Travel Distance and Stereotactic Body Radiotherapy for Localized Prostate Cancer

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PRÉCIS: Definitive prostate SBRT utilization has increased more than three-fold since 2004, with a significant increase in usage coinciding with early reports of short-term efficacy. Long-distance travel for treatment was associated with more than twice the odds of definitive prostate SBRT receipt compared to short-distance travel, suggesting that treatment decisions with unknown long-term clinical implications may be strongly driven by sociodemographic factors.

Keywords: prostate cancer, sbrt, financial toxicity, travel distance, radiation

ABSTRACT

BACKGROUND: Definitive stereotactic body radiotherapy (SBRT) represents an emerging and debated treatment option for prostate cancer, with economic savings potential and reports of short-term efficacy since 2006. We sought to define national trends in definitive prostate SBRT utilization and determine whether patterns vary by travel distance for treatment.

METHODS: The National Cancer Database (NCDB) identified 181,544 men with localized prostate cancer treated with definitive external beam radiotherapy from 2004-2012. Joinpoint regression analyzed definitive prostate SBRT trends over time, while multivariable logistic regression defined the odds for its receipt by travel distance for treatment.

RESULTS: Definitive prostate SBRT utilization increased from 1.8% in 2004 to 5.9% in 2012 (P_{trend}<0.0001), with a Joinpoint for increased utilization in 2006 (P<0.0001). Higher SBRT utilization was associated with longer travel distance for treatment, younger age, white race, more affluent zip code, academic treatment center, favorable disease characteristics, and less comorbidities (all P<0.0001). Compared to travel distances below 25 miles, 25-50 and > 50 miles of travel for treatment were associated with increasing adjusted odds of definitive prostate SBRT receipt (1.63 [95% CI 1.51-1.76] and 2.35 [95% CI 2.14-2.57], respectively, both P<0.0001).

CONCLUSION: Definitive prostate SBRT utilization increased more than three-fold since 2004, with a significant increase in usage coinciding with early reports of short-

term efficacy. Long-distance travel for treatment was associated with more than twice the odds of definitive prostate SBRT receipt compared to short-distance travel, suggesting that treatment decisions with unknown long-term clinical implications may be strongly driven by sociodemographic factors.

INTRODUCTION:

Prostate cancer is the most common non-cutaneous malignancy in men, with 161,360 new cases of prostate cancer and 26,730 deaths due to prostate cancer in the United States alone in 2017.[1] Long-course external beam radiotherapy (EBRT) is an established form of definitive therapy used for localized prostate cancer, [2] while short-course stereotactic body radiotherapy (SBRT) is a new and emerging high-dose-per fraction form of EBRT that was cautiously listed as a definitive therapy option by the National Comprehensive Cancer Network (NCCN) in 2014.[3]

SBRT can be conveniently delivered in five or fewer treatments compared to the up to 45 fractions (9 weeks) in standard-fractionated EBRT.[4] Before being cautiously listed as a potential definitive therapy option in the 2014 NCCN guidelines, definitive prostate SBRT was largely considered experimental.[4-6] An early short term report of safety and efficacy was presented in 2006, [7] and since then several phase II studies in patients with favorable risk prostate cancer have suggested SBRT is safe and efficacious. [8-14]

Given the lack of level-1 evidence and long-term results from phase II studies, definitive prostate SBRT use remains a hotly debated topic with differing expert opinions.[15] Since definitive prostate SBRT can be delivered in up to 40 fewer treatments than standard fractionated radiation, the time, travel, and cost savings that patients could incur are significant. As such, proponents argue that SBRT offers patients a cost saving and

convenient alternative to standard long-course radiation.[16, 17] Nevertheless, there is no expert consensus regarding prostate SBRT and the drivers and trends in its use are poorly understood.

Therefore, we sought to define national trends in definitive prostate SBRT utilization and determine whether utilization increased after reports of its efficacy. We also sought to determine the factors associated with receipt of definitive prostate SBRT, with a focus on distance traveled for treatment to determine the influence of sociodemographics on treatment decisions. We used the largest clinical registry in the United States to address our study aims. [18, 19]

MATERIALS AND METHODS:

Study population and Design

The study population was derived from the National Cancer Database (NCDB), a nationwide joint program of the Commission on Cancer (CoC) and the American Cancer Society (ACS) that captures 70 percent of newly diagnosed cancers diagnosed and treated at CoC accredited cancer programs. [18, 19] Patients diagnosed with localized cT1-4N0M0 prostate adenocarcinoma from 2004-2012 were identified (Site code: C61.9, International Classification of Disease for Oncology (ICD-O) code, 3rd edition: 8140) (N=888,868). Patients without information regarding tumor stage (N=18,740), Gleason score (N=36,020) or PSA level (N=108,613) were excluded. For the purposes of this study, we excluded patients treated with surgery (N=400,461), or those who received radiation therapy other than EBRT +/- brachytherapy or who received palliative intent EBRT (N=143,490); palliative intent treatments have been collected by NCDB since 2003. The final study population consisted of 181,544 patients treated with definitive prostate EBRT. Definitive prostate SBRT was defined as the use of ≤ 5 fractions of treatment modalities coded as Stereotactic radiosurgery, NOS, or Linac radiosurgery. The first year of the study was 2004, since that is the first year that the NCDB included many of the clinical variables of interest, and the last year of the study was 2012 since that is the most recent year on which data was available. Figure 1 summarizes the study population selection criteria.

The institutional review board of the Brigham and Women's Hospital/ Dana-Farber Cancer Institute approved this study.

Statistical Methods

Distribution and comparison of the clinical characteristics

Descriptive statistics were used to present the baseline characteristics, stratified by type of definitive prostate EBRT received (SBRT or standard fractionated EBRT). Categorical variables were assessed with Chi-square test and included age (stratified at age 70), race/origin, insurance status, distance traveled to treatment facility (stratified at 25 miles [approximately 60 minutes round-trip travel] and 50 miles [approximately 2 hours round-trip travel]), PSA level (stratified at 10 and 20 ng/mL), clinical tumor stage, Gleason score, hospital setting, zip code median household income, zip code education level, and residence type; continuous variables were compared with student-t test or Mann-Whiney U test as appropriate and included age and median distance to treatment facility. Travel distance was defined as the distance between patient zip code centroid and the street address of the treating facility.

SBRT Utilization Trends over Time and by Distance Traveled to Treatment Facility

For the purposes of illustration, crude definitive prostate SBRT rates by year were generated and displayed graphically. Mantel-Haenszel Chi-square test for trend was used to examine the trend for crude rates of SBRT utilization over time. To determine if any significant changes in definitive SBRT rates correlated with the publication of favorable reports in 2006, univariable Joinpoint regression analysis (Joinpoint Regression Program, Version 4.1.0) was used to analyze annual percentage changes

(APCs) over time. [20] The Joinpoint Regression Program takes trend data and tests whether any statistically significant changes in trends occur using the Monte Carlo permutation method. Points at which statistically significant changes in trends occur are termed "Joinpoints."

Estimates of Odds of Receipt of SBRT by Travel Distance to Treatment Facility and other Patient Factors

To test the null hypothesis that there is no difference in receipt of definitive prostate SBRT by travel distance to treatment facility (<25 miles [referent], 25-50miles, >50miles), univariable and multivariable logistic regressions were used to define odds ratios (OR)s and adjusted odds ratios (AOR)s for the dependent endpoint of receipt of definitive prostate SBRT, respectively. Sociodemographic covariates included in the models were age (≤70 [referent], >70]), race/origin (Non-Hispanic White [referent], African American, Non-Black Hispanic, Other Non-White), insurance status (none [referent], private, Medicaid, Medicare), zip code median household income (<$38,000 [referent], $38,000-47,999, $48,000-62,999, ≥ 63,000), residence type (metropolitan [referent], urban, rural), zip code percent education level less than high school (≥ 21% [referent], 13%-20.9%, 7-12.9%, <7%). Clinical variables included in the models were prostate-specific antigen [PSA <10ng/mL [referent], PSA 10-20ng/mL, PSA >20 ng/mL), clinical tumor stage (T1 [referent], T2, T3, T4), Gleason score (6 [referent], 7, 8-10), Charlson-Deyo comorbidity score (0 [Referent], 1, ≥2), and hospital setting (non-academic [referent], academic).

For the purposes of illustration, crude definitive prostate SBRT rates by year stratified by travel distance were generated and displayed graphically.

We used 95% confidence intervals (CI)s and a two-sided p-value<0.05 as criteria for clinical significance in all analyses. All statistical analyses were performed using SAS® version 9.4. (SAS Institute Inc., Cary, NC, USA).

RESULTS:

Distribution and comparison of the clinical characteristics

A total of 6,842 patients received SBRT for localized prostate cancer. Higher SBRT utilization was associated with longer travel distance for treatment, younger age, white race, more affluent zip code, academic treatment center, favorable disease characteristics, non-Medicaid insurance status, and less comorbidities (Table 1).

SBRT Utilization Trends over Time

Among patients treated with definitive EBRT, SBRT utilization increased year to year, from 1.8% in 2004 to 5.9% in 2012 (P_{trend}<0.0001; Figure 2). A Joinpoint for increased utilization was identified in 2006 (P<0.0001; Figure 2). The annual percent change in SBRT utilization was +13.92% from 2004-2005, +28.84 % from 2006 to 2009, and +7.09% from 2010 to 2012, with significant differences between the 2004 to 2005 and 2006 to 2009 periods (P<0.0001), but not between the 2006 to 2009 and 2010 to 2012 periods (P=0.10) (Figure 2).

Estimates of Odds of Receipt of SBRT by Travel Distance to Treatment Facility

On univariable analysis, receipt of SBRT was significantly associated with travel distance to treatment facility, race/origin, insurance status, Charlson comorbidity score, PSA level, clinical tumor stage, Gleason score, zip code median household income, zip code education level, and residence type (All P<0.004; Table 2). After robust

multivariable adjustments for all patient factors associated with receipt of SBRT, longer travel distance for treatment of 25-50 miles or beyond 50 miles was increasingly associated with higher adjusted odds of SBRT receipt when compared to travel distances below 25 miles, (1.63 [95% CI 1.51-1.76] and 2.35 [95% CI 2.14-2.57], respectively, both P<0.0001; Table 2). Crude SBRT rates over the study period stratified by travel distance are displayed in Figure 3; of note, there was an increasing trend of SBRT utilization for all patients regardless of travel distance from 2004-2012 (P_{trend} for all <0.0001), though relative differences between travel distances remained constant.

Estimates of Odds of Receipt of SBRT by other Patient Factors

Black, Hispanic, or other non-White patients were significantly less likely to receive SBRT compared to White patients (AOR 0.86 [95% CI 0.80-0.93], P=0.0001; AOR 0.52 [95% CI 0.44-0.61], P<0.0001; and AOR 0.79 [95% CI 0.68-0.91], P=0.002, respectively; Table 2). Age <70, non-Medicaid insurance, Charlson comorbidity score of 0, PSA level <10 ng/mL, clinical T1 stage, Gleason score 6, academic hospital setting, zip code median household income $\geq$ $63,000, and metropolitan residence were all significantly associated with increased odds of SBRT receipt on multivariable analysis (Table 2).

DISCUSSION:

Using the largest registry of incident prostate cancers in the United States, we found that definitive prostate SBRT utilization has increased over three-fold from 2004 to 2012, with a significant increase in usage starting in 2006 coinciding with early reports of favorable efficacy and safety. At the end of the study period, definitive SBRT rates remained modest, peaking at nearly 6%. Notably, long-distance travel for treatment was associated with more than twice the odds of definitive prostate SBRT receipt compared to short-distance travel. These findings give insight into the potential drivers of definitive SBRT utilization and thus may be able to inform patient counseling and outreach efforts.

Notably, the increased prostate SBRT utilization observed in our study was during a time when this therapy was considered experimental with unknown long-term clinical risks, and not listed in NCCN guidelines as a potential alternative to standard long-course radiation. A majority of SBRT occurred in academic cancer centers where these treatments may have been performed on clinical trial or by clinicians with clinical expertise and access to the appropriate technology and facility support to safely provide extreme hypofractionated radiotherapy. The significant uptake in prostate SBRT utilization in 2006 coincides with early presentation of favorable safety and efficacy associated with extreme hypofractionation.[7] Furthermore, a significant trend of increased SBRT utilization continued through 2012 (the end of our study period),

coinciding with the publication of several phase II clinical trials from eight cancer centers suggesting SBRT has similar early outcomes compared to other forms of radiotherapy.[8-14] Nevertheless, the absolute rate of prostate SBRT during our study period remained modest in comparison to the uptake of standard fractionation intensity modulated radiotherapy, likely given the unclear long-term implications.[21] We would expect the rate of prostate SBRT to continue increasing after being cautiously listed as a potential definitive therapy option in 2014 NCCN guidelines, and its utilization to be further guided by an ongoing phase III randomized non-inferiority clinical trial.[22]

Our finding that long-distance travel was strongly positively associated with definitive prostate SBRT suggests that treatment decisions with unknown long-term clinical implications may be strongly driven by sociodemographic factors. The reasons and directionality behind our findings can be explained by multiple competing hypotheses. One potential explanation is that patients with greater travel burden may have increased risk of economic burden and risk of financial toxicity with long-course radiation treatment (given the costs associated with time, work loss, and greater travel) that may drive treatment decisions. High economic burden has been demonstrated to be a barrier to receipt of appropriate cancer care, and travel distance is a significant factor in adherence to cancer treatment.[23, 24] As such, patients with greater travel (and/or economic burden) may be more likely to pursue short-course SBRT as a more convenient and potentially less financially burdensome treatment option.

An alternative hypothesis is that patients with the means (financial and otherwise) to travel to centers where SBRT is offered (which tend to be academic centers in metropolitan areas) are those most likely to seek out SBRT and travel long distances for the treatment. Our study showed that younger, higher SES, white, and non-Medicaid insured patients were those most likely to receive SBRT, and this group certainly represents a cohort with greater means to travel longer distances for treatment. This group of patients may be influenced to travel to centers where SBRT is offered based on information or advertisements from treating centers that short-course SBRT treatment offers an equally efficacious treatment to standard long-course treatment (especially since NCCN guidelines are not necessarily widely disseminated among patients). Ultimately, these hypotheses are not mutually exclusive, since patients are at risk of financial toxicity with cancer treatments across SES strata, including high SES patients.[25] Therefore, younger, higher SES, white patients may both 1] be more likely to have the means to travel longer distances to a center with SBRT, and also 2] may be likely to be driven by the implications of financial toxicity. Younger and higher SES patients represent a predominantly actively working population that may be at risk of the greatest delta in financial losses between long and short-course treatments given the differences in losses associated with time away from work, time in general, and cost between the two treatment approaches. Nevertheless, even after adjusting for all sociodemographic and clinic factors on multivariable analysis, travel distance remained strongly associated with SBRT receipt. Ultimately, the data provided in NCDB cannot distinguish between these and other potential hypotheses, and it is likely the case that

the drivers of the association between travel distance to treatment facility and prostate SBRT are multifactorial.

Regarding race and ethnic origin, Black and Hispanic men were observed to be significantly less likely to receive SBRT compared to white men. This finding persisted after adjusting for variables such as prostate cancer prognostic factors, travel distance, comorbidity status, age, treatment center, place of income, insurance type, and education. The reasons for this observed pattern are likely multifactorial. Prior reports have suggested that minority patients have less trust in the medical system for historical reasons, and may be less likely to receive a therapy that is considered experimental or unproven.[26-28] Furthermore, Black men tend to harbor more aggressive disease and are at a higher odds of dying from prostate cancer compared to their White counterparts, so clinicians may be less willing to recommend an experimental therapy to potentially higher risk patients when alternative proven therapies exist.[29, 30] Provider implicit bias is also a well-studied factor that may contribute to differential utilization of SBRT.[31-33] Lastly, it remains possible that there are other factors not captured in the NCDB which may contribute to racial disparities in SBRT utilization. If long-term data show that SBRT is as efficacious as current standard forms of EBRT, a concerted effort will be needed to ensure equal access to this technology, regardless of clinic-sociodemographic characteristics.

Other studies have similarly demonstrated an increasing rate of definitive prostate SBRT, but have not explored the relationships between travel distance or dissemination

of literature and SBRT utilization patterns.[16, 34] To our knowledge, this study is the first to highlight these important relationships and how travel distance to treatment facility and dissemination of favorable literature may be major drivers of SBRT utilization. Still, our results must be viewed within the limitations of the study. Although the NCDB represents the nation's largest cancer database, our study does not have data from cancer centers that are not CoC accredited and so our data may not reflect those centers. Furthermore, our study only includes data up to 2012 and so we are not able to determine SBRT rates after publication of the pooled analysis of phase II clinical trials or after the SBRT was cautiously listed as a potential definitive therapy in the 2014 NCCN guidelines.[3, 35] Lastly, the drivers and directionality of the observed associations cannot be clearly defined by the data provided in the NCDB.

Despite the potential limitations, our study is a robust and comprehensive report on the national trends and patterns of definitive prostate SBRT utilization. The absolute national rate of definitive SBRT for localized prostate cancer has increased nearly three-fold since 2004, with a significant increase in usage coinciding with early reports of favorable safety and efficacy. Long-distance travel for treatment was associated with more than twice the odds of definitive prostate SBRT receipt compared to short-distance travel, suggesting that treatment decisions with unknown long-term clinical implications may be strongly driven by sociodemographic factors. A concerted effort needs to be made to further explore definitive prostate SBRT as a safe and potentially less burdensome treatment option, balanced with an effort to ensure patients who may

be more likely to pursue SBRT are aware of the potential long-term clinical uncertainty contrary to the high-level data supporting standard treatment approaches.

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Table 1. Distribution and comparison of the clinical characteristics stratified by definitive external beam radiotherapy fractionation type. IQR (Interquartile Range), No. (Number), PSA (Prostate-Specific Antigen)

Patient Characteristic	**Received Definitive Prostate Stereotactic Body Radiotherapy N=6,842 (3.8%)**	**Received Definitive Prostate Standard Fractionated External Body Radiotherapy N=174,702 (96.2%)**
Median Age in Years (IQR)	68 (62-73)	69 (63-74)
Age in Years No. (%)*		
<70 (%)	3,940 (57.6)	89,977 (51.5)
≥70 (%)	2,902 (42.4)	84,725 (48.5)
Race/Origin No. (%)		
Non-Hispanic White	5,377 (78.6)	129,346 (74.0)
African American	1,030 (15.1)	298,936 (17.1)
Hispanic	160 (2.3)	7,497 (4.3)
Other Non-White	195 (2.9)	5,545 (3.2)
Unknown	80 (1.2)	2,421 (1.4)
Insurance Status No. (%)		
None	93 (1.4)	2,820 (1.6)
Private	2,388 (34.9)	56,621 (32.4)
Medicaid	107 (1.6)	4,859 (2.8)
Medicare	3,971 (58.0)	102,941 (58.9)
Other	152 (2.2)	4,290 (2.5)
Unknown	131 (1.9)	3,171 (1.8)
Median Travel Distance to Treatment Facility in Miles (IQR)	11.0 (5.1-23.3)	8.2 (3.9-17.6)
Travel Distance to Treatment Facility No. (%)		
<25 miles	5,235 (76.5)	146,770 (84.0)
25-50 miles	911 (13.3)	18,536 (10.6)
>50 miles	696 (10.2)	9,396 (5.4)
Charlson Comorbidity Score No. (%)		

0	5,909 (86.4)	153,666 (88.0)
1	810 (11.8)	17,596 (10.1)
2+	123 (1.8)	3,440 (2.0)
Median PSA in ng/mL (IQR)	6.2 (4.6-9.7)	7.0 (5.0-11.9)
PSA Level No. (%)		
< 10 ng/mL	5,200 (76)	119,067 (68.2)
10-20 ng/mL	944 (13.8)	32,546 (18.6)
> 20 ng/mL	698 (10.2)	230,89 (13.2)
Clinical Tumor Stage No. (%)		
T1	4,895 (71.5)	107,547 (61.6)
T2	1,823 (26.6)	58,120 (33.3)
T3	115 (1.7)	8,454 (4.8)
T4	9 (0.1)	581 (0.3)
Gleason Score No. (%)		
6	3,263 (47.7)	60,310 (34.5)
7	2,855 (41.7)	76,209 (43.6)
8-10	724 (10.6)	38,183 (21.9)
Hospital Setting No. (%)		
Academic	3,419 (50.0)	52,075 (29.8)
Non-academic	3,423 (50.0)	122,627 (70.2)
Zip Code Median Household Income No. (%)		
<$38,000	956 (14.0)	31,986 (18.3)
$38,000-47,999	1,159 (16.9)	40,366 (23.1)
$48,000-62,999	1,565 (22.9)	45,841 (26.2)
≥ 63,000	3,155 (46.1)	56,293 (32.2)
Unknown	7 (0.1)	216 (0.1)
Zip Code Education Level (percent less than high school degree) No. (%)		
≥ 21%	1,073 (15.7)	30,374 (17.4)
13%-20.9%	1,428 (20.9)	45,582 (26.1)
7-12.9%	2,120 (31.0)	56,720 (32.5
<7%	2,219 (32.4)	41,915 (24.0)

Unknown	2 (0.0)	111 (0.1)
Residence Type No. (%)		
Metropolitan	5,829 (85.2)	141,774 (81.2)
Urban	78 (1.1)	26,332 (15.1)
Rural	772 (11.3)	3,554 (2.0)
Unknown	163 (2.4)	3,042 (1.7)

*Percentage may not add up to 100 due to rounding.

Table 2. Univariable and Multivariable logistic regression defined odds ratios for receipt of definitive prostate stereotactic body radiotherapy. AOR (Adjusted Odds Ratio), CI (Confidence Interval), OR (Odds Ratio), Ref (Referent).

Patient Characteristic	**Unadjusted OR**	**P-value**	**AOR (95%CI)**	**P-value**
Travel Distance to Treatment Facility				
<25 miles	Ref		Ref	
25-50 miles	1.36 (1.26-1.46)	<.0001	1.63 (1.51-1.76)	<.0001
>50 miles	2.09 (1.92-2.27)	<.0001	2.35 (2.14-2.57)	<.0001
Age in Years				
<70	Ref		Ref	
≥70	0.78 (0.75-0.82)	<.0001	0.83 (0.78-0.87)	<.0001
Race/Origin				
Non-Hispanic White	Ref		Ref	
African American	0.83 (0.77-0.89)	<.0001	0.86 (0.80-0.93)	0.0001
Hispanic	0.51 (0.44-0.60)	<.0001	0.52 (0.44-0.61)	<.0001
Other Non-White	0.85 (0.73-0.98)	0.024	0.79 (0.68-0.91)	0.002
Insurance Status				
None	Ref		Ref	
Private	1.28 (1.04-1.58)	0.022	1.09 (0.88-1.35)	0.45
Medicaid	0.67 (0.50-0.89)	0.005	0.75 (0.56-1.00)	0.05
Medicare	1.17 (0.95-1.44)	0.140	1.27 (1.02-1.57)	0.03
Others	1.07 (0.83-1.40)	0.59	0.99 (0.76-1.29)	0.94
Charlson Comorbidity Score				
0	Ref		Ref	
1	1.20 (1.11-1.29)	<.0001	1.34 (1.24-1.44)	<.0001
2+	0.93 (0.78-1.12)	0.43	1.11 (0.92-1.34)	0.28
PSA Level				
< 10 ng/mL	Ref		Ref	
10-20 ng/mL	0.66 (0.62-0.71)	<.0001	0.79 (0.74-0.85)	<.0001
> 20 ng/mL	0.69 (0.64-0.75)	<.0001	0.94 (0.86-1.02)	0.14
Clinical Tumor Stage				
T1	Ref		Ref	

T2	0.69 (0.65-0.73)	<.0001	0.78 (0.74-0.83)	<.0001
T3	0.30 (0.25-0.36)	<.0001	0.37 (0.31-0.46)	<.0001
T4	0.34 (0.18-0.66)	0.0001	0.54 (0.28-1.05)	0.07
Gleason Score				
6	Ref		Ref	
7	0.69 (0.66-0.73)	<.0001	0.72 (0.69-0.76)	<.0001
8-10	0.35 (0.32-0.38)	<.0001	0.41 (0.37-0.44)	<.0001
Hospital setting				
Non-academic	Ref		Ref	
Academic	2.35 (2.24-2.47)	<.0001	2.14 (2.03-2.25)	<.0001
Zip Code Median Household Income				
<$38,000	Ref		Ref	
$38,000-47,999	0.96 (0.88-1.05)	0.36	1.09 (0.99-1.19)	0.09
$48,000-62,999	1.14 (1.05-1.24)	0.0001	1.26 (1.15-1.39)	0.0001
≥ 63,000	1.88 (1.72-2.02)	<.0001	2.01 (1.81-2.23)	<.0001
Zip Code Education Level (percent less than high school degree)				
≥21%	Ref		Ref	
13%-20.9%	0.89 (0.82-0.96)	0.004	0.75 (0.69-0.82)	<.0001
7-12.9%	1.06 (0.98-1.14)	0.139	0.72 (0.66-0.79)	<.0001
<7%	1.50 (1.39-1.61)	<.0001	0.77 (0.70-0.85)	<.0001
Residence Type				
Metropolitan	Ref		Ref	
Urban	0.71 (0.66-0.77)	<.0001	0.78 (0.71-0.85)	<.0001
Rural	0.53 (0.43-0.70)	<.0001	0.52 (0.41-0.65)	<.0001

Figure Legends

Figure 1. Eligibility and exclusion criteria. EBRT (External Beam Radiotherapy), N (Number), SBRT (Stereotactic Body Radiotherapy).

Figure 2. National crude rate of SBRT utilization in percent among patients who received EBRT as initial definitive therapy for localized prostate cancer. P_{trend} from 2004 to 2012 <0.0001. ^ The APC is significantly different from zero at alpha = 0.05 (P <0.0001). APC (Annual Percent Change), SBRT (Stereotactic Body Radiotherapy)

Figure 3. National crude rate of SBRT utilization in percent among patients who received EBRT as initial definitive therapy for localized prostate cancer, stratified by travel distance to treatment facility. P_{trend} from 2004 to 2012 <0.0001 for all travel distances.

Travel Distance and Stereotactic Body Radiotherapy for Localized Prostate Cancer

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RUNING HEAD: Travel Distance and Prostate SBRT

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PRÉCIS: Definitive prostate SBRT utilization has increased more than three-fold since 2004, with a significant increase in usage coinciding with early reports of short-term efficacy. Long-distance travel for treatment was associated with more than twice the odds of definitive prostate SBRT receipt compared to short-distance travel, suggesting that ~~Long-distance travel~~treatment decisions with unknown long-term clinical implications may be strongly driven by sociodemographic factors.

~~ers are more than twice as likely to receive prostate SBRT compared to short-distance travelers suggesting that economic burden is a major factor in treatment decisions and~~

~~may drive decisions toward options that alleviate potential financial toxicity but that have unknown long-term clinical implications.~~

ABSTRACT

BACKGROUND: Definitive stereotactic body radiotherapy (SBRT) represents an emerging and debated treatment option for prostate cancer, with economic savings potential and reports of short-term efficacy since 2006. We sought to define national trends in definitive prostate SBRT utilization and determine whether patterns vary by travel distance for treatment~~travel burden~~.

METHODS: The National Cancer Database (NCDB) identified 181,544 men with localized prostate cancer treated with definitive external beam radiotherapy from 2004-2012. Joinpoint regression analyzed definitive prostate SBRT trends over time, while multivariable logistic regression defined the odds for its receipt by travel distance for treatment.

RESULTS: Definitive prostate SBRT utilization increased from 1.8% in 2004 to 5.9% in 2012 (P_{trend}<0.0001), with a Joinpoint for increased utilization in 2006 (P<0.0001). Higher SBRT utilization was associated with longer travel distance for treatment~~istance travel~~, younger age, white race, more affluent zip code, academic treatment center, favorable disease characteristics, and less comorbidities (all P<0.0001). Compared to travel distances below 25 miles, 25-50 and~~or~~ > 50 miles of travel for treatment were associated with increasing adjusted odds of definitive prostate SBRT receipt (1.63 [95% CI 1.51-1.76] and 2.35 [95% CI 2.14-2.57], respectively, both P<0.0001).

CONCLUSION: Definitive prostate SBRT utilization ~~has~~ increased more than three-fold since 2004, with a significant increase in usage coinciding with early reports of short-term efficacy. ~~Notably,~~ Long-distance travel for treatment was associated with more than twice the odds of definitive prostate SBRT receipt compared to short-distance travel, suggesting that treatment decisions with unknown long-term clinical implications may be strongly driven by sociodemographic factors.

~~long-distance travelers have more than double the odds of receiving short-course SBRT compared to short-distance travelers. Economic burden appears to be a major factor in treatment decisions and may drive decisions toward options that alleviate potential financial toxicity but that have unknown long-term clinical implications.~~

INTRODUCTION:

Prostate cancer is the most common non-cutaneous malignancy in men, with 161,360 new cases of prostate cancer and 26,730 deaths due to prostate cancer in the United States alone in 2017.[1] Long-course external beam radiotherapy (EBRT) is an established form of definitive therapy used for localized prostate cancer, [2] while short-course stereotactic body radiotherapy (SBRT) is a new and emerging high-dose-per fraction form of EBRT that ~~gained cautious support~~was cautiously listed as a definitive therapy option by the National Comprehensive Cancer Network (NCCN) in 2014 ~~with the statement of, "SBRT can be considered cautiously as an alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise."~~[3]

SBRT ~~is high-dose-per fraction EBRT that~~ can be conveniently delivered in five or fewer treatments compared to the up to 45 fractions (9 weeks) in standard-fractionated EBRT.[4] Before ~~NCCN's statement of cautious support in~~being listed as a potential definitive therapy option in the 2014 NCCN guidelines, definitive prostate SBRT was largely considered experimental.[4-6] An early short term report of safety and efficacy was presented in 2006, [7] and since then several phase II studies in patients with favorable risk prostate cancer have suggested SBRT is safe and efficacious. [8-14]

Given the lack of level-1 evidence and long-term results from phase II studies, definitive prostate SBRT use remains a hotly debated topic ~~among experts~~with differing expert opinions ~~and has recently captured national headlines~~.[15] Since definitive prostate SBRT

can be delivered in up to 40 fewer treatments than standard fractionated radiation, the time, travel, and cost savings that patients could incur are significant. As such, pProponents argue that of SBRT offers patients a argue that the decrease in duration of radiotherapy from greater than 2 months to 1-2 weeks represents a significant cost savings and convenient alternative to standard long-course radiation both in terms of time and money saved and may improve access to radiation therapy.[16,17] Nevertheless, there is no expert consensus regarding prostate SBRT and the drivers and trends in its use are poorly understood.

There is an emerging body of evidence demonstrating the economic burden or "financial toxicity" that cancer patients face and that high economic burden affects treatment choice.[18,19] Since definitive prostate SBRT can be delivered in up to 40 fewer treatments than standard fractionated radiation, the time, travel, and cost savings that patients could incur are significant, particularly for long-distance travelers who are at high risk of financial toxicity where the costs of traveling and missing work for 2 months may make receiving standard long-course radiotherapy prohibitive. Definitive prostate SBRT utilization by factors associated with high economic burden such as long-distance travel has not yet been explored in the literature.

Therefore, we sought to define national trends in definitive prostate SBRT utilization and determine whether utilization increased after reports of its efficacy. We also sought to determine the factors associated with receipt of definitive prostate SBRT, with a focus on distance traveled for treatment to determine the influence of sociodemographics on treatment decisions. We used the largest clinical registry in the United States to

address our study aims. [18, 19] ~~We hypothesize that the factors that drive definitive prostate SBRT utilization are evidence demonstrating its efficacy, and factors such as long-distance travel burden that are obviously associated with greater economic burden and higher risk of financial toxicity. Therefore, the purpose of this study was to use the largest clinical registry in the United States to define national definitive prostate SBRT trends over time, and to determine whether treatment patterns vary by travel distance to treatment facility.~~

MATERIALS AND METHODS:

Study population and Design

The study population was derived from the National Cancer Database (NCDB), a nationwide joint program of the Commission on Cancer (CoC) and the American Cancer Society (ACS) that captures 70 percent of newly diagnosed cancers diagnosed and treated at CoC accredited cancer programs. [20,21] Patients diagnosed with localized cT1-4N0M0 prostate adenocarcinoma from 2004-2012 were identified (Site code: C61.9, International Classification of Disease for Oncology (ICD-O) code, 3rd edition: 8140) (N=888,868). Patients without information regarding tumor stage (N=18,740), Gleason score (N=36,020) or PSA level (N=108,613) were excluded. For the purposes of this study, we excluded patients treated with surgery (N=400,461), or those who received radiation therapy other than EBRT +/- brachytherapy or who received palliative intent EBRT (N=143,490); palliative intent treatments have been collected by NCDB since 2003. The final study population consisted of 181,544 patients treated with definitive prostate EBRT. Definitive prostate SBRT was defined as the use of ≤ 5 fractions of treatment modalities coded as Stereotactic radiosurgery, NOS, or Linac radiosurgery. The first year of the study was 2004, since that is the first year that the NCDB included many of the clinical variables of interest, and the last year of the study was 2012 since that is the most recent year on which data was available. Figure 1 summarizes the study population selection criteria.

The institutional review board of the Brigham and Women's Hospital/ Dana-Farber Cancer Institute approved this study.

Statistical Methods

Distribution and comparison of the clinical characteristics

Descriptive statistics were used to present the baseline characteristics, stratified by type of definitive prostate EBRT received (SBRT or standard fractionated EBRT). Categorical variables were assessed with Chi-square test and included age (stratified at age 70), race/origin, insurance status, distance traveled to treatment facility (stratified at 25 miles [approximately 60 minutes round-trip travel] and 50 miles [approximately 2 hours round-trip travel]), PSA level (stratified at 10 and 20 ng/mL), clinical tumor stage, Gleason score, hospital setting, zip code median household income, zip code education level, and residence type; continuous variables were compared with student-t test or Mann-Whiney U test as appropriate and included age and median distance to treatment facility. Travel distance was defined as the distance between patient zip code centroid and the street address of the treating facility.

SBRT Utilization Trends over Time and by Distance Traveled to Treatment Facility

For the purposes of illustration, crude definitive prostate SBRT rates by year were generated and displayed graphically. Mantel-Haenszel Chi-square test for trend was used to examine the trend for crude rates of SBRT utilization over time. To determine if any significant changes in definitive SBRT rates correlated with the publication of favorable reports in 2006, univariable Joinpoint regression analysis (Joinpoint Regression Program, Version 4.1.0) was used to analyze annual percentage changes (APCs) over time. [22] The Joinpoint Regression Program takes trend data and tests

whether any statistically significant changes in trends occur using the Monte Carlo permutation method. Points at which statistically significant changes in trends occur are termed "Joinpoints."

Estimates of Odds of Receipt of SBRT by Travel Distance to Treatment Facility and other Patient Factors

To test the null hypothesis that there is no difference in receipt of definitive prostate SBRT by travel distance to treatment facility (<25 miles [referent], 25-50miles, >50miles), univariable and multivariable logistic regressions were used to define odds ratios (OR)s and adjusted odds ratios (AOR)s for the dependent endpoint of receipt of definitive prostate SBRT, respectively. Sociodemographic covariates included in the models were age (≤70 [referent], >70]), race/origin (Non-Hispanic White [referent], African American, Non-Black Hispanic, Other Non-White), insurance status (none [referent], private, Medicaid, Medicare), zip code median household income (<$38,000 [referent], $38,000-47,999, $48,000-62,999, ≥ 63,000), residence type (metropolitan [referent], urban, rural), zip code percent education level less than high school (≥ 21% [referent], 13%-20.9%, 7-12.9%, <7%). Clinical variables included in the models were prostate-specific antigen [PSA <10ng/mL [referent], PSA 10-20ng/mL, PSA >20 ng/mL), clinical tumor stage (T1 [referent], T2, T3, T4), Gleason score (6 [referent], 7, 8-10), Charlson-Deyo comorbidity score (0 [Referent], 1, ≥2), and hospital setting (non-academic [referent], academic).

For the purposes of illustration, crude definitive prostate SBRT rates by year stratified by travel distance were generated and displayed graphically.

We used 95% confidence intervals (CI)s and a two-sided p-value<0.05 as criteria for clinical significance in all analyses. All statistical analyses were performed using SAS® version 9.4. (SAS Institute Inc., Cary, NC, USA).

RESULTS:

Distribution and comparison of the clinical characteristics

A total of 6,842 patients received SBRT for localized prostate cancer. Higher SBRT utilization was associated with longer travel distance for treatment, younger age, white race, more affluent zip code, academic treatment center, favorable disease characteristics, non-Medicaid insurance status, and less comorbidities (~~all *P*<0.0001;~~ Table 1).

SBRT Utilization Trends over Time

Among patients treated with definitive EBRT, SBRT utilization increased year to year, from 1.8% in 2004 to 5.9% in 2012 (P_{trend}<0.0001; Figure 2). A Joinpoint for increased utilization was identified in 2006 (P<0.0001; Figure 2). The annual percent change in SBRT utilization was +13.92% from 2004-2005, +28.84 % from 2006 to 2009, and +7.09% from 2010 to 2012, with significant differences between the 2004 to 2005 and 2006 to 2009 periods (P<0.0001), but not between the 2006 to 2009 and 2010 to 2012 periods (P=0.10) (Figure 2).

Estimates of Odds of Receipt of SBRT by Travel Distance to Treatment Facility

On univariable analysis, receipt of SBRT was significantly associated with travel distance to treatment facility, race/origin, insurance status, Charlson comorbidity score, PSA level, clinical tumor stage, Gleason score, zip code median household income, zip code education level, and residence type (All P<0.004; Table 2). After robust multivariable adjustments for all patient factors associated with receipt of SBRT, longer

travel distance for treatment of 25-50 miles or beyond 50 miles was increasingly associated with ~~a~~ higher adjusted odds of SBRT receipt when compared to travel distances below 25 miles, (1.63 [95% CI 1.51-1.76] and 2.35 [95% CI 2.14-2.57], respectively, both P<0.0001; Table 2). Crude SBRT rates over the study period stratified by travel distance are displayed in Figure 3; of note, there was an increasing trend of SBRT utilization for all patients regardless of travel distance from 2004-2012 (P_{trend} for all <0.0001), though relative differences between travel distances remained constant.

Estimates of Odds of Receipt of SBRT by other Patient Factors

Black, Hispanic, or other non-White patients were significantly less likely to receive SBRT compared to White patients (AOR 0.86 [95% CI 0.80-0.93], P=0.0001; AOR 0.52 [95% CI 0.44-0.61], P<0.0001; and AOR 0.79 [95% CI 0.68-0.91], P=0.002, respectively; Table 2). Age <70, non-Medicaid insurance, Charlson comorbidity score of 0, PSA level <10 ng/mL, clinical T1 stage, Gleason score 6, academic hospital setting, zip code median household income ≥ $63,000, and metropolitan residence were all significantly associated with increased odds of SBRT receipt on multivariable analysis (Table 2).

DISCUSSION:

Using the largest registry of incident prostate cancers in the United States, we found that definitive prostate SBRT utilization has increased over three-fold from 2004 to 2012, with a significant increase in usage starting in 2006 coinciding with early reports of favorable efficacy and safety. At the end of the study period, definitive SBRT rates remained modest, peaking at nearly 6%. Notably, ~~l~~long-distance travel for treatment was associated with more than twice the odds of definitive prostate SBRT receipt compared to short-distance travel. These findings give insight into the potential drivers of definitive SBRT utilization and thus may be able to inform patient counseling and outreach efforts.

~~ravel distances greater than 50 miles to treating facility (roughly greater than 2 hours of round-trip travel) were associated with more than twice the odds of receipt of definitive prostate SBRT when compared to travel distances less than 25 miles (roughly less than 1 hour of round-trip travel).~~

Notably, the increased prostate SBRT utilization observed in our study was during a time when this therapy was considered experimental with unknown long-term clinical risks, and not listed in NCCN guidelines as a potential alternative to standard long-course radiation. A majority of SBRT occurred in academic cancer centers where these treatments may have been performed on clinical trial or by clinicians with clinical expertise and access to the appropriate technology and facility support to safely provide extreme hypofractionated radiotherapy. The significant uptake in prostate SBRT utilization in 2006 coincides with early presentation of favorable safety and efficacy

associated with extreme hypofractionation.[7] Furthermore, a significant trend of increased SBRT utilization continued through 2012 (the end of our study period), coinciding with the publication of several phase II clinical trials from eight cancer centers suggesting SBRT has similar early outcomes compared to other forms of radiotherapy.[8-14] Nevertheless, the absolute rate of prostate SBRT during our study period remained modest in comparison to the uptake of standard fractionation intensity modulated radiotherapy, likely given the unclear long-term implications.[21] We would expect the rate of prostate SBRT to continue increasing after being cautiously listed as a potential definitive therapy option in 2014 NCCN guidelines, and its utilization to be further guided by an ongoing phase III randomized non-inferiority clinical trial.[22]

Our finding that long-distance travel was strongly positively associated with definitive prostate SBRT suggests that treatment decisions with unknown long-term clinical implications may be strongly driven by sociodemographic factors. The reasons and directionality behind our findings can be explained by multiple competing hypotheses. One potential explanation is that patients with greater travel burden may have increased risk of ~~Given the obvious increased~~ economic burden and risk of financial toxicity with long-course radiation treatment (given the costs associated with time, work loss, and greater travel) that may drive treatment decisions. ~~incurred by cancer patients with greater travel burden, short course SBRT appears to be a more salient option than for patients who otherwise have less travel burden and therefore less economic burden from long-course radiotherapy.~~ High economic burden has been demonstrated to be a barrier to receipt of appropriate cancer care, and travel distance is a significant factor in

adherence to cancer treatment.[18,23] As such, patients with greater travel and/or economic burden may be more likely to pursue short-course SBRT as a more convenient and potentially less financially burdensome treatment option.

An alternative hypothesis is that patients with the means (financial and otherwise) to travel to centers where SBRT is offered are those most likely to receive SBRT. Our study showed that younger, higher SES, white, and non-Medicaid insured patients were those most likely to receive SBRT, and this group certainly represents a cohort with greater means to travel longer distances for treatment. This group of patients may be influenced to travel to centers where SBRT is offered based on information or advertisements from treating centers that short-course SBRT treatment offers an equally efficacious treatment to standard long-course treatment (especially since NCCN guidelines are not necessarily widely disseminated among patients). Ultimately, these hypotheses are not mutually exclusive, since patients are at risk of financial toxicity with cancer treatments across SES strata, including high SES patients.[19] Therefore, younger, higher SES, white patients may both 1] be more likely to have the means to travel longer distances to a center with SBRT, and also 2] may be likely to be driven by the implications of financial toxicity. Younger and higher SES patients represent a predominantly actively working population that may be at risk of the greatest delta in financial losses between long and short-course treatments given the differences in losses associated with time away from work, time in general, and cost between the two treatment approaches. Nevertheless, even after adjusting for all sociodemographic and clinic factors on multivariable analysis, travel distance remained strongly associated

with SBRT receipt. Ultimately, the data provided in NCDB cannot distinguish between these and other potential hypotheses, and it is likely the case that the drivers of the association between travel distance to treatment facility and prostate SBRT are multifactorial. ~~Notably, the increased utilization of SBRT by long-distance travelers was observed during a time when this therapy was not approved by the NCCN and considered experimental with unknown long-term clinical risks. As such, our results suggest that for patients with greater economic burdens from cancer care such as long-distance travelers, the risks of financial toxicity may outweigh the risks of clinical toxicity even when the latter risks are poorly defined or unknown.~~

~~On one front, our findings suggest that SBRT is a promising method of radiation delivery that offers a treatment option for patients who otherwise would incur financial toxicity at a level that may deter them from treatment. However, on another front, our results suggest that patients with greater economic and financial burdens who are at risk of financial toxicity such as long-distance travelers are more likely to receive therapies that are not guideline approved or considered the standard of care. We would argue that SBRT must be explored as a modality that can alleviate economic burden and increase access to cancer care especially for long-distance travelers who may incur significant financial toxicity from daily long-course radiation treatment. However, we would also argue that efforts are needed to make standard cancer care treatments accessible to long-distance travelers and support programs are needed to reduce financial and economic barriers to receiving proven treatments.~~

Notably, a Joinpoint for significant increased national utilization of SBRT for prostate cancer was identified in 2006. This time point coincides with early presentation of favorable safety and efficacy associated with extreme hypofractionation, which suggested early biochemical failure and toxicity rates were acceptable.[7] Furthermore, a significant trend of increased SBRT usage was observed through 2012, before NCCN cautiously approved SBRT as an option for definitive therapy in 2014. The continued increase in SBRT utilization during this time period coincides with the time during which several phase II clinical trials from eight cancer centers were published suggesting SBRT has similar early outcomes compared to other forms of radiotherapy.[8-14] Interestingly, the observed uptake of SBRT utilization occurred during a period where the therapy was not yet guideline approved and still largely considered experimental given the lack of level-1 evidence or long-term data. The majority of SBRT occurred in academic cancer centers where these treatments may have been performed on clinical trial or by clinicians with clinical expertise and access to the appropriate technology and facility support to provide extreme hypofractionated radiotherapy. For now, the rate of SBRT uptake is modest in comparison to the uptake of standard fractionation intensity modulated radiotherapy, likely given the unclear long-term implications.[24] There is an ongoing phase III randomized non-inferiority clinical trial comparing outcomes between standard fractionation and extreme hypofractionation for the treatment of low-risk prostate cancer which will help address concerns about SBRT.[25] We would expect the rate of SBRT to continue to increase after a favorable pooled analysis of the aforementioned phase II clinical trials in 2013 and also NCCN's statement of cautious approval in 2014.

~~Clinical factors associated with receipt of SBRT in this study were low PSA, early T stage, early Gleason score, and better health status. Sociodemographic factors associated with higher rates of SBRT were age younger than 70, white race, non-Medicaid insurance, more affluent zip code, and metropolitan residence. Even after robust multivariable adjustment, Black and Hispanic men were less likely to receive SBRT compared to White men, and men with Medicaid were less likely to receive SBRT compared to other non-Medicaid insurance. The clinico-sociodemographic factors associated with SBRT use for localized prostate cancer highlight an interesting pattern of care. The differences between groups are likely a result of patient preferences, access to SBRT, and clinical judgment on behalf of the clinicians. Men who are younger, healthier, and who have lower-risk disease features are also more likely to receive SBRT for patient selection reasons. That is, clinicians would be more likely to select patients who have a better chance at success for an experimental therapy than patients with less favorable clinical characteristics. As an example, many of the phase II clinical trials that studied SBRT included mostly men, with low to intermediate risk disease and who were relatively young and healthy.[26] Furthermore, younger age patients are more likely to still be working and therefore the economic implications of long-course treatment are greater for that group and may be a driver toward SBRT.~~

Regarding race and ethnic origin, Black and Hispanic men were observed to be significantly less likely to receive SBRT compared to white men. This finding persisted after adjusting for variables such as prostate cancer prognostic factors, travel distance,

comorbidity status, age, treatment center, place of income, insurance type, and education. The reasons for this observed pattern are likely multifactorial. Prior reports have suggested that minority patients have less trust in the medical system for historical reasons, and may be less likely to receive a therapy that is considered experimental or unproven. [27-29] Furthermore, Black men tend to harbor more aggressive disease and are at a higher odds of dying from prostate cancer compared to their White counterparts, so clinicians may be less willing to recommend an experimental therapy to these high risk patients when alternative proven therapies exist.[30,31] Provider implicit bias is also a well-studied factor that may contribute to differential utilization of SBRT.[32-34] Lastly, it remains possible that there are other factors not captured in the NCDB which may contribute to disparities in SBRT utilization. The potential drivers of disparities described ~~hitherto~~ remain hypotheses, and would be best studied via surveys and tests of implicit bias. If long-term data show that SBRT is as efficacious as current standard forms of EBRT, a concerted effort will be needed to ensure equal access to this technology, regardless of clinic-sociodemographic characteristics.

Other studies have similarly demonstrated an increasing rate of definitive prostate SBRT, but have not explored the relationships between travel distance or dissemination of literature and SBRT patterns [16,35] To our knowledge, this study is the first to highlight these important relationships and how travel distance to treatment facility~~/economic toxicity~~ and dissemination of favorable literature may be major drivers of SBRT utilization. Still, our results must be viewed within the limitations of the study. Although the NCDB represents the nation's largest cancer database, our study does not have

data from cancer centers that are not CoC accredited and so our data likely does not reflect those centers. Furthermore, our study only includes data up to 2012 as provided by the NCDB and so we are not able to determine SBRT rates after publication of the pooled analysis of phase II clinical trials or after the SBRT was cautiously listed as a potential definitive therapy in the 2014 ~~cautious approval by~~ NCCN ~~in 2014~~guidelines.[3,26] Lastly, the drivers and directionality of the observed associations cannot be clearly defined by the data provided in the NCDB.

Despite the potential limitations, our study is a robust and comprehensive report on the national trends and patterns of definitive prostate SBRT utilization. The absolute national rate of definitive SBRT for localized prostate cancer has increased nearly three-fold since 2004, with a significant increase in usage coinciding with early reports of favorable safety and efficacy. Long-distance travel for treatment was associated with more than twice the odds of definitive prostate SBRT receipt compared to short-distance travel, suggesting that treatment decisions with unknown long-term clinical implications may be strongly driven by sociodemographic factors.~~Notably, long-distance travelers have more than double the odds of receiving short-course SBRT compared to short-distance travelers. Given the obvious increased economic burden and financial toxicity incurred by cancer patients with greater travel burden, short-course SBRT appears to be a more salient option than for patients who otherwise have less travel burden and therefore less economic burden from long-course radiotherapy.~~ A concerted effort needs to be made to further explore definitive prostate SBRT as a safe and potentially less burdensome treatment option ~~that can alleviate financial toxicity~~,

balanced with an effort to ensure patients who may be more likely to pursue SBRT have access to and are aware of the high level data supporting ~~long-distance travelers and patients at risk for economic burden are able to access standard of care treatments despite their circumstances~~standard treatment approaches.

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Table 1. Distribution and comparison of the clinical characteristics stratified by definitive external beam radiotherapy fractionation type. ~~P < 0.0001 across all patient characteristics.~~ IQR (Interquartile Range), No. (Number), PSA (Prostate-Specific Antigen)

Patient Characteristic	**Received Definitive Prostate Stereotactic Body Radiotherapy N=6,842 (3.8%)**	**Received Definitive Prostate Standard Fractionated External Body Radiotherapy N=174,702 (96.2%)**
Median Age in Years (IQR)	68 (62-73)	69 (63-74)
Age in Years No. (%)*		
<70 (%)	3,940 (57.6)	89,977 (51.5)
≥70 (%)	2,902 (42.4)	84,725 (48.5)
Race/Origin No. (%)		
Non-Hispanic White	5,377 (78.6)	129,346 (74.0)
African American	1,030 (15.1)	298,936 (17.1)
Hispanic	160 (2.3)	7,497 (4.3)
Other Non-White	195 (2.9)	5,545 (3.2)
Unknown	80 (1.2)	2,421 (1.4)
Insurance Status No. (%)		
None	93 (1.4)	2,820 (1.6)
Private	2,388 (34.9)	56,621 (32.4)
Medicaid	107 (1.6)	4,859 (2.8)
Medicare	3,971 (58.0)	102,941 (58.9)
Other	152 (2.2)	4,290 (2.5)
Unknown	131 (1.9)	3,171 (1.8)
Median Travel Distance to Treatment Facility in Miles (IQR)	11.0 (5.1-23.3)	8.2 (3.9-17.6)
Travel Distance to Treatment Facility No. (%)		
<25 miles	5,235 (76.5)	146,770 (84.0)
25-50 miles	911 (13.3)	18,536 (10.6)

>50 miles	696 (10.2)	9,396 (5.4)
Charlson Comorbidity Score No. (%)		
0	5,909 (86.4)	153,666 (88.0)
1	810 (11.8)	17,596 (10.1)
2+	123 (1.8)	3,440 (2.0)
Median PSA in ng/mL (IQR)	6.2 (4.6-9.7)	7.0 (5.0-11.9)
PSA Level No. (%)		
< 10 ng/mL	5,200 (76)	119,067 (68.2)
10-20 ng/mL	944 (13.8)	32,546 (18.6)
> 20 ng/mL	698 (10.2)	230,89 (13.2)
Clinical Tumor Stage No. (%)		
T1	4,895 (71.5)	107,547 (61.6)
T2	1,823 (26.6)	58,120 (33.3)
T3	115 (1.7)	8,454 (4.8)
T4	9 (0.1)	581 (0.3)
Gleason Score No. (%)		
6	3,263 (47.7)	60,310 (34.5)
7	2,855 (41.7)	76,209 (43.6)
8-10	724 (10.6)	38,183 (21.9)
Hospital Setting No. (%)		
Academic	3,419 (50.0)	52,075 (29.8)
Non-academic	3,423 (50.0)	122,627 (70.2)
Zip Code Median Household Income No. (%)		
<$38,000	956 (14.0)	31,986 (18.3)
$38,000-47,999	1,159 (16.9)	40,366 (23.1)
$48,000-62,999	1,565 (22.9)	45,841 (26.2)
≥ 63,000	3,155 (46.1)	56,293 (32.2)
Unknown	7 (0.1)	216 (0.1)
Zip Code Education Level (percent less than high school degree) No. (%)		
≥ 21%	1,073 (15.7)	30,374 (17.4)
13%-20.9%	1,428 (20.9)	45,582 (26.1)

7-12.9%	2,120 (31.0)	56,720 (32.5
<7%	2,219 (32.4)	41,915 (24.0)
Unknown	2 (0.0)	111 (0.1)
Residence Type No. (%)		
Metropolitan	5,829 (85.2)	141,774 (81.2)
Urban	78 (1.1)	26,332 (15.1)
Rural	772 (11.3)	3,554 (2.0)
Unknown	163 (2.4)	3,042 (1.7)

*Percentage may not add up to 100 due to rounding.

Table 2. Univariable and Multivariable logistic regression defined odds ratios for receipt of definitive prostate stereotactic body radiotherapy. AOR (Adjusted Odds Ratio), CI (Confidence Interval), OR (Odds Ratio), Ref (Referent).

Patient Characteristic	**Unadjusted OR**	**P-value**	**AOR (95%CI)**	**P-value**
Travel Distance to Treatment Facility				
<25 miles	Ref		Ref	
25-50 miles	1.36 (1.26-1.46)	<.0001	1.63 (1.51-1.76)	<.0001
>50 miles	2.09 (1.92-2.27)	<.0001	2.35 (2.14-2.57)	<.0001
Age in Years				
<70	Ref		Ref	
≥70	0.78 (0.75-0.82)	<.0001	0.83 (0.78-0.87)	<.0001
Race/Origin				
Non-Hispanic White	Ref		Ref	
African American	0.83 (0.77-0.89)	<.0001	0.86 (0.80-0.93)	0.0001
Hispanic	0.51 (0.44-0.60)	<.0001	0.52 (0.44-0.61)	<.0001
Other Non-White	0.85 (0.73-0.98)	0.024	0.79 (0.68-0.91)	0.002
Insurance Status				
None	Ref		Ref	
Private	1.28 (1.04-1.58)	0.022	1.09 (0.88-1.35)	0.45
Medicaid	0.67 (0.50-0.89)	0.005	0.75 (0.56-1.00)	0.05
Medicare	1.17 (0.95-1.44)	0.140	1.27 (1.02-1.57)	0.03
Others	1.07 (0.83-1.40)	0.59	0.99 (0.76-1.29)	0.94
Charlson Comorbidity Score				
0	Ref		Ref	
1	1.20 (1.11-1.29)	<.0001	1.34 (1.24-1.44)	<.0001
2+	0.93 (0.78-1.12)	0.43	1.11 (0.92-1.34)	0.28
PSA Level				
< 10 ng/mL	Ref		Ref	
10-20 ng/mL	0.66 (0.62-0.71)	<.0001	0.79 (0.74-0.85)	<.0001
> 20 ng/mL	0.69 (0.64-0.75)	<.0001	0.94 (0.86-1.02)	0.14

Clinical Tumor Stage				
T1	Ref		Ref	
T2	0.69 (0.65-0.73)	<.0001	0.78 (0.74-0.83)	<.0001
T3	0.30 (0.25-0.36)	<.0001	0.37 (0.31-0.46)	<.0001
T4	0.34 (0.18-0.66)	0.0001	0.54 (0.28-1.05)	0.07
Gleason Score				
6	Ref		Ref	
7	0.69 (0.66-0.73)	<.0001	0.72 (0.69-0.76)	<.0001
8-10	0.35 (0.32-0.38)	<.0001	0.41 (0.37-0.44)	<.0001
Hospital setting				
Non-academic	Ref		Ref	
Academic	2.35 (2.24-2.47)	<.0001	2.14 (2.03-2.25)	<.0001
Zip Code Median Household Income				
<$38,000	Ref		Ref	
$38,000-47,999	0.96 (0.88-1.05)	0.36	1.09 (0.99-1.19)	0.09
$48,000-62,999	1.14 (1.05-1.24)	0.0001	1.26 (1.15-1.39)	0.0001
≥ 63,000	1.88 (1.72-2.02)	<.0001	2.01 (1.81-2.23)	<.0001
Zip Code Education Level (percent less than high school degree)				
≥21%	Ref		Ref	
13%-20.9%	0.89 (0.82-0.96)	0.004	0.75 (0.69-0.82)	<.0001
7-12.9%	1.06 (0.98-1.14)	0.139	0.72 (0.66-0.79)	<.0001
<7%	1.50 (1.39-1.61)	<.0001	0.77 (0.70-0.85)	<.0001
Residence Type				
Metropolitan	Ref		Ref	
Urban	0.71 (0.66-0.77)	<.0001	0.78 (0.71-0.85)	<.0001
Rural	0.53 (0.43-0.70)	<.0001	0.52 (0.41-0.65)	<.0001

Figure Legends

Figure 1. Eligibility and exclusion criteria. EBRT (External Beam Radiotherapy), N (Number), SBRT (Stereotactic Body Radiotherapy).

Figure 2. National crude rate of SBRT utilization in percent among patients who received EBRT as initial definitive therapy for localized prostate cancer. P_{trend} from 2004 to 2012 <0.0001. ^ The APC is significantly different from zero at alpha = 0.05 (P <0.0001). APC (Annual Percent Change), SBRT (Stereotactic Body Radiotherapy)

Figure 3. National crude rate of SBRT utilization in percent among patients who received EBRT as initial definitive therapy for localized prostate cancer, stratified by travel distance. P_{trend} from 2004 to 2012 <0.0001 for all travel distances.

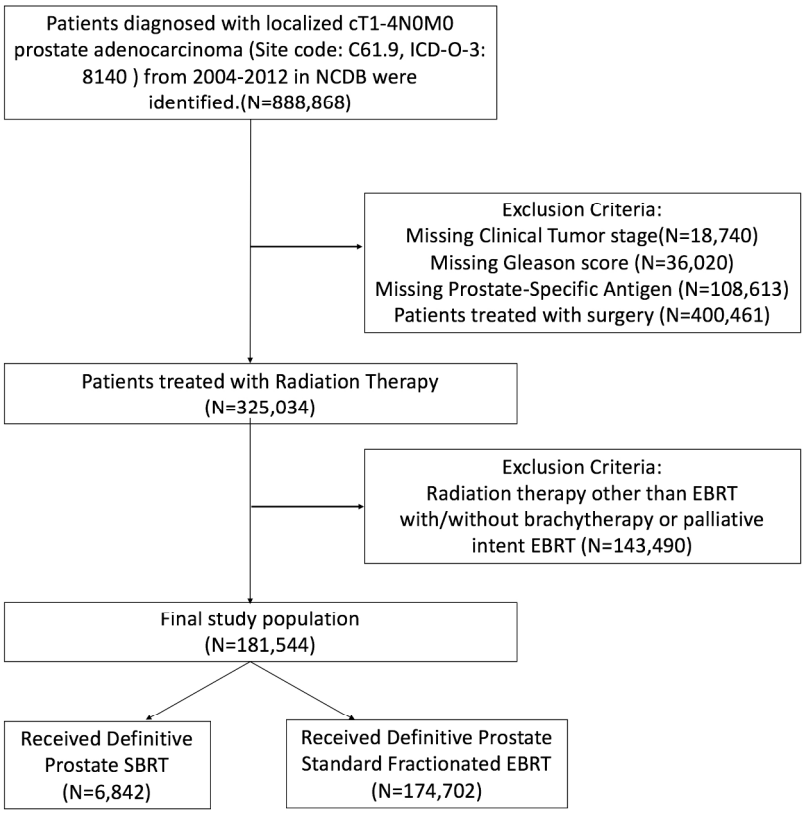

Figure 1. Eligibility and exclusion criteria. EBRT (External Beam Radiotherapy), N (Number), SBRT (Stereotactic Body Radiotherapy).

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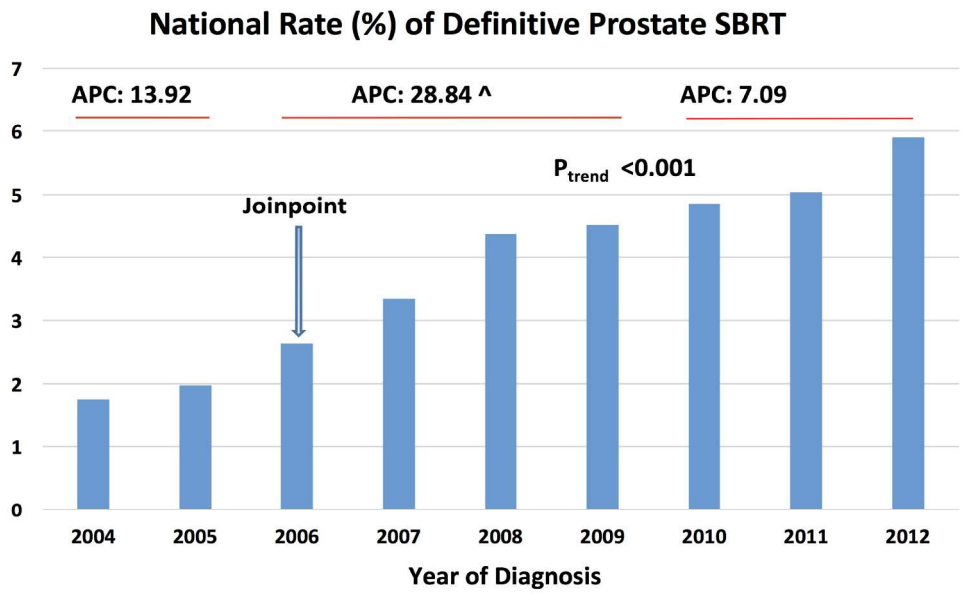

Figure 2. National crude rate of SBRT utilization in percent among patients who received EBRT as initial definitive therapy for localized prostate cancer. Ptrend from 2004 to 2012 <0.0001. ^ The APC is significantly different from zero at alpha = 0.05 (P <0.0001). APC (Annual Percent Change), SBRT (Stereotactic Body Radiotherapy)

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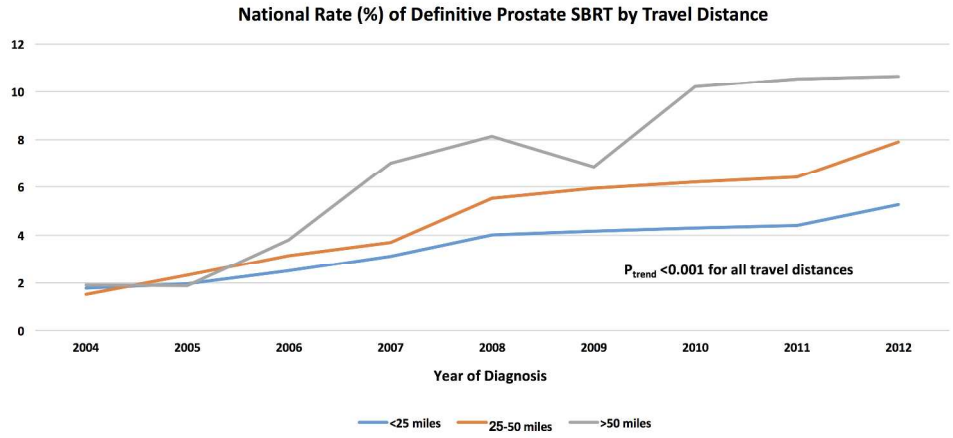

Figure 3. National crude rate of SBRT utilization in percent among patients who received EBRT as initial definitive therapy for localized prostate cancer, stratified by travel distance to treatment facility. Ptrend from 2004 to 2012 <0.0001 for all travel distances.

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