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Severe Genitourinary Toxicity Following Radiation Therapy for Prostate Cancer: How Long Does it Last?

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Abstract

Purpose—Radiation therapy (RT) is a common treatment for localized prostate cancer, but long-term data regarding treatment-related toxicities compared to observation is sparse. In this study, we evaluate the time course of grade 2–4 genitourinary (GU) toxicities in men treated with either primary radiation or observation for T1-T2 prostate cancer.

Methods and Materials—We performed a population-based cohort study, using Medicare claims data linked to the Surveillance, Epidemiology, and End Results (SEER) data. Cumulative incidence functions for time to first GU event were computed based on the competing risks model, with death before any GU event as a competing event. The generalized estimating equation (GEE) method was used to evaluate the risk ratios of recurrent events.

Results—Among patients in this study, 60,134 received RT and 25,904 underwent observation. The adjusted risk ratio for GU toxicity is 2.49 (95% CI 2.00–3.11) for 10 years and beyond. Patients who had required prior procedures for obstruction/stricture (including TURP) before RT experienced a significantly increased risk of GU toxicities: risk ratio 2.78 (95% CI 2.56–2.94)

Conclusions—This study demonstrates that the increased risk of grade 2–4 GU toxicity attributable to RT persists 10 years and beyond after treatment. Patients who had required prior procedures for obstruction/stricture experienced a higher risk of GU toxicity than those without these pre-existing conditions.

Keywords

prostate cancer; radiation therapy; Toxicity; Urinary; SEER Program

Introduction

Patients who choose to undergo prostate cancer therapy have multiple options, including radical prostatectomy, radiation therapy, and androgen deprivation therapy. Like the other treatment modalities, radiation therapy carries risks of significant side effects. For example, Mohammed et al reported the risk of urethral strictures requiring intervention to be 2%, 3%, and 10% after external beam radiation therapy (EBRT), brachytherapy, and EBRT + brachytherapy respectively. They also reported hematuria in 3%, 1%, and 2% respectively. [1]

Further complicating the decision- making process is the fact that for the majority of patients, prostate cancer is a slowly progressing disease that is frequently diagnosed in older men, so observation is often appropriate. Understanding the time course of radiation- related GU toxicity is clearly important to patient decision making. A patient would undoubtedly be more inclined to receive radiation therapy if the majority of the toxicity were limited to the first few years after radiation, as opposed to persisting for the remainder of his life. However, long-term data on genitourinary (GU) toxicity following different radiation modalities is sparse. This population-based study investigates the long-term risk and time course of GU toxicities that require intervention following radiation therapy for localized prostate cancer.

Materials and Methods

The main data source for this study is the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database, a unique resource that combines cancer, clinical and socio-demographic data. The SEER cancer registry ascertainment rate exceeds 98%. [2] There have been multiple studies verifying the validity of the Medicare database. [3–5] The agreement between SEER and Medicare data with regards to radiation treatments for prostate cancer is 93%. [6] This study cohort consisted of patients aged 66 to 85 years old diagnosed with T1-2 clinically localized prostate cancer between 1992 and 2007 (n= 283,440), who were residents of the SEER regions. Patients must have been enrolled in both Medicare Parts A and B for the 12 months before cancer diagnosis so that their co-morbidity status could be assessed [7]. Exclusion criteria included having another cancer before prostate cancer (N= 29,466), enrollment in an HMO or having private health insurance or coverage through the Veterans Administration one year before or one year after cancer diagnosis (N=120,666), metastasis within 6 months of cancer diagnosis (N= 3,243), palliative radiation treatment within 12 months of diagnosis (N= 3,200), cryotherapy or radioisotope therapy (N= 2,298), repeated brachytherapy (N=111), primary ADT not combined with radiotherapy (N=16,918), radical prostatectomy (N= 21,382) in the first 12 months after diagnosis, unless surgery was used after radiation treatment, or radiation treatment before prostate cancer diagnosis (N=118).

Our final cohort consisted of 60,134 patients treated with radiation therapy and 25,904 patients who underwent observation (no surgery, radiation therapy, or hormone therapy for at least a year after prostate cancer diagnosis). The radiation therapy cohort received radiation therapy (as defined by CPT codes) within one year of prostate cancer diagnosis. Radiation therapy was categorized as external beam radiation therapy (EBRT), brachytherapy or EBRT + brachytherapy. Patients receiving EBRT were sub- divided into three-dimensional conformal radiotherapy (3DCRT), intensity modulated radiation therapy (IMRT), or proton beam therapy. 3DCRT was defined as only 3DCRT. IMRT was defined as IMRT only or the combination of 3DCRT and IMRT. Proton beam therapy was defined as protons only or protons combined with 3DCRT or IMRT. EBRT was considered definitive if 20 or more treatments were delivered within 6 weeks.

In this study, we chose to focus on grade 2–4 toxicities that required intervention and could be reliably identified using ICD-9 procedure codes or Current Procedural Terminology (CPT) codes. The toxicities were broadly categorized into GU obstruction/stricture, cystitis, fistula, and incontinence, as defined by ICD-9 and CPT codes in Table 4 (web only). Because the most common toxicity (obstruction/stricture) occurs relatively soon after brachytherapy, we included any GU toxicity that occurred a week following radiation or later. To avoid over-counting events that were related to a single clinical problem but separated in time, we allowed only 1 event every 3 months. In addition, series of claims that crossed the boundary between one quarter and the next were counted only once if they occurred within a three-week interval. Patients in the radiation group who received a second course of radiation treatment or patients in the observation group who received any radiation treatment were censored at the time of treatment.

We used the generalized estimating equation (GEE) method with a binomial distribution and log link for risk ratio estimation of recurrent events. [8] The denominator for the binomial distribution was 4, the number of quarters in a year, and the numerator was the number of these quarters in which an event was observed. The GEE method, together with robust variance estimation, was used for estimation and statistical inference. Working correlation was used to account for within-patient correlation between multiple events. For the comparison of IMRT to proton therapy, we used an independence correlation structure with robust variance correction [8]. The Bonferroni correction was used to derive the adjusted P value for pairwise comparisons between radiation therapy modalities and observation.

Cumulative incidence functions for time to first GU event were computed based on the competing risks models, with death before any GU event as a competing event, using accommodations for competing risks as described by Putter et al.[9] Bootstrap samples of 10,000 replicates were used to obtain 95% confidence intervals for the 5-year and 10-year cumulative incidence.[10] Estimates of the unadjusted and adjusted risk ratio for comparing radiation treatment vs. observation and prior procedures for obstruction/stricture vs. no prior procedures were computed from the GEE model described above. We carried out all analyses using R (Version 2.13, R Foundation for Statistical Computing, Vienna, Austria) and SAS (Version 9.1, SAS Institute, Cary, NC). This study was IRB approved.

Results

Our study cohort consists of 86,038 patients, 60,134 who were radiated and 25,904 who underwent observation. The median follow up time was 94 months. The characteristics of the cohort are described in Table 2 (web only). The observation (compared to radiated) patients were older, more likely to reside in a low income area, and had more well differentiated cancers with lower T stage. Of the patients who were radiated, 9% had a prior procedure for obstruction/stricture; of the observation patients, 28% had a similar procedure. Of the 60,134 radiated patients, 39,690 patients were treated with EBRT, 12,738 with brachytherapy, and 7,706 with EBRT + brachytherapy.

Of the various grade 2–4 GU toxicities among all patients, the most common events were obstruction/stricture (36/1000 person-years) and cystitis (1.6/1000 person-years). The rates of GU fistula (0.1/1000 person-years) and incontinence (0.7/1000 person-years) were very low.

Regarding the time course of GU toxicities, the elevated risk persisted beyond 10 years (Figure 1A). Figure 2 shows that the adjusted elevated risk of GU toxicity for radiation versus observation increases with time. The adjusted risk ratio is 2.49 (95% CI 2.00–3.11) for 10 years and beyond, indicating that GU toxicity after radiation is a long-term problem.

Figure 3 demonstrates that having had procedures for obstruction/stricture prior to radiation increases the risk of GU toxicity afterwards. 10 years after radiation, the cumulative 10-year risk of GU toxicity for patients who had procedures for obstruction/stricture prior to radiation was 38.7%, and for those with no such history, 20.1%.

The brachytherapy modalities are associated with a higher risk of GU toxicity, as summarized in Table 1. Brachytherapy + EBRT (60 events/1000 person-years) had a higher rate of GU toxicity than brachytherapy (43/1000 person-years) or EBRT (35/1000 person-years). Among the external beam modalities, the rates of GU toxicity were relatively similar: 3DCRT (37/1000 person-years), IMRT (32/1000 person-years), protons (34/1000 person-years). For observation, the rate was 32/1000 person-years. The 5- and 10- year cumulative incidences for any first GU toxicity were: for all radiated patients (14.4% and 21.7%), brachytherapy + EBRT (19.4% and 27.8%), brachytherapy (17.6% and 23.5%), 3DCRT (12.7% and 20.1%), IMRT (12.8% and no 10- year data), protons (12.6% and no 10- year data), and observation (14.3% and 19.9%).

Variables associated with worse GU toxicity were: radiation (at all year intervals after radiation), earlier year of cancer diagnosis, worse comorbidity score, older age, state buy-in (a measure of poverty), poor tumor differentiation, prior procedure for obstruction/stricture (the single strongest predisposing factor). Southern region was associated with less GU toxicity. Higher T stage and marital status were not significant factors (Table 3).

In pairwise comparisons, all the radiation modalities resulted in more toxicity than observation. Brachytherapy + EBRT had more toxicity than brachytherapy (risk ratio: 1.23; 95% CI, 1.11–1.37). Brachytherapy, whether alone or combined with EBRT, had significantly more GU toxicity than the EBRT modalities. Among the EBRT modalities, 3DCRT had more toxicity than IMRT (risk ratio: 1.25; 95% CI, 1.08–1.44). Protons were not significantly different from either IMRT or 3DCRT. These relationships are illustrated graphically in Figure 1B.

Discussion

This is the first large-scale population-based study demonstrating that the increased risk of grade 2–4 GU toxicity attributable to radiation therapy persists 10 years and longer after treatment. In this study, procedures prior to RT for obstruction/stricture was the single strongest predictor of future GU toxicity.

That GU toxicity is a significant problem in the acute setting is well documented, especially for brachytherapy.[11, 12] Budaus et al note that acute GU toxicity is mostly related to radiation urethritis, with a peak worsening of urinary symptoms between 2–10 weeks after brachytherapy, and then 75% will return to normal within a year. [13] However, our study demonstrates that the elevated risk due to radiation is persistent. In fact, the risk ratio for GU toxicity due to radiation increases with time all the way to 10 years and beyond (Figure 2). Furthermore, of the total number of GU toxicity events in the brachytherapy patients, only 30% occur within the first year as opposed to 70% afterwards. Among the EBRT patients, the respective percentages are 20% and 80%.

Most of the brachytherapy and external beam radiation literature supports a higher risk of GU toxicity with a prior transurethral resection of the prostate (TURP), similar to our study, though there are some conflicting findings. [11, 14–17] The mechanism by which TURP confers an increased risk, per Sandhu, may be the relative devascularization of the urethra afterwards and the decreased ability to repair radiation damage.[18] Another rationale is that after TURP, the prostate base is broadened, leading to more of the bladder neck being radiated and therefore more prone to obstruction. In our paper, we included TURP patients

in a broader category of obstruction/stricture, which had a risk ratio of 2.78 (95% CI 2.56–2.94) versus no prior obstruction for GU toxicity after radiation. To illustrate the increased risk related to procedures like TURP, prior obstruction versus no prior obstruction in the EBRT patients increased the GU toxicity event rate from 29 to 92/1000 person years and increased 10- year cumulative risk from 18.2% to 37.0%.

The GU toxicity rates from this study are similar to those reported in the literature. We report 10-year cumulative incidence for any first grade 2–4 GU toxicity of 27.8%, 23.5%, 20.1% for EBRT+brachytherapy, brachytherapy, and EBRT, respectively. Memorial Sloan Kettering reported a modern series treated with IMRT to 81 Gy and 10- year follow up, and found an 18% risk of grade 2 GU toxicity. [19] Mohammed et al reported grade 2 late GU toxicity of 28%, 22% and 21% in a large series of patients treated with EBRT + brachytherapy, brachytherapy or EBRT, respectively. In their study, only older age and radiation modality were significantly associated with GU toxicity on multivariate analysis. [1] In this study, the GU toxicity rate for observation patients was also high at 19.9%, and at first glance only slightly less than the radiated patients, though it should be noted that these patients were significantly older and had more prior procedures for obstruction/strictures than their radiated counterparts.

This study has certain limitations. The results of retrospective SEER-Medicare studies depend largely on the accuracy of ICD-9 and CPT codes used. In this case, we chose to focus on toxicities requiring procedural intervention because the accuracy of procedures is much higher than that of diagnosis codes alone. We admit that some codes may not be completely specific to the desired toxicity. For example, we used 57.93 (control of postoperative hemorrhage of bladder) and 52001 (cystourethroscopy with irrigation and evacuation of multiple obstructing clots) to search for cystitis, though both could potentially be utilized in other clinical situations. Additionally, there is selection bias in that patients who chose observation were older and had more prior procedures for obstruction/stricture, presumably leading to higher subsequent GU toxicity, thus likely underestimating the true impact of radiation on GU toxicity. Also, patients who decline treatment initially (observation group) might also be less willing to undergo procedures for subsequent urinary symptoms. Another limitation is that our cohort of patients was aged between 66–85 years old, and so our results may not be completely applicable to younger patients. There are also subtle differences between SEER-Medicare and the general US population: the SEER-Medicare population is less frequently white, less poverty prone, more urban dwelling, and may have lower rates of cancer mortality. Furthermore, as health maintenance organization (HMO) enrollees tend to be younger and healthier than their non- HMO counterparts, excluding them may bias this cohort towards an older population.[2] Finally, we have little data as to the specifics of treatment, such as the total dose given, dose per fraction, prostate volume, radiation beam orientation or how conservatively the nearby normal structures such as the rectum, bladder, or penile bulb were spared from radiation.

Conclusions

This is the first large-scale population-based study demonstrating that the time course of severe GU toxicity after prostate radiation is persistent, and that the elevated risk lasts more than ten years.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

RT	Radiation therapy
SEER	Surveillance, Epidemiology, and End Results
GU	Genitourinary
TURP	Transurethral resection of prostate
EBRT	External beam radiation therapy
3DCRT	Three dimensional conformal radiation therapy
IMRT	Intensity modulated radiation therapy
ADT	Androgen deprivation therapy

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No. at risk

Radiation	60134	57481	43351	30104	18377	9066	4632
Observation	25904	23764	16418	10763	6411	3497	1889

Figure 1.

Figure 1A: Event Rate of Genitourinary Toxicity After Radiation by Treatment Group for all Patients

Event rates were calculated for each year time interval and multiple events were used.

Figure 1B: Age Adjusted Event Rate of Genitourinary Toxicity After Radiation by Radiation Therapy Modality for all Patients.

Event rates were calculated for each year time interval and multiple events were used.

Figure 2. Adjusted Risk Ratio for GU Toxicity, Radiation versus Surveillance by Time Interval
 Adjusted risk ratios were derived from regression model including all patients (radiation and surveillance) for genitourinary toxicity. Model was adjusted for year of cancer diagnosis, co-morbidity, age group, clinical stage at diagnosis, SEER regions, race, marital status, state buy-in, cancer grade, and prior GU procedures before radiation. Error bars indicate 95% confidence intervals.

Figure 3. Effect of Procedures for Obstruction/Stricture Prior to Radiation on Incidence of GU Toxicity Following Radiation

Cumulative incidence functions for time to first GU event were computed based on the competing risks models, with death before any GU event as a competing event.

Table 1
Event Rate of Genitourinary Toxicity by Radiation Therapy Modalities and Prior GU Procedures

	Any Radiation (n = 60,134) Events/Person-Year (Rate per 1000)	All EBRT (n = 39,690) Events/Person-Year (Rate per 1000)	Brachy only (n = 12,738) Events/Person-Year (Rate per 1000)	Brachy plus EBRT (n = 7,706) Events/Person-Year (Rate per 1000)	Surveillance (n = 25,904) Events/Person-Year (Rate per 1000)
Any GU toxicity					
All patients	15411/388085(40)	9056/260243(35)	3328/77634(43)	3027/50209(60)	5368/166997(32)
No prior obstruction/stricture	12043/354175(34)	6734/235059(29)	2779/72688(38)	2530/46429(54)	2767/119329(23)
Prior obstruction/stricture	3368/33910(99)	2322/25184(92)	549/4946(111)	497/3780(131)	2601/47668(55)

Abbreviations: GU, Genitourinary; EBRT, External beam radiation; Brachy, Brachytherapy.