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Clinical-Prostate cancer

National practice patterns for lymph node irradiation in 197,000 men receiving external beam radiotherapy for localized prostate cancer

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Abstract

Purpose: Controversy surrounds the benefit of pelvic lymph node irradiation (PLN-RT) in localized prostate cancer (CaP). Our objective was to determine the practice patterns and predictors of PLN-RT in a national cohort.

Materials and methods: The National Cancer Data Base (2005−2015) was leveraged to obtain men diagnosed with nonmetastatic CaP treated with external beam radiotherapy ($n = 197{,}378$). Multivariable logistic regressions were used to assess temporal trends and factors associated with PLN-RT.

Results: PLN-RT occurred in 37% of patients overall, which increased to 41% by 2015. When stratified by risk group, there was no significant difference in PLN-RT over time in low, favorable intermediate, unfavorable intermediate, or high-risk CaP. PLN-RT increased for men with very high-risk disease (51%−60%; odds ratio per year 1.34, 95% confidence inrerval 1.06−1.70, $P = 0.013$). Increased odds of PLN-RT was associated with higher risk disease, addition of hormone therapy, treatment at community hospitals, and shorter patient travel distance to treatment facilities. Surprisingly, 26% and 34% of low and favorable intermediate risk CaP received PLN-RT, respectively. Predictors of PLN-RT among these patients included treatment at a community practice and use of brachytherapy or hormone therapy.

Conclusions: PLN-RT occurred in about one-third of men receiving external beam radiotherapy and increased over time, mostly in men with very high-risk CaP for unclear reasons. Of concern, over one-quarter of low-risk men receive PLN-RT. Further work is needed to understand the heterogeneity in PLN-RT use. We await the completion of RTO G 09-24 to better understand the role of PLN-RT for men with localized CaP.

Keywords: Prostatic neoplasms; United States; Epidemiology; Radical prostatectomy; Radiotherapy; Brachytherapy

1. Introduction

Prostate cancer (CaP) is the second most common malignancy in men, with an estimated incidence of 120 newly diagnosed cases per 100,000 men in the United States [1]. The National Comprehensive Cancer Network (NCCN) recommends external beam radiotherapy (EBRT) with androgen deprivation therapy (ADT) as a primary treatment option for unfavorable intermediate-, high-, and very high-risk clinically localized CaP. The addition of pelvic lymph node irradiation (PLN-RT) can be considered for these men based on the increased potential for harboring micrometastatic nodal disease [2]. However, conflicting evidence from retrospective and prospective randomized trials has made the purported benefits of PLN-RT controversial [3,4].

Amid this controversy, it is currently unknown how frequently PLN-RT is performed and what factors influence its usage. We hypothesized that PLN-RT use has increased with time according to NCCN recommendations and sought to better understand the contemporary role of PLN-RT for localized CaP.

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2. Material and methods

2.1. Data source and patients

Following Northwestern University institutional review board exemption, we derived our cohort from the latest release of the National Cancer Data Base (NCDB) CaP participant user file with data through 2015. The NCDB is a hospital-based cancer registry comprised of more than 1,500 hospitals accredited by the American College of Surgeons Commission on Cancer [5]. Based on estimates from the American Cancer Society, the NCDB captured about 53% of all new CaP cases diagnosed in the United States in 2015 [6,7].

We included all men diagnosed with localized adenocarcinoma of the prostate from 2005 through 2015 who underwent EBRT with or without brachytherapy and ADT as their primary definitive treatment within 1 year of diagnosis ($n = 265,763$, 100%). We excluded men with unknown information on EBRT target (prostate vs. prostate and lymph nodes; $n = 20,767$, 7.8%). Men were also excluded if they lacked information on patient and facility characteristics ($n = 6,934$, 2.6%) or tumor risk details including clinical stage, biopsy Gleason score, and pretreatment prostatic-specific antigen (PSA; $n = 28,610$, 10.8%). Finally, to minimize bias in temporal trends, we excluded men from facilities that did not contribute patients each year throughout the study period in the NCDB ($n = 12,074$, 4.5%).

2.2. Covariates

All covariates assessed in multivariable analyses were chosen a priori (Table 1). Patient characteristics included year of diagnosis, age at diagnosis, race/ethnicity defined as non-Hispanic white, non-Hispanic black, Hispanic, or other/unknown, and comorbidities defined by the Charlson comorbidity index. Distance traveled from residence to treatment facility was defined by distance between the center of the patient's zip code or city and the hospital. Patient regional education was defined as high school attainment level. Both regional education and income levels were derived from 2012 American Community Survey data, which averaged values from 2008 to 2012. Patient home regions were defined as metropolitan, urban, or rural were based on county populations as defined by the United States Department of Agriculture Economic Research Service. The NCDB also captures data on patient insurance type defined as the primary payer of medical expenses.

Tumor characteristics included International Society of Urological Pathology (ISUP) grade grouping, with increasing grade group representing higher grade disease, clinical T stage, and pretreatment PSA. Risk group was defined using NCCN guidelines [2].

Treatment facilities were categorized by geographic region within the United States. Facility type within the

Table 1
Cohort characteristics.

Covariate	*n* (%)
All	197,378 (100)
Year of diagnosis	
2005	19,347 (9.8)
2006	20,504 (10.4)
2007	21,902 (11.1)
2008	20,253 (10.3)
2009	16,912 (8.6)
2010	18,285 (9.3)
2011	18,688 (9.5)
2012	15,516 (7.9)
2013	15,037 (7.6)
2014	14,949 (7.6)
2015	15,985 (8.1)
Age, y	
Median (IQR)	69 (64−74)
Gleason grade group	
1	61,478 (31.2)
2	59,505 (30.2)
3	31,467 (15.9)
4	26,179 (13.3)
5	18,749 (9.5)
Pretreatment PSA, ng/dl	
Median (IQR)	7.0 (5.0−11.6)
Clinical stage	
cT1	2,575 (1.3)
cT2	167,588 (84.9)
cT3	26,581 (13.5)
cT4	634 (0.3)
Risk group	
Low	37,928 (19.2)
Favorable intermediate	44,752 (22.7)
Unfavorable intermediate	42,734 (21.7)
High	59,509 (30.2)
Very high	12,455 (6.3)
Comorbidities	
0	169,342 (85.8)
1	23,021 (11.7)
>1	5,015 (2.5)
Race/ethnicity	
White	140,914 (71.4)
Black	30,688 (15.6)
Hispanic	7,638 (3.9)
Unknown/other	18,138 (9.2)
Geographic location	
North East	51,601 (26.1)
North Central	50,938 (25.8)
South	57,951 (29.4)
West	36,888 (18.7)
Facility type	
Community	18,403 (9.3)
Comprehensive	96,245 (48.8)
Academic	62,746 (31.8)
Other	19,984 (10.1)
Insurance type	
Medicare	119,376 (60.5)
Private	60,862 (30.8)
Medicaid	5,621 (2.9)
Uninsured	2,819 (1.4)
Other government	5,691 (2.9)
Unknown	3,009 (1.5)
Income	
<$38,000	34,917 (17.7)

(*continued*)

Table 1 (***Continued***)

Covariate	*n* (%)
$38,000–47,999	44,631 (22.6)
$48,000–$62,999	52,095 (26.4)
$63,000+	65,735 (33.3)
Nonhigh school educated in patient's zip code	
≥21%	32,071 (16.3)
13%–20.9%	50,314 (25.5)
7%–12.9%	65,534 (33.2)
<7%	49,459 (25.1)
Distance traveled to treatment facility	
≤60 miles	185,996 (94.2)
60–120 miles	5,020 (2.5)
>120 miles	6,362 (3.2)
Patient's county type	
Metropolitan	165,379 (83.8)
Urban/rural	31,999 (16.2)
Brachytherapy	
No	171,774 (87.0)
Yes	25,604 (13.0)
ADT	
No	108,312 (54.9)
Yes	83,791 (42.5)
Unknown	5,275 (2.7)
Nodal irradiation	
No	125,033 (63.4)
Yes	72,345 (36.7)

ADT = androgen deprivation therapy; IQR = interquartile range; PSA = prostate-specific antigen.

NCDB is defined by number of new cancer patients the facility contributed to the NCDB yearly: community (>100), comprehensive (>500), and academic (>500 and offer graduate medical training).

Finally, the receipt of simultaneous primary brachytherapy or ADT if received within 1 year of diagnosis was included in multivariable analyses.

2.3. Outcomes

Our primary outcome was the receipt of PLN-RT and our main covariate of interest was year of diagnosis with the hypothesis that use of PLN-RT increased over time for men diagnosed with high-risk, localized disease. In the NCDB, PLN-RT was defined as radiation to the pelvis as part of the treatment with a boost to the prostate while prostate radiation alone was defined as radiation directed at the prostate with or without the seminal vesicle but not including regional lymph nodes.

We also explored the effects of tumor risk and patient facility characteristics on the primary outcome. Our secondary outcome was overall survival following PLN-RT vs. prostate irradiation alone.

2.4. Statistical analyses

For univariable comparisons, Pearson's chi-squared analyses were used. In multivariable analyses, logistic regressions were used. In all multivariable analyses, PSA was assessed as a continuous variable of the log of PSA. Analyses were stratified by risk groups defined by the NCCN [2]. Low-risk disease was cT1-2a, PSA < 10 ng/ml, and Gleason grade group 1. Favorable intermediate risk included any man with 1 intermediate-risk characteristics (cT2b-c disease, PSA 10–20 ng/ml, or Gleason grade groups 2). Unfavorable intermediate risk was defined by more than 1 intermediate-risk characteristics or Gleason grade group 3. High risk included men with cT3a disease, PSA > 20ng/ml or Gleason grade group 4 or 5, and no primary Gleason pattern 5 disease. Very high risk included all men with either cT3b-4 disease or any primary Gleason pattern 5. A 2-sided $P < 0.05$ was considered significant for all analyses and the statistics package Stata 13.0 (College Station, TX) was used.

3. Results

3.1. Cohort characteristics

In total 197,378 men were included in the final cohort (Table 1). The median age was 69 years and 71% were white. A total of 61% of men were Gleason grade groups 1 or 2, median PSA was 7.0 ng/ml, and 86% were clinical stage T1-2. Combination brachytherapy was performed in 13% of patients, and ADT was received by 43% of men.

3.2. Trends in nodal irradiation

A total of 72,345 (36.7%) men received EBRT with PLN-RT (Fig. 1). From 2005 to 2015, the use of PLN-RT overall, increased from 36.9% to 41.1% ($P < 0.001$). PLN-RT was stable among men with low-risk disease (2005 27.3%, 2015 25.6%; $P = 0.170$), favorable intermediate-risk disease (2005 33.2%, 2015 33.7%; $P = 0.6$), and unfavorable intermediate risk (2005 36.5%, 2015 36.8%;

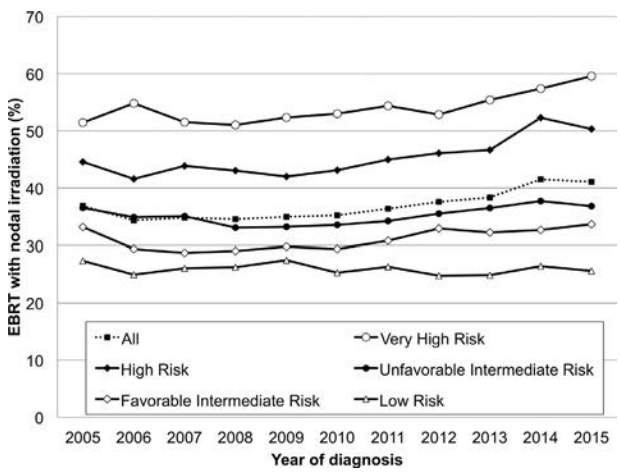

Fig. 1. Temporal trends in external beam radiotherapy with nodal irradiation

EBRT = external beam radiotherapy.

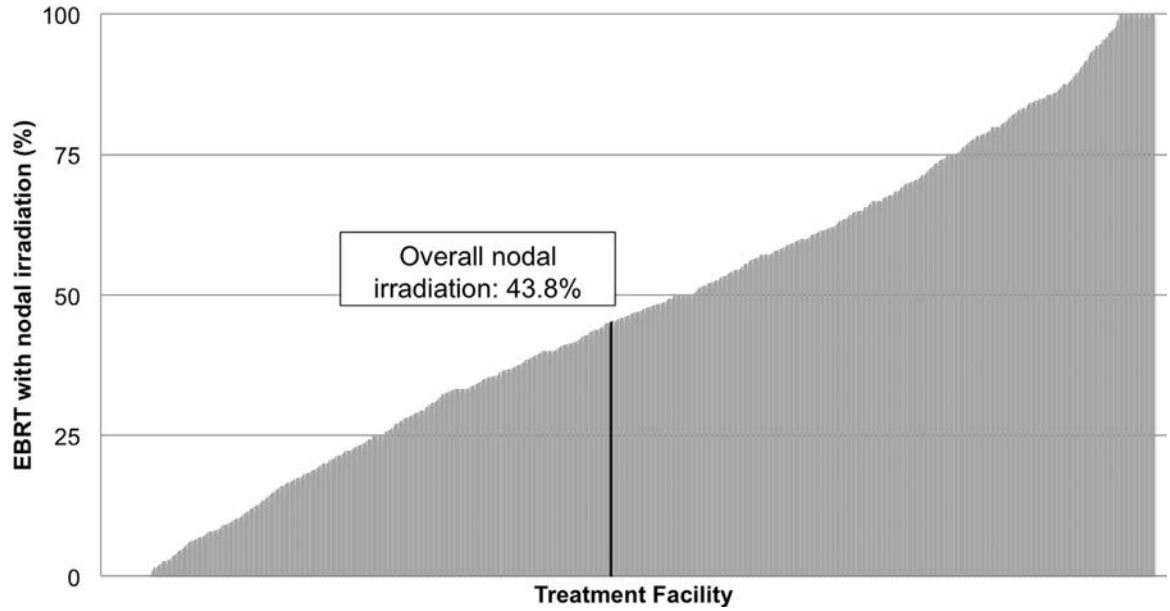

Fig. 2. Frequency of external beam radiotherapy with nodal irradiation based on treatment facility for men with unfavorable intermediate-, high-, and very high-risk prostate cancer

EBRT = external beam radiotherapy.

P = 0.8). PLN-RT increased among men with high-risk disease from 44.6% to 50.3% ($P < 0.001$) as well as in men with very high-risk disease from 51.4% to 59.6% ($P < 0.001$). PLN-RT among men with unfavorable intermediate-, high-, or very high-risk disease was 43.8% and varied greatly by the 1,074 treatment facilities analyzed (Fig. 2).

3.3. Multivariable analysis

When accounting for all covariates, the use of PLN-RT did not significantly change from 2005 to 2015 (odds ratio [OR] 1.06, 95% confidence interval [CI] 0.92−1.23, P = 0.4; Fig. 3). PLN-RT also did not change significantly over time when stratifying men by low- (P = 0.5), favorable intermediate- (P = 0.8), unfavorable intermediate- (P = 0.7), or high-risk disease (P = 0.057). PLN-RT did significantly increase among men with very high-risk disease (OR 1.34, 95% CI 1.06−1.70, P = 0.013).

Among all men, each increasing Gleason grade group was associated with increasing use of PLN-RT (Figs. 3 and 4). While only 28% of men in grade group 1 received PLN-RT, 53% in grade group 5 received PLN-RT (OR 2.08, 95% CI 1.88−2.30, $P < 0.001$). Increasing pretreatment PSA via log of PSA (OR 1.09, 95% CI 1.06−1.12, $P < 0.001$) and clinical stage were also associated with increasing use of PLN-RT. Compared to white men (36%), Hispanic men were more likely to receive nodal radiation (41%; OR 1.29, 95% CI 1.02−1.64, P = 0.033). Treatment at an academic facility (compared to community) and greater travel distance to treatment facility (traveling >120 miles compared to <60 miles) also resulted in lower rates of PLN-RT (OR 0.75, 95% 0.57−0.98, P = 0.036 and OR 0.57, 95% CI 0.39−0.85, P = 0.006, respectively). The greatest disparities in PLN-RT by facility type were seen among men with lower risk disease who were treated with greater frequency at community treatment facilities (Fig. 5).

Use of brachytherapy was not associated with PLN-RT, while receipt of ADT was associated with increased use (OR 1.28, 95% CI 1.18−1.38, $P < 0.001$). When stratified by risk group, ADT use was associated with increased use of PLN-RT among men with unfavorable intermediate-, high-, and very high-risk CaP (all $P < 0.001$; Fig. S). Brachytherapy was associated with increased use of PLN-RT only among men with unfavorable intermediate-risk CaP ($P < 0.001$).

A separate logistic regression analysis was performed among men with low- and favorable intermediate-risk CaP, for whom there are no recommendations for use of PLN-RT (Table S1). Covariates associated with use of PLN-RT included Gleason grade group 2 vs. 1 (OR 1.19, 95% CI 1.11−1.28, $P < 0.001$), geographic location, academic vs. community treatment facility (OR 0.73, 95% CI 0.53−0.99, P = 0.044), being uninsured vs. having Medicare (OR 1.22, 95% CI 1.00−1.49, P = 0.049), living >120 miles from the treatment facility (OR 0.51, 95% CI 0.32−0.81, P = 0.004), receipt of brachytherapy (OR 1.31, 95% CI 1.01−1.71, P = 0.043), and receipt of ADT (OR 1.21, 95% CI 1.10−1.34, $P < 0.001$).

3.4. Survival analyses

Median follow-up was 64 months (IQR 39−92 months). On multivariable analysis, receipt of EBRT directed at lymph nodes was associated with worse overall survival

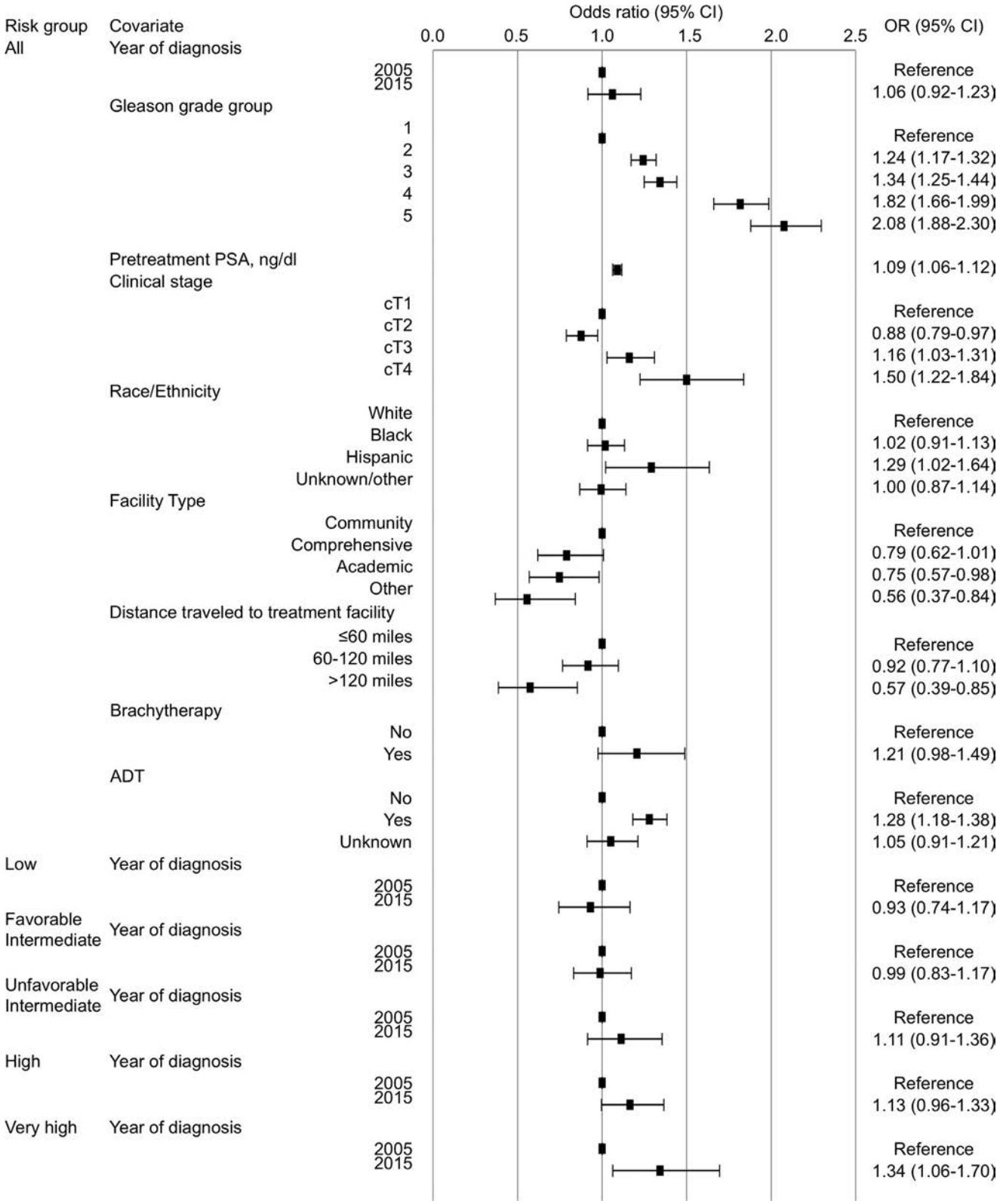

Fig. 3. Logistic regression for odds of receiving lymph node irradiation

All covariates in Table 1 were included in the multivariable model except for risk group. CI = confidence interval; OR = odds ratio; PSA = prostate-specific antigen.

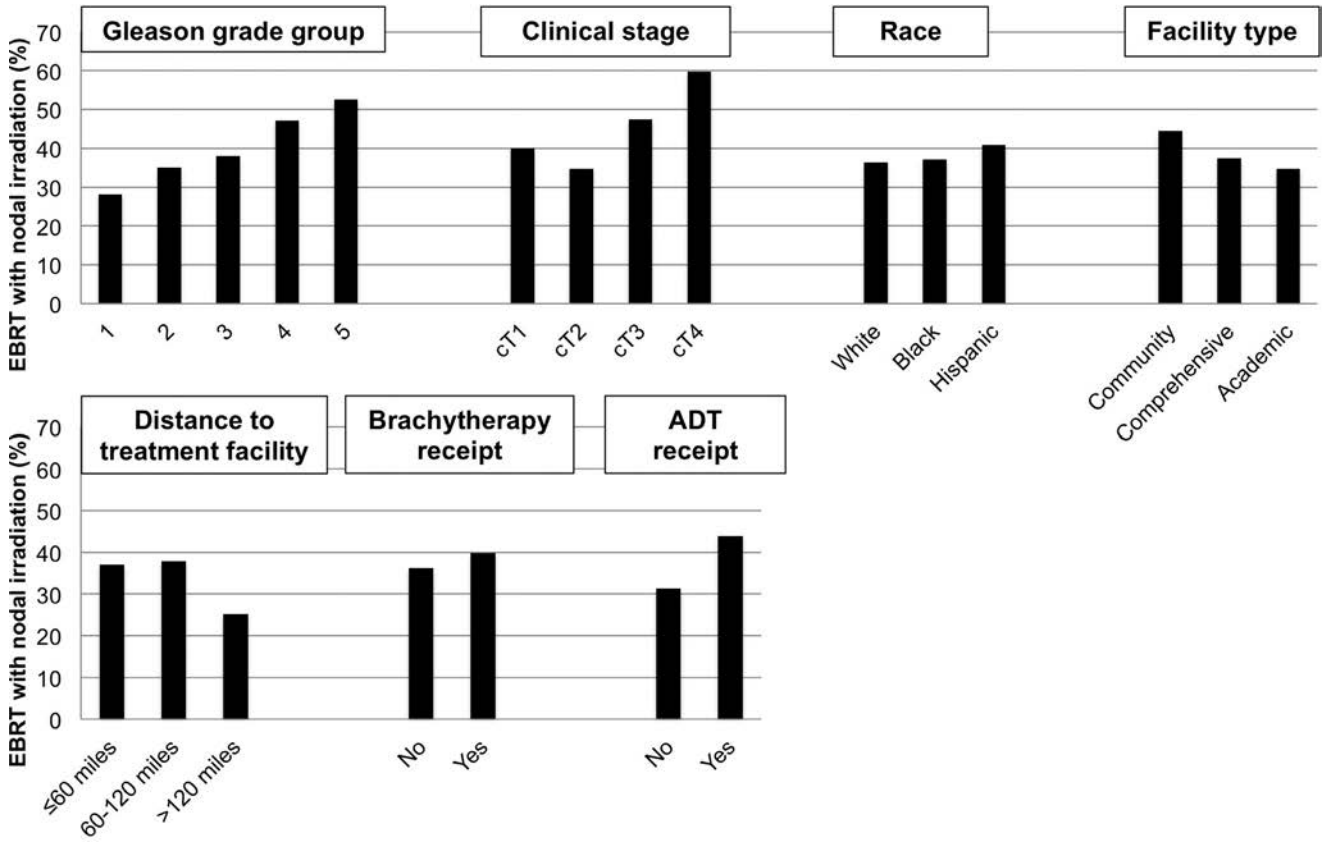

Fig. 4. Stratified frequency of external beam radiotherapy with nodal irradiation
For all within-group analyses using chi-squared analyses, $P < 0.001$. EBRT = external beam radiotherapy.

among all men (HR 1.11, 95% CI 1.09−1.14, $P < 0.001$; Table S2). PLN-RT did not have a significant survival impact in men with very high-risk disease.

4. Discussion

In this large, national registry study, the use of PLN-RT increased over time among men with very high-risk CaP but has remained stable among all other risk groups. Currently, there is no definitive consensus on the use of PLN-RT in the treatment of nonmetastatic CaP, but there are trends from the current study that raise questions and concerns. One primary concern is that 25% to 35% of low and favorable intermediate-risk men continue to receive PLN-RT despite modern studies demonstrating a ≤5% risk of distant metastasis with prostate-only radiotherapy (PORT) [8].

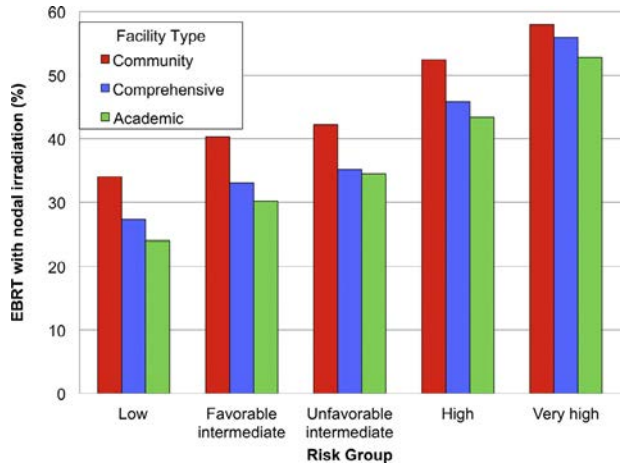

Fig. 5. Frequency of external beam radiotherapy with nodal irradiation stratified by facility type and risk group
EBRT = external beam radiotherapy.

There have been multiple shifts in the use of radiotherapy and PLN-RT over the past few decades. Among those who received EBRT, the use of whole pelvis radiotherapy (WPRT) declined from 92% in 1989 to 23% in 1999 [9]. Our study is the first to show PLN-RT increased modestly from 36.9% to 41.1% among men receiving primary EBRT from 2005 to 2015. However, when adjusting for relevant covariates, treatment year did not predict for PLN-RT. The only risk group in which later year was associated with increases in PLN-RT on adjusted analyses was for men with very high-risk disease.

Increasing use of PLN-RT for very high-risk disease may be reflective of prior retrospective studies suggesting a benefit of WPRT in patients with increased risk of lymph node involvement [10−12]. While retrospective studies have suggested a possible benefit with WPRT, 2 major randomized trials examining the efficacy of WPRT have shown mixed results [3,4]. In 2007, the preliminary results

of GETUG-01 were published showing no benefit of WPRT over PORT after 5 years of follow-up [13]. After 11 years of follow-up, GETUG-01 did not find a significant difference in overall, progression-free, or recurrence-free survival [4]. The initial results of RTOG 94-13 demonstrated there was a benefit in progression-free survival favoring WPRT plus neoadjuvant hormones [3]. Recently, updated data from this trial with a median follow-up of 8.8 years confirmed the superiority of WPRT over PORT when paired with neoadjuvant hormonal therapy [14]. Some of the earlier conflicting data, however, from both prospective and retrospective studies likely influenced the great variability in the use of PLN-RT seen in the NCDB based on treatment facility.

Importantly, the benefit seen in RTOG 94-13 in terms of progression free survival (28.4% for WRPT vs. 23.5% for PORT with neoadjuvant hormonal therapy at 10 years) came at a cost of significantly increased high-grade gastrointestinal toxicity [14]. Further prospective data on men with high-risk disease will be needed to evaluate the net benefits of PLN-RT. Currently, RTOG 0924 (NCT01368588) is accruing patients to assess the efficacy of WPRT in men with both intermediate- and high-risk features [15]. Data from the NCDB showed worse overall survival for PLN-RT, but these analyses should be interpreted with caution given that patients at higher risk, despite being adjusted for on multivariable analysis, typically received PLN-RT and notably survival follow-up was relatively brief.

We observed that patients who were treated at an academic institution or traveled a greater distance to a treatment facility were less likely to receive PLN-RT. These data are evocative of prior studies showing men with CaP were less likely to receive radiation compared to surgery if they lived further from a treatment center [16]. Additionally, patients are more likely to travel longer distances for treatment if treatment is done at an academic institution [17]. We speculate patients traveling longer distances to receive EBRT are doing so to receive care at center's of excellence that are more likely abiding by guideline use of PLN-RT which may explain the association between longer travel distance and lower use of PLN-RT.

The high use of PLN-RT in men with low- and favorable intermediate-risk CaP is concerning given there are no current recommendations for its use in this group with concern for increased toxicity from radiation [2]. Factors associated with increased use of PLN-RT in this group were similar to the overall cohort. These included high tumor grade and treatment at a community treatment facility. While a portion of these patients may have been upgraded on subsequent prostate biopsy, a large amount of this PLN-RT may represent overtreatment.

In the NCDB, Hispanic men were more likely to receive pelvic PLN-RT compared to white men. Few studies exist in the literature surrounding CaP specifically in Hispanic men, but Hosain et al. found that healthcare providers in Houston were less likely to discuss surgery and watchful waiting compared to radiation therapy with Hispanic patients [18]. Physician assumptions and biases about patients based on racial/ethnic differences may play a role in recommending different treatments.

Our study has limitations. Data were obtained from the NCDB, so our sample consisted of information only from Commission on Cancer-accredited facilities that contributed data to the NCDB and is not a comprehensive population-based data set. However, the NCDB captured around 53% of all new CaP cases in the US in 2015 suggesting our findings are likely reflective of real-world practice patterns [6,7]. The retrospective nature of the NCDB does not allow us to account for unmeasured variables. Accordingly, we were unable to account for long-term vs. short-term ADT and we do not make a distinction between neoadjuvant, adjuvant, or salvage ADT. Given, however, that all treatments in this study needed to be given within 1 year of diagnosis based on inclusion criteria, we suspect salvage ADT was rarely the form of ADT measured. Additionally, we relied on the coding for radiation field for our primary outcome. A nuanced data such as this in a large dataset may be subject to inaccuracies, but for now these data from the NCDB are the best estimate of national practice patterns.

While most EBRT cases consist of standard long-course radiation, stereotactic body radiotherapy (SBRT) was an experimental and emerging treatment modality in the 2000s for CaP before being listed as a possible treatment option in the 2014 NCCN guidelines. While the inclusion of SBRT cases may have affected our results, the number of patients receiving SBRT relative to standard EBRT during our study's time period is small (3.8% vs. 96.2%) [19]. Finally, we are unable to account for the field size used during nodal radiation and there could be significant variation that we cannot report.

5. Conclusions

In a national cohort of men with nonmetastatic CaP, PLN-RT occurred in about one third of those receiving primary EBRT including 25% to 35% of low- and favorable intermediate-risk men. Further understanding to the variability in PLN-RT use and why PLN-RT was less common among men treated at academic centers and those who traveled further to their treatment facility is warranted.

Conflicts of interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urolonc.2018.12.022.

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