The burden of overtreatment: comparison of toxicity between single and combined modality radiation therapy among low risk prostate cancer patients

Renjian Jiang, MPH,[1] Jeffrey J. Tomaszewski, MD,[2] Kevin C. Ward, PhD,[1] Robert G. Uzzo, MD,[3] Daniel J. Canter, MD[4]

[1]Department of Epidemiology, Rollins School of Public Health,Emory University, Atlanta, Georgia, USA
[2]Division of Urology, MD Anderson Cancer Center at Cooper, Rowan University School of Medicine, Camden, New Jersey, USA
[3]Division of Urologic Oncology, Fox Chase Cancer Center, Temple University School of Medicine, Philadelphia, Pennsylvania, USA
[4]Department of Urology, Albert Einstein Medical Center, Philadelphia, Pennsylvania, USA

JIANG R, TOMASZEWSKI JJ, WARD KC, UZZO RG, CANTER DJ. The burden of overtreatment: comparison of toxicity between single and combined modality radiation therapy among low risk prostate cancer patients. *Can J Urol* 2015;22(1):7648-7655.

Introduction: *To compare radiation related toxicities among men with low risk prostate cancer treated with single or multimodal radiation therapy.*

Materials and methods: *The SEER-Medicare linked database was used to assess the relationship between treatment type and toxicity among men with low risk prostate cancer treated with brachytherapy (BT), external beam radiation therapy (EBRT), or combined therapy between 2004 and 2007. Inverse probability of treatment weighting was utilized to minimize selection bias and control for confounding. Multivariate logistic regression models were used to explore the relationship between treatment and outcomes.*

Results: *Overall 1915 (43.9%), 1893 (43.4%), and 555 (12.7%) patients were treated with EBRT, BT, and combined therapy, respectively. In univariate analyses, combined modality radiation was more toxic than BT alone for GU incontinence (56.76% versus 49.08%), GU obstruction (21.26% versus 19.70%), and erectile dysfunction (22.52% versus 22.24%) ($p < 0.01$, all comparisons). Compared to EBRT alone, combined modality radiation was more toxic for GI bleeding (7.21% versus 6.21%), GU incontinence (56.76% versus 29.24%), GU obstruction (21.26% versus 14.15%), and erectile dysfunction (22.52% versus 15.35%) ($p < 0.01$, all comparisons). Among the most frequent radiation toxicity events, the probability of treatment associated toxicity was highest for patients receiving combined modality treatment and lowest for the group treated with EBRT. After multivariate adjustment, EBRT alone demonstrated protective effects against GU obstruction (OR 0.56 [CI 0.50-0.63]), GI bleeding (OR 0.57 [CI 0.48-0.67]), GU incontinence (OR 0.39 [CI 0.36-0.43]), and erectile dysfunction (OR 0.68 [CI 0.61-0.76]) when compared to combined therapy.*

Conclusions: *The use of combined modality radiation therapy in low risk prostate cancer patients is discordant with clinical guidelines and associated with a significantly increased burden of associated toxicity when compared to EBRT monotherapy. Prudent patient selection and judicious use of combined therapy among men with low risk prostate cancer represents a targetable area to reduce the burden of overtreatment.*

Key Words: external beam radiation therapy, prostate cancer, interstitial brachytherapy, toxicity, morbidity

Accepted for publication October 2014

Acknowledgments: This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the Applied Research Program, NCI; the Office of Research, Development and Information, CMS; Information Management Services (IMS), Inc.; the Georgia SEER Registry under contract HHSN261201000025C with the NCI; and the SEER Program registries in the creation of the SEER-Medicare database.

Address correspondence to Dr. J. J. Tomaszewski, MD Anderson Cancer Center, 3 Cooper Plaza, # 411, Camden, NJ 08103 USA

Introduction

The clinical significance of many low risk prostate cancers has been questioned while awareness of significant prostate cancer overdiagnosis increases.[1] The major concern of overdiagnosis is the resultant overtreatment that often follows. In the United States, the majority of men with screen-detected tumors receive aggressive treatment (up to 91% in the PLCO trial),[2] and such treatment is unlikely to yield a survival benefit in those with indolent disease or in men older than 65 years.[3]

Prostate cancer treatment can result in a considerable decrease in quality of life as a result of potentially

persistent urinary, sexual, and bowel dysfunction,[4] the impact of which may be exacerbated by the increased utilization of aggressive therapy for low risk disease.[5] Among men with low risk disease, the use of advanced treatment technologies such as intensity-modulated radiation therapy (IMRT) has increased from 32% to 44% from 2004 to 2009.[6] Likewise, combined external beam radiation therapy (EBRT) and brachytherapy (BT) has been associated with increased rates of genitourinary and gastrointestinal toxicity,[7] and may reduce health-related quality of life.[4,8] While current clinical practice guidelines do not support the use of combination therapy for low risk prostate cancer, upward of 45% of patients in some geographic regions will receive combination therapy.[8] Given the regional increase in the utilization of combination therapy,[8] we compare radiation related toxicities among men over the age of 65 with low risk prostate cancer treated with single or multimodal radiation therapy.

Materials and methods

Study cohort

The Surveillance, Epidemiology and End Results (SEER)-Medicare database[9] was used to identify men over the age of 65 diagnosed with clinically localized, low risk prostate cancer[10] between 2004 and 2007. Patients with an unknown month of diagnosis, missing data on education and poverty, or unknown value of lymph node involvement or distant metastasis were excluded, Figure 1. To facilitate an unbiased comparison of baseline comorbidity in the year prior to diagnosis and to maximize the potential for the complete capture of health services in the claims data during the period of post-treatment toxicity assessment, 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 treatment initiation were also excluded.

Medicare claims covering the calendar period 2003-2010 were then used for comorbidity assessment and to identify 6264 patients who received radiation therapy for prostate cancer within 6 months following diagnosis. Radiation was identified in the claims data and categorized by modality using Healthcare Common Procedure Coding System (HCPCS) or Current Procedural Terminology (CPT) codes. For those patients with documented radiation therapy initiation in month 6, the subsequent month of claims was reviewed to ensure combined radiation therapy was identified where provided. Patients initiating radiation therapy in 2008 were excluded to ensure a full 3 year period of toxicity data was available for all patients. The final cohort of 4363 patients consisted of 1915 patients treated with EBRT, 1893 patients treated with BT, and 555 patients treated with combined therapy (both EBRT and BT).

Outcomes

Treatment related outcomes of interest 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 were used to identify medical procedures related to grade 3 or grade 4 toxicity events.[11] Individual events evaluated include: GI bleeding/ulceration, GI fistula, GI stricture, GI colostomy, GU stricture/obstruction, GU incontinence, GU cystitis, GU fistula, and erectile dysfunction (ED). The final outcome measure in each toxicity category was defined as a binary outcome. Patients with documented pre-existing ED were not counted as radiation-related ED in the post-treatment period.

Control variables

Variables analyzed include race, age at diagnosis, marital status, SEER region, census tract measure of income and education, year of diagnosis, AJCC stage, prostate-specific antigen (PSA) value, and Charlson Comorbidity Index (CCI). All non-ordinal categorical variables were coded as dummy variables. Ordinal categorical variables were coded using their original values. Considering the effect of geographic variation on prostate cancer treatment choice,[5,8,12,13] SEER regions were divided into three categories according to the percentage of patients treated with combined modality radiation, Table 1. Poverty was defined as the percentage of individuals living below the federal poverty level, while education was defined by the percentage of individual's ≥ 25 years old with less than 12 years of education. Medicare claim-based comorbidity indices (CCI) were calculated and grouped (0, 1, and ≥ 2) using the SAS Macro reflecting the Deyo and Romano adaptation of the CCI.[14]

Statistical analysis

Patient characteristics were compared between treatment groups using ANOVA tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. In univariate analysis of toxicity, treatment modalities were compared using Chi-square test and post hoc multiple comparisons for proportions.[15] Multivariate logistic regression models were used to adjust potential confounders and assess interaction while exploring the relationship between treatment and outcomes. Modeling for GU fistula was

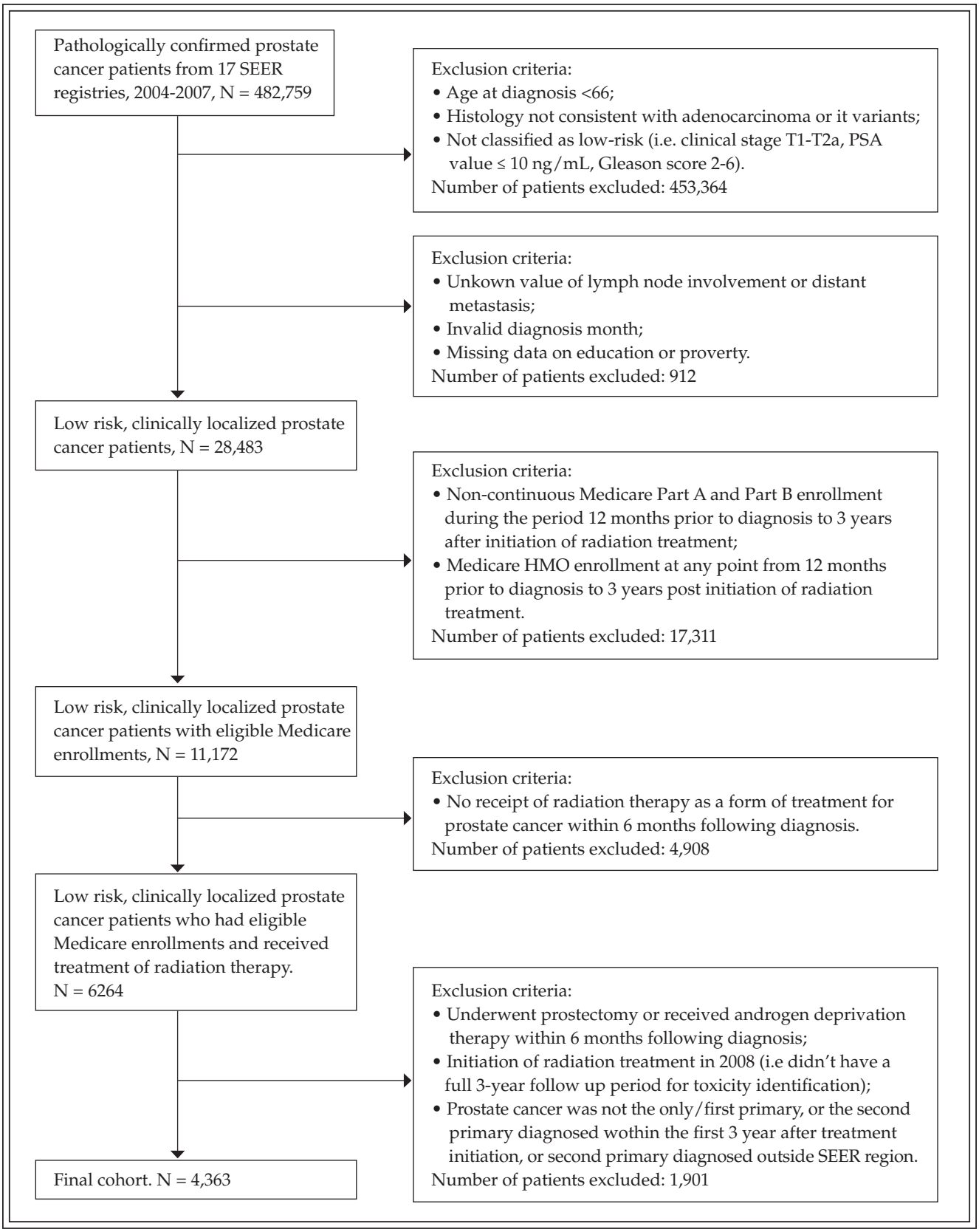

Figure 1. Definition of a study cohort of 4,363 men with clinically localized low-risk prostate adenocarcinoma.

TABLE 1. **Distribution of radiation modality across SEER regions[+]**

SEER region	Radiation modality			p value (ANOVA/ Chi-square test)
	Combined count[a] (row %)	EBRT only[b] (row %)	Brachy only[c] (row %)	
Rural Georgia	< 11 (61.54%)	< 11 (23.08%)	< 11 (15/38%)	
Atlanta	86 (49.43%)	26 (14.94%)	62 (35.63%)	
Greater Georgia	154 (30.92%)	181 (36.35%)	163 (32.73%)	
San Jose	22 (23.66%)	21 (22.58%)	50 (53.76%)	
Iowa	20 (13.70%)	76 (52.05%)	50 (34.25%)	
New Jersey	98 (13.70%)	398 (52.93%)	256 (34.04%)	
San Francisco	15 (12.00%)	35 (28.00%)	75 (60.00%)	< .001
New Mexico	< 11 (10.77%)	< 63 (61.54%)	< 28 (27.69%)	
Kentucky	27 (9.00%)	114 (38.00%)	159 (53.00%)	
Los Angeles	17 (8.59%)	130 (65.66%)	51 (25.76%)	
Connecticut	25 (8.59%)	142 (48.63%)	125 (42.81%)	
Detroit	20 (7.87%)	153 (60.24%)	81 (31.89%)	
Louisiana	21 (6.60%)	100 (31.45%)	197 (61.95%)	
Seattle	14 (5.67%)	62 (25.10%)	171 (69.23%)	
Utah	< 11 (2.86%)	< 40 (10.48%)	< 333 (86.67%)	
Greater California	17 (2.36%)	382 (53.06%)	321 (44.58%)	
Hawaii	< 11 (1.59%)	< 450 (65.08%)	<231 (33.33%)	
Total	555 (12.72%)	1915 (43.89%)	< 231 (43.39%)	

SEER region totals were suppressed to prevent obtaining actual number of cells with fewer than 11 patients according to the Seer Medicare reporting rules; SEER = Surveillance, Epidemiology and End Results Program; [+]the distribution presented is sorted by combined modality radiation usage in descending order; [a]combined modality of external beam radiation and radioactive implants (brachytherapy); [b]external beam radiation only; [c]brachytherapy only

not performed due to infrequent event occurrence. Inverse probability of treatment weighting (IPTW) was utilized to assist in balancing the distribution of observed baseline characteristics between the treatment groups in an effort to minimize selection bias and control for confounding. A multinomial logistic regression model was used to estimate the generalized propensity scores (GPS) for each of the three radiation treatments. IPTW's were then generated based on the GPS for each individual patient. Finally, baseline characteristic comparisons and multivariate comparison of toxicity events were conducted with IPTW adjustment. Statistical analyses were performed using SAS software version 9.3 (SAS Institute, Inc., Cary, NC, USA). All p values were 2-sided and significance was set at the 0.05 level. The Emory University Institutional Review Board approved the study.

Results

A significant regional difference in utilization of radiation by modality was observed ($p < 0.01$), Table 1. Within SEER regions of Georgia, combined modality therapy was the predominant radiation therapy administered. Significant differences among treatment groups were observed for age, race, marital status, education, SEER region, clinical stage, and PSA, Table 2. Generally, patients treated with combined modality radiation therapy were younger with lower PSA. They were also more likely to be married (82.70% [combined] versus 75.30% [EBRT] and 79.71% [BT]; $p < 0.001$). African American men comprised a larger proportion of the combined modality treatment group relative to the other modalities (12.25% [combined] versus 9.45% [EBRT] and 8.08% [BT]; $p < 0.001$). Following IPTW adjustment, demographic and clinical characteristics

TABLE 2. **Baseline demographic and treatment related characteristics in study cohort**

Characteristics	Radiation modality				
	Combined modality[a] Mean (std)/ count (%)	EBRT only[b] Mean (std)/ count (%)	Brachy only[c] Mean (std)/ count (%)	p value (ANOVA/ Chi-square test)	IPTW[#] adjusted p value
Age at diagnosis	71.99 (4.08)	72.96 (4.28)	72.11 (3.98)	< .001	0.10
Race				< .001	0.35
White	471 (84.86%)	1596 (83.34%)	1646 (86.95%)		
Black	68 (12.25%)	181 (9.45%)	153 (8/08%)		
Other	16 (2.88%)	138 (7.21%)	94 (4.97%)		
Marital status				< .001	0.10
Married	459 (82.70%)	1442 (75.30%)	1509 (79.71%)		
Unmarried	78 (14.05%)	319 (16.66%)	303 (16.01%)		
Unknown	18 (3.24%)	151 (8.04%)	81 (4.28%)		
Education				< .001	0.14
0.00%-33.33%	201 (36.22%)	588 (30.70%)	648 (34.23%)		
33.34%-66.66%	154 (27.75%)	664 (34.67%)	623 (32.91%)		
66.67%-100.00%	200 (36.04%)	663 (34.62%)	622 (32.86%)		
Poverty				0.06	0.21
0.00%-4.99%	228 (41.08%)	694 (36.24%)	651 (34.39%)		
5.00%-9.99%	137 (24.68%)	499 (26.06%)	557 (29.42%)		
10.00%-14.99%	77 (13.87%)	310 (16.19%)	283 (14.95%)		
15.00%-19.99%	58 (10.45%)	172 (8.98%)	183 (9.67%)		
20.00%+	55 (9.91%)	240 (12.53%)	219 (11.57%)		

[a]combined modality of external beam radiation and radioactive implants (brachytherapy); [b]external beam radiation only; [c]brachytherapy only; [#]IPTW = inversed probability of treatment weight

were no longer statistically different across treatment groups, Table 2, suggesting the IPTW adjustment was successful in balancing the observed baseline differences.

The most frequent radiation related toxicity events were GU incontinence (41.35%), ED (19.25%) and GU obstruction (17.47%), while GU fistula (< 0.01%) occurred infrequently, Table 3. After IPTW adjustment, combined modality radiation was more toxic than BT alone for GU incontinence (56.76% versus 49.08%), GU obstruction (21.26% versus 19.70%), and ED (22.52% versus 22.24%) ($p < 0.01$, all comparisons). Compared to EBRT alone, combined modality radiation was more toxic for GI bleeding (7.21% versus 6.21%), GU incontinence (56.76% versus 29.24%), GU obstruction (21.26% versus 14.15%), and ED (22.52% versus 15.35%) ($p < 0.01$, all comparisons). Among the most frequent radiation toxicity events, the probability of treatment associated toxicity was highest for patients receiving combined modality treatment and lowest for the group treated with EBRT.

Multivariate logistic regression modeling by toxicity event identified no significant interaction effects. After controlling for potential confounders (race, age at diagnosis, marital status, SEER region, census tract measures of income and education, year of diagnosis, PSA value, and CCI) and adjusting with IPTW, both EBRT (OR 0.56 [CI 0.50-0.63]) and BT (OR 0.89 [CI 0.80-0.98]) demonstrated protective effects against GU obstruction when compared to combined modality treatment. EBRT showed a protective effect against GI bleeding (OR 0.57 [CI 0.48-0.67]), GU incontinence (OR 0.39 [CI 0.36-0.43]), and ED (OR 0.68 [CI 0.61-0.76]) compared to combined therapy, Table 4.

Discussion

Widespread use of PSA testing has led to unnecessary biopsies and significant overdiagnosis and treatment of low risk prostate cancers, many of which were unlikely to have caused harm. To help reduce prostate cancer treatment related morbidity, current guidelines recommend against the routine use of PSA prostate cancer screening for most men.[16] Patients with clinically

TABLE 3. **Comparison of radiation related toxicity events among different radiation modality groups before modeling**

	Radiation modality					
Toxicity events	**Combined modality[a] (n = 652)**	**EBRT only[b] (n = 2231)**	**Brachy only[c] (n = 2206)**	**Total cases**	**p value Chi-square test**	**IPTW[#] adjusted p value**
GI bleeding/ ulceration[d]	40 (7.21%)	119 (6.21%)	171 (9.03%)	330 (7.56%)	< 0.01*	< 0.01[+]
GI colostomy[d]	32 (4.14%)	102 (5.33%)	85 (4.49%)	210 (4.81%)	0.35	< 0.01[+]
GI fistula[d]	< 11 (< 1.98%)	13 (0.68%)	12 (0.63%)	< 36 (< 0.83%)	0.2	0.54
GI stricture[d]	< 11 (< 1.98%)	33 (1.72%)	30 (1.58%)	< 74 (< 1.70%)	0.88	0.79
GU cystitis[e]	13 (2.34%)	22 (1.15%)	72 (3.80%)	107 (2.45%)	< 0.01*	< 0.01
GU fistula[e]	< 11 (< 1.98%)	< 11 (0.05%)	< 11 (0.57%)	< 33 (< 0.58%)		
GU incontinence[e]	315 (56.76%)	560 (29.24%)	929 (49.08%)	1804 (41.35%)	< 0.01[+]	< 0.01[+]
GU obstruction[e]	118 (21.26%)	271 (14.15%)	373 (19.70%)	762 (17.47%)	< 0.01-	< 0.01[+]
Erectile dysfunction	125 (22.52%)	294 (15.35%)	421 (22.24%)	840 (19.25%)	< 0.01-	< 0.01[+]

exact totals for groups with fewer than 11 patients cannot be reported as a result of SEER-Medicare reporting rules; [+]SEER = Surveillance, Epidemiology and End Results Program; [a]combined modality of external beam radiation and radioactive implants (brachytherapy); [b]external beam radiation only; [c]brachytherapy only; [d]gastrointestinal; [e]genitourinary; [f]Fisher's Exact test result; [#]IPTW = inversed probability of treatment weight; *post-hoc multiple comparison test[15] indicate significant difference between b and c; [+]post-hoc multiple comparison test[15] indicate significant difference across all groups.; -post-hoc multiple comparison test[15] indicate significant difference between a and b, b and c.; `post-hoc multiple comparison test[15] indicate significant difference between a and c, b and c.

TABLE 4. **Comparison of effect estimates in each toxicity event category (combined modality of external beam radiation and radioactive implants as reference)**

Toxicity events	**Effect estimates[a] (RR, 95% CI) before IPTW[f] Adjustment**		**Effect estimates[a] (RR, 95% CI) after IPTW[f] adjustment**	
	EBRT only[b]	**Brachy only[c]**	**EBRT only[b]**	**Brachy only[c]**
GI bleeding[d]	0.65 (0.44, 0.96)	0.97 (0.66, 1.42)	0.57 (0.48, 0.67)	0.94 (0.81, 1.09)
GI colostomy[d]	1.42 (0.88, 2.30)	1.20 (0.74, 1.96)	1.63 (1.31, 2.02)	1.44 (1.16, 1.80)
GI fistula[d]	0.53 (0.20, 1.28)	0.49 (0.19, 1.27)	0.68 (0.42, 1.09)	0.75 (0.47, 1.19)
GI stricture[d]	1.13 (0.50, 2.50)	1.05 (0.46, 2.39)	1.22 (0.87, 1.72)	1.13 (0.80, 1.60)
GU cystitis[e]	0.52 (0.25, 1.06)	1.85 (0.98, 3.47)	0.78 (0.54, 1.12)	2.77 (2.08, 3.69)
GU incontinence[e]	0.35 (0.28, 0.42)	0.83 (0.68, 1.02)	0.39 (0.36, 0.43)	0.98 (0.90, 1.07)
GU obstruction[e]	0.60 (0.47, 0.78)	0.91 (0.72, 1.17)	0.56 (0.50, 0.63)	0.89 (0.80, 0.98)
Erectile dysfunction	0.66 (0.52, 0.84)	1.04 (0.82, 1.33)	0.68 (0.61, 0.76)	1.02 (0.92, 1.13)

[a]effect estimates generated from logistic regression model controlled for all potential confounders (race, age at diagnosis centered to its mean, marital status, SEER region, census tract measures of income and education, year of diagnosis, PSA value, Charlson Comorbidity Index). (Race is dropped from GI stricture model because it was found collinear with the model intercept); SEER = Surveillance, Epidemiology and End Results Program; SEER Regions were grouped by percentage of eligible subjects treated with combined modality radiation; [b]external beam radiation only; [c]brachytherapy only; [d]gastrointestinal.; [e]genitourinary; [f]inversed probability of treatment weight

localized prostate cancer have favorable long term overall and cancer specific survival regardless of treatment choice.[17] Overtreatment of low risk disease is associated with significant morbidity and men undergoing radical prostatectomy or radiotherapy for localized prostate cancer experience declines in all functional outcomes throughout early, intermediate, and long term follow up.[17] In addition, there is a substantially greater burden of urinary health problems among elderly prostate cancer survivors.[18]

In the current cohort, nine individual radiation therapy associated toxicity events were analyzed following treatment for low risk prostate cancer. GU incontinence (41.4%), ED (19.3%) and GU obstruction (17.5%) were the most frequently encountered events, and patients treated with combined modality radiation therapy were at significantly increased risk of developing GI bleeding, GU incontinence, GU obstruction, and ED when compared to patients treated with EBRT alone. Less than 33 (actual number masked to protect small cell counts) cases of GU fistula were identified among 4363 eligible patients, which reflect the exceptionally low cumulative incidence of GU fistula among low risk prostate cancer patients treated with radiation therapy. When comparing combined modality radiation therapy to BT alone, fewer significant differences in toxicity events were observed. This may indicate that the excessive morbidity associated with combined modality therapy is largely driven by the addition of BT.

Although combined modality radiation therapy is associated with reduced prostate cancer-specific mortality when compared to EBRT monotherapy for patients with high risk disease,[19] no survival benefit has been demonstrated in patients with low risk disease. The NCCN[20] and AUA[16] guidelines both recommend radiation monotherapy for patients with low risk prostate cancer. We observed a significant regional variation in the receipt of combined modality therapy, and alarmingly upward of 48% of patients in some regions (Atlanta, rural Georgia) were subjected to non-guideline concordant combined modality treatment. The significant geographic variation in the utilization of combination therapy persisted following multivariate adjustment and the observed differences remained quite large (results not shown), which reflects the influence of regional variation on treatment choice. Others have previously shown a similar effect of geography and provider on treatment modality.[5,8]

Men with low risk disease have extremely low rates of 10 year cancer-specific mortality and may provide the ideal circumstances in which treatment-associated toxicity and patient comorbidity may be safely applied to prostate cancer decision-making.[21] Among men with significant comorbidity, guidelines recommend non-aggressive treatment[21] to avoid morbidities that can significantly affect quality of life.[22-24] In one series, at least 54% of men with low risk prostate cancer and significant comorbidities (CCI ≥ 3) were overtreated.[25] In the current cohort, approximately 10% of men in all treatment groups had a CCI score of 2 or greater while around 19% had a CCI score of 1. Men with CCI scores of 1 and 2 have significantly elevated risks of long term non-prostate cancer mortality,[25] leading some to suggest significant comorbidity should be a strong relative contraindication to aggressive treatment.[21] This was not observed in our study as there were no significant differences in treatment modality (single versus multimodal) by comorbidity score. Prudent patient selection and judicious use of combined therapy among men with low risk prostate cancer represents a targetable area to reduce the burden of overtreatment.

Kim et al reported comparable rates of GU (19.4%)[26] and GI (3.5%)[27] toxicities following combination therapy. Although the current cohort only included toxicity events occurring within 3 years of treatment, the increased risk of radiation associated grade 2-4 GU and GI toxicities can persist 10 years or more after treatment.[26,27] Radiation related toxicities can have a significant impact on men's health-related quality of life, and men treated with radiation have been shown to have a 2.2 times greater likelihood of developing major depression.[28] The direct effect of treatment decisions on quality of life in men with prostate cancer make consideration of radiation related toxicity important. Our data provide clinician's with an additional metric to help adequately counsel men considering combined modality radiation therapy.

The cohort of low risk prostate cancer patients examined provides an optimal population to explore the effects of treatment related toxicity. However there are significant limitations associated with the use of payment-based claims data to assess treatment related toxicity, and the clinical validity of using ICD-9 codes for quality monitoring has been questioned.[29] Because they are designed for billing, disentangling comorbid conditions from complications is particularly challenging. In an audit of ICD-9 hospital coded discharge diagnoses, fewer than 60% of diagnoses had supportive clinical evidence available to confirm the coded condition.[29] We therefore utilized procedure codes as opposed to diagnosis codes in an attempt to more accurately enumerate treatment related toxicities. Nonetheless, the observed rates of GU incontinence and obstruction in this study are higher than previously reported by studies relying on patient-reported outcomes.[30] While this could be partially explained by higher baseline rates of these treatment related toxicities in the general Medicare population due to advanced age, it is also feasible to postulate that a multidisciplinary

team over-utilizing combination brachytherapy and EBRT may be more likely to perform unnecessary procedures in the postoperative period, leading to an overestimation of toxicity. Therefore, an increase in procedure claims does not necessarily indicate an increase in toxicity. A phase III trial of combined EBRT and BT versus BT alone (RTOG 0232) for patients with intermediate risk PC has recently closed to accrual. Results from this trial will help determine if combination therapy is associated with increased complications. In the interim, the current cohort highlights the potential burden of over-treatment among men with low-risk disease and identifies an actionable target to reduce morbidity.

Conclusions

Among SEER-Medicare patients, the use of combined modality radiation therapy to treat men with low risk prostate cancer is discordant with clinical guidelines and associated with higher rates of payment claims for procedures indicating a possible association with development of GI/GU toxicities and impairment of sexual function when compared to EBRT monotherapy. Prudent patient selection and judicious use of combined therapy among men with clinically localized low risk prostate cancer represents a targetable area to reduce the burden of overtreatment. □

References

1. Welch HG, Black WC. Overdiagnosis in cancer. *J Natl Cancer Instit* 2010;102(9):605-613.
2. Andriole GL, Crawford ED, Grubb RL 3rd et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009;360(13):1310-1319.
3. Wilt TJ, Brawer MK, Jones KM et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012;367(3):203-213.
4. Sanda MG, Dunn RL, Michalski J et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* 2008;358(12):1250-1261.
5. Hamilton AS, Albertsen PC, Johnson TK et al. Trends in the treatment of localized prostate cancer using supplemented cancer registry data. *BJU Int* 2011;107(4):576-584.
6. Jacobs BL, Zhang Y, Schroeck FR et al. Use of advanced treatment technologies among men at low risk of dying from prostate cancer. *JAMA* 2013;309(24):2587-2595.
7. Lee WR, Bae K, Lawton C et al. Late toxicity and biochemical recurrence after external-beam radiotherapy combined with permanent-source prostate brachytherapy: analysis of Radiation Therapy Oncology Group study 0019. *Cancer* 2007;109(8):1506-1512.
8. Quek RG, Master VA, Ward KC et al. Determinants of the combined use of external beam radiotherapy and brachytherapy for low-risk, clinically localized prostate cancer. *Cancer* 2013;119(2):3619-3628.
9. Institute NC. SEER-Medicare: Medicare Claims Files. 2013.
10. D'Amico AV, Whittington R, Malkowicz SB et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280(11):969-974.
11. Kim S, Shen S, Moore DF et al. Late gastrointestinal toxicities following radiation therapy for prostate cancer. *Eur Urol* 2011; 60(5):908-916.
12. Krupski TL, Kwan L, Afifi AA, Litwin MS. Geographic and socioeconomic variation in the treatment of prostate cancer. *J Clin Oncol* 2005;23(31):7881-7888.
13. Skinner J, Weinstein JN, Sporer SM, Wennberg JE. Racial, ethnic, and geographic disparities in rates of knee arthroplasty among Medicare patients. *N Engl J Med* 2003;349(14):1350-1359.
14. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;45(6):613-9.
15. Westfall PH, Wolfinger, R.D. Closed multiple testing procedures and PROC MULTTEST. *Observations* 2000.
16. Carter HB, Albertsen PC, Barry MJ et al. Early detection of prostate cancer: AUA guideline. *J Urol* 2013;190(2):419-426.
17. Resnick MJ, Koyama T, Fan KH et al. Long-term functional outcomes after treatment for localized prostate cancer. *N Engl J Med* 2013;368(5):436-445.
18. Kopp RP, Marshall LM, Wang PY et al. The burden of urinary incontinence and urinary bother among elderly prostate cancer survivors. *Eur Urol* 2013;64(4):672-679.
19. Shen X, Keith SW, Mishra MV, Dicker AP, Showalter TN. The impact of brachytherapy on prostate cancer-specific mortality for definitive radiation therapy of high-grade prostate cancer: a population-based analysis. *Int J Radiat Oncol Biol Phys* 2012; 83(4):1154-1159.
20. Mohler JL, Armstrong AJ, Bahnson RR et al. Prostate cancer, Version 3.2012: featured updates to the NCCN guidelines. *J Natl Compr Canc Netw* 2012;10(9):1081-1087.
21. Daskivich TJ, Chamie K, Kwan L et al. Overtreatment of men with low-risk prostate cancer and significant comorbidity. *Cancer* 2011;117(10):2058-2066.
22. Gore JL, Kwan L, Lee SP, Reiter RE, Litwin MS. Survivorship beyond convalescence: 48-month quality-of-life outcomes after treatment for localized prostate cancer. *J Natl Cancer Instit* 2009;101(12):888-892.
23. Stanford JL, Feng Z, Hamilton AS et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. *JAMA* 2000;283(3):354-360.
24. Talcott JA, Manola J, Clark JA et al. Time course and predictors of symptoms after primary prostate cancer therapy. *J Clin Oncol* 2003;21(21):3979-3986.
25. Daskivich TJ, Chamie K, Kwan L et al. Comorbidity and competing risks for mortality in men with prostate cancer. *Cancer* 2011;117(20):4642-4650.
26. Kim S, Moore DF, Shih W et al. Severe genitourinary toxicity following radiation therapy for prostate cancer--how long does it last? *J Urol* 2013;189(1):116-121.
27. Kim S, Shen S, Moore DF et al. Late gastrointestinal toxicities following radiation therapy for prostate cancer. *Eur Urol* 2011;60(5): 908-916.
28. Reeve BB, Stover AM, Jensen RE et al. Impact of diagnosis and treatment of clinically localized prostate cancer on health-related quality of life for older Americans: a population-based study. *Cancer* 2012;118(22):5679-5687.
29. McCarthy EP, Iezzoni LI, Davis RB et al. Does clinical evidence support ICD-9-CM diagnosis coding of complications? *Med Care* 2000;38(8):868-76.
30. Lee WR, DeSilvio M, Lawton C et al. A phase II study of external beam radiotherapy combined with permanent source brachytherapy for intermediate-risk, clinically localized adenocarcinoma of the prostate: preliminary results of RTOG P-0019. *Int J Radiat Oncol Biol Phys* 2006;64(3):804-809.