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Androgen deprivation therapy use with post-prostatectomy radiotherapy in the Prostate Cancer Outcomes Registry Victoria

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Abstract

Introduction: The aim of this study is to evaluate the use of androgen deprivation therapy (ADT) with post-prostatectomy radiotherapy (PPRT) in a population-based cohort of Australian men.
Methods: This is a prospective cohort of men with localised prostate cancer captured in the Prostate Cancer Outcomes Registry Victoria (PCOR-Vic), who received PPRT between January 2010 and December 2015. The primary outcome was ADT use with PPRT. Multivariate logistic regressions were used to identify patient, tumour and institutional factors influencing ADT use.
Results: 485 men were included in this study – 115 (24%) had pT2 disease, 231 (48%) pT3a, 134 (28%) pT3b and 5 (1%) pT4. Eighteen (4%) men had ISUP grade 1 disease, 139 (29%) ISUP grade 2, 170 (35%) ISUP grade 3 and 158 (33%) ISUP grade 4/5, while 267 (64%) men had positive surgical margins. Median time from prostatectomy to PPRT was 8.1 months (IQR = 5.3–13.9). Sixty-six (14%) patients had ADT with PPRT. In multivariate analyses, men who had increased age (OR = 1.06; 95% CI = 1.01–1.11), seminal vesicle involvement (OR = 3.81; 95% CI = 1.63–8.91) and underwent treatment in regional centres (OR = 2.17; 95% CI = 1.08–4.33) were more likely to have ADT with PPRT.
Conclusion: We reported that 14% of men treated with PPRT received ADT in a population-based cohort of Australian men, which was less than half of the proportion of ADT use with PPRT in the US. It will be of interest to evaluate the uptake of ADT with PPRT in the coming years following recent publications of level 1 evidence confirming overall survival benefits of ADT with PPRT.

Key words: androgen deprivation; post-prostatectomy; prostate cancer; radiotherapy; registry.

Introduction

A significant number of men with localised prostate cancer treated with radical prostatectomy (RP) will develop local and biochemical recurrence,[1,2] and the risk could be as high as 70% for men with high-risk features such as extra-prostatic extension or seminal vesicle invasion.[3,4] Adjuvant or early salvage post-prostatectomy radiotherapy (PPRT) has been shown to be associated with oncological and overall survival benefits in prospective randomised controlled trials,[5–7] but men with aggressive prostate cancer are still at risk of disease progression and distant metastases despite PPRT. Recent long-term follow-up results of RTOG-9601and GETUG-AFU16, have provided level 1 evidence supporting the use of androgen deprivation therapy (ADT) with PPRT to

further improve disease control and overall survival.[8,9] In this study, we aimed to evaluate the pattern of ADT use with PPRT in an Australian population-based cohort of men with prostate cancer, and to evaluate the factors associated with ADT use with PPRT.

Methods

Study population

The study comprised men with prostate cancer from the Prostate Cancer Outcome Registry Victoria (PCOR-Vic). Detailed patient recruitment and data collection methodology for PCOR-Vic has been previously described.[10] For this study, we only included men with localised prostate cancer who had RP as their primary treatment and subsequently had PPRT between January 2010 and December 2015.

Primary outcomes and covariates

The primary outcome of interest was ADT use with PPRT, as a binary outcome. There was no information on type or duration of ADT given the nature of data collection in PCOR-Vic. Covariates included in the analyses were: age at PPRT, year of PPRT, PSA level at prostate cancer diagnosis, International Society of Urological Pathology (ISUP) grade group,[11] pathological stage, RP surgical margin status and PPRT treatment institutions, which were classified into public or private, and metropolitan or regional.

Statistical analyses

Differences in covariates between men who received ADT vs. no ADT were analysed using Pearson's chi-squared test. Univariate and multivariate logistic regression analyses were used to estimate the effect of each factor associated with likelihood of ADT use with PPRT. Covariates with $P < 0.1$ in univariate analyses were included in the multivariate analyses. A two-sided P-value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed using STATA/IC 13 (STATA Corp, College Station, TX, USA).

Results

A total of 485 men treated with RP and PPRT were included in this study. Baseline characteristics of the study population are summarised in Table 1. Of the patients included in this study, 115 (24%) had organ-confined disease (pT2), 231 (48%) had extracapsular extension (pT3a), 134 (28%) had seminal vesicle invasion (pT3b) and 5 (1%) had bladder/rectum invasion (pT4). Prostate cancer was classified based on ISUP grade group – 18 (4%), 139 (29%), 170 (35%) and 158 (33%) had ISUP grade group 1, 2, 3 and 4/5 respectively. 312 (64%) had positive surgical margins on RP. The median time from RP to RT was 8.1 months (IQR: 5.3–13.9 months).

There were 66 (14%) patients who had ADT with PPRT. Men who had ADT were older (mean = 65.7) compared to men who did not have ADT (mean = 63.4) ($P = 0.006$). Men with higher ISUP grade group were more likely to have ADT ($P < 0.001$) – 11%, 3%, 12% and 25% of men with ISUP Grade 1, 2, 3 and 4/5 respectively (Fig. 1a). Men with non-organ confined disease were more likely to have ADT ($P < 0.001$) – 7% pT2, 10% pT3a, 25% pT3b and 20% pT4 had ADT (Fig. 1b). There was no statistically significant difference in ADT use between men with positive (14%) and negative (12%) surgical margins ($P = 0.5$) (Fig. 1c). There was also no difference in ADT use in men who had PPRT at different intervals post-RP ($P = 0.8$) (Fig. 1d). Men treated in regional centres (23%) were more likely to have ADT compared to those treated in metropolitan centres (12%) ($P = 0.01$) (Fig. 1e), but there was no significant difference in ADT use in men treated in public (12%) vs. private centres (18%) ($P = 0.1$) (Fig. 1f).

In multivariate analyses, patient age, pathological stage and treatment centres were independently associated with ADT use with PPRT (Table 2). For every year increase in age, there was a relative 6% (95% CI = 1.01–1.11, $P = 0.02$) increase in likelihood of ADT use with PPRT. Men with seminal vesicle involvement were 3.8 (95% CI = 1.6–8.9, $P = 0.002$) times more likely to have ADT compared to men with organ-confined disease. Men treated in regional centres were 2.2 times (95% CI = 1.1–4.3, $P = 0.03$) more likely to have ADT with PPRT.

Discussion

The establishment of PCOR-Vic has provided an excellent platform for risk-adjusted evaluation of patterns of care for men with prostate cancer in Victoria.[12] Over the years, we have reported the pattern of RT practice as part of a multimodality treatment for men with prostate cancer using the extensively collected data in PCOR-Vic, including the pattern of adjuvant RT use following RP,[13] ADT use with definitive prostate RT[14,15] and brachytherapy-based prostate RT.[16] Using the same database, we evaluated the pattern of ADT use in the PPRT setting in this study, and reported that 14% of men treated with PPRT between 2010 and 2015 in Victoria received ADT. This is less than half of the proportion of men who received ADT with PPRT (32%) in the US National Cancer Database (NCDB) between 2004 and 2012.[17]

We did not observe any increase in uptake of ADT use with PPRT over the study period from 2010 to 2015. This is despite an initial report of RTOG-9601 that was presented at the ASTRO meeting in 2010, which showed significant benefits of ADT use with PPRT, in terms of PSA progression-free survival, with a median follow-up of 7 years.[18] It is likely that clinicians at large are still

Table 1. Baseline characteristics of men who had ADT vs. no ADT

	No ADT *N* = 419 (86%)	ADT *N* = 66 (14%)	All *N* = 485	*P*-value
Age at PPRT (year), mean (SD)	63.4 (6.5)	65.7 (5.8)	63.7 (6.5)	0.006
Serum PSA at diagnosis (ng/L), median (IQR)	7.2 (5.5–10.2)	8.2 (5.8–13)	7.2 (5.6–10.8)	0.07
<10	306 (73%)	38 (58%)	334 (71%)	0.08
10–20	75 (17%)	18 (27%)	93 (19%)	
>20	31 (7%)	8 (12%)	39 (8%)	
Unknown	7 (2%)	2 (3%)	9 (2%)	
ISUP Grade, *n* (%)				
1 (GS 3 + 3)	16 (4)	2 (3)	18 (4)	<0.001
2 (GS 3 + 4)	133 (32)	4 (6)	139 (29)	
3 (GS4 + 3)	150 (36)	20 (30)	170 (35)	
4/5 (GS 8/9/10)	118 (28)	40 (61)	158 (33)	
Pathological stage, *n* (%)				
pT2	107 (26)	8 (12)	115 (24)	<0.001
pT3a	207 (49)	24 (36)	231 (48)	
pT3b	101 (24)	33 (50)	134 (28)	
pT4	4 (1)	1 (2)	5 (1)	
Positive margin, *n* (%)				
No	152 (36%)	21 (32%)	173 (36%)	0.5
Yes	267 (64%)	45 (68%)	312 (64%)	
Time from RP to PPRT (month), median (IQR)	8.3 (5.3–14.1)	7.5 (5.7–10.3)	8.1 (5.3–13.9)	0.2
<6 month	134 (32%)	24 (36%)	158 (33%)	0.7
6–12 month	155 (37%)	26 (39%)	181 (37%)	
12–24 month	98 (23%)	12 (18%)	110 (23%)	
>24 month	32 (8%)	4 (6%)	36 (7%)	
RT centre type, *n* (%)				
Public	322 (77)	45 (68)	367 (76)	0.1
Private	97 (23)	21 (32)	118 (24)	
RT centre location, *n* (%)				
Metropolitan	370 (88)	51 (77)	421 (87)	0.01
Regional	49 (12)	15 (23)	64 (13)	
Year of PPRT, *n* (%)				
2010	38 (9)	5 (8)	43 (9)	0.9
2011	60 (14)	7 (11)	67 (14)	
2012	95 (23)	18 (27)	113 (23)	
2013	80 (19)	12 (18)	92 (19)	
2014	77 (18)	12 (18)	89 (18)	
2015	69 (16)	12 (18)	81 (17)	

awaiting the final publication of the study prior to adoption of the evidence into clinical practice. With the recent publication of the RTOG-9601, which showed overall survival benefits of ADT use with PPRT, it will be of interest to evaluate the adoption of this practice in the coming years. Nonetheless, we also observed low uptake of ADT use in the definitive prostate RT setting in Victoria,[14] despite ample level 1 evidence confirming overall survival benefits of ADT with definitive prostate RT since early 2010,[19–22] suggesting that in general there is a lag in adoption of evidence into radiation oncology practice.

The pattern of low uptake of ADT with PPRT was also observed throughout Australia and New Zealand. In a survey conducted by the RANZCR Faculty of Radiation Oncology Genitourinary Group (FROGG) in 2012, radiation oncologists with an interest in uro-oncology were asked to complete a survey regarding treatment recommendation for a 54-year-old man post-RP, who had Gleason 4 + 4 disease with bilateral seminal vesicle involvement (pT3b), positive surgical margins, negative node status (N0) and detectable PSA (0.4 ng/mL) 8 weeks post-RP.[23] Of the 46 radiation oncologists who responded, only one-third recommended ADT in conjunction with PPRT.

It is important to bear in mind that there is a significant prostate cancer heterogeneity in men treated with PPRT, and ADT use may not be appropriate and necessary for every one of them.[24] In the exploratory subgroup analyses in the RTOG-9601 study, Shipley *et al.*[8] reported that overall survival benefits of ADT was most evident in men with high-risk features such as positive surgical margin, pre-PPRT PSA >0.7 ng/mL and Gleason 7 and above. In our study, however, the only high-risk feature associated with the use of ADT with PPRT in

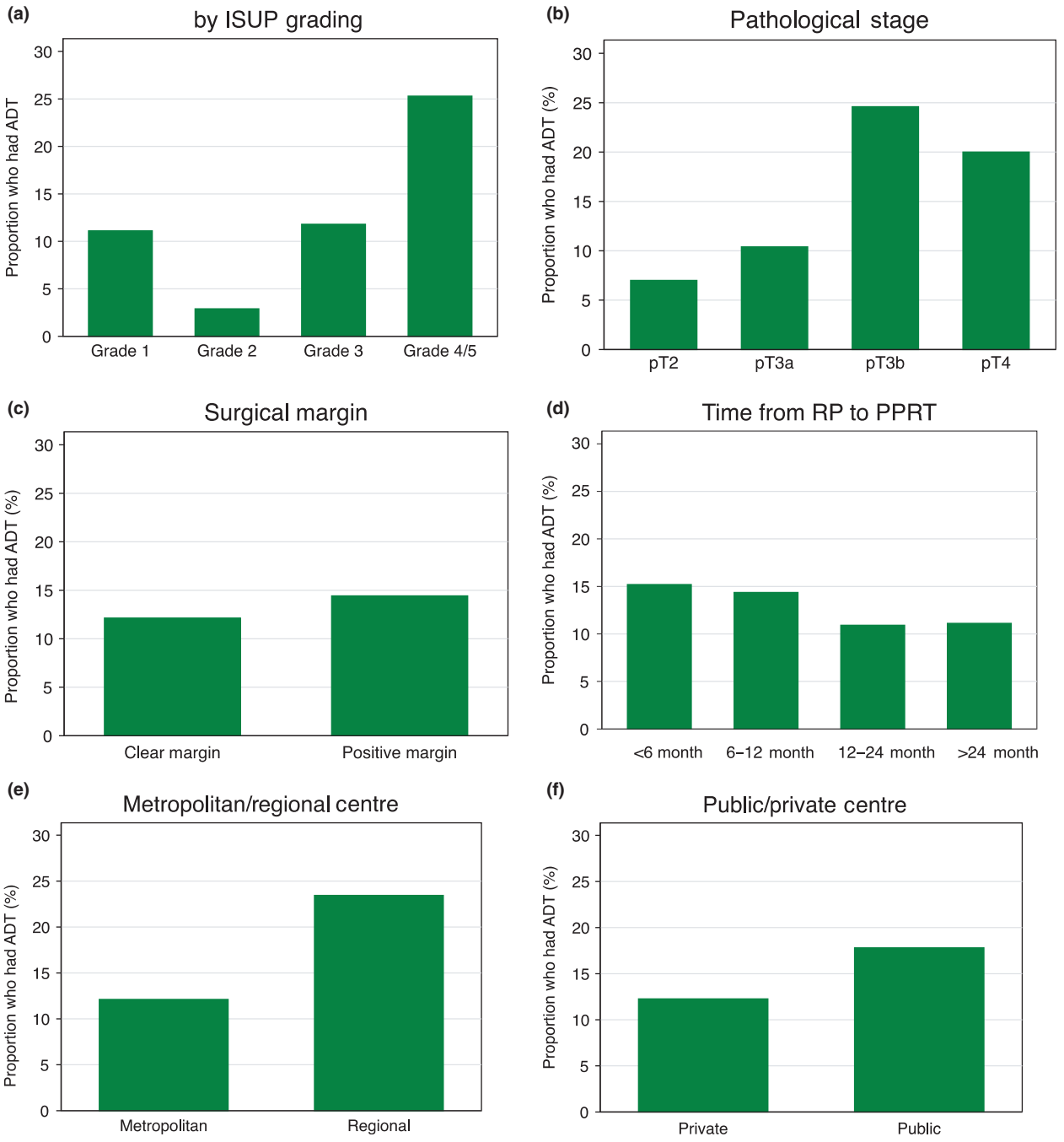

Fig. 1. Proportion of men who received ADT with PPRT, stratified by ISUP grading (a), pathological stage (b), surgical margin (c), interval between RP and PPRT (d), metropolitan-regional centres (e), and public-private centres (f).

multivariate analyses was pathological stage. Also, older patients were more likely to have ADT. Given the wide spectrum of side effects associated with ADT, ranging from risk of osteoporosis and cardiovascular events, to metabolic changes and sexual dysfunction, as well as cognitive impairment and Alzheimer's disease,[25–27] we postulated that younger patients were less likely to be willing to accept these side effects, and hence the lower use of ADT with PPRT in younger patients.

Apart from patient and tumour factors, we also observed that institution factors were significant determinants of ADT use – patients treated in regional centres

Table 2. Univariate and multivariate logistic regressions of factors associated with ADT use with PPRT

	Univariate OR (95% CI)	*P*-value	Multivariate OR (95% CI)	*P*-value
Age at PPRT	1.06 (1.02–1.11)	0.006	1.06 (1.01–1.11)	0.02
Serum PSA at diagnosis				
<10	1.0 (Ref.)		1.0 (Ref.)	
10–20	1.93 (1.04–3.57)	0.04	1.42 (0.73–2.74)	0.3
>20	2.08 (0.89–4.85)	0.09	1.51 (0.61–3.74)	0.4
ISUP Grade				
1	1.0 (Ref.)		–	–
2	0.24 (0.04–1.49)	0.1	–	–
3	1.07 (0.23–4.99)	0.9	–	–
4/5	2.71 (0.60–12.31)	0.1	–	–
Pathological stage				
pT2	1.0 (Ref.)		1.0 (Ref.)	
pT3a	1.55 (0.67–3.57)	0.3	1.36 (0.58–3.20)	0.5
pT3b	4.37 (1.93–9.91)	<0.001	3.81 (1.63–8.91)	0.002
pT4	3.34 (0.33–33.55)	0.3	4.29 (0.39–47.16)	0.2
Positive margin				
No	1.0 (Ref.)		–	–
Yes	1.22 (0.70–2.12)	0.5	–	–
Time from RP to RT				
<6 months	1.0 (Ref.)			
6–12 months	0.94 (0.51–1.71)	0.8	–	–
12–24 months	0.68 (0.33–1.43)	0.3	–	–
>24 months	0.70 (0.23–2.15)	0.5	–	–
RT centre type				
Public	1.0 (Ref.)		–	–
Private	0.65 (0.37–1.14)	0.1	–	–
RT centre location				
Metropolitan	1.0 (Ref.)		1.0 (Ref.)	
Regional	2.22 (1.16–4.25)	0.02	2.17 (1.08–4.33)	0.03
Year of RT				
2010	1.0 (Ref.)		–	–
2011	0.89 (0.26–3.00)	0.8	–	–
2012	1.44 (0.50–4.16)	0.5	–	–
2013	1.14 (0.37–3.47)	0.8	–	–
2014	1.18 (0.39–3.61)	0.8	–	–
2015	1.32 (0.43–4.03)	0.6	–	–

were more likely to receive ADT with PPRT, after adjusting for other covariates. This pattern of higher proportion of ADT use in regional centres was also observed in our earlier study in the definitive prostate RT setting.[14] While we postulated that patient preference may again come into play, such that men in regional centres were more willing to accept the side effects of ADT compared with men in metropolitan centres, we could not discount the possibility of preferential ADT prescription by clinicians i.e. clinicians in regional centres were possibly more likely to prescribe ADT with PPRT. This could be due to metropolitan clinicians' lack of awareness of published level 1 evidence, or their belief that the side effects outweigh the survival benefits of ADT. We do not have information to confirm or refute any of these hypotheses, and this offers potential areas for future research in order to identify the barriers and facilitators for adoption of ADT use with PPRT, from both patients' and clinicians' perspective.

There are several other limitations in the current study, which are inherent limitations of PCOR-Vic database. These include the lack of information on RT dose and fractionations as well as type and duration of ADT use. One of the possible avenues to overcome these limitations in future study using the PCOR-Vic data is through data-linkage with other population-based administrative database such as the Victorian Radiotherapy Minimum Data Set, which captures detailed RT information in the state of Victoria, as well as the Pharmaceutical Benefit Scheme, which will provide details on type and duration of ADT.

In summary, we report the contemporary patterns of ADT use with PPRT in a population-based cohort of Australian men with prostate cancer, with only 14% receiving ADT with PPRT. It will be of great interest to evaluate the pattern of uptake of ADT with PPRT in the coming years, following the publications of the RTOG 9601 and

GETUG-AFU16 findings. With long-term follow-up, it will also be interesting to evaluate if the pattern of ADT use with PPRT in a population-based real-life clinical setting translates into overall survival differences as observed in the trials.

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