



Utilization of IMRT and Brachytherapy for Low-Risk and Intermediate-Risk Prostate Cancer Patients: Analysis of the Real-World Scenario

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Abstract

Purpose: Two main techniques in radiation therapy (RT) for the treatment of low-risk and intermediate-risk prostate cancer (PCa) are intensity-modulated radiation therapy (IMRT) and brachytherapy (BT). In this study, the pattern of utilization of IMRT, low dose-rate (LDR) BT, and high dose-rate (HDR) BT has been evaluated using a large hospital based registry database.

Methods: We analyzed a very large data set of N0, M0, non-surgical, stage T1-T2c prostate cancer patients diagnosed between 2004 and 2015 from the National Cancer Database (NCDB). Based on the RT techniques used, we considered three groups of patients: (1) IMRT (n=61,159; 48.4%) who received an initial as well as a boost treatment with the IMRT, (2) BT LDR (n=43,293; 34.3%), and (3) BT HDR (n=21,938; 17.3%). A total dose of 70-81Gy for IMRT was considered. For brachytherapy, LDR and HDR or unspecified brachytherapy was considered as monotherapy. Patients were stratified according to the National Comprehensive Cancer Network (NCCN) guidelines into: low-risk [clinical stage T1-T2a, Gleason Score (GS) of ≤ 6 (Grade Group 1), and Prostate-specific antigen (PSA) of < 10 ng/mL] and intermediate-risk [clinical stage T2b-T2c, GS of 7 (Grade Groups 2 and 3), and PSA of 10-20 ng/mL]. OS probability was determined using the Kaplan-Meier estimator. Propensity-score matched (PSM) analysis was performed for each risk group (low and intermediate) for the three research treatment modalities (IMRT, BT LDR, and BT HDR). IBM SPSS software was used for statistical analysis; p-value < 0.05 was considered statistically significant.

Results: There has been a relative increase in IMRT usage for the treatment of both low-risk (29% to 53%) and intermediate-risk (53% to 77%) PCa patients from 2004 to 2015. Observed comparable median OS in low-risk and intermediate-risk patients in these three modalities IMRT (74.8/63.4 mo.), LDR (77.7/65.7 mo.) and HDR (83.5/72.1 mo.).

Conclusion: The pattern of utilization of RT modality seems inclined toward increased use of IMRT over brachytherapy (59% vs. 41%) for both the low-risk and intermediate-risk PCa patients. Over the years, use of IMRT increased more in low-risk patient group than in intermediate-risk group.

Keywords: prostate cancer (PCa); overall survival, pattern of treatment; brachytherapy for PCa; IMRT for PCa

Abbreviations: RT: Radiation Therapy; IMRT: Intensity-Modulated Radiation Therapy; BT: Brachytherapy; LDR: Low Dose-Rate; NCDB: National Cancer Database; HDR: High Dose-Rate; NCCN: National Comprehensive Cancer Network; GS: Gleason Score; PSA: Prostate-Specific Antigen; PSM: Propensity-Score Matched; ACS: American College of Surgeons; HR: Hazard Ratios.

Introduction

Prostate cancer (PCa) is one of the most common cancers among men in US, with a 12.1% lifetime probability of developing the cancer (as per statistics from 2015-2017). The disease accounts for slightly above 21% of new cancer diagnoses in men every year [1]. Despite a high prevalence rate, prostate cancer accounts for about 10% of primary cancer-related deaths in men, however, has a 98% survival rate [2]. PCa patients often die due to inter current illnesses or secondary issues stemming from the original cancer and complications of treatment modalities, such as failure in the pulmonary circulation and heart failure [3]. Nonetheless, this disease remains of utmost interest to cancer researchers. PCa patients are currently stratified into three risk groups (low, intermediate, and high) based on three main factors: clinical T stage, Gleason score (now histologically compressed into Grade Groups), and PSA levels [4]. A wide array of treatment modalities is used consistently and preferentially to manage each individual's condition related to age, risk group, demographic, treatment center, and personal preferences, among many other factors. Surgery (prostatectomy), brachytherapy, intensity-modulated radiation therapy, hormonal therapy, and combination of multiple modalities are some of the commonly used treatment modalities [5]. Clinical guidelines regarding various treatment modalities have proven each of them to be safe, giving patients increased autonomy to choose a treatment plan of their preference [6].

IMRT is widely used as a standard treatment technique for prostate cancer [7]. IMRT's dose escalation is advantageous in cancer control without increasing toxicity [8-10]. There is evidence that high-dose IMRT (up to 81 Gy) yields high efficacy in preventing biochemical failure with acceptable side effects over the course of 10 years [11]. Meanwhile, BT's benefits include high dose conformity within the target volume, coupled with a rapid dose fall-off in adjacent organs and normal tissues. There is also a relatively short treatment period with excellent functional outcomes [12]. BT is advantageous in overcoming overall organ motion, and sparing nearby organs and at the same time delivering a very high dose. This allows for a thorough and concise biological

planning [12]. Even though BT is valuable in treating localized, low-risk prostate cancer, it is neither utilized frequently nor practiced uniformly across the nation [12-14]. To date, there have been limited randomized clinical studies performed to investigate the effectiveness of individual treatments for prostate cancer and they remain inconclusive unlike some other types of studies, due to lack of concrete control groups and possibilities of confounding variables [15,16]. Randomized attempts to assess such differences of effectiveness between various treatment modalities have been prematurely closed, due to decreases in longitudinal active surveillance and thus potential resulting toxicities [17]. Hence, randomized data directly comparing the efficacy and survival outcome of IMRT vs brachytherapy is currently lacking on a national scale [13].

This paper retrospectively investigates trends that are representative of prostate cancer management in the US population (i.e., a real-world scenario). Using the NCDB, data was accumulated from an extensive variety of centers across the country that differ in factors such as demographics served, size of the institution, research intent, etc. This large, diverse database may help us to reduce some of the biases expressed by big cancer centers and instead uncover the outcomes in community-based and smaller treatment centers across the country. We hope that clinicians and researchers may use these analyses to adjust or provide further guidance to their current practices of treating this prevalent disease.

Materials and Methods

Data Source

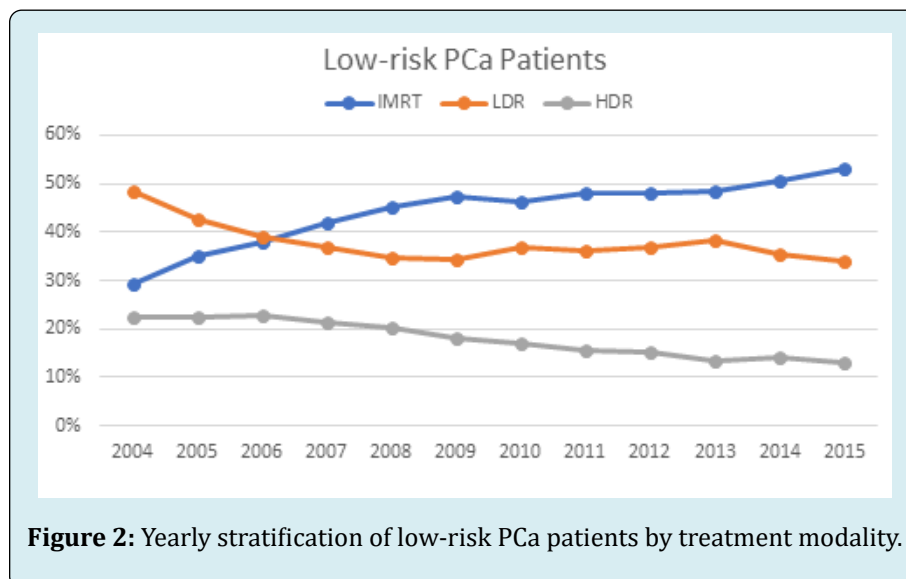
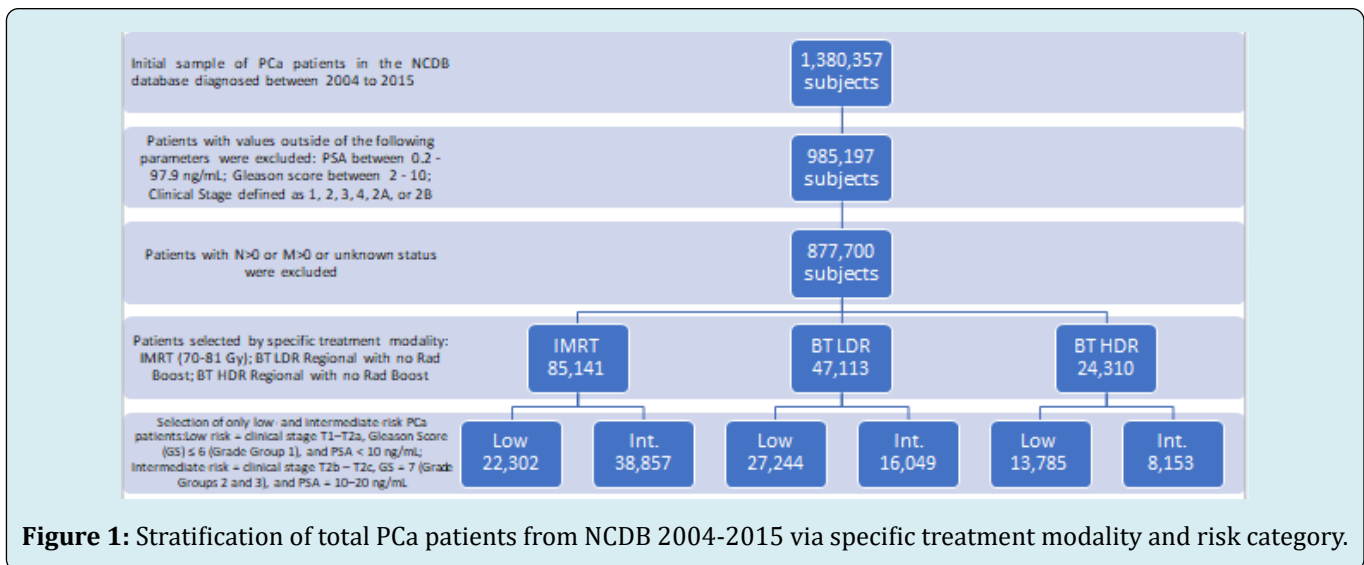
The NCDB is a nationwide clinical oncology database cosponsored by the American College of Surgeons and the American Cancer Society. Data is extracted from hospital registries of 1,500+ cancer-accredited facilities and represents an estimated 70% of all cancer cases across the United States. The information obtained from the NCDB included patient's demographics, facility type/location, cancer characteristics, Charlson/Deyo scores, treatment modality, and survival data for prostate cancer patients from 2004 to 2015. The records of these patients in the database were de-identified and sent to researchers for analysis after the approval of their research proposals. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the conclusions drawn from the data by the investigators in this study.

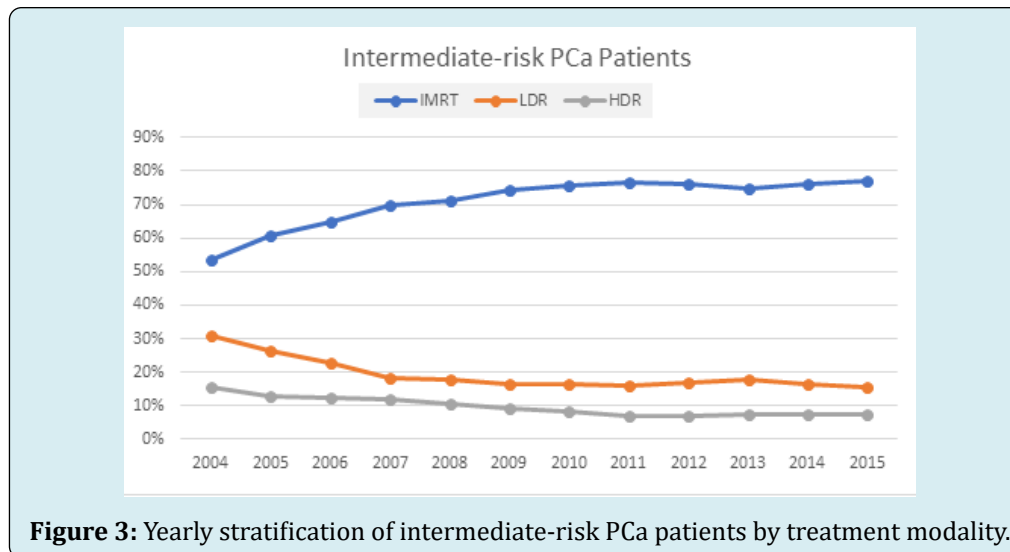
Subject Selection

A total of 1,380,357 patients were identified with prostate cancer diagnosis from 2004 to 2015. Of these, patients with

PSA levels between 0.2-97.9 ng/mL, Gleason score between 2-10, and Clinical Stage defined as 1, 2, 3, 4, 2A, or 2B were considered, yielding 985,197 subjects. Only patients with the American Joint Committee on Cancer (AJCC) N0 and M0 were considered for the analysis; the rest were excluded (Figure 1). From the remaining 877,700 subjects, PCa patients who underwent prostatectomy surgery/chemotherapy or had unknown surgery/chemotherapy status were also excluded. Finally, only the patients treated with IMRT (70-81 Gy), BT LDR, and BT HDR were included. Total subject frequency by treatment modality was as follows: 85,141 IMRT patients, 47,113 BT LDR patients, and 24,310 BT HDR patients. These patient groups were then stratified by risk, according to

the NCCN guidelines into two categories: low-risk [clinical stage T1-T2a, GS \leq 6 (Grade Group 1), and PSA < 10 ng/mL] and intermediate-risk [clinical stage T2b-T2c, GS = 7 (Grade Groups 2 and 3), and PSA = 10-20 ng/mL]. To be eligible for these categories, patients had to meet all three necessary criteria. Other T2 patients (i.e., T2-undefined) that met the GS and PSA criteria were also considered. Patients not categorized specifically into these two groups were excluded as out-of-scope for this study. Patient stratification is shown in (Figure 1). The yearly breakdown and utilization of treatment modality of the studied patient population from 2004 to 2015 are illustrated in (Figures 2 & 3).





Based on the specific radiotherapy technique used, we considered two treatment groups of patients from the eligible sample: (1) IMRT group (n=61,159; 48.4%), inclusive of initial + IMRT boost treatment, and (2) BT only group (n=65,231; 51.6%), who were treated with either low-dose-rate (LDR), high-dose-rate (HDR), or any other unspecified brachytherapy. The total dose considered was 70-81Gy for IMRT. The 70-81 Gy IMRT dosage was inclusive of the following patterns: 70-81 Gy in initial/primary IMRT with no additional Boost and 45-51 Gy with an in initial IMRT plan followed by a 25-30 Gy IMRT Boost plan. For Brachytherapy, only monotherapy was considered utilizing LDR, HDR, or unspecified brachytherapy.

Definition of Variables

The year of diagnosis was separated into periods from 2004-2007, 2008-2011, and 2012-2015. Age was stratified into groups of under 65, 65-69, 70-74, and more than 74 years old. The race was defined as white, black, other, or unknown. Insurance was categorized as private, government (including Medicare, Medicaid, and other government), or no insurance. Charlson-Deyo comorbidity index was recorded as the summation of comorbid conditions and was scored as 0, 1, 2, with a score of 0 representing no comorbid conditions recorded [18]. The 2013 US Department of Agriculture Rural-Urban Continuum was used to define metropolitan, urban, and rural areas. Counties in metropolitan areas were coded metropolitan, counties with an urban population of ≥ 2500 but those not in a metropolitan area were termed urban, and counties with an urban population of < 2500 were termed rural. Residential areas were stratified by median income into less than \$38,000, \$38,000-\$47,999, \$48,000-\$62,999, and \$63,000 and above; the statuses of a small set of patients were unknown. Similarly, the education levels of the residential areas were separated by percentage of

residents without high school degrees: $< 7\%$, 7-12.9%, 13-20.9%, $> 21\%$, and unknown. Distance from the residence to the facility was calculated as that between the center of the patient's zip code and the treating facility's mailing address. Facilities were primarily classified as academic/research-based or non-academic centers, with the status of 10 facilities unknown. Facility location was defined as:

- Northeast: CT, MA, ME, NH, NJ, NY, PA, RI, and VT.
- South: AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV.
- Midwest: IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI.
- West: AZ, AK, CA, CO, ID, HI, MT, NM, NV, OR, UT, WA, and WY.

Facilities were also stratified by the volume of cases seen, ranging from ≤ 100 , 101-200, 201-300, and > 300 cases. Classification of cases into T-Stages was divided into Stages 1, 2, 2A, 2B, or unknown. Lastly, the use of hormone therapy for PCa was included as yes, no, or unknown.

Statistical Analysis

To account for confounding variables, propensity score matching (PSM) was performed for patients treated with IMRT or BT LDR or BT HDR, for both risk groups (low and intermediate). Patients in the IMRT group were well matched with patients in the BT LDR group and the BT HDR group on the following characteristics: age of the patient, race of the patient, distance from the facility, year of diagnosis, clinical T stage, hormone therapy, duration of radiation (days from the start of radiation to the end of radiation), and the number of days between treatment starting and the day of diagnosis. The primary endpoint was median OS. Propensity score matching (1-1 nearest neighbor matching without replacement) was employed to match the three treatment groups using the caliper match algorithm described by Coca-

Perrailon, with the caliper width set to 0.01 [19]. These outcomes were assessed with a log-rank test, and the hazard ratios (HR) were determined by univariate Cox regression. Outcomes of survival probability were determined using a Kaplan-Meier estimator. IBM SPSS software (version 26.0) was used for the overall statistical analysis. For this study, a p-value <0.05 was considered statistically significant.

Disclaimer

This study was carried out as per the guidelines, data dictionary, and accompanying de-identified files provided by the NCDB. The findings of this study are neither endorsed nor verified by the NCDB, they are independently concluded by the listed investigators.

Results

Gross Breakdown

A total of 126,390 patients were selected in this study

after all pertaining inclusion and exclusion criteria had been applied. The breakdown of the total post-inclusion and post-exclusion sample (126,390 subjects) was performed via risk stratification: 63,331 subjects (50.1% of total) being classified as low-risk and 63,059 subjects (49.9%) are being classified as intermediate-risk. The individual risk categories were then further stratified into respective treatment modalities as shown in (Figure 1). These modalities are subsequently trended over the course of the study period in Figures 2 and 3. Demographical breakdown by treatment modality is as follows: 65,231 patients (51.6% of total) that underwent brachytherapy and 61,159 patients (48.4%) that underwent 70-81 Gy IMRT. Baseline characteristics, including patient demographics, facility type, stage of disease and treatment for low- and intermediate-risk categories are shown in (Table 1). These baseline characteristics for each risk group are broken down further by treatment modality in (Table 2). It appeared that in both low-risk and intermediate-risk groups, younger patients with private insurance were more likely to receive BT as primary therapy (Table 1).

Baseline characteristics	Number of Low-risk patients (%)	Number of Intermediate-risk patients (%)
Overall (n)	63331	63059
Year of Diagnosis		
2004 – 2007	28692 (45.3)	19414 (30.8)
2008 – 2011	23291 (36.8)	23074 (36.6)
2012 – 2015	11348 (17.9)	20571 (32.6)
Age (years)		
Less than 65	26506 (41.9)	18426 (29.2)
65 – 69	15957 (25.2)	14699 (23.3)
70 – 74	13193 (20.8)	15398 (24.4)
More than 74	7675 (12.1)	14536 (23.1)
Race		
White	52579 (83.0)	51096 (81.0)
Black	8643 (13.6)	9634 (15.3)
Other	1367 (2.2)	1651 (2.6)
Unknown	742 (1.2)	678 (1.1)
Insurance Status		
Private	27396 (43.3)	20299 (32.2)
Government	34505 (54.5)	41304 (65.5)
None	565 (0.9)	683 (1.1)
Unknown	865 (1.4)	773 (1.2)
Residential Setting		
Metro	50928 (80.4)	50228 (79.7)

Urban	9545 (15.1)	9665 (15.3)
Rural	1274 (2.0)	1498 (2.4)
Unknown	1584 (2.5)	1668 (2.6)
Median Income (residential area)		
Less than \$38,000	10001 (15.8)	10591 (16.8)
\$38,000 - \$47,999	14462 (22.8)	14263 (22.6)
\$48,000 - \$62,999	16639 (26.3)	17061 (27.1)
\$63,000 and more	21692 (34.3)	20670 (32.8)
Unknown	537 (0.8)	474 (0.8)
Without high school degree (residential area), %		
Less than 7	16648 (26.3)	16371 (26.0)
7 - 12.9	21629 (34.2)	21228 (33.7)
13 - 20.9	15526 (24.5)	15609 (24.8)
21 and higher	9031 (14.3)	9427 (14.9)
Unknown	497 (0.8)	424 (0.7)
Distance from facility to residence, miles		
Less than 5	17661 (27.9)	18191 (28.8)
5 - 9.9	14484 (22.9)	14597 (23.1)
10 - 24.9	17373 (27.4)	17249 (27.4)
25 and higher	13336 (21.1)	12618 (20.0)
Unknown	477 (0.8)	477 (0.8)
Facility Type		
Non-academic	46377 (73.2)	45563 (72.3)
Academic/research	16944 (26.8)	17495 (27.7)
Unknown	10 (0.0)	1 (0.0)
Facility Location		
Northeast	15325 (24.2)	14377 (22.8)
South	22481 (35.5)	21162 (33.6)
Midwest	16979 (26.8)	18165 (28.8)
West	8536 (13.5)	9353 (14.8)
Unknown	10 (0.0)	1 (0.0)
Facility volume, cases		
Less than 100	28250 (44.6)	31560 (50.0)
101 - 200	14798 (23.4)	16310 (25.9)
201 - 300	10352 (16.3)	7515 (11.9)
More than 300	9931 (15.7)	7674 (12.2)
T stage		
1	19200 (30.3)	2656 (4.2)
2	41668 (65.8)	31695 (50.3)
2A	1617 (2.6)	25760 (40.9)
2B	844 (1.3)	2935 (4.7)

Unknown	2 (0.0)	13 (0.0)
Prostate-specific antigen		
Between 0.2 to 2.9 ng/mL	6606 (10.4)	3963 (6.3)
Between 3 to 6.9 ng/mL	43068 (68.0)	29467 (46.7)
Between 7 and 10.0 ng/mL	13657 (21.6)	13536 (21.5)
Between 10.1 and 20 ng/mL	-----	16093 (25.5)
Total Gleason Score		
Less than 6	1734 (2.7)	360 (0.6)
6	61597 (97.3)	10801 (17.1)
7	-----	51898 (82.3)
Radiotherapy		
IMRT	22302 (35.2)	38857 (61.6)
BT LDR	27344 (43.0)	16049 (25.5)
BT HDR	13785 (21.8)	8153 (12.9)
Hormonal Therapy		
No	51155 (80.8)	39695 (62.9)
Yes	10024 (15.8)	21855 (34.7)
Unknown	2152 (3.4)	1509 (2.4)

Table 1: Baseline characteristics of all patients with low- or intermediate-risk prostate cancer who received IMRT or BT LDR or BT HDR (n=126,390), p-value < 0.001.

Low Risk	IMRT (n = 22302)	BT LDR (n = 27244)	BT HDR (n = 13785)
Year of Diagnosis			
2004 – 2007	8424 (37.8)	13061 (47.9)	7207 (52.3)
2008 – 2011	9115 (40.9)	9436 (34.6)	4740 (34.4)
2012 – 2015	4763 (21.4)	4747 (17.4)	1838 (13.3)
Age (years)			
Less than 65	7631 (34.2)	12348 (45.3)	6527 (47.3)
65 – 69	5735 (25.7)	6910 (25.4)	3312 (24.0)
70 – 74	5274 (23.6)	5297 (19.4)	2622 (19.0)
More than 74	3662 (16.4)	2689 (9.9)	1324 (9.6)
Race			
White	18029 (80.8)	23214 (85.2)	11336 (82.2)
Black	3484 (15.6)	3321 (12.2)	1838 (13.3)
Other	542 (2.4)	433 (1.6)	392 (2.8)
(Unknown = 742)			
Insurance Status			
Private	7956 (35.7)	12682 (46.5)	6758 (49.0)
Government	13727 (61.6)	14038 (51.5)	6740 (48.9)
None	263 (1.2)	191 (0.7)	111 (0.8)
(Unknown = 865)	356 (1.6)	333 (1.2)	176 (1.3)

Residential Setting			
Metro	18353 (82.3)	21009 (77.1)	11566 (83.9)
Urban	3052 (13.7)	4766 (17.5)	1727 (12.5)
Rural	359 (1.6)	696 (2.6)	219 (1.6)
(missing = 1584)			
Median Income (residential area)			
Less than \$38,000	3765 (16.9)	4371 (16.0)	1865 (13.5)
\$38,000 - \$47,999	4993 (22.4)	6608 (24.3)	2861 (20.8)
\$48,000 - \$62,999	6100 (27.4)	7131 (26.2)	3408 (24.7)
\$63,000 and more	7289 (32.7)	8849 (32.5)	5554 (40.3)
(missing = 537)			
Without high school degree (residential area), %			
Less than 7			
7 - 12.9	5616 (25.2)	6962 (25.6)	4070 (29.5)
13 - 20.9	7616 (34.1)	9406 (34.5)	4607 (33.4)
21 and higher	5493 (24.6)	6720 (24.7)	3313 (24.0)
(missing = 497)	3433 (15.4)	3892 (14.3)	1706 (12.4)
Distance from facility to residence, miles			
Less than 5	7591 (34.0)	6631 (24.3)	3439 (24.9)
5 - 9.9	5649 (25.3)	5650 (20.7)	3185 (23.1)
10 - 24.9	6054 (27.1)	7575 (27.8)	3744 (27.2)
25 and higher	2868 (12.9)	7133 (26.2)	3335 (24.2)
(missing = 477)			
Facility Type			
Non-academic	16323 (73.2)	20638 (75.8)	9416 (68.3)
Academic/research	5978 (26.8)	6601 (24.2)	4365 (31.7)
(missing = 10)			
Facility Location			
Northeast	6324 (28.4)	5925 (21.7)	3076 (22.3)
South	6973 (31.3)	10494 (38.5)	5014 (36.4)
Midwest	6469 (29.0)	7243 (26.6)	3267 (23.7)
West	2535 (11.4)	3577 (13.1)	2424 (17.6)
(missing = 10)			
Facility volume, cases			
Less than 100	12898 (57.8)	10308 (37.8)	5044 (36.6)
101 - 200	4028 (18.1)	6873 (25.2)	3897 (28.3)
201 - 300	3247 (14.6)	4896 (18.0)	2209 (16.0)
More than 300	2129 (9.5)	5167 (19.0)	2635 (19.1)
T stage			
1	7783 (34.9)	8175 (30.0)	3242 (23.5)

2	13434 (60.2)	18183 (66.7)	10051 (72.9)
2A	771 (3.5)	528 (1.9)	318 (2.3)
2B	313 (1.4)	358 (1.3)	173 (1.3)
(missing = 2)			
Hormonal Therapy			
No	18503 (83.0)	21502 (78.9)	11150 (80.9)
Yes	2977 (13.3)	4836 (17.8)	2211 (16.0)
(unknown = 2152)			

Table 2: Comparative utilization of IMRT, BT LDR, and BT HDR for low-risk and intermediate-risk prostate cancer patients (p-value <0.001).

Trends In Utilization

As observed in Figures 2 and 3, there was a decline in usage of BT (both LDR and HDR) in the treatment of low- and intermediate-risk PCa patients from 2004-2015. While year-to-year variations may not fully adhere to the gross pattern over the 11 years, the overall trend of BT utilization declined over this timespan. In contrast, a relative increase in the usage of IMRT in both risk categories was observed.

Univariable Analyses of Patient Population

In the low-risk population, overall survival was significantly increased with races other than black or white, incomes greater than \$38,000, treatment at an academic/research facility, and facility volume >200 patients seen. Within the low-risk population, poorer survival was associated with increasingly rural areas, government-insured and uninsured populations, areas with greater percentages of those without high school diplomas (starting at less than 7%), facilities located in the South and the Midwest, and patients who underwent hormonal therapy. Univariable analyses differed when compared to the intermediate-risk population group. Significant differences in overall survival were no longer present with patients living in rural areas,

patients without insurance, residential areas with median incomes between \$38,000-\$47,999, and those undergoing hormonal therapy. However, facility locations in the South and the Midwest were still significantly associated with poorer survival (in comparison to the Northeast).

Multivariable Analyses of Patient Populations

Multivariable Cox proportional hazard models is shown in Table 3 to better understand survival trends. Hazard ratios are superior in effectively capturing the effects of the variables studied over the entire duration of the Kaplan-Meier curve, rather than at a single point as is done by the median survival statistic [20]. In addition, such analysis allows for further understanding of survival trends if carried out with propensity score matching. Within the low-risk population, the multivariable analysis indicated significantly increased overall survival associated with relatively younger patients, incomes greater than \$63,000, the West (geographical location of the facility), and usage of BT LDR and BT HDR. Additionally, poorer survival outcomes were significantly associated with government insurance and areas with greater percentages of those without high school diplomas 13% or greater. The same trends were noticed in the multivariable analyses of the intermediate-risk population group.

Factor	Univariable		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Low-risk				
Year of Diagnosis				
2004 – 2007	1	0.75	1	0.311
2008 – 2011	1.01 (0.96 – 1.06)	0.344	1.03 (0.97 – 1.10)	0.998
2012 – 2015	0.94 (0.82 – 1.07)		1.00 (0.85 – 1.18)	
Age (years)				
Less than 65	1	<0.001	1	<0.001
65 – 69	1.69 (1.56 – 1.78)	<0.001	1.32 (1.22 – 1.43)	<0.001

70 – 74	2.30 (2.16 – 2.45)	<0.001	1.78 (1.65 – 1.93)	<0.001
More than 74	3.65 (3.43 – 3.89)		2.80 (2.59 – 3.04)	
Race				
White	1	0.418	1	0.098
Black	1.03 (0.96 – 1.10)	<0.001	1.06 (0.99 – 1.15)	0.011
Other	0.67 (0.56 – 0.80)		0.79 (0.65 – 0.95)	
Insurance				
Private	1	<0.001	1	<0.001
Government	2.23 (2.12 – 2.35)	<0.001	1.44 (1.35 – 1.54)	0.014
None	1.55 (1.20 – 2.01)		1.41 (1.07 – 1.84)	
Residential Setting				
Metro	1	<0.001	1	0.256
Urban	1.19 (1.12 – 1.26)	<0.001	1.04 (0.97 – 1.12)	0.009
Rural	1.43 (1.24 – 1.64)		1.22 (1.05 – 1.42)	
Median Income (residential area)				
Less than \$38,000	1	<0.001	1	0.018
\$38,000 - \$47,999	0.87 (0.81 – 0.93)	<0.001	0.91 (0.85 – 0.99)	0.003
\$48,000 - \$62,999	0.77 (0.72 – 0.82)	<0.001	0.89 (0.82 – 0.96)	<0.001
\$63,000 and more	0.64 (0.60 – 0.68)		0.82 (0.74 – 0.90)	
Without high school degree (residential area), %				
Less than 7	1	<0.001	1	0.002
7 – 12.9	1.18 (1.12 – 1.26)	<0.001	1.11 (1.04 – 1.19)	<0.001
13 – 20.9	1.38 (1.30 – 1.47)	<0.001	1.22 (1.12 – 1.32)	<0.001
21 and higher	1.49 (1.39 – 1.60)		1.26 (1.14 – 1.39)	
Distance from Facility to Residence, Miles				
Less than 5	1	---	1	---
5 – 9.9	0.93 (0.88 – 0.99)	0.025	1.00 (0.94 – 1.07)	0.909
10 – 24.9	0.92 (0.87 – 0.98)	0.005	0.99 (0.94 – 1.06)	0.924
25 and higher	0.95 (0.89 – 1.01)	0.107	0.90 (0.83 – 0.97)	0.006
Facility Type				
Non-academic	1	<0.001	1	0.176
Academic/research	0.85 (0.81 – 0.90)		0.96 (0.91 – 1.02)	
Facility Location				
Northeast	1	<0.001	1	0.195
South	1.20 (1.14 – 1.27)	0.001	1.04 (0.98 – 1.11)	0.666
Midwest	1.11 (1.04 – 1.17)	<0.001	0.99 (0.92 – 1.05)	<0.001
West	0.74 (0.68 – 0.80)		0.78 (0.72 – 0.85)	
Facility Volume, Cases				
Less than 100	1	0.511	1	0.8

101 -- 200	1.02 (0.97 - 1.08)	<0.001	1.01 (0.95 - 1.07)	0.005
201 -- 300	0.87 (0.82 - 0.93)	<0.001	0.91 (0.85 - 0.97)	0.168
More than 300	0.82 (0.77 - 0.87)		0.95 (0.89 - 1.02)	
T stage				
1	1	0.838	1	0.903
2	1.02 (0.83 - 1.27)	0.523	0.99 (0.79 - 1.24)	0.484
2A	0.92 (0.70 - 1.20)	0.063	0.91 (0.69 - 1.19)	0.179
2B	1.07 (0.99 - 1.16)		1.07 (0.97 - 1.17)	
Radiotherapy				
IMRT	1	<0.001	1	<0.001
BT LDR	0.75 (0.71 - 0.79)	<0.001	0.85 (0.81 - 0.90)	<0.001
BT HDR	0.69 (0.65 - 0.73)		0.83 (0.78 - 0.88)	
Hormonal Therapy				
No	1	<0.001	1	0.125
Yes	1.14 (1.08 - 1.21)		0.96 (0.91 - 1.01)	
Intermediate-risk				
Year of Diagnosis				
2004 - 2007	1	0.955	1	0.828
2008 - 2011	0.99 (0.95 - 1.05)	0.464	1.01 (0.95 - 1.06)	0.977
2012 - 2015	0.97 (0.89 - 1.06)		0.99 (0.89 - 1.11)	
Age (years)				
Less than 65	1	<0.001	1	<0.001
65 - 69	1.39 (1.30 - 1.49)	<0.001	1.19 (1.10 - 1.28)	<0.001
70 - 74	1.76 (1.65 - 1.87)	<0.001	1.48 (1.37 - 1.59)	<0.001
More than 74	2.70 (2.55 - 2.87)		2.31 (2.15 - 2.49)	
Race				
White	1	0.579	1	0.386
Black	0.98 (0.93 - 1.04)	<0.001	1.03 (0.96 - 1.10)	0.009
Other	0.77 (0.67 - 0.88)		0.82 (0.71 - 0.95)	
Insurance				
Private	1	<0.001	1	<0.001
Government	1.85 (1.77 - 1.95)	0.212	1.33 (1.26 - 1.42)	0.526
None	1.17 (0.92 - 1.48)		1.08 (0.84 - 1.39)	
Residential Setting				
Metro	1	<0.001	1	0.706
Urban	1.12 (1.07 - 1.19)	0.005	0.99 (0.93 - 1.05)	0.821
Rural	1.20 (1.06 - 1.35)		1.02 (0.89 - 1.16)	
Median Income (residential area)				
Less than \$38,000	1	0.007	1	0.098
\$38,000 - \$47,999	0.92 (0.87 - 0.98)	<0.001	0.94 (0.88 - 1.01)	0.024

\$48,000 - \$62,999	0.85 (0.80 - 0.90)	<0.001	0.92 (0.85 - 0.99)	<0.001
\$63,000 and more	0.69 (0.65 - 0.73)		0.80 (0.73 - 0.87)	
Without high school degree (residential area), %				
Less than 7	1	<0.001	1	0.092
7 - 12.9	1.16 (1.10 - 1.22)	<0.001	1.05 (0.99 - 1.12)	<0.001
13 - 20.9	1.32 (1.25 - 1.39)	<0.001	1.15 (1.07 - 1.23)	<0.001
21 and higher	1.37 (1.29 - 1.46)		1.20 (1.10 - 1.32)	
Distance from facility to Residence, Miles				
Less than 5	1	0.001	1	0.087
5 - 9.9	0.91 (0.88 - 0.96)	0.001	0.95 (0.90 - 1.01)	0.334
10 - 24.9	0.91 (0.87 - 0.96)	0.013	0.97 (0.92 - 1.03)	0.012
25 and higher	0.93 (0.88 - 0.98)		0.91 (0.85 - 0.98)	
Facility Type				
Non-academic	1	<0.001	1	0.089
Academic/research	0.87 (0.83 - 0.91)		0.96 (0.91 - 1.01)	
Facility Location				
Northeast	1	<0.001	1	0.289
South	1.15 (1.09 - 1.21)	<0.001	1.03 (0.97 - 1.10)	0.492
Midwest	1.11 (1.05 - 1.17)	<0.001	1.02 (0.96 - 1.09)	<0.001
West	0.85 (0.80 - 0.91)		0.85 (0.79 - 0.91)	
Facility volume, cases				
Less than 100	1	<0.001	1	0.079
101 -- 200	0.92 (0.88 - 0.96)	0.002	0.96 (0.91 - 1.01)	0.025
201 -- 300	0.90 (0.85 - 0.96)	<0.001	0.92 (0.86 - 0.99)	0.061
More than 300	0.85 (0.80 - 0.91)		0.94 (0.87 - 1.00)	
T stage				
1	1	0.605	1	---
2	1.04 (0.90 - 1.20)	0.105	0.99 (0.91 - 1.22)	0.502
2A	1.16 (0.97 - 1.38)	0.346	0.91 (0.95 - 1.38)	0.151
2B	1.07 (0.93 - 1.22)		1.05 (0.91 - 1.22)	0.503
Radiotherapy				
IMRT	1	<0.001	1	<0.001
BT LDR	0.75 (0.72 - 0.79)	<0.001	0.83 (0.79 - 0.88)	<0.001
BT HDR	0.68 (0.64 - 0.73)		0.82 (0.77 - 0.88)	
Hormonal Therapy				
No	1	0.001	1	0.343
Yes	1.08 (1.03 - 1.12)		0.98 (0.94 - 1.02)	

Table 3: Unadjusted and adjusted hazard ratios (HR) for respective univariate and multivariate Cox proportional hazard models of overall survival in low-risk and intermediate-risk prostate cancer patients who received IMRT or BT LDR or BT HDR.

Survival Outcomes

Trends in survival are presented in Table 4. Median OS was calculated as the number of months from a patient's diagnosis to last contact or death. Outcomes

were distinguishable by both risk category and treatment modality. All data points were found to be significant with $p < 0.001$ (Table 4).

Risk	IMRT	BT LDR	BT HDR	p-value
Low	74.84	77.73	83.65	<0.001
Intermediate	63.37	65.68	72.11	<0.001

Table 4: Median OS (months) for low- (n=63,331) and intermediate-risk (n=63,059) PCa patients.

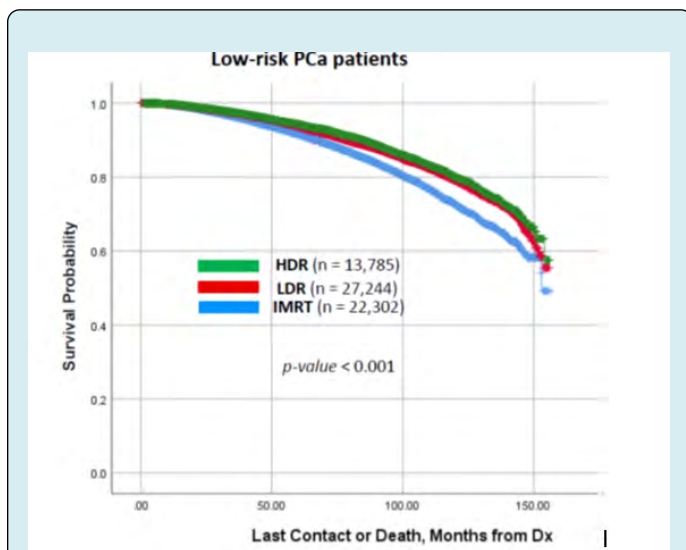


Figure 4: Kaplan-Meier curve for cumulative survival of low-risk patient prostate cancer (PCa) patients treated with IMRT, BT LDR, and BT HDR.

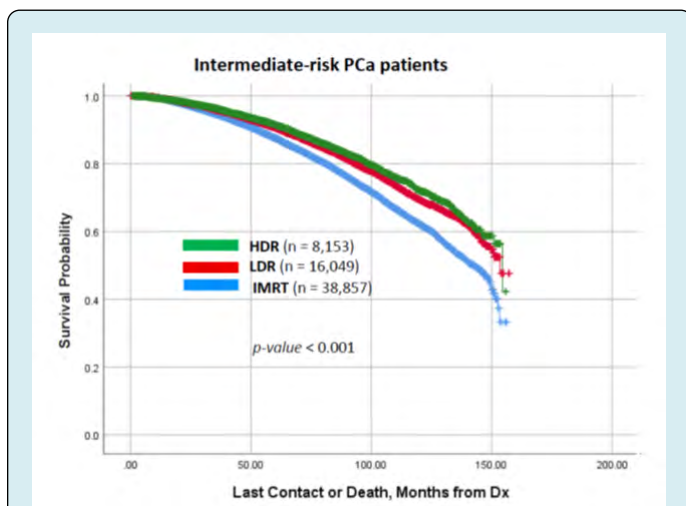


Figure 5: Kaplan-Meier curve for cumulative survival of intermediate-risk patient prostate cancer (PCa) patients treated with IMRT, BT LDR, and BT HDR.

As expected, the low-risk population group exhibited better survival figures than the intermediate-risk group across the respectively matched treatment groups. Appeared that the OS for BT HDR treatment group was slightly better than other two groups (i.e. IMRT and BT LDR). Kaplan-Meier survival curves (Figures 4 and 5), shows better OS achieved by BT over IMRT. As seen in these curves, there is a clear superiority of BT HDR in OS for both low- and intermediate-risk populations. IMRT maintained the relatively lower cumulative survival than BT groups in both risk groups.

Propensity Score Matching

Propensity score matching between IMRT, BT LDR, and BT HDR groups in low- and intermediate-risk patients was performed to address confounding patient demographics, cancer characteristics, and treatment differences between the groups. Variables included in the PSM analysis were age, race, comorbidity, distance from the facility, year of diagnosis, clinical stage of treatment, hormone therapy, number of days from the day of diagnosis to start of treatment, and number of days between start and end of radiation treatment. Patients were then paired 1:1 based on these propensity scores using the “greedy” nearest-neighbor matching algorithm without replacement [21]. Patient order was randomized while drawing matches to prevent a drastically shrunken pool of potential matches for those appearing later in a fixed-order list. Standardized differences were estimated before and after matching to evaluate the balance of covariates, and a match tolerance level of 0.01 was used (i.e., standardized differences < 0.1 indicated balance between the treatment groups). Following 1:1 propensity score-matching, OS between matched IMRT, BT LDR, and BT HDR cohorts was examined by Kaplan-Meier analysis using the Klein-Moeschberger methodology [22]. For the low-risk patient group, the PSM for all patients combined resulted in a cohort consisting of 31,491 patients, well-matched and divided between IMRT, BT LDR, and BT HDR. We followed the same approach for the intermediate-risk patient group, and the PSM cohort consisted of a 21,135-patients, well-matched and divided between IMRT, BT LDR, and BT HDR.

The post-PSM median OS for these two groups are presented in (Table 5).

Risk	IMRT	BT LDR	BT HDR	p-value
Low	77.75	84.40	81.38	<0.001
Intermediate	68.11	72.61	72.05	

Table 5: Median OS (months) for low- (n=31,491) and intermediate-risk (n=21,135) PCa patients, post-PSM.

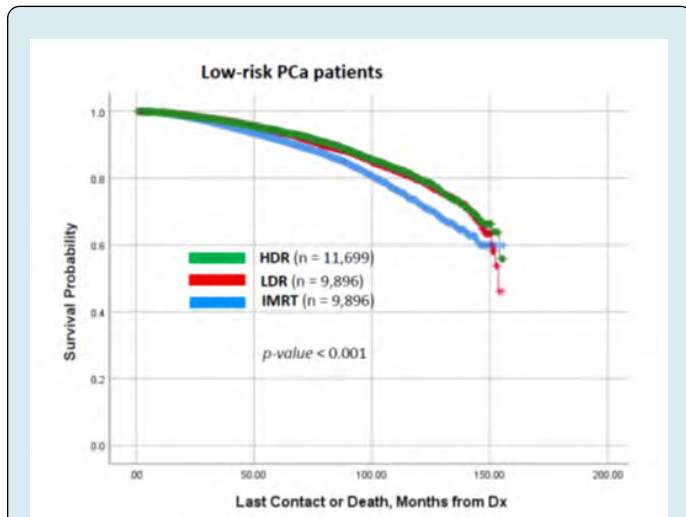


Figure 6: Kaplan-Meier curve for cumulative survival of low-risk patient prostate cancer (PCa) propensity score-matched patients treated with IMRT, BT LDR, and BT HDR.

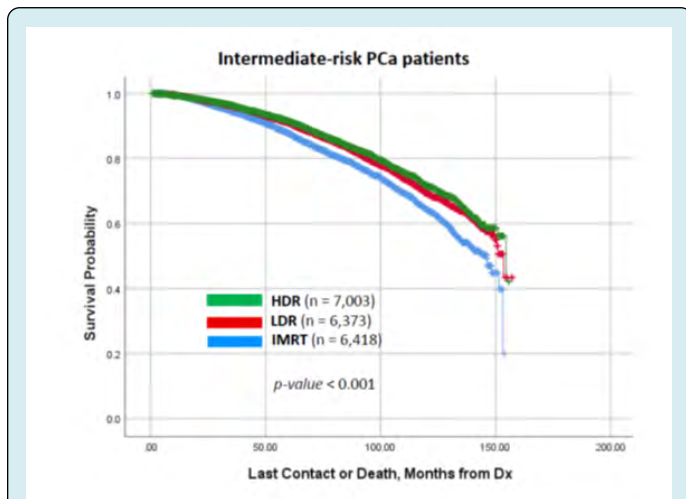


Figure 7: Kaplan-Meier curve for cumulative survival of intermediate-risk patient prostate cancer (PCa) propensity score-matched patients treated with IMRT, BT LDR, and BT HDR.

There were differences in median OS trends after the PSM analysis. Contrary to the longer median OS of BT HDR previously, median OS after PSM was longest in the BT LDR

in (Table 5).

group in both low- (84.40 months) and intermediate-risk (72.61 months) patients. In the low-risk group, BT LDR had 3.7% higher median OS than BT HDR and 8.6% longer than IMRT. The intermediate-risk group showed BT LDR to have only 0.8% higher median OS than BT HDR but 6.6% higher than IMRT. Consistent with the findings above, post-PSM Kaplan-Meier curves show significant survival differences with matched datasets for both the low-risk patient group (Figure 6) and the intermediate-risk patient group (Figure 7).

Discussion

The increased use of IMRT compared to brachytherapy (LDR and HDR combined) was the first notable observation in this study. Increasing usage of IMRT may reflect a possible treatment preference throughout the US for similar patient population groups. This is in alignment with the report by Mohler J, et al. that IMRT has established itself as the standard radiotherapy treatment for prostate cancer, and its usage accounting for nearly 80% of all radiotherapy modalities [23]. This is an important finding. Prior report by Glazer, et al. [24] looking at NCDDB data also showed similar pattern of declined use of brachytherapy in intermediate- and high-risk PCa. The main difference between their study and the current study is that they included both intermediate- and high-risk patients and compared between brachytherapy boost and IMRT dose escalation. Several other reports also commented on this alarming trend in decrease in utilization of brachytherapy altogether [25-27]. However, it is unclear why the use of IMRT is increasing in the past decade compared to the use of BT. The reasons could be multifactorial including current reimbursement model and decreased availability of a well-trained physician performing brachytherapy treatment. Unfortunately, further exploration in this regard is beyond the scope of this study.

The median OS for all three modalities (IMRT, BT LDR and BT HDR) were comparable, BT appeared slightly better. When the survival points were analyzed by propensity score matching, the same trend continued. We also observed, as shown in Table 2, younger patients with private insurance were more likely to receive BT compared to older patients with government insurance where IMRT was a preferential treatment. This may be to some extent responsible for better

OS of patients who had brachytherapy. Interestingly, high volume centers with > 300 patients had more BT treatment compared to centers with <100 patients where IMRT was preferred. The reasons are unknown, but it is possible that younger patients received BT because of the convenience of shorter treatment course versus older people who are considered higher risk for anesthesia required for BT.

Main aims of this study were to 1) investigate the usage rates of IMRT (70-81 Gy), BT LDR, and BT HDR in the treatment of prostate cancer on a national scale, and 2) analyze corresponding baseline characteristics and survival outcomes of each treatment modality. A key focus of this paper was to analyze trends that are representative of low- and intermediate-risk prostate cancer management in the US population. We acknowledge that the quality of our results may not be equivalent to those of a randomized trial due to inherent selection bias with retrospective data, which we attempted to minimize by doing PSM analysis but nonetheless is present. However, this large data set is composed of real-world practices across the country where a majority of patients are treated. Usage of PSM statistical technique with the observational data points in the NCDB database allows us to partially mimic some characteristics of any randomized study. PSM allows for estimation of population-average treatment effects, in contrast to regression-based approaches [28]. The results in this study may aid in general clinical decision-making or adjust the clinical practice for prostate cancer treatment.

We acknowledge that there are several limitations in this study, they include:

- The lack of information/guidelines regarding the choice of treatment in each patient. For example, patients and urologists tend to avoid BT for higher-risk cancers and thus may lead to treatment selection bias. Follow-up therapies after initial treatment were not considered.
- The total patient dataset from 2004-2015 may not be uniform in length of follow-up for each subject, as subjects from earlier timeframes are probable to have longer follow-up periods than those from more recent timeframes. While this did not impact results in our study, analysis of distinct, mature follow-up groups may show more compelling differences in future studies.
- There is potential availability bias as only accredited hospitals input data in the NCDB registry.
- Differences in other important clinical endpoints (quality of life, adverse events, and other toxicities) were not assessed.
- There is missing toxicity-related data. With that being said, survival is the most important outcome with treatment according to the NCCN guidelines [29].

The greatest strength of this study resides with the usage of a nationwide cancer database; it provides a large number of patients that could be representative of actual prostate cancer treatment throughout the US and avoids influences that are typically present in single-institution studies. The database is also homogenous in the stratification of the sample, with objective criteria separating the patients into low- and intermediate-risk groups. Despite these strengths, the presence of numerous limitations means further investigation is warranted.

Conclusion

This large-scale, analysis of the NCDB data showed that a preferential treatment existed for non-surgical, non-chemotherapy, low- and intermediate-risk prostate cancer patients from 2004-2015. There was a trend of increased utilization of IMRT over the years. Increased utilization of IMRT for low-risk patients was more prominent than for intermediate-risk patients. The overall survival in all three modalities were comparable. Randomized trials and longer observation periods of retrospective data would be desirable to confirm these findings.

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