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Neoadjuvant Androgen Deprivation Therapy Prior to Radical Prostatectomy: Recent Trends in Utilization and Association with Postoperative Surgical Margin Status

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ABSTRACT

Purpose. In this study, we sought to describe the contemporary trends in utilization of neoadjuvant androgen deprivation therapy (ADT). As a secondary endpoint, we assessed the community-level effect of neoadjuvant ADT on positive surgical margins after radical prostatectomy (RP).

Methods. Using the National Cancer Database (2004–2014), we identified patients with clinically localized prostate cancer (PCa) [cT1-4N0M0] treated with RP. The estimated annual percentage change (EAPC) mixed linear regression methodology was used for temporal trend analysis of neoadjuvant ADT. Observed differences in baseline characteristics between patients treated with neoadjuvant ADT versus those who were not were then controlled for using an inverse probability of treatment weighting (IPTW) approach. IPTW-adjusted analyses were then performed to examine the odds of positive surgical margins.

Results. Overall, 8184 (2.12%) and 377,843 (97.88%) individuals with PCa were treated with neoadjuvant ADT prior to RP versus RP only, respectively. There was a consistent trend in decreasing use of neoadjuvant ADT over time, with a nadir observed in 2011 [EAPC − 8.08; 95% confidence interval (CI) − 11.7 to − 4.32; $p < 0.05$]. In IPTW-adjusted analyses, the odds of positive surgical margins were lower in patients receiving neoadjuvant ADT with low-risk [odds ratio (OR) 0.65; 95% CI 0.51–0.84; $p < 0.001$] and intermediate-risk [OR 0.76; 95% CI 0.69–0.85; $p < 0.001$] PCa.

Conclusions. After a period of steady decline, there appears to be a modest trend towards increased utilization of neoadjuvant ADT in more recent years. We found an association between neoadjuvant ADT and decreased odds of positive surgical margins among low- and intermediate-risk patients.

Prostate cancer (PCa) is the most common non-skin malignancy, with nearly 3.3 million men living with PCa in the US. A majority (64%) of these individuals are elderly, i.e. over 70 years of age.[1] While a large proportion of these men present with early-stage localized disease, some of whom do not require immediate or deferred treatment, approximately half will be treated with androgen deprivation therapy (ADT) at some stage.[2]

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The use of ADT is fairly established in the metastatic PCa setting, as well as being an adjunct of primary external beam radiation therapy for unfavorable intermediate- and high-risk PCa; however, the use of ADT in the perioperative setting is much more controversial. Studies have shown that neoadjuvant ADT prior to radical prostatectomy (RP) is associated with lower positive surgical margin rates, but no sustainable effect on survival has been described.[3–5] For these reasons, and given the concern for the significant side effects of ADT,[6] neoadjuvant ADT prior to RP is not recommended in any guidelines or best practice statements.[7,8]

Against this backdrop, the prescription of ADT was historically a lucrative practice for urologists and medical oncologists, with reimbursements of up to 95% of the average wholesale price for gonadotropin-releasing hormone (GnRH) agonists. In the 1990s, treatment with ADT almost doubled, and approximately 50% of patients diagnosed with PCa received ADT for different indications within 1 year of diagnosis. The Medicare Modernization Act of 2003 significantly impacted ADT reimbursement, and, following this, ADT use decreased by over 50%.[9–11]

Most recently, given the US FDA approval of novel ADT agents, we are reconsidering the role of ADT in the neoadjuvant setting. For example, a recently published trial assigned patients to either enzalutamide or enzalutamide + dutasteride + GnRH agonist prior to RP, and found minimal response to neoadjuvant enzalutamide alone, as well as response to combined therapy similar to historical controls.[12] Several other trials of neoadjuvant therapy are ongoing or have suggested a benefit for neoadjuvant therapy in certain populations.[13,14]

On the basis of these considerations, we performed a descriptive analysis of contemporary trends in the use of neoadjuvant ADT in a nationwide hospital-based setting. As a secondary endpoint, we assessed the community-level effect of neoadjuvant ADT on positive surgical margins after RP. Finally, we examined the effect of neoadjuvant ADT on overall survival among patients with high-risk PCa and no comorbidity.

MATERIAL AND METHODS

Data Source

The National Cancer Database (NCDB), a joint program of the American Cancer Society and the Commission on Cancer, is a hospital-based database that contains information on patterns of cancer care and outcomes. The NCDB collects data on all newly diagnosed malignancies since 1989, and includes information on more than 29 million unique cancer cases seen in more than 1500 Commission on Cancer-accredited programs in the US and Puerto Rico. Approximately 70% of incident neoplasms in the US are reported to the NCDB.[15]

Study Population and Treatment Groups

We identified 1,294,126 men diagnosed with PCa between 2004 and 2014 in the NCDB (International Classification of Diseases for Oncology, Third Edition [ICD-0-3] code C61.9). Of these, we selected 947,981 men with adenocarcinoma and no metastasis to the lymph nodes or other organs at the time of PCa diagnosis (cT1–T4N0M0). We excluded individuals who were not treated with RP ($n = 533{,}956$) and those with unknown surgical margin status ($n = 3686$). We also excluded patients with unknown National Comprehensive Cancer Network (NCCN) risk group status ($n = 21{,}834$), as well as individuals with missing follow-up data ($n = 152$) or the treatment of ADT ($n = 2326$). Our final cohort consisted of 386,027 patients.

Definition of Treatment Groups

The eligible population was defined according to the receipt of neoadjuvant ADT therapy prior to surgery. This was undertaken by comparing the date of surgery with the date of initiation of hormone therapy. Men for whom the date of hormone therapy was prior to the date of RP surgery were defined as undergoing neoadjuvant therapy.

Other Variables

We abstracted patient-level variables, including age at diagnosis, race, baseline Charlson Comorbidity Index (CCI), insurance status, and year of diagnosis. Socioeconomic variables were estimated using household income and education level from the patients' county of residence. Travel distance, as well as hospital type and location, were also abstracted. Cancer characteristics included clinical tumor (cT) stage, surgical margin status, value of PSA (< 10 ng/ml, 10–20 ng/ml, > 20 ng/ml, and unknown) and the classification of NCCN risk groups (low: T1-T2, Gleason score ≤ 6 and PSA < 10 ng/ml; intermediate: T2b-T2c, Gleason score 7 or PSA 10–20 ng/ml; high: T3a, Gleason score 8–10 or PSA > 20 ng/ml; very high: T3b–T4 or primary Gleason pattern 5, or four or more cores with a Gleason score of 8–10).

Endpoint

Our primary analytical endpoint was receipt of neoadjuvant ADT prior to surgery, while our secondary

endpoints were the presence of positive surgical margins at RP and overall survival in high-risk patients with no comorbidity.

Statistical Analyses

Interquartile ranges (IQRs) and medians were generated for continuous variables, and frequencies and proportions were generated for categorical variables. Differences in continuous and categorical variables between neoadjuvant ADT and RP only were examined using the Mann–Whitney test and the Chi-square test, respectively. The proportion of patients receiving neoadjuvant ADT was reported for each study year, and temporal trend analysis was evaluated using the estimated annual percentage change (EAPC) mixed linear regression methodology.[16]

We examined the effect of neoadjuvant ADT on the odds of positive surgical margins at RP. Analyses were first performed among all patients, and then in subgroups stratified according to NCCN risk groups. Therefore, four separate analyses were performed. To account for selection bias, observed differences in baseline characteristics between patients treated with neoadjuvant ADT versus those who were not were controlled for with a weighted propensity score analysis. To assess the fit of the propensity logistic regression score model, we used the goodness-of-fit approach of Lemeshow and Hosmer.[17] Each patient was weighted by the inverse probability of receiving neoadjuvant ADT in order to balance out observable characteristics between the groups, a method known as inverse probability of treatment weighting (IPTW).[18] The balance between patient characteristics in pre- and post-weighted groups was also assessed using standardized differences (SDs) and by comparing their distribution with unweighted data.[19] In addition, we used Kernel density plots to depict the pre- and post-IPTW adjustment distribution of propensity scores in each treatment group. If the two groups had similar Kernel density plots, then the distribution of confounders likely balance across groups.

Finally, IPTW-adjusted Kaplan–Meier curves were used to compare overall survival between high-risk patients who received neoadjuvant ADT between 2004 and 2013 and those who did not. Patients treated in 2014 were excluded due to inadequate follow-up data on survival in the NCDB. We only included patients with high-risk disease and no comorbidity as other patient groups would not be expected to die in the follow-up period available for this study.[20] The proportional hazards assumption was tested using the approach described by Grambsch and Therneau.[21] An IPTW-adjusted Cox regression model was fitted to assess the effect of neoadjuvant ADT on OS.

All statistical analyses were performed using Stata® version 14.0 (StataCorp LLC, College Station, TX, USA). The two-sided statistical significance was defined as a p value < 0.05. An Institutional Review Board waiver was obtained prior to the study in accordance with institutional regulations when dealing with de-identified previously collected data.

RESULTS

Baseline Characteristics

Overall, 386,027 men were eligible for our cohort. Between 2004 and 2014, 377,843 (97.88%) and 8184 (2.12%) individuals with PCa were treated with RP only versus neoadjuvant ADT prior to RP, with a median follow up of 56.90 months and 65.28 months, respectively.

Unweighted and Weighted Baseline Patient Characteristics

Table 1 shows all unweighted and weighted baseline characteristics of PCa patients with T1-4N0M0, stratified according to receipt of neoadjuvant ADT prior to RP. Calculated mean SDs of unweighted data showed that both study cohorts differed significantly with respect to socioeconomic, demographic, clinical, and cancer characteristics.

The Kernel density plots in Fig. 1 show the pre- and post-IPTW adjustment distribution of propensity scores of each treatment cohort. Post-IPTW variations are almost similar across the study arms, suggesting that all confounders are balanced across the two therapy groups.

Table 1 shows that all SDs of the weighted group were $< 10\%$, indicating that individuals who received neoadjuvant ADT and RP versus RP only were subsequently comparable according to the variables we considered.

Figure 2 shows the proportion of patients receiving neoadjuvant ADT over time, where EAPC = − 8.08 (95% confidence interval [CI] − 11.7 to − 4.32; $p < 0.05$)

Effect of Neoadjuvant Androgen Deprivation Therapy (ADT) on Margin Status

Table 2 shows the IPTW-adjusted ORs of neoadjuvant ADT and RP versus RP alone on the prediction of positive surgical margins according to the NCCN groups and in the whole cohort. The receipt of neoadjuvant ADT prior to RP in low- and intermediate-risk patients was associated with lower rates of positive surgical margins [odds ratio (OR) 0.65 and 0.76; all $p < 0.001$].

TABLE 1 Baseline characteristics for all patients (n = 386,027) with neoadjuvant ADT and RP versus RP alone, between 2004 and 2014 in the National Cancer Data Base (weighted and unweighted population)

Variables	Unweighted			Weighted (%)		
	RP only [no neo-ADT] (%)	Neo ADT and RP (%)	Stand. difference (%)	RP only	Neo ADT and RP	Stand difference (%)
No. of patients (%)	377,843 (97.88)	8184 (2.12)		98.00	2.00	
Age, years [mean (SD)]	60.84 (7.08)	63.04 (7.28)	30.70	60.89 (7.08)	61.49 (7.24)	8.40
Age group (years)						
< 65	254,411 (67.33)	4457 (54.46)	− 26.60	67.06	63.83	− 6.80
≥ 65	123,432 (32.67)	3727 (45.54)	26.60	32.94	36.17	6.80
Race						
White	317,010 (83.90)	6921 (84.57)	1.80	83.91	83.03	− 2.40
Black	44,563 (11.79)	850 (10.39)	− 4.50	11.77	12.57	2.40
Other	9859 (2.61)	264 (3.23)	3.70	2.62	2.61	− 0.01
Unknown	6411 (1.70)	149 (1.82)	0.90	1.70	1.79	0.70
CCI						
0	316,129 (83.67)	6696 (81.82)	− 4.90	83.63	82.76	− 2.30
1	54,693 (14.48)	1298 (15.86)	3.90	14.51	15.32	2.30
2	7021 (1.86)	190 (2.32)	3.20	1.87	1.92	0.40
Year of diagnosis						
2004	17,976 (4.76)	763 (9.32)	17.90	4.86	5.79	4.20
2005	18,855 (4.99)	541 (6.61)	6.90	5.03	6.26	5.30
2006	23,810 (6.30)	667 (8.15)	7.10	6.34	7.05	2.80
2007	32,450 (8.59)	782 (9.56)	3.40	8.61	8.90	1.0
2008	43,336 (11.47)	908 (11.09)	− 1.20	11.46	12.40	2.90
2009	45,396 (12.01)	860 (10.51)	− 4.80	11.98	12.13	0.50
2010	43,287 (11.46)	785 (9.59)	− 6.10	11.42	10.92	− 1.60
2011	45,354 (12.00)	774 (9.46)	− 8.20	11.95	10.77	− 3.70
2012	37,081 (9.81)	694 (8.48)	− 4.60	9.78	9.00	− 2.70
2013	36,378 (9.63)	713 (8.71)	− 3.20	9.61	8.92	− 2.40
2014	33,920 (8.98)	697 (8.52)	− 1.60	8.97	7.85	− 4.00
Insurance						
Private	245,321 (64.93)	4261 (52.07)	− 26.30	64.65	61.38	− 6.80
Medicaid	6456 (1.71)	184 (2.25)	3.90	1.72	1.70	− 0.10
Medicare	111,899 (29.62)	3404 (41.59)	25.20	29.87	33.00	6.70
Other government	5317 (1.41)	92 (1.12)	− 2.50	1.40	1.54	1.20
Not insured	5023 (1.33)	123 (1.50)	1.50	1.33	1.44	0.90
Unknown	3827 (1.01)	120 (1.47)	4.10	1.02	0.94	− 0.80
Income						
High	249,724 (66.09)	4829 (59.01)	− 14.70	65.94	62.92	− 6.30
Low	125,567 (33.23)	3305 (40.38)	14.90	33.39	36.29	6.10
Unknown	2552 (0.68)	50 (0.61)	− 0.80	0.67	0.79	1.30
Education						
High	245,377 (64.94)	4992 (61.00)	− 8.20	64.86	62.09	− 5.80
Low	130,085 (34.43)	3142 (38.39)	8.20	34.51	37.12	5.40
Unknown	2381 (0.63)	50 (0.61)	− 0.20	0.63	0.79	1.90
Counties						
Metro	309,067 (81.80)	6257 (76.45)	− 13.20	81.68	80.75	− 2.40
Urban	50,785 (13.44)	1488 (18.18)	13.00	13.54	14.39	2.40

TABLE 1 continued

Variables	Unweighted			Weighted (%)		
	RP only [no neo-ADT] (%)	Neo ADT and RP (%)	Stand. difference (%)	RP only	Neo ADT and RP	Stand difference (%)
Rural	7071 (1.87)	259 (3.16)	8.30	1.90	2.04	1.00
Unknown	10,920 (2.89)	180 (2.20)	− 4.40	2.88	2.82	− 0.30
Facility type						
Academic	165,237 (43.73)	3430 (41.91)	− 3.70	43.69	40.48	− 6.50
Non-academic	212,219 (56.17)	4750 (58.04)	3.80	56.21	59.44	6.50
Unknown	387 (0.10)	4 (0.05)	− 1.90	0.10	0.10	− 0.60
Great-circle distance						
First	172,700 (45.71)	3574 (43.67)	− 4.10	45.66	45.94	0.60
Second	132,689 (35.12)	2767 (33.81)	− 2.80	35.09	34.80	−0.60
Third	70,135 (18.56)	1797 (21.96)	8.50	18.63	18.48	− 0.40
Unknown	2319 (0.61)	46 (0.56)	− 0.70	0.61	0.78	2.0
Location						
East	156,940 (41.54)	2642 (32.28)	− 19.30	41.34	40.32	− 2.10
Center	157,262 (41.62)	4103 (50.13)	17.10	41.80	43.29	3.00
West	63,254 (16.74)	1435 (17.53)	2.10	16.76	16.31	− 1.20
Unknown	387 (0.10)	4 (0.05)	− 1.90	0.10	0.10	− 0.60
Surgical margins						
Negative	296,154 (78.38)	6164 (75.32)	− 7.30	78.31	79.08	1.90
Positive	81,689 (21.62)	2020 (24.68)	7.30	21.69	20.92	− 0.19
cT stage						
1	260,131 (68.85)	4481 (54.75)	− 29.30	68.55	68.72	0.40
2	108,013 (28.59)	3004 (36.71)	17.40	28.76	28.16	− 1.30
3	9463 (2.50)	659 (8.05)	25.00	2.62	3.03	2.50
4	236 (0.06)	40 (0.49)	8.10	0.1	0.1	0.50
PSA (ng/mL)						
< 10	293,728 (77.74)	5021 (61.35)	− 36.20	77.39	74.99	− 5.60
10–20	37,122 (9.82)	1495 (18.27)	24.50	10.01	11.10	3.50
> 20	19,212 (5.08)	1256 (15.35)	34.40	5.30	6.01	3.10
Unknown	27,781 (7.35)	412 (5.03)	− 9.60	7.30	7.91	2.30
NCCN risk group						
Low	107,203 (28.37)	1138 (13.91)	− 36.00	28.06	25.30	− 6.30
Intermediate	207,027 (54.79)	3293 (40.24)	− 29.50	54.48	55.01	1.10
High	58,959 (15.60)	3293 (40.24)	57.10	16.13	18.11	5.30
Very high	4654 (1.23)	460 (5.62)	24.30	1.33	1.57	2.00

ADT androgen deprivation therapy, *SD* standard deviation, *CCI* Charlson Comorbidity Index, *PSA* prostate-specific antigen, *NCCN* National Comprehensive Cancer Network, *RP* radical prostatectomy

Effect of Neoadjuvant ADT on Overall Survival in High-Risk Patients

Figure 3 shows the IPTW-adjusted Kaplan–Meier curves for high-risk patients without comorbidity between 2004 and 2013. The receipt of neoadjuvant ADT prior to RP was associated with worse overall survival (median survival was not estimable in both groups). Furthermore, IPTW-adjusted Cox regression analysis showed that the receipt of neoadjuvant ADT prior to RP was associated with a 1.39-fold increased risk of death among men with high-risk disease and no comorbidity (hazard ratio 1.39, 95% CI 1.01–1.91; $p = 0.040$).

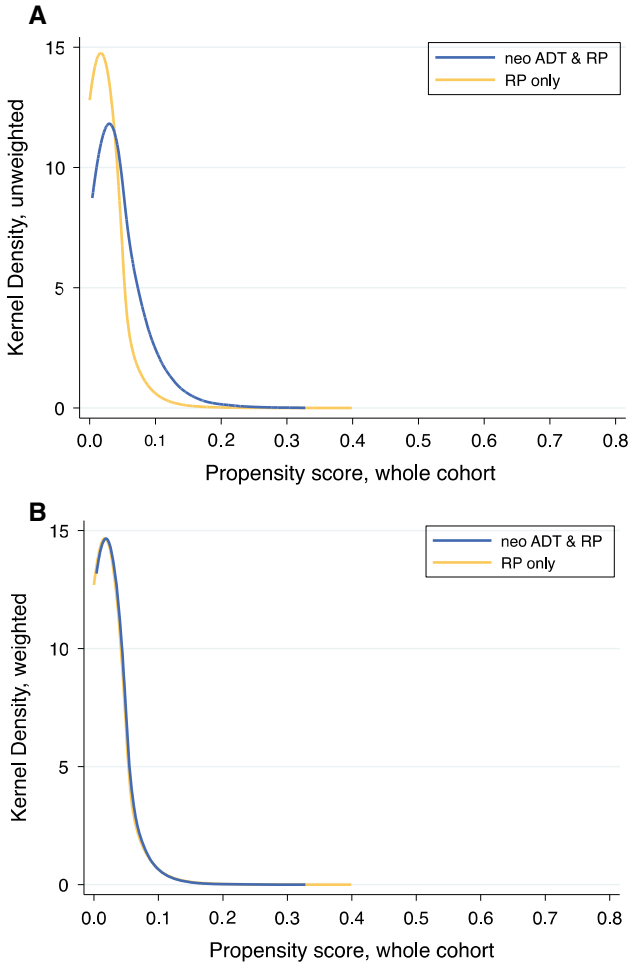

FIG. 1 The Kernel density plots demonstrating covariate balance **a** pre and **b** post inverse probability of treatment weighting adjustment for the receipt of neoadjuvant ADT. *ADT* androgen deprivation therapy, *RP* radical prostatectomy

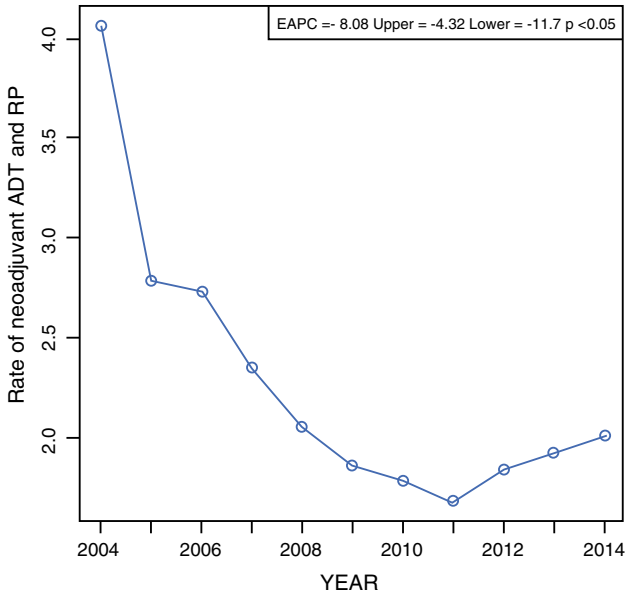

FIG. 2 Proportion of patients receiving neoadjuvant ADT over time, calculated using the EAPC. *ADT* androgen deprivation therapy, *EAPC* estimated annual percentage change, *RP* radical prostatectomy

DISCUSSION

Within our study period, the findings presented here show the utilization of neoadjuvant ADT peaked in 2004, at 4.07% of all individuals who underwent RP. This steadily downtrended in the years to follow, eventually reaching a nadir of 1.68% in 2011. However, of note, there has more recently been a modest increase back to 2.01% from 2012 to 2014. This trend corresponds to the FDA approval of novel anti-androgen agents such as abiraterone and enzalutamide. The ADT utilization observed in this study is generally consistent with what has been observed in prior studies,[9,11] which is likely the consequence of multiple factors, including changes in both reimbursement and practice patterns, as well as the introduction of novel agents in the early 2010s. Of particular relevance to this discussion is the restructuring of Medicare reimbursement policies in 2003 that drove down reimbursement by over 50%, thereby removing a powerful financial incentive for ADT prescribing. However, based on the findings of prior studies, it is likely that lower reimbursement does not fully explain the utilization patterns observed here. For example, a study comparing majority salaried (academic) urologists with majority non-salaried (non-academic) urologists showed that their patterns of ADT use over the period in question were similar despite assumed differences in financial incentivization.[11] Furthermore, a 16.8% decrease in the use of LHRH agonists was noted from 2003 to 2007 in the US among practitioners within the Veterans Health Administration, for whom changes in fee-for-service ADT reimbursement would have presumably had no direct effect on personal income or behavior.[22] It has therefore been postulated that beyond loss of financial motivators, some practitioners were swayed against unindicated ADT use as awareness of associated adverse effects such as osteoporosis, anemia, cardiovascular disease, metabolic syndrome, and impaired quality of life became clearer and there remained no clear benefit for neoadjuvant ADT in terms of biochemical recurrence or survival.[23–27]

According to our results, receiving neoadjuvant ADT was associated with a lower odds of positive surgical margins at the time of prostatectomy (OR 0.85, 95% CI 0.79–0.90; $p < 0.001$). In subanalyses, this association was only true among low- and intermediate-risk groups and did not persist among those with high- or very high-risk disease. Margin status at RP has been previously utilized as a meaningful clinical outcome, given that it has been shown

TABLE 2 Propensity-adjusted effect of neoadjuvant ADT and RP versus RP alone on prediction of positive surgical margins in the whole cohort and stratified to National Comprehensive Cancer Network subgroups

	Odds ratio	95% CI	*p* value
Whole cohort	0.85	0.79–0.90	< 0.001
Low risk	0.65	0.51–0.84	< 0.001
Intermediate risk	0.76	0.69–0.85	< 0.001
High risk	1.08	1.00–1.16	0.077
Very high risk	1.14	0.91–1.44	0.258

OR odds ratio, *CI* confidence interval, *ADT* androgen deprivation therapy, *RP* radical prostatectomy

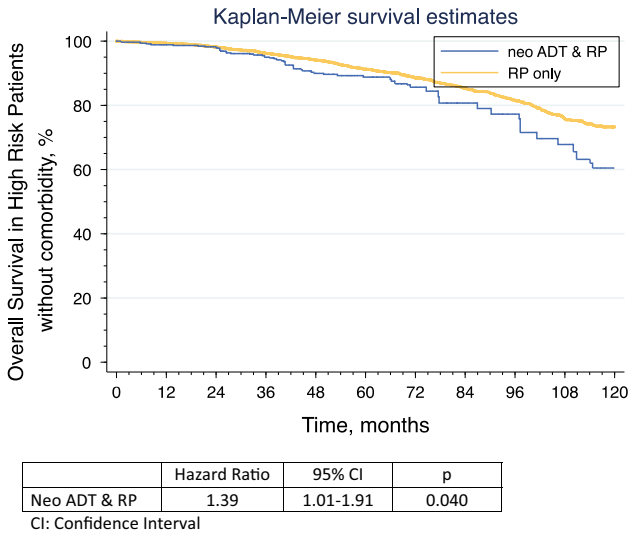

FIG. 3 Propensity score-adjusted overall survival in 3931 patients (high risk and no comorbidity) between 2004 and 2013. *ADT* androgen deprivation therapy, *RP* radical prostatectomy, *CI* confidence interval

in some studies to be an independent predictor of biochemical progression among those with intermediate- and high-risk disease. However, it is notable that this has not been the case in PCa studies of neoadjuvant ADT.[28–30] Why margin status has not shown a meaningful connection to recurrence-free or overall survival in men receiving ADT is contentious, although may be related to the fact that many of the groups studied were fairly heterogeneous and not weighted towards those who may benefit the most from neoadjuvant therapy (i.e. those with higher-risk disease). Additionally, past trials were likely underpowered and may not have had the necessary follow-up.[28] Conversely, however, the pathological endpoint of negative margins may simply lose its typical clinical significance and association with meaningful survival endpoints when it becomes a byproduct of neoadjuvant ADT rather than a feature of innate tumor biology.

It is possible that the absence of a relationship seen between ADT use and margin status in the higher-risk groups seen here is a reflection of the population in whom neoadjuvant ADT is now most likely to be employed. While no overall or disease-free survival benefit has been shown for integrating neoadjuvant ADT outside the scope of advanced disease, a continued desire to improve outcomes among high- and very high-risk patients has motivated recent clinical trials to potentially define a role. Along with the previously mentioned decrease in the positive margin rate, a meta-analysis of these data has shown benefits in the decreased likelihood of nodal involvement, lower pathologic T stage, and increased rates of organ-confined disease.[31] Despite lacking overall or disease-free survival benefit, these encouraging shorter-term endpoints may have led more providers to integrate neoadjuvant ADT into their practice patterns for select high-risk patients prior to RP, thereby leading to the slight positive trend in use we have shown from 2011 to 2014. Among practitioners in the community employing ADT more frequently prior to RP, it is conceivable that a greater proportion of patients with the most adverse characteristics (and highest de novo risk of positive margins at the time of prostatectomy) may have been preferentially selected for neoadjuvant therapy. This may explain the worse OS among men with high-risk disease and no comorbidity who received neoadjuvant ADT rather than neoadjuvant ADT itself truly being associated with a negative impact on survival.

Our retrospective study has certain limitations. Based on the difference of patient numbers in both groups, we used IPTW to attempt to correct for selection bias by accounting for baseline patient characteristic differences, including age at diagnosis, year of diagnosis, or pathological features. Additionally, our database itself has some limitations. For example, no information is available for some potential patient or institutional-level confounders, such as performance status, postoperative complications, cardiovascular disease, treating surgeon, or institutional volume. Furthermore, we could only measure OS in the high-risk group due to the low number of deaths in other groups. We also lacked the ability to discern specific therapies within neoadjuvant ADT as the database does not provide granularity beyond a single all-encompassing code. Lastly, it is conceivable that our follow-up period may be too short to

fully characterize significant differences in OS, given that a relatively small number of men undergoing RP (even for high-risk disease) will die of PCa within 5 years.

CONCLUSIONS

We have presented the most contemporary data on the use of neoadjuvant ADT in the treatment of PCa patients prior to prostatectomy, showing that after a period of steady decline, there appears to be a modest trend towards increased utilization in more recent years. In our cohort, there is an association between neoadjuvant ADT and decreased risk of positive surgical margins, which exists only among low- and intermediate-risk patients. Further randomized, prospective studies are needed to delineate the true effect of neoadjuvant ADT regimens on margin status, as well as to determine their impact on survival endpoints and which patient subsets may be most appropriate to target for treatment.

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