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Comparison of Toxicity between Single Modality Radiation Therapy and Combined Modality Radiation Therapy among Early Stage Prostate Cancer Patients

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By

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Bachelor of Medicine

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Abstract

Comparison of Toxicity between Single Modality Radiation Therapy and Combined Modality Radiation Therapy among Early Stage Prostate Cancer Patients

By Renjian Jiang

Background: For early stage prostate cancer, conservative management is generally considered appropriate as most of these cancers are quite slow growing in nature. Aggressive therapy is sometimes used in the management of early stage disease but needs to be evaluated in the context of health related quality of life and post-treatment morbidity. This study aims to compare radiation related toxicities (gastrointestinal, genitourinary, sexual function) for early stage prostate cancer patients over the age of 65 who were treated with either a more conservative single modality or a more aggressive multimodality radiation therapy approach.

Methods: A population-based cohort study was conducted using Surveillance, Epidemiology and End Result (SEER) data linked to Medicare data. Cumulative incidence was used to calculate the probability of each outcome event of interest (toxicity).Multivariate logistic regression models were used to adjust potential confounders and assess interaction while exploring the relationship between treatment and outcomes.

Result: The final cohort of 9,202 patients consisted of 4,567patientstreated with external beam radiation only, 3,039 patients treated with brachytherapy alone, and 1,596 patients treated with combined modality radiation treatment of both external radiation and brachytherapy. Generally, patients treated with combined modality radiation therapy tended to be slightly younger, with a higher T stage, higher Gleason Score and a larger number of existing comorbidities. Among the 9 toxicity events evaluated in this study, the most frequent radiation related toxicity events were GU Incontinence (38.31%)**,** Erectile Dysfunction (23.36%) and GU Obstruction (16.59%). The least frequent event was GU Fistula (0.07%).A significant protective effect (OR<1) of external beam radiation only compared to combined modality therapy was found for GI Fistula, GU Cystitis and Erectile Dysfunction. Significant protective effects (OR<1) for both external beam radiation therapy alone and brachytherapy alone, compared to combined modality radiation therapy, were found in models for GU Incontinence and GU Obstruction.

Conclusions: Decisions regarding the use of combined modality radiation therapy to treat low risk, clinically localized prostate cancer patients should be carefully made by health providers in conjunction with their patients considering both the high survival rate of disease in these patients and the increased risk in multiple radiation related toxicity events.

Key Words: SEER, Medicare, Prostate Cancer, Radiation, Toxicity

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Table of Contents

Background

Prostate cancer is the leading incident cancer among men in the U.S. and comprises 29% of all male cancers (1). As the average life expectancy of U.S. males continues to increase due to advances in the treatment of cardiovascular, pulmonary and other chronic diseases, the effects of prostate cancer treatment on health related quality of life will become an increasingly more important issue for men with this disease. As such, there is currently considerable interest in the role of prostate cancer treatment modalities among the elderly population with localized disease.

Prostate cancer treatment modalities include surgery (radical prostatectomy), radiation therapy (radioactive implants/ brachytherapy and external beam radiation therapy), high-intensity focused ultrasound (HIFU), chemotherapy, cryosurgery, hormonal therapy, or some combination of the above (2-4). Better survival (both prostate cancer-specific and all-cause) has been observed in early stage prostate cancer patients of all ages treated with prostatectomy or brachytherapy compared to patients receiving no definitive therapy (5) . No significant survival difference has been observed, however, for either of the two definitive treatments above relative to the other (5).

Despite the survival advantage inferred by treatment, all treatments have potential side effects that can negatively impact an individual's quality of life. Prostate cancer patients treated with surgery have a higher risk of urinary leakage and erection dysfunction (6-9) while patients treated with radiation therapy have a higher risk of radiation toxicity such as bowel urgency (10, 11). Among patients treated with radiation therapy, Michael et al. found that for low-risk prostate cancer patients, 7-year biochemical tumor control was superior for intraoperatively planned brachytherapy compared with high-dose intensity-modulated external beam radiation therapy (12).Treatment with brachytherapy (brachytherapy alone or brachytherapy combined with external beam radiation) was also found to be associated with reduced prostate cancer-specific mortality compared with external beam radiation alone among high grade prostate cancer patients (13). However, a significant increase

in grade 2 urinary and rectal symptoms was observed following brachytherapy compared with intensity-modulated radiation therapy (12).

For early stage prostate cancer, conservative management is generally considered appropriate as most of these cancers are quite slow growing in nature. This is especially true among older patients. Aggressive therapy is sometimes used in the management of early stage disease but needs to be evaluated in the context of health related quality of life and post-treatment morbidity. This study aims to compare radiation related toxicities (gastrointestinal, genitourinary, sexual function) for early stage prostate cancer patients over the age of 65 who were treated with either a more conservative single modality or a more aggressive multimodality radiation therapy approach.

Methods

Data Source

SEER-Medicare data are publically available following application review and reflect the linkage of two large population-based sources of data that provide detailed information about Medicare beneficiaries with cancer.

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) is an authoritative source of information on cancer incidence and survival in the United States. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 28 percent of the US population.

SEER-Medicare links the SEER registry data to Medicare administrative and health care claims data, which include 97% of US residents aged 65 years and older (14).Medicare claims are provided in three major file types that can be used for identifying information regarding comorbidities, treatments received, and procedures related to interventions for various post-treatment complications. The Medicare Provider Analysis and Review file (MEDPAR/ Inpatient Claims), includes all Medicare Part A short stay, long stay, and skilled nursing facility

(SNF) inpatient claims; the Carrier Claims file (NCH/ Physician Claims) includes all Medicare Part B physician/ supplier claims; and the Outpatient Claims files contains Part B claims from institutional outpatient providers (15).

Study Cohort

Between diagnosis years 2004 and 2007, 70,103 patients over the age of 66were identified in the SEER-Medicare data with a clinically localized, low risk diagnosis of prostate cancer defined by the following criteria: AJCC T stage of T1c-T2, Gleason's Score of 6 or 7, and prostate specific antigen (PSA) value less than or equal to 20.This cohort excluded patients with prostate cancer diagnosed at autopsy or from death certificate only and also excluded patients within an unknown month or year of diagnosis in SEER data. To facilitate an unbiased comparison of baseline comorbidity and to maximize the potential for the complete capture of health services in the claims data, patients who were enrolled in a Medicare health maintenance organization or not enrolled in both Medicare Part A and Part B for the study duration of 1 year before diagnosis to 3 years after diagnosis were also excluded. These enrollment exclusions narrowed down the cohort to 27,025 patients with continuous enrollment in the Medicare fee-for-service claims for further analyses.

We next used Medicare claims, covering the calendar period 2003-2009, to identify14,318 patients who received radiation therapy as a form of treatment for prostate cancer within 6months following diagnosis. Radiation was identified in the claims data using Healthcare Common Procedure Coding System (HCPCS) or Current Procedural Terminology (CPT) codes (Appendix 1). 5,042 patients who were treated by prostatectomy or androgen deprivation therapy in addition to radiation within 6months after diagnosis were then excluded followed by the exclusion of an additional 74 patients with missing values in race, education, or poverty.

The final cohort of 9,202 patients consisted of 4,567 patients treated with external beam radiation only, 3,039 patients treated with brachytherapy alone, and 1,596 patients treated with combined modality radiation treatment of both external radiation and brachytherapy.

Outcomes

The treatment related outcomes of interest in this study were categorized in three general groups: gastrointestinal (GI) toxicity, genitourinary (GU) toxicity and sexual function. CPT codes or International Classification of Diseases, ninth revision (ICD-9) procedure codes (Appendix 1) were used to identify grade 3 or grade 4 toxicity events under these general categories above which required intervention (10).Individual events being evaluated were: GI Bleeding/ Ulceration, GI Fistula, GI Stricture, GI Colostomy, GU Stricture/ Obstruction, GU incontinence, GU Cystitis, GU Fistula, and Erectile Dysfunction.

Interventions related to radiation toxicity were searched in the Medicare claims starting from the date of first radiation treatment through three years post-treatment. Diagnosis and procedures were counted together for events under each toxicity category. The final outcome measure in each toxicity category was defined as a binary outcome (true) if any event happened within the time period of interest.

Control Variables

We obtained patient level demographic information from the SEER registry data, and comorbididity, clinical and treatment related information from the Medicare claims. Variables obtained for analyses in this study included race/ ethnicity, age at diagnosis, marital status, SEER region, census tract measures of income and education, year of diagnosis, AJCC stage, Gleason score, PSA value, year of radiation, Inpatient Claims Comorbidity Index, Physician Claims Comorbidity Index, and Outpatient Claims Comorbidity Index.
All non-ordinal categorical variables were coded as dummy variables. Race/ ethnicity was defined into 6 categories (white/ black/ Asian/ Hispanic/ North American Native/ other) using white as reference; marital status was defined into 6 categories (single/ married/ separated/ divorced/ widowed/ unknown) using married as reference; year of diagnosis was defined into 4 categories (2004/ 2005/ 2006/ 2007) using year of 2004 as reference; year of radiation was defined into 5 categories (2004/ 2005/ 2006/ 2007/ 2008) using year of 2004 as reference; SEER region was defined into 17 categories (San Francisco/ Connecticut/ Detroit/ Hawaii/ Iowa/ New Mexico/ Seattle/ Utah/ Atlanta/ San Jose/ Los Angeles/ Rural Georgia/ Greater California/ Kentucky/ Louisiana/ New Jersey/ Greater Georgia) using Greater Georgia as reference. Ordinal categorical variables were

coded using their original values. Gleason Score was defined according to its value of 6 or 7; AJCC stage was defined into categories of T1c, T2a, T2b, or T2c in accordance with its coding system in SEER data. Continuous variables were kept in their original value. PSA value has a range from 1- 20; poverty was measured by the percentage of individuals living below the Federal poverty level in a given census tract, and education was defined by the percentage of individuals ≥25 years old with less than 12 years of education in a given census tract. Medicare claim-based comorbidity indices were calculated using the SAS Macro reflecting the Deyo adaptation of the Charlson comorbidity index, with several procedure codes that reflect the Romano adaptation (16, 17).

Statistical Analysis

Patient characteristics were compared between treatment groups using ANOVA tests and post-hoc tukey pairwise tests for continuous variables and chi-square tests for categorical variables. Fisher's exact tests were used for categorical variables with expected values less than 5. Cumulative incidence was used to calculate the probability of each outcome event of interest (toxicity). Multivariate logistic regression models were used to adjust potential confounders and assess interaction while exploring the relationship between treatment and outcomes. Non-ordinal categorical variables were coded as dummy variables in these models.
Collinearity was assessed separately in the models for each outcome event. After assessing collinearity, AJCC stage was found to be collinear with the model intercepts and was dropped from all models. In addition, age at diagnosis was centered to its mean in every model. Product terms of exposures (treatment groups) and potential confounders were evaluated for interaction using likelihood ratio tests and confounding was assessed using a ten percent rule within the Gold Standard Point Estimate. The final models for each toxicity event were decided after assessing the gain in precision following the removal of variables not deemed to be confounders in the model. Since multiple dummy variables and continuous variables appeared in models with interaction terms, extraordinarily large numbers of combinations needed to be assessed for risk ratio estimation. To avoid these large combinations, in models containing significant interaction terms continuous variables involved in the interactions were re-coded as ordinal categorical variables and dummy variables were re-coded according to the

effect estimate in models before interaction assessment. Statistical analyses were performed using SAS software version 9.2 (SAS Institute, Inc., Cary, NC). All P-values are 2-sided at 0.05 significant levels. This study was approved by the Emory University Institutional Review Board.

Results

As shown in Table 1, significant differences across treatment groups appeared for most variables in this study. Generally, patients treated with combined modality radiation therapy tended to be slightly younger, with a higher T stage, higher Gleason Score and a larger number of existing comorbidities. They also tended to be from census tracts with slightly lower percentages of the population in the tract living below the Federal poverty level. African American men comprised a larger percentage of the combined modality treatment group relative to the other single modality therapy groups as did the SEER region of Georgia where the combined modality therapy was the predominate radiation therapy administered.

Among the 9 toxicity events evaluated in this study, the most frequent radiation related toxicity events were GU Incontinence (38.31%)**,** Erectile Dysfunction (23.36%) and GU Obstruction (16.59%). The least frequent event was GU Fistula (0.07%).

Table 2 presents the probabilities of experiencing each toxic outcome event of interest among the men receiving each type of treatment modality. Probabilities of the events under the categories of GI Bleeding/ Ulceration, GU Cystitis, GU Incontinence, GU Obstruction and Erectile Dysfunction were significantly different among the radiation treatment groups. Probabilities of events were generally highest among the combined modality treatment group and lowest among the group treated with beam radiation therapy. Overall, combined modality therapy and brachytherapy generally had similar probabilities of the individual events.

Multivariate logistic regression models were developed for each individual toxicity event as described previously. Significant interaction terms were found in the multivariate regression models of GI Bleeding and GU Incontinence. Since a large combination of interaction terms can poses some difficultly in model

interpretation and in confounding assessment, non-exposure interaction terms were re-coded to reduce the number of interaction term combinations. Age at diagnosis centered to its mean was converted from a continuous variable to an ordinal categorical variable according to its 25%, 50%, and 75% percentiles; the Physician Claims Comorbidity Index was converted from a continuous variable to an ordinal variable coded as 0, 1, or 2+; race/ ethnicity were converted into three category dummy variables of White, Black, and Other using white as the reference group; SEER registries were divided into a protective group, an increased risk group and a reference group according to the OR values of each registry in models before interaction assessment. After re-coding, significant interaction terms were no longer found in GU Incontinence model but they remained in the GI Bleeding model. As such and due to the large number of interaction terms in the model, we were not able to produce effect estimates for this toxicity event. Multivariate models for GU Fistula events were also not run as a result of too few events during the 3 year follow-up period.

In Table 3, we compare the Gold Standard models controlling for all potential confounders (race/ ethnicity, age at diagnosis, marital status, SEER region, census tract measures of income and education, year of diagnosis, PSA value, Gleason Score, year of radiation, Inpatient Claims Comorbidity Index, Physician Claims Comorbidity Index, and Outpatient Claims Comorbidity Index) with the most precise models obtained after confounding assessment. Decisions regarding the optimal model are shown in the last column of Table 3. A significant protective effect (OR<1) of external beam radiation only compared to combined modality therapy was found for GI Fistula, GU Cystitis and Erectile Dysfunction. Significant protective effects (OR<1) for both external beam radiation therapy alone and brachytherapy alone (compared to combined modality radiation therapy) were found in models for GU Incontinence and GU Obstruction.

Discussion

In this study, we evaluated 9 individual radiation related toxicity events (GI Bleeding/ulceration, GI Obstruction/ Stricture, GI Fistula, GI colostomy, GU Obstruction/ Stricture, GU Cystitis, GU Fistula, GU Incontinence, and Erectile Dysfunction) among different radiation treatment modality groups for patients

diagnosed with clinically localized low risk prostate cancer. Our study result showed that patients treated with combined modality radiation therapy were generally younger, with a higher T stage, higher Gleason Score, a larger number of existing comorbidities and tended to be from census tracts with slightly lower percentages of the population in the tract living below the Federal poverty level compared to patients treated with single modality radiation therapy (EBRT only/ Brachytherapy only). These results were consistent with previous studies (10, 18) and correspond with the common understanding that younger patients tend to be more resilient to more aggressive therapies. Cost-effectiveness studies (19) also showed that combined modality radiation therapy was more expensive than single modality therapy and thus demands the patients to have the financial means for the treatment. Although several studies found combined modality radiation therapy to be associated with reduced prostate cancer-specific mortality compared with external beam radiation alone among high-grade prostate cancer patients (13), the survival benefits of combined therapy were not shown to outweigh the effect on toxicity and the patient's quality of life. For clinically localized, low risk prostate cancer in older patients, morbidity control and quality of life may be the most important factors for consideration in regard to treatment choice as survival has not been shown to be superior from one treatment modality over another in this group of patients.

Among the 9 toxicity events evaluated in our study, the most frequent radiation related toxicity events were GU Incontinence (38.31%)**,** Erectile Dysfunction (23.36%) and GU Obstruction (16.59%). Significant differences were found in all three of these events between different treatment modality groups both before and after modeling adjustment. Early stage prostate cancer patients treated with combined modality radiation therapy were found to be at higher risk of developing GU Incontinence and GU Obstruction compared to patients in both single modality radiation groups. They were also at higher risk of developing Erectile Dysfunction, GI Fistula and GU Cystitis, however, this only held when compared to those treated with external beam radiation therapy alone. Only 6 cases of GU fistula were identified within 3 years after radiation initiation among 9,202 eligible patients. As such, the number of cases was too sparse to allow valid logistic model calculations. This

result reflects the exceptionally low cumulative incidence of GU fistula among early stage prostate cancer patients treated with radiation therapy alone and is not surprising.

Strengths& Weaknesses

Strengths of this study include a clearly defined cohort of low risk, clinically localized prostate cancer patients, which provide an optimal population to explore the effects of treatment related toxicity due to the exceptional cancer specific survival in this group. The risk of radiation related toxicity in this population becomes exceptionally important as treatment decisions have been shown to have direct effects on quality of life. By identifying individual toxicity events rather than general categories, we were able to provide more detailed information on radiation related toxicity events. This approach should support health care providers with better information to provide patients regarding potential risks associated with individual treatments.

In previous studies, the physician claims comorbidity index were shown to be a strong predictive factor for treatment decision and radiation related toxicity, however, its distribution was without significance across the different radiation treatment modality groups in this study. This phenomenon might be caused by the fact that our cohort consists of early stage cancer patients who have continuous eligible enrollment from one year before prostate cancer diagnosis till three years afterwards. With the exclusion of patients with non-continuous enrollment, some underlining differences might be homogenized and the generalizability of the study might be limited to a certain degree. This rationale may also explain why the physician claims comorbidity index was not found to be an influential confounder in any of the regression models of our study.

Non-ordinal categorical variables were strictly coded as dummy variables in this study to avoid arbitrarily adding ordinal value to these variables. However, this coding strategy posed difficulties for confounding assessment when significant interactions appeared in models. Large combinations of interaction terms prohibited confounding assessment even after recoding the interaction terms. In follow-up studies in the future, different coding strategies might be applied to find a better solution to this problem.

Conclusions

Decisions regarding the use of combined modality radiation therapy to treat low risk, clinically localized prostate cancer patients should be carefully made by health providers in conjunction with their patients considering both the high survival rate of disease in these patients and the increased risk in multiple radiation related toxicity events. Morbidity control and quality of life may be the most important factors for consideration in regard to treatment for these patients.

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Tables

Table 1. Baseline Demographic and Treatment Related Characteristics in Study Cohort

Characteristics	Radiation Modality			P-Value (ANOVA/Chi-Square Test)	ANOVA Post-hoc Tukey Pairwise Test
	a. Combined Modality Mean(Std) /Count (Pct)	b.EBRT Only Mean(Std) /Count (Pct)	c. Brachy Only Mean(Std) /Count (Pct)		
Age at Diagnosis*	72.45 (4.26)	73.61 (4.56)	72.59 (4.27)	<.001	<.005 for b and a, b and c
Race*					
White	1349 (84.52%)	3813 (83.49%)	2679 (88.15%)	<.001	
Black	187 (11.72%)	455 (9.96%)	211 (6.94%)		
Asian	22 (1.38%)	109 (2.39%)	61 (2.01%)		
Hispanic	14 (0.88%)	60 (1.31%)	26 (0.86%)		
N. Am. Native	0 (0.00%)	7 (0.15%)	8 (0.26%)		
Other	24 (1.50%)	123 (2.69%)	54 (1.78%)		
Marital Status*					
Single	74 (4.64%)	315 (6.90%)	191 (6.28%)	<.001	
Married	1273 (79.76%)	3356 (73.48%)	2406 (79.17%)		
Separated	14 (0.88%)	21 (0.46%)	4 (0.13%)		
Divorced	74 (4.64%)	179 (3.92%)	115 (3.78%)		
Widowed	99 (6.20%)	307 (6.72%)	192 (6.32%)		
Unknown	62 (3.88%)	389 (8.52%)	131 (4.31%)		
Education*	16.39(11.84)	17.25(12.35)	16.33(12.05)	<.001	<.005 for b and a, b and c
Poverty*	9.09 (7.95)	10.03 (8.89)	9.59 (7.97)	<.001	<.005 for a and b
Year of Diagnosis*					
2004	350 (21.93%)	1007 (22.05%)	703(23.13%)	0.01	
2005	375 (23.50%)	1044 (22.86%)	762(25.07%)		
2006	466 (29.20%)	1228 (26.89%)	815(26.82%)		
2007	405 (25.38%)	1288 (28.20%)	759(24.98%)		
Year of Radiation					
2004	256 (16.04%)	722 (15.81%)	503(16.55%)	0.18	
2005	387 (24.25%)	1019 (22.31%)	754(24.81%)		
2006	402 (25.19%)	1169 (25.60%)	763(25.11%)		
2007	451 (28.26%)	1323 (28.97%)	824(27.11%)		
2008	627 (6.27%)	334 (7.31%)	195(6.42%)		

*: Difference Significant at α=0.05 level.

a. Combined modality of external beam radiation and radioactive implants (brahcy therapy).

b. External beam radiation only.

c. Radioactive implant (Brachy) only.

+. SEER refers to Surveillance, Epidemiology and End Results Program.

Table 1. Baseline Demographic and Treatment Related Characteristics in Study Cohort (continued)

Characteristics	Radiation Modality			P-Value (ANOVA/Chi-Square Test)	ANOVA Post-hoc Tukey Pairwise Test
	a. Combined Modality Mean(Std) /Count (Pct)	b.EBRT Only Mean(Std) /Count (Pct)	c. Brachy Only Mean(Std) /Count (Pct)		
SEER region*+					
Connecticut	86 (5.39%)	354 (7.75%)	188(6.19%)	<.001	
Detroit	56 (3.51%)	449 (9.83%)	135(4.44%)		
Hawaii	7 (0.44%)	123 (2.69%)	37(1.22%)		
Iowa	38 (2.38%)	184 (4.03%)	67(2.20%)		
New Mexico	13 (0.81%)	117 (2.56%)	30(0.99%)		
Seattle	89 (5.58%)	181 (3.96%)	323(10.63%)		
Utah	17 (1.07%)	29 (0.63%)	185 (6.09%)		
Kentucky	87 (5.45%)	246 (5.39%)	218 (7.17%)		
Louisiana	63 (3.95%)	225 (4.93%)	251 (8.26%)		
New Jersey	170 (10.65%)	814 (17.82%)	378(12.44%)		
California	264 (16.54%)	1364 (29.87%)	870(28.63%)		
Georgia	706 (44.24%)	481 (10.53%)	357(11.75%)		
AJCC T Stage*					
T1c	1173(73.50%)	3503 (76.70%)	2390(78.64%)	<.001	
T2a	156 (9.77%)	493 (10.79%)	333 (10.96%)		
T2b	85 (5.33%)	120 (2.63%)	86 (2.83%)		
T2c	182 (11.40%)	451 (9.88%)	230 (7.57%)		
Gleason*					
6	756 (47.37%)	2783 (60.94%)	2389 (78.61%)	<.001	
7	840 (52.63%)	1784 (39.06%)	650 (21.39%)		
PSA*	0.67 (0.33)	0.71 (0.34)	0.61(0.27)	<.001	<.005 for a and b and c
Inpatient Claim Comorbidity* Index	0.005 (0.112)	0.000 (0.000)	0.001 (0.044)	<.001	<.005 for a and b
Phsician Claim Comorbidity Index	0.39 (0.69)	0.38 (0.75)	0.34(0.69)	0.07	
Outpatient Claim Comorbidity Index	0.07 (0.29)	0.09 (0.37)	0.07(0.35)	0.09	

*: Difference Significant at α=0.05 level.

a. Combined modality of external beam radiation and radioactive implants (brahcy therapy).

b. External beam radiation only.

c. Radioactive implant (Brachy) only.

+. SEER refers to Surveillance, Epidemiology and End Results Program.

Table 2. Comparison of Radiation Related Toxicity Events among Different Radiation Modality Groups before Modeling

Toxicity Events	Radiation Modality						Total Cases		P-Value (Chi-Square Test)
	a. Combined Modality (n=1596)		b.EBRT Only (n=4567)		c. Brachy Only (n=3039)				
[d]GI Bleeding/ Ulceration*	186	11.65%	324	7.09%	299	9.84%	809	8.79%	<0.01
[d]GI colostomy	94	5.89%	242	5.30%	150	4.94%	486	5.28%	0.39
[d]GI Fistula	22	1.38%	36	0.79%	24	0.79%	82	0.89%	0.07
[d]GI Stricture	31	1.94%	94	2.06%	55	1.81%	180	1.96%	0.74
[e]GU Cystitis*	51	3.20%	51	1.12%	99	3.26%	201	2.18%	<0.01
[e]GUFistula	1	0.06%	2	0.04%	3	0.10%	6	0.07%	[f]0.09
[e]GUIncontinence*	896	56.14%	1198	26.23%	1431	47.09%	3525	38.31%	<0.01
[e]GU Obstruction*	339	21.24%	616	13.49%	572	18.82%	1527	16.59%	<0.01
Erectile Dysfunction*	440	27.57%	883	18.24%	877	28.86%	2150	23.36%	<0.01

a. Combined modality of external beam radiation and radioactive implants (brahcy therapy).
b. External beam radiation only.
c. Radioactive implant (Brachy) only.
d. Gastrointestinal.
e. Genitourinary.
f. Fisher's Exact test result

Table 3. Comparison of Effect Estimates in Each Toxicity Event Category (combined modality of external beam radiation and radioactive implants as reference)

Toxicity Events	[a]Gold Standard (GS) Model Effect Estimates (RR, 95% CI)		Most precise model under 10% confounding assessment rule[f]	Most Precise Model Effect Estimates (RR, 95% CI)		Final Model Chosen
	[b]EBRT Only	[c]Brachy Only		[b]EBRT Only	[c]Brachy Only	
[d]GI colostomy	1.03 (0.79, 1.35)	0.95 (0.71, 1.27)	Confounder in model: SEER Region	0.97 (0.74, 1.27)	0.80 (0.68, 1.19)	[a]GS model
[d]GI Fistula*	0.52 (0.29, 0.94)	0.54 (0.29, 1.03)	Confounder in model: None	0.57 (0.33, 0.97)	0.57 (0.32, 1.02)	[a]GS model
[d]GI Stricture	0.80 (0.51, 1.24)	0.78 (0.48, 1.26)	Confounder in model: Age at Diagnosis (centered to mean), SEER Region, Year of Radiation	0.82 (0.53, 1.26)	0.80 (0.50, 1.28)	Precise model
[e]GU Cystitis*	0.33 (0.21, 0.50)	1.09 (0.74, 1.60)	Confounder in model: None	0.34 (0.23, 0.51)	1.02 (0.72, 1.44)	Precise model
[e]GUIncontinence**	0.26 (0.24, 0.30)	0.71 (0.62, 0.81)	Confounder in model: None	0.28 (0.25, 0.31)	0.70 (0.62, 0.79)	[a]GS model
[e]GU Obstruction**	0.48 (0.41, 0.56)	0.80 (0.68, 0.94)	Confounder in model: SEER Region	0.48 (0.41, 0.57)	0.81 (0.69, 0.95)	Precise model
Erectile Dysfunction*	0.64 (0.55, 0.74)	1.12 (0.96, 1.30)	Confounder in model: None	0.59 (0.51, 0.67)	1.07 (0.93, 1.22)	Precise model

*: Effect Estimates significant for External Beam Radiation Therapy only using combined modality therapy as reference at α=0.05 level.

**: Effect Estimates significant for both External Beam Radiation Therapy only and Radioactive Implant Therapy only using combined modality therapy as reference at α=0.05 level.

a.Gold Standard model: Model controlled for all potential confounders (race/ ethnicity, age at diagnosis centered to its mean,marital status, SEER region, census tract measures of incomeand education, year of diagnosis, PSAvalue, Gleason score, year of radiation, Inpatient Claims Comorbidity Index, Physician Claims Comorbidity Index, Outpatient Claims Comorbidity Index).

b. External beam radiation only.

c. Radioactive implant (Brachy) only.

d. Gastrointestinal.

e. Genitourinary.

f. Within 10% interval of Gold Standard Model point estimate.

Appendix

Appendix 1. CPT and ICD-9 codes for treatment identifications

Type of	Category		CPT and ICD9 Codes
Cancer Therapy	Radiation	Brachytherapy	77326, 77327, 77328, 77776, 77777, 77778, 77781, 77782, 77783, 77784, 77790, 77799, Q3001, 92.2, 77785, 77786, 77787, 77799, 9227, 55860, 55862, 55865, 55859, 55875, C1715, C1717, C1719, C1728, C2634, C2635, C2636, C2638, C2639, C2640, C2641
		Conformal radiation therapy	77305, 77310, 77315, 77321, 77371, 77372, 77373, 77402, 77403, 77404, 77406, 77407, 77408, 77409, 77411, 77412, 77413, 77414, 77416,77422, 77423, 92.24, 92.26, 77401
		IMRT	77301, 77418, 0073T
	Androgen Deprivation	Orchiectomy	G9132, 54520, 54522, 54530, 54535, 54690, 62.3, 62.41, 62.42
		Hormone Therapy	54520, 54522, 54530, 54535, 54690, J1050, J1051, J1950, J3315, J9202, J9217, J9218, J9219, J9165, S0175, C9216, C9430, G0356, J0128, S0165, S9560, 62.4, 62.41, 62.42
	Surgery	MIRP	55866
		ORP	55810, 55812, 55815, 55840, 55842, 55845, 60.5

Appendix 2. CPT and ICD-9 codes for toxicity event identifications

Type of	Category		CPT and ICD9 Codes
Morbidity	Gastrointestinal (GI)	GI bleeding, ulceration	45300, 45317, 45330, 45334, 45382, 46614, 48.31,48.32
		GI fistula	44660, 44661, 45800, 45805, 45820, 45825, 46270, 46275, 46280, 46285, 46288, 46706, 46707, 46710, 46712, 46740, 46742, 45800, 45805, 45820, 45825, 48.73, 48.93, 49.1, 49.73, 57.83, 57.83
		GI stricture	45150, 45303, 45340, 45386, 45500, 45905 , 45910, 46604, 46700, 96.22, 96.23
		GI colostomy	45563, 45110-45123, 46.1–46.14
	Genitourinary (GU)	GU Obstruction/strictures	52275 , 52276, 52281, 52282, 52283, 52510, 52601, 52612, 2614, 52620, 52630, 53010, 53400, 53405, 53410, 53415, 53420, 3425, 53431, 53443, 53600, 53601, 53605, 53620, 53621, 53850, 53852, 52275-76, 52281, 52510, 53010, 53400, 53405, 53410, 53415, 53420, 53425, 53600-01, 53605, 53620-21, 53852, 52282, 52283, 57.85, 57.91, 57.92, 58.0, 58.1, 58.31-58.39, 58.47, 58.5, 58.6, 60.95, 60.2-60.29
		GU Cystitis	52001, 52601, 52630, 53850, 57.93
		GU Fistula	44660, 44661, 53520, 51595, 51596, 51590, 53520, 57.83 ,57.84, 58.43
		GU Incontinence	788.30 - 788.39, 599.82, 51715, 51840, 51841, 53440, 53442, 53445-53449, 51736, 51725, 51726, 51772, 51784-5, 51792, 51795, 51797-8, 51741, 53446-9, 53431
	Sexual Dysfunction	Erectile	607.84, 64.94, 64.95, 64.96, 64.97, 54400, 54401, 54402, 54405, 54406, 54407, 54408, 54409, 54410, 54411, 54415, 54416, 54417, C1007, C1813, C2622, C3500 C8514, C8516, C8534, L7900, 54231, 54235, J0270, J0275, J2440, J2760