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A Nationwide Persistent Underutilization of Adjuvant Radiotherapy in North American Prostate Cancer Patients

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Original Study

A Nationwide Persistent Underutilization of Adjuvant Radiotherapy in North American Prostate Cancer Patients

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Abstract

Adjuvant radiotherapy (aRT) after radical prostatectomy has been shown to benefit patients with adverse pathology. We have found that from 2004 to 2015, only 11.7% of eligible patients received aRT and identified the magnitude of influence that each variable had on the utilization of aRT; thus, identifying a severe underutilization of aRT within a large, contemporary, North American cohort.

Objective: To examine the utilization of adjuvant radiotherapy (aRT) in contemporary prostate cancer patients with adverse pathological features at radical prostatectomy (RP). **Methods:** We identified 189,240 patients with adverse features at RP (positive margin, stage ≥pT3a, and/or pN1 disease), from 2004 to 2015, within the National Cancer Database, and validated our findings within Surveillance, Epidemiology, and End Results (SEER) program. We examined the utilization of patients with aRT with adverse features at RP and patients with very aggressive disease (at least 2 of the following: ≥pT3b, pathological Gleason 8-10, and pN1). Regression analysis examined the relationship of various predictors of utilization adjusting to confounders. Pseudo R^2 analysis examined the magnitude of influence that each variable had on the decision to use aRT. **Results:** Within the National Cancer Database cohort, only 11.7% of our patients received aRT. In patients with very aggressive disease, aRT utilization rate was 28.9%. Within the SEER cohort, 16.3% of patients with any adverse features at time of RP received aRT. In patients with very aggressive disease, only 30% of patients received aRT. Further, year of diagnosis, Gleason grade, pathologic stage, and positive surgical margin were the variables that had the greatest influence on the decision to use aRT, and that positive surgical margin, type of institution at which care was received, and lymph node involvement were the most influential variables in patients with very aggressive disease. **Conclusions:** The current standard of care in the United States represents a significant underutilization of aRT in eligible patients with prostate cancer. Urgent efforts are necessary to address this quality-of-care concern.

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Introduction

Prostate cancer is the second-most common cause of cancer-specific mortality in North American men.[1] A common treatment for these patients, especially those with localized disease, is radical prostatectomy (RP).[2,3] Among men receiving surgery, upward of 40% display indicators of aggressive disease and adverse pathology,[3] and approximately 50% to 70% of these men will go on to develop biochemical recurrence.[4-6] Although multiple randomized controlled clinical trials have elucidated that such patients can benefit from adjuvant radiotherapy(aRT),[4,7,8] only 10% of these individuals end up receiving this treatment modality in clinical practice.[9] This represents a stark underutilization of aRT, and highlights a quality-of-care concern.[9,10]

Although several reports have examined this issue in patients with any adverse pathology, none have examined it in individuals with very aggressive disease, which is the population that seems to benefit the most from aRT.[11,12] Given the trials data,[4,7,8] and recent updates of the guidelines,[13,14] we hypothesized that there would be an increase in the utilization of aRT over time in patients with any

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adverse pathological features, as well as in those with very aggressive pathological features (at least 2 of the following: pT3b or higher, pathological Gleason 8-10, and pN1). We tested this hypothesis using the National Cancer Database (NCDB) and validated our findings within a Surveillance, Epidemiology, and End Results (SEER) cohort. Thus, evaluating the trend within a hospital-based registry, and validating our results within a population-based registry. Moreover, we assessed which variables had the greatest influence on the decision to use aRT.

Methods

Study Population

The NCDB is a clinical oncology database jointly sponsored by the American College of Surgeons and the American Cancer Society. It is sourced from hospital registry data that are collected in more than 1500 Commission on Cancer–accredited facilities. Data represent approximately 70% of newly diagnosed cancer cases nationwide across the United States.[15]

We identified a total of 192,543 patients with histologically confirmed nonmetastatic adenocarcinoma of the prostate, diagnosed between 2004 and 2015, within the NCDB. All these patients received an RP, and had at least 1 indicator of adverse pathology: ≥pT3a stage, positive surgical margin (PSM), and/or lymph node invasion (LNI). Detailed inclusion/exclusion criteria are provided in Supplemental Figure 1 in the online version. We then excluded 3303 patients with missing data, leaving us with 189,240 patients in our cohort.

External Validity

The data for the external validation was abstracted from the SEER database. The SEER database is publicly available and maintained by the National Cancer Institute. This database includes approximately 26% of the US population, and predominantly represents the states of Alaska, California, Connecticut, rural Georgia, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah, as well as the metropolitan areas of Atlanta, Detroit, Los Angeles, Monterey, Oakland, San Francisco, San Jose, and Seattle. We identified a total of 45,350 patients with histologically confirmed nonmetastatic adenocarcinoma of the prostate, diagnosed between 2004 and 2015. All of the patients received an RP, and had at least 1 indicator of adverse pathology: ≥pT3a stage, PSM, and/or LNI.

Covariates

For the NCDB cohort, variables including age at diagnosis, race (non-Hispanic White, non-Hispanic Black, or other), baseline Charlson Comorbidity Index (CCI) category (0, 1, or ≥2), and insurance status (not insured, private insurance/managed care, Medicare, Medicaid, or other) were abstracted. We estimated socioeconomic variables using household income quartiles (≤38,000, 38,000-47,999, 48,000-62,999, ≥63,000). Hospital type (community cancer program, comprehensive community cancer program, academic/research program, or integrated network cancer program) was also abstracted, as well as disease characteristics including year of diagnosis, prostate-specific antigen (PSA) value, pathological tumor stage (≤pT3a, pT3b, and pT4), pathological nodal stage (pN0, pN1, or pNx), pathological Gleason score (≤6, 3 + 4, 4 + 3, and ≥8), and surgical margin status (negative or positive). Similar variables were extracted for the SEER cohort, except for CCI and hospital type, which are not available in SEER.

Endpoints

The main endpoint examined within this study was the utilization rate of aRT over the study period. Patients were classified as receiving aRT if radiotherapy was administered within 12 months after surgery in the NCDB cohort, or if the sequence of treatment variable in SEER indicated radiation therapy after surgery. Secondarily, we examined which variables were predictors of utilization of aRT over the course of the study period, and the magnitude of influence that each independent predictor had on the decision to use aRT

Statistical Analyses

Median and interquartile ranges (IQRs) were reported for continuous variables, and frequencies and proportions were reported for categorical variables. The Mann-Whitney U test and χ^2 tests were used to compare medians and proportions, respectively.

Our statistical analysis consisted of 2 main steps. First, in the entire cohort, the Cochran-Armitage trend test was used to examine the statistical significance of changes in aRT utilization over the study period. Next, multivariable logistic regression analysis tested the relationship between year of diagnosis, and aRT utilization, after adjusting to all available covariates. Pseudo R^2 was calculated to assess what proportion of the variance of the logistic model each variable was responsible for. Second, the same aforementioned analyses were repeated exclusively in patients with very aggressive disease at surgery, defined as harboring 2 or more of the following: pT3b disease or higher, pathological Gleason score 8-10, and/or LNI.

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Two-sided statistical significance was defined as a P value $< .05$. An institutional review board waiver was obtained before the study was conducted, in accordance with institutional regulation when dealing with de-identified previously collected data.

Results

Descriptive Characteristics

Descriptive statistics are presented in Table 1. Median (IQR) of age and PSA value were 62.0 years (57.0-67.0), and 6.3 ng/ml (4.7-10.0), respectively. Most patients had a pathological Gleason 3 + 4 (40.8%), pathological pT3a or lower disease (68.6%), PSMs (65.2%), and pathological N0 disease (65.1%).

Within the NCDB cohort, only 22,320 (11.8%) patients received aRT. These patients were younger (median: 61 vs. 62 years), had a higher PSA value (median: 7.7 vs. 6.2 ng/mL), a higher-grade disease (Gleason score ≥8: 40.8% vs. 17.2%), a more advanced T stage (pT3b or higher: 41.6% vs. 16.0%), higher PSM rate (74.2% vs. 63.4%), and higher rate of pN1 disease (13.3% vs. 6.6%) than their counterparts who did not receive aRT (all $P <$ .0001). The rate of aRT utilization changed from 12.9% in 2004% to 12.2% in 2015 (Figure 1, $P = .009$). In patients with very aggressive disease, the overall utilization rate of aRT was 28.9%, and this changed from 27.9% in 2004% to 29.6% in 2015 (Figure 2, $P = .4$). Overall, the proportion of patients who had very aggressive

Table 1 Descriptive Statistics in 189,240 Patients With Adverse Pathological Features on Radical Prostatectomy Specimen, Diagnosed Between 2004 and 2015, Within the National Cancer Database

Characteristics	Entire Cohort n = 189,240	Observation n = 166,920 (88.2%)	Adjuvant Radiotherapy n = 22,320 (11.8%)	*P* Value
Age (IQR)	62 (57-67)	62 (57-67)	61 (56-66)	<.0001
Median PSA (IQR)	6.3 (4.7-10)	6.2 (4.6-9.6)	7.7 (5.2-14.1)	<.0001
Race				<.0001
White	159,527 (82.9)	138,559 (83.0)	18,429 (82.6)	
Black	23,728 (12.3)	20,314 (12.2)	2873 (12.9)	
Other	5846 (3.0)	4927 (2.9)	772 (3.5)	
Annual median income, $				.009
≤38,000	26,475 (13.8)	22,864 (13.7)	3121 (14.0)	
38,000-47,999	41,009 (21.3)	35,742 (21.4)	4666 (20.9)	
48,000-62,999	52,631 (27.3)	45,591 (27.3)	6290 (28.2)	
≥63,000	71,152 (37.0)	61,627 (36.9)	8082 (36.2)	
Charelson comorbidity index				<.0001
0	158,883 (82.5)	137,485 (82.4)	18,649 (83.6)	
1	29,504 (15.3)	25,807 (15.5)	3200 (14.3)	
≥2	4156 (2.2)	3628 (2.17)	471 (2.1)	
Pathologic tumor stage				<.0001
≤pT3a	131,990 (68.6)	119,441 (71.6)	10,335 (46.3)	
pT3b	34,448 (17.9)	25,199 (15.1)	8672 (38.9)	
pT4	2124 (1.1)	1476 (0.88)	603 (2.7)	
Gleason grade				<.0001
≤6	27,181 (14.1)	25,380 (15.2)	1247 (5.6)	
3 + 4	78,616 (40.8)	71,583 (42.9)	5665 (25.4)	
4 + 3	39,606 (20.6)	38,895 (20.3)	5107 (22.9)	
≥8	38,467 (20.0)	28,748 (17.2)	9116 (40.8)	
Lymph node invasion				<.0001
pN0	125,520 (65.2)	108,909 (65.3)	14,534 (65.1)	
pN1	14,190 (7.4)	11,025 (6.6)	2974 (13.3)	
pNx	48,229 (25.1)	42,905 (25.7)	4387 (19.7)	
Surgical margin				<.0001
Negative	63,992 (33.2)	57,736 (34.6)	5474 (24.5)	
Positive	125,691 (65.2)	106,645 (63.4)	16,552 (74.2)	
Year of diagnosis				<.0001
2004	11,478 (6.0)	11,478 (6.0)	9794 (5.9)	
2005	11,805 (6.1)	11,805 (6.1)	10,108 (6.1)	
2006	13,425 (7.0)	13,425 (7.0)	11,604 (7.0)	
2007	15,404 (8.0)	15,404 (8)	13,352 (8)	
2008	15,790 (8.2)	15,790 (8.2)	13,604 (8.2)	
2009	16,451 (8.5)	16,451 (8.5)	14,076 (8.4)	
2010	18,710 (9.7)	18,710 (9.7)	16,246 (9.7)	
2011	19,763 (10.3)	19,763 (10.3)	17,275 (10.4)	
2012	16,795 (8.7)	16,795 (8.7)	14,754 (8.8)	
2013	17,005 (8.8)	17,005 (8.8)	14,953 (9.0)	
2014	17,075 (8.9)	17,075 (8.9)	14,832 (8.9)	
2015	18,842 (9.8)	18,842 (9.8)	16,322 (9.8)	
Facility Type				<.0001
Community cancer program	10,830 (5.6)	8722 (5.2)	1848 (8.3)	
Comprehensive community cancer program	77,411 (40.2)	65,620 (39.3)	10,230 (45.8)	

Table 1 Continued

Characteristics	Entire Cohort n = 189,240	Observation n = 166,920 (88.2%)	Adjuvant Radiotherapy n = 22,320 (11.8%)	*P* Value
Academic research program	81,758 (425)	72,725 (43.6)	7934 (35.6)	
Integrated network cancer program	22,385 (11.6)	19,720 (11.8)	2283 (10.2)	
Insurance status				<.0001
Not insured	3082 (1.6)	2595 (1.56)	439 (2.0)	
Private insurance/managed care	114,950 (60.0)	99,264 (59.5)	13,588 (60.8)	
Medicaid	4379 (2.3)	3610 (2.2)	691 (3.1)	
Medicare	62,887 (32.7)	55,093 (33.0)	6827 (30.6)	
Other government	2927 (1.5)	2411 (1.4)	486 (2.2)	

Abbreviations: IQR = interquartile range; PSA = prostate-specific antigen.

disease steadily increased from 8.6% in 2004% to 15.6% in 2015 (Figure 3, $P < .0001$).

Regression Analysis Predicting aRT Utilization in Patients With Adverse Pathological Features

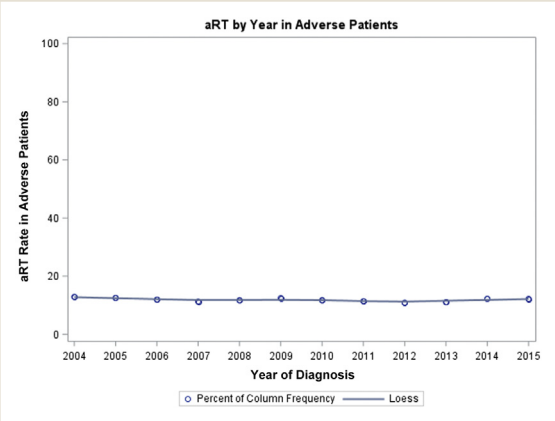
In patients with any adverse pathologic features, when comparing with 2004, year showed to be an independent predictor of decreased utilization of aRT. For example, patients undergoing aRT in 2006 were equally as likely to receive aRT as patients in 2004 (Table 2, odd ratio [OR] 0.937; 95% confidence interval [CI], 0.846-1.038; $P = .21$), whereas similar patients in 2012 (OR 0.747; 95% CI, 0.681-0.820; $P < .0001$) and 2015 (OR 0.780; 95% CI, 0.713-0.853; $P \leq .0001$) were less likely.

Higher-grade disease was also a predictor of receipt of aRT, as patients with Gleason grade 3 + 4 (Table 2, OR 1.745; 95% CI, 1.614-1.886; $P < .0001$), Gleason grade 4 + 3 (OR 3.001; 95% CI, 2.768-3.253; $P < .0001$), and Gleason grade 8 or higher (OR 4.948; 95% CI, 4.568-5.361; $P < .0001$), were all more likely to receive aRT than patients with Gleason 6 or lower disease. Further, patients with pT3b (OR 2.946; 95% CI, 2.833-3.063; $P < .0001$) and pT4 (OR 2.823; 95% CI, 2.512-3.171; $P < .0001$) were more likely to undergo aRT than were patients with pT3a disease, as were patients with PSMs (OR 2.194; 95% CI, 2.112-2.279; $P < .0001$), when compared with patients with negative surgical margin. Patients with known lymph node involvement were more likely to undergo aRT (OR 1.195; 95% CI, 1.132-1.262; $P < .0001$), whereas patients with unknown lymph node involvement were less likely (OR 0.75; 95% CI, 0.713-0.800; $P < .0001$).

The type of facility in which a patient was diagnosed is also an independent predictor of use of aRT. When compared with a community cancer program, patients who receive care at an academic/research program (Table 2, OR 0.505; 95% CI, 0.471-0.542; $P \leq .0001$), comprehensive community cancer program (OR 0.754; 95% CI, 0.704-0.809; $P \leq .0001$), and integrated network cancer program (OR 0.597; 95% CI, 0.549-0.649; $P \leq .0001$), were all less likely to receive aRT. Last, a patient with only 1 CCI (Table 2, OR 0.886; 95% CI, 0.844-0.930; $P < .0001$) was less likely to receive aRT than a patient without any comorbidities, and a patient with 2 or more (OR 0.938; 95% CI, 0.836-1.053; $P = .2780$) was equally as likely.

In these patients, pathologic stage, Gleason grade, and PSM had the greatest impact on the decision to use aRT, as evidenced by the fact that they were responsible for 27.6%, 21.8%, and 17.3% of variance of the pseudo R^2, respectively.

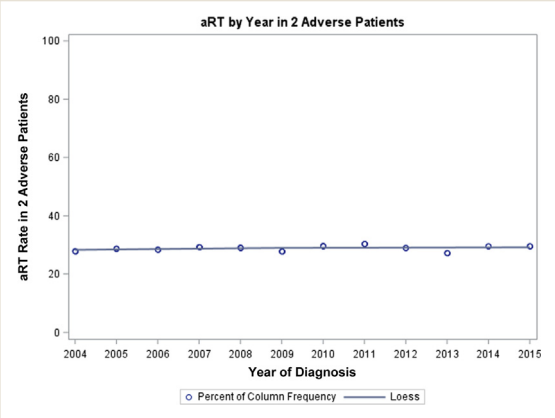
Figure 1 Year-per-Year Trend Analysis of Adjuvant Radiotherapy (aRT) Utilization in 189,240 Patients With Prostate Cancer With Adverse Pathological Features on Radical Prostatectomy Specimen, Diagnosed Between 2004 and 2015, Within the National Cancer Database



Regression Analysis Predicting aRT Utilization in Patients With Very Aggressive Disease

In patients with very aggressive disease, the year of diagnosis did not seem to affect the likelihood that patients would undergo aRT. For example, patients in 2006 (Table 3; OR 1.068; 95% CI, 0.859-1.329; $P = .55$), and 2012 (OR 1.134; 95% CI, 0.938-1.372; $P = .19$) were equally as likely to undergo aRT as were patients in 2004. Conversely, patients in 2015 were more likely to undergo aRT compared with patients in 2004 (OR 1.231; 95% CI, 1.025-1.1.478; $P = .03$). Other independent predictors of utilization mirrored the trends seen in patients with adverse pathological features, and are highlighted in Table 3.

Figure 2 Year-per-Year Trend Analysis of Adjuvant Radiotherapy (aRT) Utilization in 20,583 Patients With Prostate Cancer With Very Aggressive Disease Features on Radical Prostatectomy Specimen, Diagnosed Between 2004 and 2015, Within the National Cancer Database

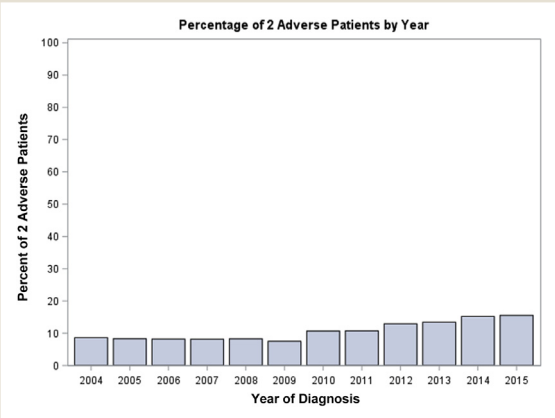


In these patients, positive surgical margin, and the type of program at which care was received had the greatest positive impact on the decision to use aRT, as evidenced by the fact that they were responsible for 48.4% and 13.2% of the variance of pseudo R^2 (Table 3), Increasing age at diagnosis was shown to have the greatest negative impact on the decision to use aRT, as evidenced by its responsibility for 11.3% of the variance of pseudo R^2.

External Validity

Descriptive data of the SEER cohort are provided in Supplemental Table 1 (see the online version). Our findings were confirmed within the SEER cohort. In the SEER cohort, the overall utilization of aRT in patients with any adverse pathology from 2004 to 2015 was 16.3%, and this changed from 17.4% in 2004% to 17.1% in 2015 (Supplemental Figure 2 see the online version, $P = .50$). In patients with very aggressive disease, the overall utilization of aRT was 30.0%, and this varied from 27.1% in 2004% to 29.8% in 2015 (Supplemental Figure 3, $P = .11$). Regression analysis for predictors of aRT utilization showed similar results and are detailed in Supplemental Tables 2 and 3 (see the online version).

Figure 3 Year-per-Year Analysis of the Rate of Patients With Very Aggressive Disease Among all Patients With Adverse Pathological Features on Radical Prostatectomy Specimen, Diagnosed Between 2004 and 2015, Within the National Cancer Database



Discussion

Several randomized controlled trials and retrospective data have shown the beneficial impact of aRT on cancer control outcomes in patients with adverse pathological features. However, previous reports showed the utilization of this treatment modality to be limited at best. For example, a study examining NCDB data between 2004 and 2011 identified that only 9.9% of patients with aggressive disease had received aRT.[9] However, no recent update on aRT utilization is available, and previous reports do not go beyond 2011.[9,16] Moreover, recent reports[11,12] showed that patients with very aggressive disease features are those who benefit the most from aRT, but no report has examined the utilization of this treatment modality in these individuals. Further, the variables that influence aRT decision-making have not been evaluated. To address this void, we set out to examine the utilization of aRT in contemporary patients with any adverse pathology and in those with very aggressive pathological features.

Our analyses yielded several findings worth highlighting. For example, in the NCDB cohort, the rate of aRT utilization in patients with any adverse pathological feature was 11.7% overall, with no clinically meaningful change over the years. Similarly, although aRT utilization was somewhat higher in patients with very aggressive disease features, the rate of aRT hardly changed throughout the study period. Similar numbers were observed in the SEER cohort. Our findings also show that in patients with adverse pathological features, a patient in 2015 was less likely to receive aRT than a similar patient in 2004, as year of diagnosis was shown to be an independent negative predictor of receipt of aRT. Such observations ascertain the general underutilization of aRT in clinical practice and confirm that there is no improvement in treatment trends, even in the most contemporary of patients. In addition, our findings highlight the severe underutilization of aRT in individuals with very aggressive disease features. Indeed, less than a third of such individuals receive aRT, even though such treatment has been demonstrated to decrease the 10-year clinical progression rate from 42.1% to 10.1%, and the 10-year overall mortality rate from 37.3% to 24.4% in these individuals.[11] Similar to how there is little argument about the benefit that patients with positive lymph node involvement receive from early androgen deprivation therapy,[17,18] most experts would agree that these high-risk patients with very aggressive pathology would need multimodal treatment after prostatectomy to minimize the risk of very early local relapse. Thus, making it very worrisome that even in a population in which there is little controversy over the benefit of aRT, the utilization of such a treatment modality is only 28.9%. This represents a significant quality-of-care concern, and an area for possible improvement.

Our work retains importance in light of ongoing trials and analyses, namely the RAVES and RADICALS-RT trials, and the

Table 2 Predictors of Use of aRT in 189,240 Patients With Adverse Pathological Features on Radical Prostatectomy Specimens, Diagnosed Between 2004 and 2015, Within the National Cancer Database

Predictors of Utilization of aRT									
Variable	**Univariate Odds Ratio**	**95% CI Lower Limit**	**95% CI Upper Limit**	***P* Value**	**Multivariate Odds Ratio**	**95% CI Lower Limit**	**95% CI Upper Limit**	***P* Value**	**% of Pseudo R^2**
PSA	1.016	1.015	1.017	<.0001	1.005	1.004	1.006	<.0001	0.54
Age	0.989	0.987	0.991	<.0001	0.975	0.972	0.978	<.0001	2.79
CDCC comorbidity									0.32
0	Reference				Reference				
1	0.914	0.878	0.951	<.0001	0.886	0.844	0.93	<.0001	
2+	0.957	0.868	1.055	.3765	0.938	0.836	1.053	.28	
Race									
White	Reference				Reference				
Black	1.063	1.02	1.109	.0041	1.047	0.992	1.105	.095	0.01
Other	1.178	1.09	1.273	<.0001	1.175			.0008	
Year of diagnosis									0.62
2004	Reference				Reference				
2005	0.969	0.896	1.048	.4277	0.985	0.887	1.094	.7843	
2006	0.918	0.85	0.99	.027	0.937	0.846	1.038	.2133	
2007	0.859	0.797	0.925	<.0001	0.851	0.769	0.942	.0018	
2008	0.899	0.835	0.967	.0045	0.897	0.811	0.992	.0335	
2009	0.962	0.895	1.034	.2904	0.847	0.764	0.94	.0017	
2010	0.9	0.838	0.966	.0037	0.918	0.839	1.006	.0659	
2011	0.869	0.81	0.933	<.0001	0.873	0.798	0.955	.0031	
2012	0.826	0.767	0.889	<.0001	0.747	0.681	0.82	<.0001	
2013	0.839	0.779	0.903	<.0001	0.744	0.678	0.816	<.0001	
2014	0.94	0.875	1.01	.092	0.783	0.715	0.838	<.0001	
2015	0.938	0.874	1.007	.0755	0.78	0.713	0.853	<.0001	
Type of program									5.18
Community cancer program	Reference				Reference				
Academic program	0.515	0.487	0.544	<.0001	0.505	0.471	0.542	<.0001	
Comprehensive community cancer program	0.736	0.697	0.777	<.0001	0.754	0.704	0.809	<.0001	
Integrated network cancer program	0.546	0.511	0.584	<.0001	0.597	0.549	0.649	<.0001	
Positive surgical margin	1.637	1.585	1.691	<.0001	2.194	2.112	2.279	<.0001	17.28

Table 2 Continued

Predictors of Utilization of aRT									
Variable	**Univariate Odds Ratio**	**95% CI Lower Limit**	**95% CI Upper Limit**	***P* Value**	**Multivariate Odds Ratio**	**95% CI Lower Limit**	**95% CI Upper Limit**	***P* Value**	**% of Pseudo R^2**
Pathologic stage									27.56
≤pT3a	Reference				Reference				
pT3b	3.978	3.854	4.106	<.0001	2.946	2.833	3.063	<.0001	
pT4	4.723	4.287	5.203	<.0001	2.823	2.512	3.171	<.0001	
Pathologic lymph node involvement									0.50
pN0	Reference				Reference				
pN1	2.021	1.934	2.112	<.0001	1.195	1.132	1.262	<.0001	
pNx	0.766	0.739	0.794	<.0001	0.755	0.713	0.8	<.0001	
Gleason grade									21.75
≤6	Reference				Reference				
3 + 4	1.611	1.512	1.715	<.0001	1.745	1.614	1.886	<.0001	
4 + 3	3.067	2.876	3.269	<.0001	3.001	2.768	3.253	<.0001	
≥8	6.453	6.068	6.862	<.0001	4.948	4.568	5.361	<.0001	
Income									0.25
<38,000									
$38,000-$47,99	0.956	0.911	1.004	.07	0.972	0.915	1.032	.3581	
$48,000-$62,999	1.011	0.966	1.058	.6479	1.061	1.002	1.124	.0434	
$63,000+	0.961	0.92	1.004	.0763	1.072	1.013	1.134	.0158	
Insurance status									0.40
Not insured	Reference				Reference				
Medicaid	1.131	0.994	1.288	.0622	1.201	1.022	1.411	.0261	
Medicare	0.732	0.66	0.813	<.0001	0.945	0.827	1.079	.4011	
Government (other)	1.192	1.035	1.371	.0145	1.399	1.176	1.665	.002	
Private insurance/managed care	0.809	0.73	0.897	<.0001	0.962	0.846	1.094	.5533	

Abbreviations: aRT = adjuvant radiotherapy; CDCC = Charlson/Deyo combined comorbidity score; CI = confidence interval; PSA = prostate-specific antigen.

Table 3 Predictors of Use of aRT in 20,583 Patients With Prostate Cancer with Very Aggressive Disease Features on Radical Prostatectomy Specimen, Diagnosed Between 2004 and 2015, Within the National Cancer Database

Predictors of Utilization of aRT									
Variable	**Univariate Odds Ratio**	**95% CI Lower Limit**	**95% CI Upper Limit**	***P* Value**	**Multivariate Odds Ratio**	**95% CI Lower Limit**	**95% CI Upper Limit**	***P* Value**	**% of Pseudo R^2**
PSA	1.002	1	1.004	.018	0.999	0.997	1.001	.4025	0.06
Age	0.971	0.967	0.975	<.0001	0.968	0.962	0.974	<.0001	11.27
CDCC comorbidity									1.72
0	Reference				Reference				
1	0.914	0.878	0.951	<.0001	0.843	0.769	0.923	.0002	
2+	0.957	0.868	1.055	.02	0.79	0.636	0.982	.033	
Race									
White	Reference				Reference				
Black	0.929	0.844	1.022	.1304	0.927	0.831	1.034	.1728	0.53
Other	1.117	0.952	1.311	.1762	1.176	0.984	1.405	.0755	
Year of diagnosis									1.51
2004	Reference				Reference				
2005	1.046	0.857	1.275	.66	1.083	0.863	1.359	.4924	
2006	1.028	0.848	1.248	.7766	1.068	0.859	1.329	.5523	
2007	1.07	0.888	1.29	.4753	1.132	0.916	1.399	.2511	
2008	1.059	0.88	1.276	.5422	1.117	0.906	1.376	.2998	
2009	0.994	0.823	1.202	.9544	1.086	0.877	1.344	.4486	
2010	1.093	0.921	1.296	.3087	1.213	1.001	1.47	.0491	
2011	1.127	0.952	1.334	.166	1.229	1.017	1.487	.0332	
2012	1.055	0.891	1.249	.5352	1.134	0.938	1.372	.1938	
2013	0.968	0.818	1.146	.7062	1.012	0.838	1.224	.8979	
2014	1.085	0.921	1.279	.3311	1.179	0.98	1.419	.081	
2015	1.087	0.924	1.278	.3131	1.231	1.025	1.478	.0264	
Type of program									13.17
Community cancer program	Reference				Reference				
Academic program	0.567	0.501	0.643	<.0001	0.563	0.489	0.649	<.0001	
Comprehensive community cancer program	0.843	0.744	0.955	.0073	0.818	0.711	0.941	.005	
Integrated network cancer program	0.726	0.625	0.844	<.0001	0.691	0.584	0.817	<.0001	
Positive surgical margin	2.2	2.064	2.345	<.0001	2.132	1.989	2.285	<.0001	48.39
Pathologic stage									1.24
≤pT3a	Reference				Reference				

Table 3 Continued

Predictors of Utilization of aRT									
Variable	**Univariate Odds Ratio**	**95% CI Lower Limit**	**95% CI Upper Limit**	***P* Value**	**Multivariate Odds Ratio**	**95% CI Lower Limit**	**95% CI Upper Limit**	***P* Value**	**% of Pseudo R^2**
pT3b	1.541	1.385	1.715	<.0001	1.273	1.116	1.452	.003	
pT4	1.88	1.598	2.211	<.0001	1.36	1.124	1.646	.0016	
Pathologic lymph node involvement									3.43
pN0	Reference				Reference				
pN1	0.778	0.731	0.828	<.0001	0.788	0.723	0.859	<.0001	
pNx	0.977	0.836	1.143	.7733	0.903	0.757	1.078	.2596	
Gleason grade									0.27
≤6	Reference				Reference				
3 + 4	0.876	0.362	2.117	.7686	0.813	0.27	2.448	.713	
4 + 3	1.001	0.418	2.399	.9974	0.939	0.314	2.805	.9104	
≥8	1.129	0.474	2.687	.7842	0.961	0.323	2.86	.9436	
Income									1.16
<$38,000									
$38,000-$47,99	1.014	0.914	1.126	.7897	0.987	0.879	1.108	.82	
$48,000-$62,999	1.102	0.997	1.217	.057	1.063	0.95	1.188	.2854	
$63,000+	1.105	1.004	1.216	.0404	1.13	1.014	1.259	.0273	
Insurance status									0.80
Not insured	Reference				Reference				
Medicaid	1.139	0.862	1.507	.3596	1.083	0.797	1.471	.6091	
Medicare	0.843	0.676	1.052	.1304	1.031	0.803	1.324	.8103	
Government (other)	1.55	1.136	2.113	.0057	1.495	1.061	2.106	.0216	
Private insurance/managed care	1.144	0.919	1.424	.2298	1.081	0.849	1.376	.5273	

Abbreviations: aRT = adjuvant radiotherapy; CDCC = Charlson/Deyo combined comorbidity score; CI = confidence interval; PSA = prostate-specific antigen.

ARTISTIC meta-analysis. In short, these studies have preliminarily found no evidence that aRT improves event-free survival compared with early salvage radiotherapy (sRT), despite treating 2 to 3 times as many patients with radiotherapy.[19,20] These findings may lead to omission or delay of radiation in the future. However, these preliminary results should not yet shape clinical care, as they are based off of studies with short follow-up (5 and 8 years), and studies that assessed freedom from biochemical failure (FFBF), which has been shown to not be an adequate surrogate for overall survival.[21-25] Further, achieving similar rates of FFBF between aRT and early sRT requires strict, diligent follow-up that is much more feasible within the setting of a clinical trial, and may not be achievable on a nationwide scale in real clinical practice. In addition, with regard to these studies, further work is still required to accurately identify which patients still require aRT to avoid very early local relapse and potential subsequent metastases. Our work fills this void in the interim. Specifically, we have shown that patients with very aggressive disease, likely the ones that will have early local relapse, are receiving a necessary treatment modality in fewer than 30% of cases. Moreover, patients with very aggressive pathology comprise fewer than 20% of patients within these new, prospective trials.[19] Thus, the question of aRT versus sRT in patients with very aggressive pathology will remain unanswered, for the foreseeable future.

Moreover, our work is the first to identify the main influencers of the decision to use aRT. Specifically, we showed that stage (27.6% pseudo R^2), grade (21.8% pseudo R^2), and PSM (17.3% pseudo R^2) explained most of the decision to use aRT in patients with any adverse pathological features, and that nodal status had a very low influence on this decision. This may be suboptimal in light of reports showing that local disease features and nodal status are the main influencers of cancer mortality, whereas PSM is not necessarily quite as influential.[26,27] Likewise, PSM was the main influencer of the decision to use aRT in patients with very aggressive features, as it explained almost 50% of decision process. However, data seem to suggest that all these individuals will benefit from aRT, regardless of the surgical margin status. It is important to note that it is not necessarily possible to deduct the influence of a variable solely based off of its hazard ratio (HR). For example, Gleason 3 + 4, 4 + 3, and 8 + have respective HRs of 1.89, 3.25, and 5.36, yet they are responsible for 21.8% of the decision to use aRT. Comparatively, stage pT3b and pT4 disease have respective HRs of 3.06 and 3.17, and they are responsible for 27.6% of the decision to use aRT. This emphasizes the importance of these analyses, as they identify the influence of a variable beyond simply the HR.

Our studies corroborate and add to various studies investigating these topics, while examining the use of aRT in both hospital and population-based registries. Specifically, our rate of aRT in patients with aggressive disease was 11.7%, which is similar to prior studies done by Kalbasi et al,[9] who identified a rate of 9.9% between 2004 and 2011, and Maurice et al,[16] who identified a rate of 7.5% between 2004 and 2009, thus suggesting that the use of aRT was uncommon before 2011. In addition, our study identified that the use of aRT was uncommon and unchanged in patients with very aggressive disease within a more contemporary cohort, thus indicating that even though there are recent guidelines and studies that have elucidated the benefit of aRT, it is still being severely underused. Interestingly, our analyses showed that the type of hospital where patients received care also proved to be predictor of receipt of aRT, as patients with adverse pathological features are less likely to receive aRT while being treated at an academic institution (OR 0.505, $P < .0001$), and most likely to receive aRT when being treated at a community cancer program. This finding further corroborates Kalbasi et al,[9] as they observed that patients treated at the highest volume centers were less likely to receive aRT. The cause of such an observation warrants further investigation.

Our study is not without limitations. For example, there was no centralized pathological review within our study. This may seem to be a limitation, but antithetically it also may act as a strength, as it lends reproducibility and applicability of our results to clinical practice within the United States. Moreover, postsurgical PSA nadir and functional outcomes are not captured within the NCDB and SEER datasets and these are important determinants of secondary treatment after prostatectomy. Further, both datasets capture the initial course of treatment after diagnosis, and as such do not capture salvage radiation therapy. Moreover, the NCDB does not capture secondary treatments accurately, and as such we could not evaluate the utilization of sRT or early sRT in our cohort. Further, we have no data regarding toxicity and quality of life, which have an impact on the decision to use aRT.

Conclusion

On a national level, there is a severe underuse of aRT, which did not improve over time. This is true even in patients with very aggressive pathological features, in whom there is little controversy regarding the beneficial impact of aRT. As such, our findings highlight an important quality-of-care concern, and urgent efforts are needed to improve the current practice pattern in the United States.

Clinical Practice Points

- Multiple randomized clinical control trials have elucidated the benefit of adjuvant radiotherapy after radical prostatectomy for patients who have adverse pathology at the time of prostatectomy.
- Further, studies have shown that there is a historic underutilization of this treatment modality in eligible patients, but these studies have not looked beyond the year 2011, nor has a study examined the current utilization of aRT on a population level.
- Our work has found that there is currently a jarring underutilization of aRT (11.7%) in eligible patients.
- Moreover, we have shown that there is an underutilization of aRT (28.9%) in patients with very aggressive disease, which are patients who would benefit the most from this treatment modality. This is especially worrisome, considering that these are patients who most experts would agree require multimodal treatment.
- Further, we have identified, for the first time, the magnitude of influence that each available variable has on the decision to utilize aRT.
- Our work highlights a suboptimal quality of care, within a large, contemporary North American cohort, that should be rectified immediately.

Disclosure

Firas Abdollah is a consultant for GenomeDx Biosciences. The remaining authors have stated that they have no conflicts of interest.

CRediT authorship contribution statement

Nikola Rakic: Conceptualization, Writing - original draft, Writing - review & editing, Methodology, Investigation, Project administration. **Akshay Sood:** Conceptualization, Methodology, Data curation, Investigation, Writing - review & editing. **Deepansh Dalela:** Conceptualization, Methodology, Data curation, Investigation. **Sohrab Arora:** Conceptualization, Methodology, Investigation, Data curation, Writing - review & editing. **Ulyana Malovana:** Data curation, Writing - original draft. **Jacob Keeley:** Formal analysis, Data curation, Methodology. **Craig Rogers:** Conceptualization, Investigation, Methodology, Writing - review & editing. **James Peabody:** Conceptualization, Investigation, Methodology, Writing - review & editing. **Mani Menon:** Conceptualization, Investigation, Methodology, Writing - review & editing. **Firas Abdollah:** Conceptualization, Investigation, Methodology, Writing - review & editing, Writing - original draft, Writing - review & editing.

Supplemental Data

Supplemental tables and figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.clgc.2020.05.001.

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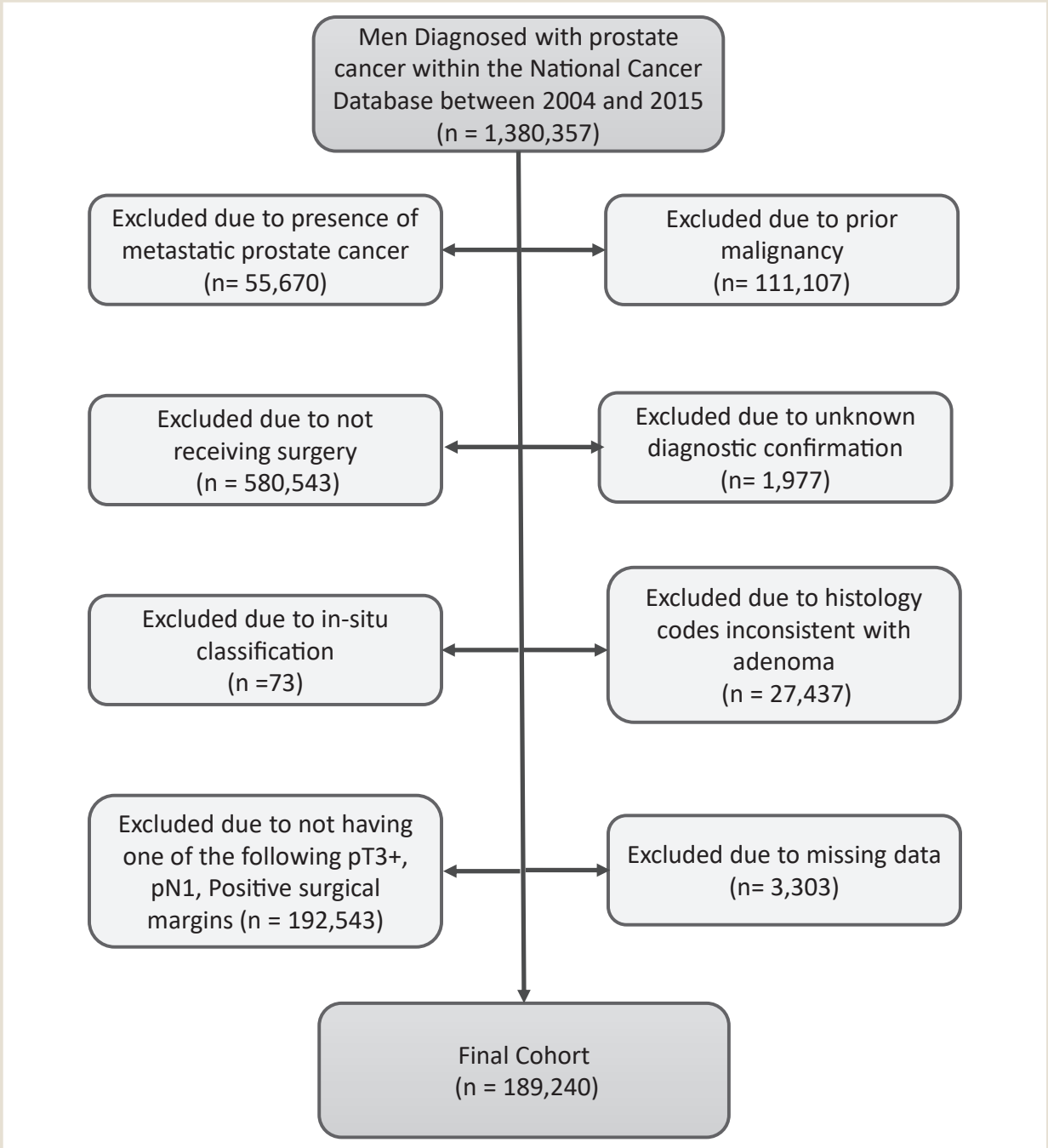
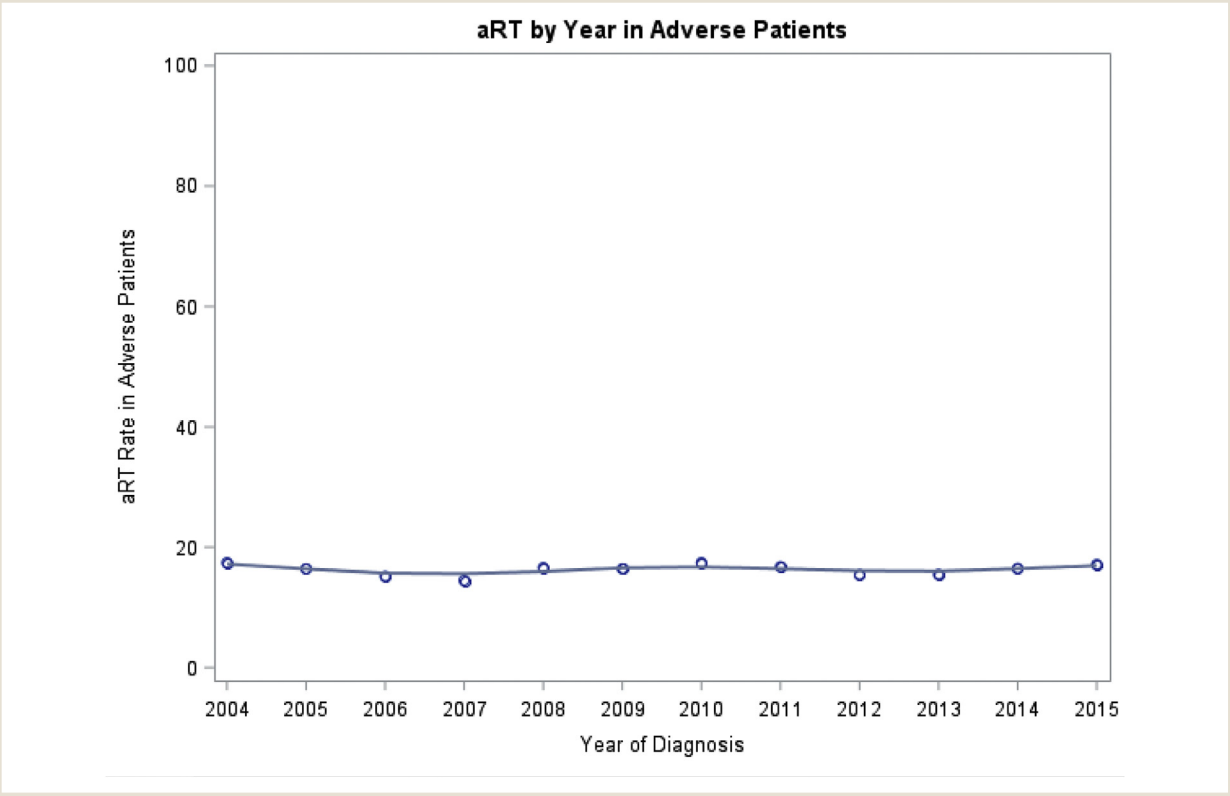
Supplemental Data

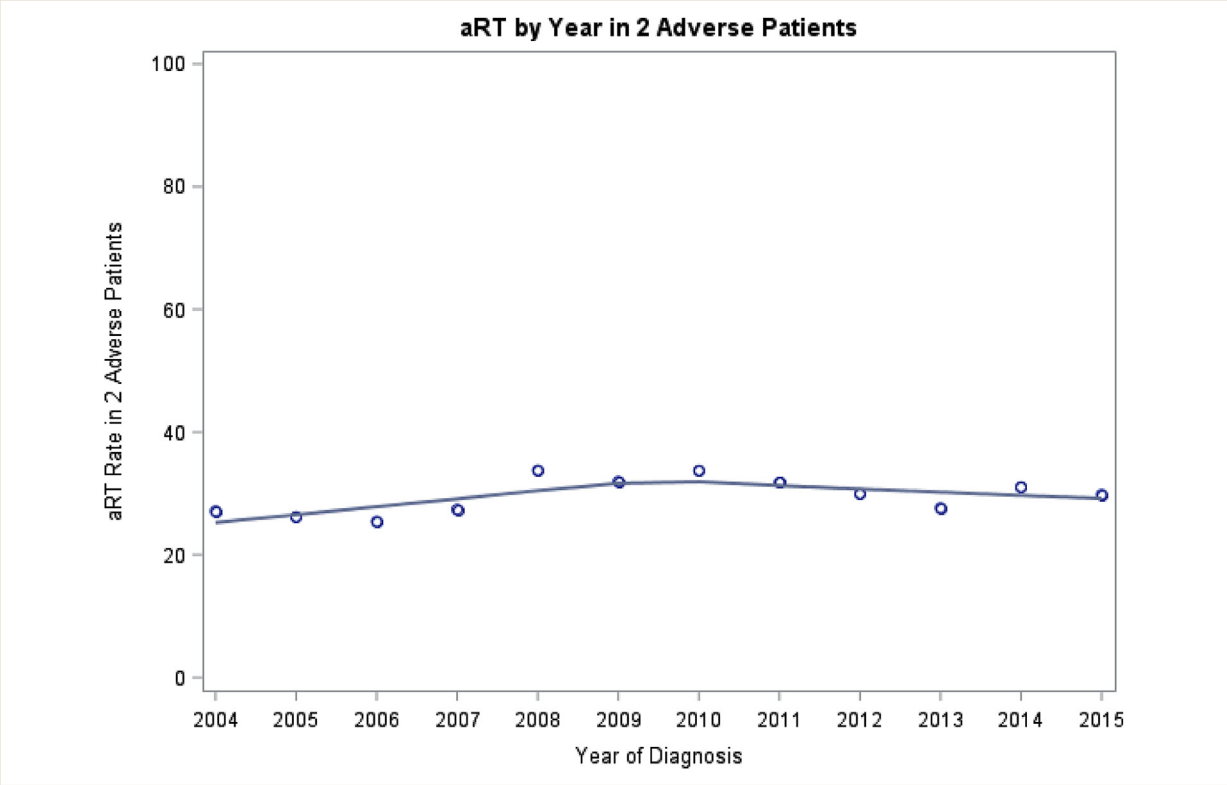
Supplemental Figure 1 Inclusion/Exclusion Criteria for Patients With Adverse Pathological Features on Radical Prostatectomy Specimen, Diagnosed From 2004 to 2015, Within the National Cancer Database



Supplemental Figure 2 **Year-per-Year Trend Analysis of Adjuvant Radiotherapy (aRT) Utilization in 45,350 Patients With Prostate Cancer With Adverse Pathological Features on Radical Prostatectomy Specimen, Diagnosed Between 2004 and 2015, Within the Surveillance, Epidemiology, and End Results (SEER) Database**



Supplemental Figure 3 Year-per-Year Trend Analysis of Adjuvant Radiotherapy (aRT) Utilization in 8366 Patients With Prostate Cancer With Very Aggressive Disease Features on Radical Prostatectomy Specimen, Diagnosed Between 2004 and 2015, Within the Surveillance, Epidemiology, and End Results (SEER) Database



Supplemental Table 1 Descriptive Statistics in 45,350 Patients With Adverse Pathological Features on Radical Prostatectomy Specimen, Diagnosed Between 2004 and 2015, Within the Surveillance, Epidemiology, and End Results Database

Characteristics	Entire Cohort n = 45,350	Observation n = 37,865	Adjuvant Radiotherapy n = 7385	*P* Value
Age (IQR)	63 (57-67)	63 (58-67)	62 (57-66)	<.0001
Median PSA (IQR)	7.2 (5.1-11.7)	7.0 (5.0-11.1)	8.5 (5.6-15.4)	<.0001
Race				.0004
White	36,809 (81.2)	30,878 (81.3)	5931 (80.3)	
Black	5575 (12.3)	4629 (12.2)	946 (12.8)	
Other	2563 (5.7)	2077 (5.5)	486 (6.6)	
Pathologic tumor stage				<.0001
≤pT3a	29,074 (64.1)	25,738 (67.8)	3336 (45.2)	
pT3b	12,493 (27.6)	9337 (24.6)	3156 (42.7)	
pT4	3776 (8.3)	2885 (7.6)	891 (12.1)	
Gleason grade				<.0001
≤6	3420 (7.5)	3195 (8.4)	225 (3.1)	
3 + 4	16,842 (37.1)	15,094 (39.8)	1748 (23.7)	
4 + 3	11,269 (24.9)	9348 (24.6)	1921 (26.0)	
≥ 8	12,178 (26.9)	8995 (23.7)	3183 (43.1)	
Lymph node invasion				<.0001
pNo	39,710 (87.6)	33,704 (88.8)	6006 (81.3)	
pN1	5308 (11.7)	3,69 (10.5)	1339 (18.1)	
pNx	332 (0.7)	292 (0.8)	40 (0.5)	
Year of diagnosis				.0066
2004	2805 (6.2)	2316 (6.1)	489 (6.6)	
2005	2650 (5.8)	2215 (5.8)	435 (5.9)	
2006	3098 (6.8)	2628 (6.9)	470 (6.4)	
2007	3736 (8.2)	3195 (8.4)	541 (7.3)	
2008	3848 (8.5)	3209 (8.5)	639 (8.7)	
2009	4212 (9.3)	3521 (9.3)	691 (9.4)	
2010	4270 (9.4)	3526 (9.3)	744 (10.1)	
2011	4362 (9.62)	3632 (9.6)	730 (9.9)	
2012	3928 (8.7)	3322 (8.8)	606 (8.2)	
2013	3872 (8.5)	3273 (8.6)	599 (8.1)	
2014	3963 (8.7)	3310 (8.7)	653 (8.8)	
2015	4606 (10.2)	3818 (10.1)	788 (10.7)	

Abbreviations: IQR = interquartile range; PSA = prostate-specific antigen.
Values are n (%) unless otherwise indicated.

Supplemental Table 2 Predictors of Use of aRT in 45,350 Patients With Adverse Pathological Features on Radical Prostatectomy Specimen, Diagnosed Between 2004 and 2015, Within the Surveillance, Epidemiology, and End Results Database

Predictors of Utilization of aRT								
Variable	**Univariate Odds Ratio**	**95% CI Lower Limit**	**95% CI Upper Limit**	***P* Value**	**Multivariate Odds Ratio**	**95% CI Lower Limit**	**95% CI Upper Limit**	***P* Value**
PSA	1.033	1.032	1.034	<.0001	1.008	1.006	1.01	<.0001
Age	1.005	1.002	1.008	.001	0.973	0.97	0.977	<.0001
Race								
White	Reference				Reference			
Black	1.094	1.031	1.161	.003	0.977	0.899	1.061	.5791
Other	1.427	1.314	1.549	<.0001	1.269	1.158	1.39	.0009
Year of diagnosis								
2004	Reference				Reference			
2005	0.958	0.861	1.066	.4303	0.889	0.762	1.036	.1321
2006	0.832	0.749	0.924	.0006	0.757	0.652	0.879	.0003
2007	0.815	0.736	0.902	<.0001	0.704	0.609	0.814	<.0001
2008	0.952	0.862	1.051	.3277	0.844	0.733	0.971	.0178
2009	0.977	0.885	1.077	.6364	0.783	0.678	0.904	.0008
2010	1.047	0.949	1.153	.3598	0.89	0.777	1.02	.0942
2011	0.993	0.9	1.096	.891	0.841	0.734	0.964	.0128
2012	1.006	0.907	1.115	.9096	0.696	0.605	0.802	<.0001
2013	1.104	0.996	1.224	.06	0.724	0.629	0.834	<.0001
2014	1.224	1.104	1.356	.0001	0.743	0.646	0.854	<.0001
2015	1.4	1.268	1.546	<.0001	0.797	0.697	0.912	.0009
Pathologic stage								
≤6	Reference				Reference			
pT3b	9.797	9.338	10.278	<.0001	4.435	4.19	4.694	<.0001
pT4	8.951	8.267	9.692	<.0001	4.528	4.134	4.96	<.0001
Pathologic lymph node involvement								
pNo	Reference				Reference			
pN1	7.015	6.569	7.49	<.0001	1.183	1.095	1.277	<.0001
pNx	1.01	0.81	1.258	.9324	0.943	0.642	1.385	.7659
Gleason grade								
<6	Reference				Reference			
3+4	3.399	3.117	3.707	<.0001	1.676	1.441	1.949	<.0001
4+3	9.074	8.304	9.915	<.0001	2.757	2.367	3.211	<.0001
≥8	20.72	19.018	22.574	<.0001	4.308	3.706	5.008	<.0001

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

Supplemental Table 3 Predictors of Use of aRT in 8366 Patients With Prostate Cancer With Very Aggressive Disease Features on Radical Prostatectomy Specimen, Diagnosed Between 2004 and 2015, Within the Surveillance, Epidemiology, and End Results Database

Predictors of Utilization of aRT								
Variable	**Univariate Odds Ratio**	**95% CI Lower Limit**	**95% CI Upper Limit**	***P* Value**	**Multivariate Odds Ratio**	**95% CI Lower Limit**	**95% CI Upper Limit**	***P* Value**
PSA	1.001	0.999	1.004	<.0001	1	0.997	1.003	.9528
Age	0.972	0.966	0.978	<.0001	0.969	0.962	0.976	<.0001
Race								
White	Reference				Reference			
Black	0.858	0.739	0.997	.0459	0.803	0.684	0.942	.0071
Other	1.281	1.062	1.545	.0098	1.322	1.088	1.606	.0049
Year of diagnosis								
2004	Reference				Reference			
2005	0.954	0.7	1.3	.7642	0.926	0.668	1.285	.6454
2006	0.918	0.689	1.223	.5593	0.942	0.695	1.277	.7006
2007	1.015	0.771	1.338	.9146	1.064	0.796	1.422	.676
2008	1.372	1.049	1.794	.0208	1.44	1.086	1.91	.0114
2009	1.263	0.961	1.66	.0944	1.236	0.922	1.657	.1562
2010	1.369	1.052	1.781	.0193	1.393	1.054	1.839	.0196
2011	1.253	0.963	1.632	.0932	1.308	0.989	1.729	.0596
2012	1.15	0.883	1.497	.3008	1.142	0.864	1.51	.3498
2013	1.027	0.787	1.341	.844	1.089	0.822	1.443	.5504
2014	1.21	0.934	1.569	.1496	1.273	0.967	1.675	.0849
2015	1.142	0.886	1.472	.3043	1.235	0.944	1.617	.124
Pathologic stage								
≤6	Reference				Reference			
pT3b	1.355	1.16	1.583	.0001	1.33	1.101	1.606	.003
pT4	1.588	1.324	1.904	<.0001	1.508	1.22	1.864	.0001
Pathologic lymph node involvement								
pNo	Reference				Reference			
pN1	0.828	0.754	0.91	<.0001	0.883	0.776	1.004	.0578
pNx	0.626	0.269	1.455	.2762	0.94	0.381	2.319	.8924
Gleason grade								
<6	Reference				Reference			
3+4	1.615	0.456	5.716	.4575	2.209	0.485	10.06	.3054
4+3	1.954	0.559	6.824	.2938	2.581	0.573	11.622	.2169
≥8	2.184	0.632	7.551	.2172	3.003	0.671	13.447	.1505

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