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Yuxian Sun Date

Whether the Proton Beam Radiation Leads to Less Second Malignancies among Localized Prostate Cancer Patients

By

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Master of Public Health

Biostatistics and Bioinformatics

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By

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B.A.
University of Science and Technology Beijing
2018

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Abstract

Whether the Proton Beam Radiation Leads to Less Second Malignancies among Localized Prostate Cancer Patients

By Yuxian Sun

Background: The primary radiotherapies for prostate cancer patients include three-dimensional conformal radiation therapy (3D-CRT), Intensity-modulated radiation therapy (IMRT), Photon beam radiation therapy (Photon therapy), Brachytherapy, and Proton beam radiation therapy (Proton therapy). Although these treatment methods can be curative, radiation carcinogenesis arises as a unique major concern.

Methods and Materials: NCDB prostate PUF cancer cases diagnosed from 2004 to 2016 were queried for patient with localized disease and treated by radiation as the first course of treatment plan. ANOVA and chi-square tests were used to assess the univariate association of radiotherapies and all covariates. Absolute Standardized Difference was used to check the significance of the association. The univariate logistic regression and multivariate logistic regression methods were used to assess the association of secondary tumor with all covariates. Subgroup analysis was also performed. The pairwise propensity score method was used to reduce selection bias through balancing baseline covariates.

Results: Proton therapy resulted in reduced odds of secondary cancers when compared to other radiation therapies. After applying the propensity score weighting method, selection bias was eliminated (all ASD below 0.2). Photon/IMRT/3D-CRT resulted in higher odds of secondary cancers when compared with Proton therapy (OR: 4.31 (95%CI: 4.07-4.56)). In comparing Brachytherapy versus Proton therapy as the reference group, the odds of secondary tumors were also statistically significant (OR: 3.45 (95%CI:3.21-3.70)). The association of secondary tumor was modified by the race-ethic groups, the year of diagnosis groups, and the gleason groups in comparison to Proton vs. Photon/IMRT/3D-CRT and Proton vs. Brachy. NH-White patients had higher odds ratio with Photon/IMRT/3D-CRT therapy (OR:5.04 (95%CI: 4.73-5.37)) or Brachytherapy (OR:3.95 (95%CI: 3.64-4.28)) comparing with Proton therapy. Patients from earlier year of diagnosis had higher odds ratio due to longer follow-up. Patients with lower Gleason score had much higher odds ratio in comparison to Proton vs. Photon/IMRT/3D-CRT (OR:6.64 (95%CI: 6.02-7.34)) and Proton vs. Brachy (OR:5.12 (95%CI: 4.54-5.77)).

Conclusion: Proton therapy had the least risk of developing secondary tumors compared with therapies of other radiation modalities. The propensity score weighting method could eliminate bias in observation since our data was well balanced with propensity score adjustment.

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Contents

1. Introduction

Prostate cancer is cancer that develops in the prostate.[1] Importantly, this is one of the most common cancers among men and is the sixth leading cause of cancer deaths in men globally. Prostate cancer is also the second leading cause of cancer death in the United States.[2] According to the American Cancer Society, the estimated number of new cases of prostate cancer is 174,650, and the estimated number of deaths was 31,620 in 2019. In other words, one in nine American men may be diagnosed with prostate cancer in their lifetime, and about 1 in 41 men will die of this disease. Although the incidence rate and death rate have declined over the last decade, both rates still maintain high. [3] Most cases in prostate cancer are localized, which is defined as cancer only occurring in the prostate with no identifiable regional lymph nodes or distant metastases. [4] [5] Among cases diagnosed from 2008 to 2014 and followed through 2015, the 5-year relative survival rate of localized prostate cancer is above 99%. [3]

The primary treatment options for localized prostate cancer include active surveillance, radiation therapy, and surgery. Active surveillance means patients only use a series of tests, including PSA testing and physical examinations to monitor the development of the disease. [5] Radiotherapy has been considered to be one of the most effective treatment methods. [6] According to different types of radiation modalities, the techniques can be divided into five kinds, including three-dimensional conformal radiation therapy (3D-CRT), Intensity-modulated radiation therapy (IMRT), Photon beam radiation therapy (Photon therapy), Brachytherapy, and Proton beam radiation therapy (Proton therapy). [7] Both 3D-CRT and IMRT use X-rays. Photon therapy focuses on X-rays or gamma-rays and uses a special machine called a linear accelerator to non-invasively deliver the beams from the surface of the body and penetrate the tumor. [8] For 3D-CRT, special machines are used in advance to find the location as well as the position of the tumor. After tumor mapping, physicians distribute X-rays beams to the malignant tumor from different directions. IMRT is more advanced than 3D-CRT. Both IMRT and 3D-CRT are commonly used external beam

radiotherapies. The difference between 3D-CRT and IMRT is the machine of IMRT can move around the patients to deliver beams. Brachytherapy is a kind of internal radiation therapy, and it uses small radioactive pellets that are placed directly into the prostate to release targeted radiation. [9] Proton therapy is the newest method, which delivers beams of the proton to the tumor, minimizing radiation loss when approaching the target. In this way, adjacent normal tissues receive much less off-target radiation. [10] Proton therapy seems to be more effective than the other techniques due to its unique properties, but there is no enough evidence to confirm the efficacy since it is not widely used. Proton therapy needs a special device, which is very expensive, so it is not available in many centers. [11]

Although the five treatment methods can be curative and play an important role in prostate cancer therapy, they also have many side effects that impact a patient's quality of life. Those usually include urinary incontinence, urinary irritates symptoms, infertility, scarring of the urethra, trouble obtaining or sustaining an erection, radiation cystitis, and gastrointestinal effects. [12] [4] In addition, radiation carcinogenesis arises as a unique major concern for radiotherapy as follow-up time becomes longer.[13]

A meta-analysis review concluded there was an increased risk of developing second malignancies of the bladder, colon, and rectum compared with patients unexposed to radiotherapy. [13] Secondary malignancies are defined as the same kind of cancer cells spread from the primary place and develop new tumors in other places.[14] Similarly, several other studies investigated whether a single radiation modality increases the risk of secondary tumors. There was an increased risk of developing bladder cancer and rectal cancer for men who had prostate cancer and received external beam radiotherapy. [7] Further, there was a small increased risk of bladder cancer for patients who had prostate cancer receiving Brachytherapy. [15] In a comparison of radiation modalities among patients with thymic tumors, there was a significant reduction in secondary malignancies for patients who received Proton therapy compared with IMRT.[16]

Clinical data support there is a lower incidence of secondary tumors after Proton therapy compared with historical photon data.[10] Among studies looking at Proton therapy compared to Photon therapy, there is a lower risk of developing secondary tumors with Proton therapy. [17] [18]

There are many studies on the incidence of secondary cancer by Proton radiotherapy, but these studies mainly focus on cancer other than prostate cancer. In addition, there is no comprehensive comparison of radiotherapy methods for prostate cancer. Physicians and prostate cancer patients should be aware of the side effects of developing second malignancies when making clinical care decisions. In addition, the rate of secondary cancer should be carefully evaluated as curing one cancer, but creating a second cancer is highly problematic. To address these gaps in the literature about comparisons of radiotherapies for prostate cancer and the risk of secondary cancers, the purpose of this study is to assess the risk of developing second cancers among patients who have prostate cancer receiving those five radiation modalities. We aimed to examine the question by querying the National Cancer Database 2004-2016.

2. Method

2.1 Data Source

Our data was from a retrospective cohort study obtained from The National Cancer Database. The National Cancer Database, a joint project between the American College of Surgeons and American Cancer Society that provides deidentified data from over 1500 hospitals affiliated with the Commission on Cancer program, which represents approximately 70% of new cancer diagnoses in the United States. The Participant User File (PUF) was a publicly available file consisting of the NCDB dataset for each cancer type.[19]

2.2 Study population

All of the NCDB prostate PUF cancer cases diagnosed from 2004 to 2016 were initially included in this study. Then the following selections and exclusions were made:

Inclusions:

- Patients with localized prostate cancer: AJCC Clinic T1-3N0M0
- Patients with age> 40 years
- Patients with invasive tumor behaviors
- Patients whose current cancer diagnosis was the only one of the first in the sequence
- Study cohorts of Proton, Brachytherapy, IMRT, 3D-CRT, and Photon
- Radiation treatment volume of prostate, pelvis, and prostate

Exclusions:

- Patients with any metastasis cases
- Patients aged ≤ 40 years
- Patients receiving palliative care
- Patients with chemotherapy

2.3 Outcome Measures

The primary outcome is the presence of a secondary tumor, which was defined by the sequence number. The sequence number records as the sequence number of malignant or *in situ* tumors over the lifetime of the patients. If patients only had one malignant in his lifetime, then the sequence was 00. A sequence number of 01 means the current cancer diagnosis is the first of two or more independent malignant in a patient's lifetime. A sequence number of 02 indicates the present prostate cancer is the second of two or more independent malignant in a patient's lifetime.

In this study, we only considered cases with a sequence number of 00 and 01. If the sequence number was 00, then this patient only had one tumor diagnosis during his lifetime, which was prostate cancer, and no other secondary tumors. We also included patients with sequence number 01, which indicates a patient was diagnosed first with prostate cancer and then developed at least one other malignant, or a secondary tumor(s) after the initial prostate cancer. With this definition, we know for sure that a patient with sequence number = 01 had another tumor developed later. In contrast, for a patient with sequence number >= 2, we are not 100% sure whether there is another tumor diagnosis after the current prostate cancer. In this study, we will focus on the rate of second tumor or the proportion of sequence number = 01, and compare it across different radiation therapies for localized prostate cancer patients.

2.4 Study Cohorts

The study cohorts were defined by radiation therapy, regional treatment modality, boost treatment modality, and total radiation dose (the sum of regional radiation dose and boost radiation dose). Radioactive implants or combinations of beam radiation with radioactive implants or radioisotopes were defined as Brachytherapy. If it was Proton beam radiation, then it was Proton therapy. EBRT included Photon beam radiation (Photon therapy), three-dimensional conformal radiation therapy (3D-CRT) and Intensity-modulated radiation therapy (IMRT).

2.5 Study Variables

In this study, we considered a bunch of baseline characteristics based on patient' demographics including age at diagnosis, race (White, Black and Other/Unknown), ethnicity (Spanish Hispanic vs. Not Spanish Hispanic). We also included patient's residential symptoms consisting of the median income quartiles between 2008 and 2012 in residence zip code (< $38,000, $38,000-

$47,999, $48,000-$62,999, $63,000+) and treating facility characteristics e.g. Facility type (Non-Academic/Research Program vs. Academic/Research Program). Disease characteristics including Charlson-Deyo Score, Year of diagnosis, AJCC Clinical T stage, Gleason Score, PSA, the addition of concomitant androgen deprivation therapy (ADT), and whether surgery was part of first-course treatment were obtained.

Variables that might have an impact on rate of the secondary tumor of prostate cancer were listed in Table 1. Further explanations were provided in the footnote of Table 1. Race and Spanish Hispanic origin were combined as Race- Ethnic Groups such as NH-White, NH-Black, Asian-Indians-Pac, and Other/Unknown.

2.6 Statistical Method

Descriptive statistics were used to describe count data with percentages for categorical variables and mean with standard deviations, median with Q1 and Q3 for continuous variables. ANOVA and Chi-square tests were used to assess the univariate association of three radiation modalities (Brachy, Photon/IMRT/3D-CRT and Proton) with all covariates listed in Table 1. Absolute Standardized Difference (ASD) was also used to illustrate the net magnitude of difference in variable distribution by study cohorts. Unlike p-value, ASD is not impacted by sample size. The formula of Absolute Standardized Difference was shown below[20],

$$|d| = \left| \frac{100 \times (\bar{x}_T - \bar{x}_C)}{\sqrt{\frac{s_T^2 + s_C^2}{2}}} \right|$$

Where $\bar{x}_T$ and $\bar{x}_C$ were the sample mean of the treatment group and the control group while s_T and s_C indicated the respective sample variance of the treatment group and the control group.

Logistic regression model was utilized to assess the association of using Proton therapy as well as the association of secondary with all covariates. The formula of the linear logistic regression model was shown below,

$$Logit(p) = \log\left(\frac{P(y=1)}{1-p(y=1)}\right) = \beta_0 + \beta x$$

$$p = \frac{e^{\beta_0+\beta x}}{1+e^{\beta_0+\beta x}}$$

Where p was the probability of the outcome being 'success', y was the outcome and x was the independent variable. The multivariate model for the probability of using Proton therapy fitted followed by a backward variable elimination under selection criteria of p-value<0.05. The odds ratio with 95% confidence interval was reported at the same time.

Subgroup analysis (Proton vs. Photon/IMRT/3D-CRT; Proton vs. Brachy; Photon/IMRT/3D-CRT vs. Brachy) was performed to check the significance of the overall effect as well as the interaction terms (Race-Ethnic Groups, Year of diagnosis, and Gleason). Furthermore, the study was stratified by year of diagnosis to compare the percentage of secondary tumors of different radiation modalities. Since patients using Proton therapy were subject to a large selection bias, the pairwise propensity score method was used to reduce the covariate imbalance among Proton vs. Brachy, Proton vs. EBRT, and Proton vs. EBRT. In the pairwise propensity score method, the probability of treatment assignment ($Y = 1$), also called the propensity score, was computed from a logistic regression using radiation modality as the outcome and the baseline characteristics as covariates. The formula of the propensity score was shown as[21],

$$\sigma(X_i) = \Pr(Y = 1|X)$$

Where $\sigma(X_i)$ was the propensity score, i was the particular participant and X was the covariate.

In this study, matching weights were computed as propensity scores based on the other groups. For example, when comparing Proton versus Photon/IMRT/3D-CRT, we used the estimated probability of Photon/IMRT/3D-CRT as the weight for Proton and the estimated probability of Proton as the weight for Photon/IMRT/3D-CRT. After assigning the matching weights, the distributions of covariates are roughly the same across the radiation modality groups. In this way, the impact of potential confounders was fairly balanced out. In the final weighted sample, Absolute Standardized Difference (ASD) was computed again for balance checking of baseline characteristics in these three comparison groups after matching. Multivariate logistic regression models were constructed in the comparison groups to estimate the significance of the overall effects as well as the interaction terms (Race-Ethnic Groups, Year of diagnosis, and Gleason) with propensity score adjustment. All statistical significance in this study was determined as two-tailed tests at an alpha of 0.05 or as ASD at 0.2. SAS 9.4 (SAS Institute, Inc. Cary, NC) and SAS macros were used to perform all statistical analysis.[22]

3. Results

3.1 Overall patients' baseline characteristics and differences by study cohorts. (Table 1)

A total of 366,976 patients who met the selection and exclusion criteria were included in this study. Of these, 5,931 patients received Proton therapy. The demographic details of the included patients were summarized in Table 1, along with its univariate association with the three radiation modalities. Most patients were treated at the Non-Academic Program (70.9%), and aged above 65 years (61%). Most patients were NH-White (76%). The Gleason score of the majority of patients was below 7 (77.5%), and the PSA values were below 10 (70.1%). More patients were included with an earlier diagnosed year (37.6%, 25.0%, 19.7%, 17.7%). The majority of the patients did not have surgery (92.9%) as first-course therapy. The distribution of radiation modalities used were as follows: Photon/IMRT/3D-CRT therapy (58.8%), Brachy (39.6%), and Proton (1.6%).

Table 1 shows the specific demographics data in those three groups with its p-value as well as ASD. All p-values were significant in the univariate analysis (all $p < 0.05$) and most ASD values were above 0.2.

Most patients using Photon/IMRT/3D-CRT (70.8%) as well as Brachytherapy (73.8%) were from Non-Academic Program while most patients using Photon therapy (94.2%) were from an Academic Program. The reason of this difference might be because Proton therapy requires a special treatment machine. That was also the reason why patients with higher median income quartiles tended to use Proton therapy more since Proton therapy was more expensive than other radiotherapy methods. Comparing patients using Brachy, Photon/IMRT/3D-CRT, patients using Proton therapy tended to be younger, have a lower Charlson-Deyo Score (88.9% vs. 85.5% or 85%), and a lower PSA (81.6% vs. 77.6% or 64.8%). All of these indicated most patients using Proton therapy might be healthier than patients using other radiotherapies.

3.2 Association with the rate of the secondary tumor in the original sample. (Figure 1, Figure 2, Table 2)

The percentages of secondary tumor declined by year of diagnosis specifically for Photon/IMRT/3D-CRT as well as Brachytherapy and in each group of the year of diagnosis, those two groups had larger percentage of the secondary tumor comparing with Proton (Figure 1.). The reason for higher rate of Photon/IMRT/3D-CRT and Brachytherapy may due to a longer follow-up with those patients diagnosed in earlier years. But the Proton group seemed flat over years. As in Figure 2, the difference between the Proton group and the Photon/IMRT/3D-CRT group were larger after stratified by age, such as the difference during 2004-2007 (7% vs. 10%).

The univariate and multivariate associations between secondary tumors and covariates are presented in Table 2. In the univariate association analysis, all variables were significantly

associated with secondary tumors (all $p < 0.05$). While in the multivariate association analysis, Gleason and surgery were removed from the final model. In the multivariate association analysis in Table 2, patients using Proton therapy were less likely to develop secondary tumors than the other two radiation modality groups (Brachy- OR: 3.51, 95%CI: 2.83-4.37; Photon/IMRT/3D-CRT- OR: 4.29, 95%CI: 3.45-5.34). However, patients elder than 65 years of age (>65: (OR:1.54, 95%CI: 1.50-1.59)) and higher Charlson-Score (2+: (OR:1.35, 95%CI: 1.25-1.45)) had more risk to develop secondary tumors were less likely to use Proton therapy ((>65: (OR:0.85, 95%CI: 0.81-0.90); 2+: (OR:0.52, 95%CI: 0.42-0.65)) (Table 1). In this way, it was hard to determine whether Proton therapy reduced the risk of secondary malignancies, or the Proton therapy happened to be used by patients with a lower risk of developing secondary tumors.

3.3 Association with the rate of the secondary tumor in propensity score weighted sample. (Figure 3, Table 3)

The propensity score method was applied to mitigate the impact of the selection bias of Proton therapy. After adding the weight from the propensity score matching method, selection bias was eliminated. In Figure 3, it was very clear that before applying the propensity score method, some variables were not well balanced in each of the comparison group (Proton vs. Photon/IMRT/3D-CRT: Facility type, ADT, PSA; Proton vs. Brachy: Facility type, Year of diagnosis, ADT; Photon/IMRT/3D-CRT vs. Brachy: Gleason, ADT, Surgery) but after adjusting by the propensity score method, the ASD values of all variables were less than 0.2 in all three subgroups which meant they were well balanced.

Table 3 shows the results of the overall models and the interaction models in subgroup analysis in the matched data. In Table 3, Photon/IMRT/3D-CRT therapy compared to the reference group, Proton, led to higher odds of secondary cancers (OR: 4.31 (95%CI: 4.07-4.56)). Similarly, Photon/IMRT/3D-CRT resulted in higher odds of secondary cancers when compared to Brachy as

the reference group (OR: 1.22 (95%CI: 1.18-1.25)). In comparing Brachytherapy versus Proton therapy as the reference group, the odds of secondary tumors were also statistically significant (OR: 3.45 (95%CI:3.21-3.70)). From this analysis, Proton therapy results in reduced odds of secondary cancers when compared to other radiation therapies. In the meantime, the association of secondary tumor was modified by the race-ethic groups, the year of diagnosis groups, and the gleason groups in comparison to Proton vs. Photon/IMRT/3D-CRT and Proton vs. Brachy. NH-White patients had higher odds ratio if they choose to use Photon/IMRT/3D-CRT (OR:5.04 (95%CI: 4.73-5.37)) or Brachytherapy (OR:3.95 (95%CI: 3.64-4.28)) comparing with Proton therapy. In other words, NH-White patients may benefit from Proton the most. When analyzing the year of diagnosis groups in comparison to all three groups, patients from earlier year of diagnosis had higher odds ratio due to longer follow-up. Patients with lower gleason score had much higher odds ratio comparing those with higher gleason score in comparison to Proton vs. Photon/IMRT/3D-CRT (OR:6.64 (95%CI: 6.02-7.34)) and Proton vs. Brachy (OR:5.12 (95%CI: 4.54-5.77)). This may indicate patients with lower gleason score should use the Proton therapy due to reduced rates of secondary tumors.

4. Discussion

The purpose of this study was to compare the secondary tumors among patients with primary prostate cancers following different radiation therapy modalities. Given the increasing attention to secondary tumors, this work aimed to provide additional evidence to guide prostate cancer treatment. While several studies focused on radiotherapy, prostate cancer lacks comprehensive research in this area. In addition, the use of Proton therapy, that has been shown to be effective in the treatment of many other cancers, needs to be further explored for prostate.

Our first key finding is that Proton therapy does have the least risk to developing secondary tumors compared with therapies of other radiation modalities. Patients using Photon/IMRT/3D-

CRT therapy were more likely to develop secondary malignancies although they were often the first treatment choice for many people. The superiority of Proton therapy is consistent with many previous studies. Eaton BR *et al*. compared Proton therapy with Photon and IMRT and found that Proton therapy resulted in the greatest reduction in risk of developing secondary tumors.[9] In a cohort study at Harvard Cyclotron in Cambridge, Proton therapy was shown not to increase the risk of secondary tumors.[15] Our study is novel in that it is the first to compares secondary tumors of prostate cancer using five radiotherapies at the same time. Similarly, J. Vogel *et al*. demonstrated that fewer patients with thymoma developed secondary tumors using adjuvant Proton therapy compared with Photon therapy.[14] Sethi RV *et al*. also had consistent findings with patients with retinoblastoma.[16]

Another key finding from this study is that our data is well balanced after applying the propensity score matching method so it may be considered as a good choice to use the propensity score matching method to reduce selection bias in observational study. Austin PC demonstrated that an observational study can be treated as randomized controlled trials within a propensity score matched sample.[21] Our findings support this application and illustrate this point. Future studies should consider the use of propensity score matching in order to reduce biases.

Finally, our results show that NH-White patients are more likely to develop secondary tumors. At the same time, they have higher probability of using Proton therapy than other patients after adjusting for all covariates of interest. These results suggest this treatment method should be given priority and given the advantages of Proton therapy, healthcare and governmental measures should be taken to reduce patient costs and improve access to these therapies.

There are several limitations to our study. Our study was an observational study and the data used for analysis was from a registry database. The first limitation is that we could not find a specific variable to represent the incidence of secondary tumor. As a result, we used sequence numbers as our outcome due to the availability of data in NCDB. In this case, we only knew whether patients

developed secondary tumors, however there was no more information on the secondary tumor. For example, by using the sequence number, we only knew patients had other cancers besides prostate cancer, but we did not know what the other cancers were. Those other cancers might not be induced by radiotherapies, an example of which would be skin cancer, which results from over exposure to ultraviolet light. In this case, these secondary cancers would have no connection to radiation and our analysis might overestimate the strength of this association. Furthermore, without more detailed clarification of sequence number, how this number is recorded and updated, there is a possibility that our findings are incomplete. Lastly, because we used data from The National Cancer Database, there is a risk of data entry error or missing data, in which too many outliers could potentially impact our models. Future research involving a prospective study is still needed in order to confirm the findings from this study.

5. Conclusion

In this study, we compared the secondary malignancies among different radiation modality therapies. The results suggest that Proton therapy is least likely to induce secondary tumors compared with Photon/IMRT/3D-CRT, and Brachytherapy. This work has implications for physicians and patients, who should be aware of this advantage when making treatment choices. The propensity score matching method is found to effectively reduce selection bias, which should be implemented when analyzing observational data. Future research should focus on the association not only between secondary tumor and radiotherapies, but also between first tumor and secondary tumors. Prospective studies will be able to advance this work further.

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7. Figures and Tables

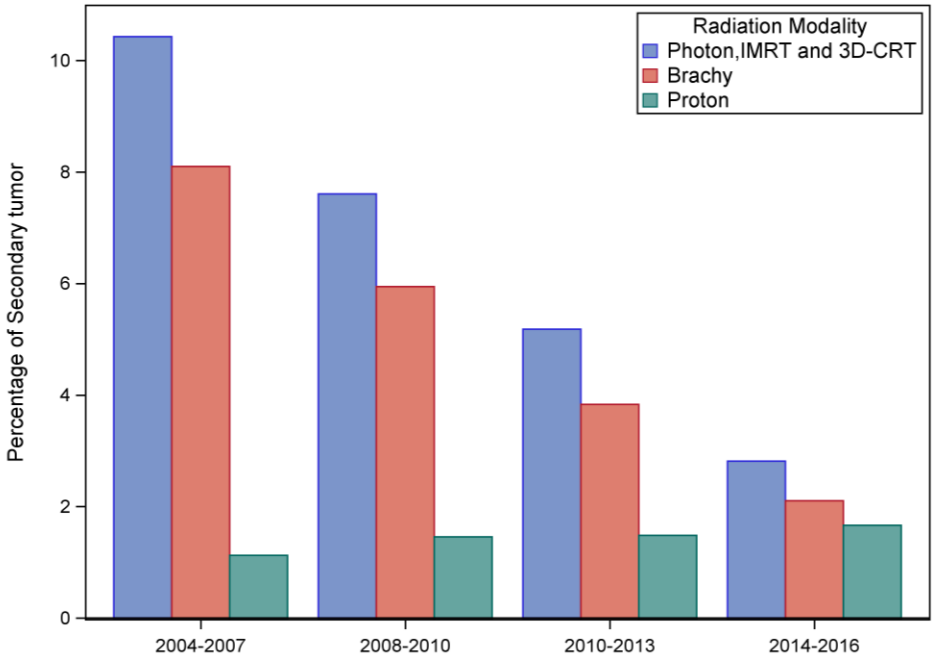


Figure 1 Percentage of Secondary tumor by Year of Diagnosis

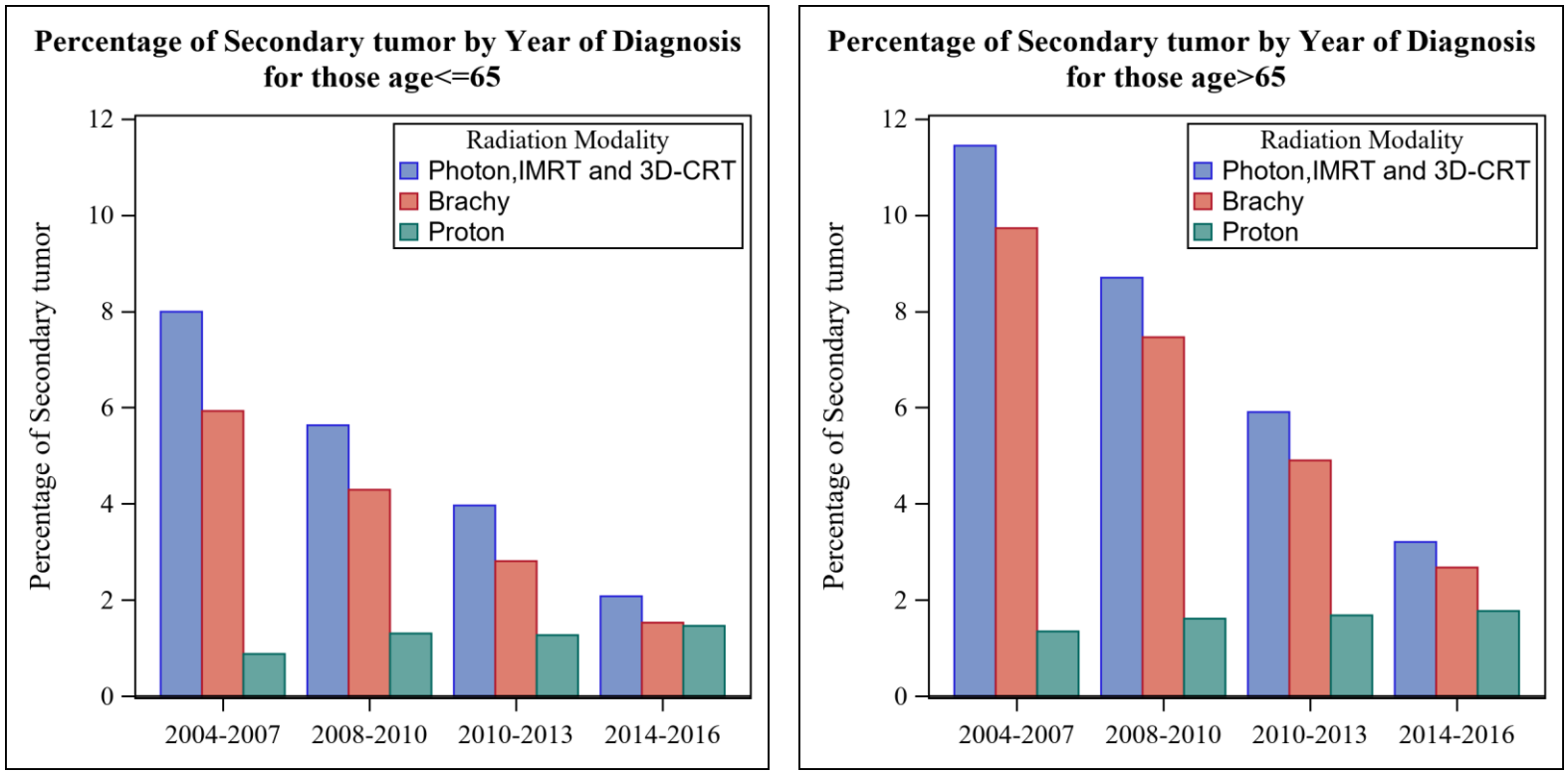
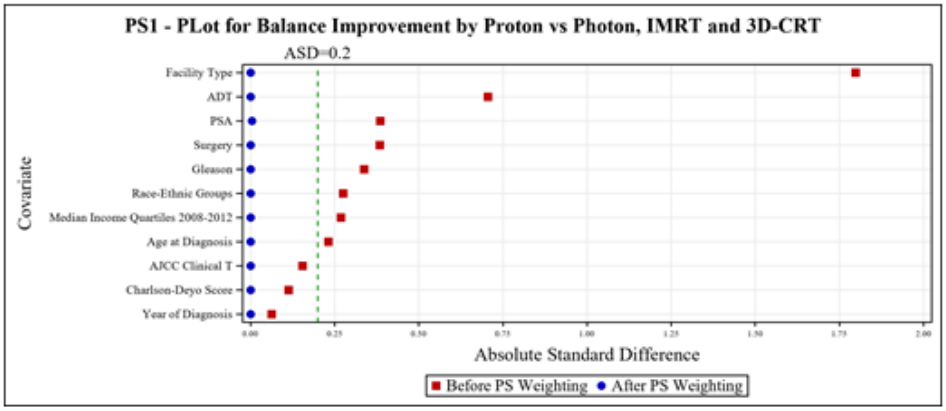
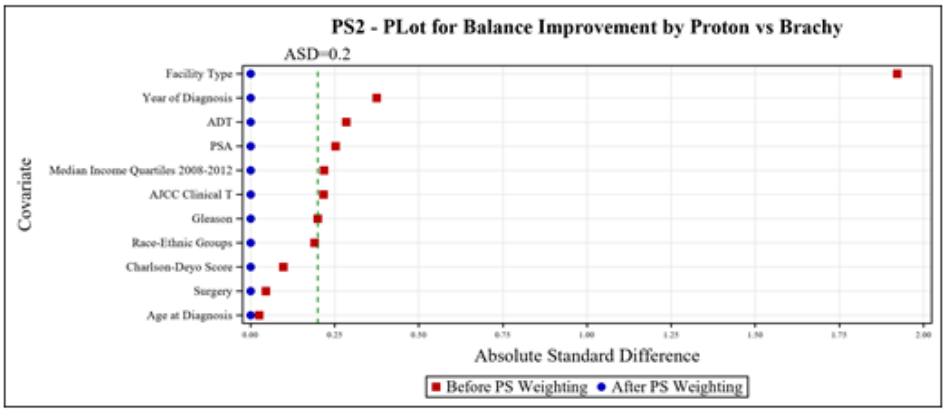


Figure 2 Percentage of Secondary tumor at Year of Diagnosis by Age. Left: <= 65 years old; Right: > 65 years old.





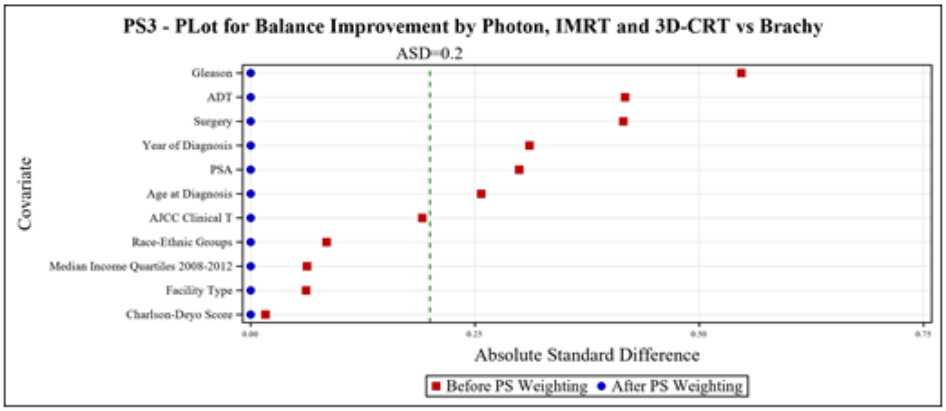


Figure 3 Summary of covariates balance improvement measured by the absolute standardized difference before and after propensity score matching in pairwise sample

Table 1 Baseline characteristics for the study population by the study cohorts and the multivariable logistic regression for factors predict the utilization of Proton therapy

Demographics and Clinical Characteristics	Total N (%)	Univariate Association with Radiation Modalities (All p-value <0.001)				Logistic Regression Model for the Probability of Proton Usage	
		Brachy N (%)	EBRT N (%)	Proton N (%)	ASD	Odds Ratio (95% CI)	P*
Facility Type							
Non-Academic/Research Program	260207 (70.9)	107077 (73.8)	152788 (70.8)	342 (5.8)	1.93	-	-
Academic/Research Program	106769 (29.1)	38066 (26.2)	63114 (29.2)	5589 (94.2)	1.93	43.02 (38.52-48.04)	<.001
Age at Diagnosis							
Missing	0.00	-	-	-	-	-	-
<=65	142948 (39.0)	67188 (46.3)	73082 (33.8)	2678 (45.2)	0.26	-	-
>65	224028 (61.0)	77955 (53.7)	142820 (66.2)	3253 (54.8)	0.26	0.85 (0.81-0.90)	<.001
Mean (Std)	67.47 (7.92)	65.9 (7.6)	68.6 (7.9)	66 (7.8)	0.34	-	-
Median (Q1, Q3)	68 (62, 73)	66 (61, 72)	69 (63, 74)	66 (61, 71)	-	-	-
Median Income Quartiles 2008-2012							
Missing	2065	-	-	-	-	-	-
< $38,000	64788 (17.8)	24067 (16.7)	40169 (18.7)	552 (9.3)	0.27	-	-
$38,000-$47,999	83348 (22.8)	32881 (22.8)	49349 (23)	1118 (18.9)	0.10	1.47 (1.32-1.64)	<.001
$48,000-$62,999	96898 (26.6)	37562 (26.1)	57716 (26.9)	1620 (27.4)	0.03	1.48 (1.34-1.64)	<.001
>=$63,000	119877 (32.9)	49616 (34.4)	67647 (31.5)	2614 (44.3)	0.27	1.54 (1.40-1.70)	<.001
Charlson-Deyo Score							
0	313003 (85.3)	124115 (85.5)	183617 (85)	5271 (88.9)	0.11	-	-
1	43533 (11.9)	17600 (12.1)	25353 (11.7)	580 (9.8)	0.08	0.92 (0.84-1.00)	0.060
2+	10440 (2.8)	3428 (2.4)	6932 (3.2)	80 (1.3)	0.12	0.52 (0.42-0.65)	<.001
Year of Diagnosis							
2004-2007	138106 (37.6)	67791 (46.7)	68625 (31.8)	1690 (28.5)	0.38	-	-
2008-2010	91601 (25.0)	36421 (25.1)	53806 (24.9)	1374 (23.2)	0.05	1.25 (1.16-1.35)	<.001
2011-2013	72402 (19.7)	23435 (16.1)	47483 (22)	1484 (25)	0.22	1.63 (1.51-1.75)	<.001
2014-2016	64867 (17.7)	17496 (12.1)	45988 (21.3)	1383 (23.3)	0.30	1.90 (1.76-2.05)	<.001
AJCC Clinical T							
T1	247220 (67.4)	105601 (72.8)	137890 (63.9)	3729 (62.9)	0.21	-	-
T2	105635 (28.8)	36944 (25.5)	66628 (30.9)	2063 (34.8)	0.20	1.70 (1.60-1.80)	<.001
T3	14121 (3.8)	2598 (1.8)	11384 (5.3)	139 (2.3)	0.19	1.25 (1.04-1.49)	0.016
Cohort							

Photon/IMRT/3D-CRT	215902 (58.8)	-	-	-	-	-	-
Brachy	145143 (39.6)	-	-	-	-	-	-
Proton	5931 (1.6)	-	-	-	-	-	-
Race-Ethnic Groups							
NH-White	279005 (76.0)	113198 (78)	160730 (74.4)	5077 (85.6)	0.28	3.29 (2.95-3.66)	<.001
NH-Black	59743 (16.3)	22471 (15.5)	36887 (17.1)	385 (6.5)	0.33	-	-
Asian-Indians-Pac	8021 (2.2)	2861 (2)	4991 (2.3)	169 (2.8)	0.06	2.96 (2.45-3.58)	<.001
Hispanic	14881 (4.1)	4382 (3)	10244 (4.7)	255 (4.3)	0.09	2.69 (2.29-3.17)	<.001
Other/Unknown	5326 (1.5)	2231 (1.5)	3050 (1.4)	45 (0.8)	0.07	1.05 (0.76-1.43)	0.773
Gleason							
2-6	140432 (38.3)	76672 (52.8)	61088 (28.3)	2672 (45.1)	0.52	1.23 (1.11-1.37)	<.001
7	143703 (39.2)	48721 (33.6)	92417 (42.8)	2565 (43.2)	0.20	1.17 (1.06-1.29)	0.002
8-10	67821 (18.5)	12849 (8.9)	54353 (25.2)	619 (10.4)	0.45	-	-
Unknown	15020 (4.1)	6901 (4.8)	8044 (3.7)	75 (1.3)	0.21	-	-
PSA							
Unknown	13093 (3.6)	7712 (5.3)	5342 (2.5)	39 (0.7)	0.28	-	-
<10	257345 (70.1)	112595 (77.6)	139908 (64.8)	4842 (81.6)	0.39	-	-
10-20	58501 (15.9)	15783 (10.9)	41902 (19.4)	816 (13.8)	0.24	0.99 (0.92-1.07)	0.855
>20	38037 (10.4)	9053 (6.2)	28750 (13.3)	234 (3.9)	0.34	0.49 (0.43-0.56)	<.001
ADT							
No	210159 (57.3)	99428 (68.5)	105941 (49.1)	4790 (80.8)	0.70	-	-
Yes	148300 (40.4)	41901 (28.9)	105361 (48.8)	1038 (17.5)	0.70	0.32 (0.30-0.35)	<.001
Unknown	8517 (2.3)	3814 (2.6)	4600 (2.1)	103 (1.7)	0.06	-	-
Surgery							
No	340970 (92.9)	143181 (98.6)	191966 (88.9)	5823 (98.2)	0.41	-	-
Yes	25685 (7.0)	1840 (1.3)	23738 (11)	107 (1.8)	0.41	0.21 (0.17-0.25)	<.001
Unknown	321 (0.1)	122 (0.1)	198 (0.1)	1 (0)	0.03	-	-

ASD: absolute standardized difference.

The P-value is calculated by ANOVA for continuous covariates and Chi-square test for categorical variable.

Table 2 Summary based on univariate and multivariable logistic regression with the secondary tumor

Demographics and Clinical Characteristics	UVA Odds Ratio (95% CI)	MVA Odds Ratio (95% CI)
Cohort		
Photon/IMRT/3D-CRT	5.20 (4.19-6.45)*	4.29 (3.45-5.34)*
Brachy	4.56 (3.67-5.66)*	3.51 (2.83-4.37)*
Proton	-	-
Age at Diagnosis		
>65	1.70 (1.65-1.75)*	1.54 (1.50-1.59)*
<=65	-	-
Race-Ethnic Groups		
NH-White	1.39 (1.33-1.44)*	1.25 (1.20-1.31)*
Asian-Indians-Pac	0.95 (0.85-1.06)	0.88 (0.78-0.98)
Hispanic	0.84 (0.77-0.91)*	0.77 (0.71-0.84)*
Other/ Unknown	0.50 (0.42-0.59)*	0.47 (0.40-0.56)*
NH-Black	-	-
Facility Type		
Academic/Research Program	0.79 (0.77-0.82)*	0.90 (0.88-0.93)
Non-Academic/Research Program	-	-
Year of Diagnosis		
2014-2016	0.26 (0.25-0.28)8	0.25 (0.24-0.26)*
2011-2013	0.48 (0.47-0.50)*	0.48 (0.46-0.50)*
2008-2010	0.73 (0.71-0.75)*	0.73 (0.71-0.76)*
2004-2007	-	-
Charlson-Deyo Score		
2+	1.19 (1.10-1.28)*	1.35 (1.25-1.45)*
1	1.12 (1.08-1.17)*	1.21 (1.16-1.26)*
0	-	-
AJCC Clinical T		
T3	1.01 (0.94-1.09)	0.95 (0.89-1.02)
T2	1.18 (1.15-1.21)*	1.06 (1.03-1.09)*
T1	-	-
PSA		
Unknown	0.97 (0.90-1.04)	-
<10	-	-
10-20	1.07 (1.03-1.11*	.05 (1.01-1.09)*
>20	1.06 (1.01-1.10)*	1.04 (1.00-1.09)
Gleason		
Unknown	0.97 (0.90-1.04)	-
2-6	1.03 (0.99-1.07)	-
7	0.97 (0.93-1.01)	-
8-10	-	-
ADT		
Unknown	1.09 (1.00-1.19)*	-
Yes	1.23 (1.20-1.26)8	1.14 (1.11-1.17)*
No	-	-
Surgery		

Unknown	0.99 (0.63-1.54)	-
Yes	0.84 (0.79-0.88)*	-
No	-	-
Median Income Quartiles 2008-2012		
>=$63,000	0.94 (0.90-0.98)*	0.89 (0.85-0.92)*
$48,000-$62,999	1.03 (0.99-1.07)	0.97 (0.93-1.01)
$38,000-$47,999	1.03 (0.99-1.07)	0.96 (0.92-1.00)
< $38,000	-	-

In Multivariable logistic regression, backward selection with an alpha level of removal of .05 was used. The following variables were removed from the model: Gleason, and Surgery.

*P-value <0.05.

Table 3 Summary based on multivariable logistic regression model and interaction model in weighted sample (subgroup analysis)

	Proton vs. Photon/ IMRT/3D-CRT[1]		**Proton vs. Brachy[2]**		**Photon/IMRT/ 3D-CRT vs. Brachy[3]**	
Covariate	**Odds Ratio (95% CI)**	**Interaction p-value**	**Odds Ratio (95% CI)**	**Interaction p-value**	**Odds Ratio (95% CI)**	**Interaction p-value**
Overall	4.31 (4.07-4.56)*	-	3.45 (3.21-3.70)*	-	1.22 (1.18-1.25)*	-
Race-Ethnic Groups	-	<.001	-	<.001	-	0.943
NH-White	5.04 (4.73-5.37)*	-	3.95 (3.64-4.28)*	-	1.22 (1.18-1.25)*	-
Other	1.96(1.72-2.23)*	-	1.79 (1.52-2.11)*	-	1.21 (1.14-1.29)*	-
Year of Diagnosis Groups		<.001		<.001		0.361
2004-2007	8.82 (7.89-9.85)*	-	6.80 (5.93-7.81)*	-	1.24 (1.20-1.29)*	-
2008-2010	5.05 (4.46-5.71)*	-	4.47 (3.84-5.21)*	-	1.19 (1.13-1.26)*	-
2011-2013	3.05 (2.73-3.41)*	-	2.14 (1.85-2.48)*	-	1.21 (1.12-1.30)*	-
2014-2016	1.51 (1.34-1.71)*	-	1.23 (1.05-1.44)	-	1.13 (1.01-1.27)*	-
Gleason Groups	-	<.001	-	<.001	-	0.724
2-6	6.64 (6.02-7.34)*	-	5.12 (4.54-5.77)*	-	1.21 (1.16-1.26)*	-
7+	3.30 (3.08-3.54)*	-	2.63 (2.41-2.88)*	-	1.22 (1.18-1.27)*	-

*Odds ratio significant at 0.05.

[1]Reference group is Proton.

[2]Reference group is Proton.

[3]Reference group is Brachy.

The P-value is calculated by the interaction model.