 4. **Univariate and multivariate analyses of factors for overall survival**

Factor	Univariate	Multivariate	Odds ratio (95% confidence interval)
Stage	ns	-	-
PSA (log)	0.012	ns	-
Gleason score	< 0.0001	< 0.0001	2.0 (1.5-2.7)
Year of treatment	ns	-	-
Radiation dose	ns	-	-
Age	ns	-	-
ADT < 6 v 6-12 m	ns	ns	-
ADT < 6 v 12-24 m	ns	ns	-
ADT < 6 v > 24 m	0.0025	0.0016	0.3 (0.15-0.59)

Discussion

The most convincing evidence of the benefit of long term ADT has been reported by Bolla et al.[2] In this trial, patients who received 3 years of adjuvant goserelin experienced significantly improved 5-year OS and disease free survival (DFS) compared to patients not treated with ADT.[2,3] The majority of patients in this study, however, had locally advanced T3 or T4 disease. Only one-third of these patients had PSA > 10 ng/ml and the proportion of patients with PSA > 20 ng/ml was unknown. The 5-year OS rate of 62% without ADT and 78% with 3 years of ADT represented a significant improvement in a specific subset of patients with high-risk disease. However, the generalizability of long term ADT use to other prostate cancer patient populations is limited since only one-third of patients in that study had PSA > 10ng/ml and the proportion of patients with PSA > 20 ng/ml was unknown. Furthermore, the widespread applicability of a 3-year course of ADT may be limited due to poor tolerance in some patients. Data from the Radiation Therapy Oncology Group 9202 study suggested that only patients with Gleason score 8-10 had a survival benefit from longer duration of ADT (4). We accordingly believe that additional research with randomized trials are necessary to determine whether ADT durations shorter than 3 years may be equally effective, and ongoing and completed studies may answer this question in due course.

Using a shorter course of ADT, D'Amico et al demonstrated that the use of 6 months of ADT in combination with EBRT conferred an OS survival advantage at 5 years compared to EBRT alone (88% versus 78%).[8] Most patients in this study, however, had early stage disease and few (12%) presented with PSA levels > 20 ng/ml. In another report, D'Amico et al also demonstrated improved outcomes in terms of time to PSA recurrence, prostate cancer-specific mortality and all-cause mortality using 6 months of ADT in conjunction with RT. In this analysis, 25% of patients had presenting PSA > 20 ng/ml, 47% had Gleason scores 7 or higher, and 11% had T3 disease.[9]

A study from the National Cancer Institute of Canada evaluating neoadjuvant hormonal treatment found no significant differences in outcomes with 8 months versus 3 months of ADT before RT. The difference in duration of ADT between the two arms of this trial may not have been large enough to translate into a statistically significant benefit in outcomes. Furthermore, 26% of patients in this study had low-risk disease and may not benefit from ADT. Finally, while the results suggested improved 5 year DFS in the 8-month ADT arm for high-risk patients, this difference did not reach statistical significance.[17]

In higher risk patients, such as those in the present series, our previous report suggested that the use of at least 12 months of ADT has a significant positive impact on all outcomes studied.[10] In the current analysis, our objective was to expand on prior work to further refine the definition of optimal duration of ADT in patients presenting with PSA > 20 ng/ml. The present results suggest that longer duration of ADT may be more beneficial. For bNED outcomes, a statistically significant advantage was seen for durations of ADT of 12-24 months and > 24 months compared to shorter durations. However, the improvement in CSS and OS was limited to patients who received > 24 months of ADT.

There are several other strategies available to improve outcomes in high-risk patients with prostate cancer such as dose escalation[18-21] by means of intensity modulated radiotherapy and/or brachytherapy boost, [22,23] and the

addition of pelvic RT.[24] It remains unclear, however, whether a combination of these strategies will further improve outcomes.

While the present study's findings serve to highlight the potential benefit of long ADT duration in optimizing bNED and survival, it has several limitations. An important limitation is the lack of a comparable control group treated with EBRT alone to assess the value of any length of ADT. Due to the retrospective nature of the analysis, selection bias is introduced by clinicians recommending different durations of ADT for each patient. Follow-up time in this study also varied between the treatment groups. It has been postulated that in the contemporary era where PSA availability, screening, and patient and physician awareness have all increased, improved patient outcomes may be attributed in part to within-stage migration. This translates into a more favorable presentation of prostate cancer patients seen today[25] with correspondingly favorable results following therapy. This effect appears even more significant when high-risk patients are considered. Similar findings have been reported in patients treated with radical prostatectomy.[26] Finally, the upward shift in Gleason score described during the last 15 years is another factor that can lead to improved outcomes in patients treated in more recent years.[27] Acknowledging these limitations, the observed outcomes in this study appear to be consistent with those of major randomized trials and would suggest that durations of ADT shorter than 24 months may be less effective than longer durations in patients presenting with PSA > 20 ng/ml.

Conclusion

This study supports the contention that ADT recommendations should be considered in the context of presenting PSA levels and suggests that longer duration of ADT (> 24 months) is associated with improved bNED, CSS, and OS compared to shorter durations in patients who present with PSA levels > 20 ng/ml treated with EBRT. □

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