Published in final edited form as:

Eur Urol. 2011 November ; 60(5): 908–916. doi:10.1016/j.eururo.2011.05.052.

Late Gastrointestinal Toxicities Following Radiation Therapy for Prostate Cancer

Sung Kim^{a,b,e}, Shunhua Shen^a, Dirk F. Moore^{a,c}, Weichung Shih^{a,c}, Yong Lin^{a,c}, Hui Li^a, Matthew Dolan^b, Yu-Hsuan Shao^a, and Grace L. Lu-Yao^{a,d,e,*}

^aThe Cancer Institute of New Jersey, New Brunswick, NJ, USA

^bDepartment of Radiation Oncology, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ, USA

^cDepartment of Biostatistics, The School of Public Health, University of Medicine and Dentistry of New Jersey, Piscataway, NJ, USA

^dDepartment of Medicine, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ, USA

^eThe Dean and Betty Gallo Prostate Cancer Center, New Brunswick, NJ, USA

Abstract

Background—Radiation therapy is commonly used to treat localized prostate cancer; however, representative data regarding treatment-related toxicities compared with conservative management are sparse.

Objective—To evaluate gastrointestinal (GI) toxicities in men treated with either primary radiation or conservative management for T1–T2 prostate cancer.

*Corresponding author: The Cancer Institute of New Jersey, 195 Little Albany Street, Room 5534, New Brunswick, NJ 08903, Tel.: (732) 235 8830, Fax: (732) 235 8808, luyao@umdnj.edu.

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Author contributions: Grace L. Lu-Yao had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lu-Yao, Kim, Shao.

Acquisition of data: Lu-Yao.

Analysis and interpretation of data: Lu-Yao, Kim, Moore, Shih, Lin, Shen, Li, Dolan, Shao.

Drafting of the manuscript: Lu-Yao, Kim, Moore, Shih, Lin, Shen, Li, Dolan, Shao.

Critical revision of the manuscript for important intellectual content: Lu-Yao, Kim, Moore, Shih, Lin, Shen, Li, Dolan, Shao.

Statistical analysis: Lu-Yao, Moore, Shih, Lin, Shen.

Obtaining funding: Lu-Yao.

Administrative, technical, or material support: None.

Supervision: Lu-Yao.

Other (specify): None.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Disclaimers: This study uses the Linked SEER-Medicare Database. The project described was supported by award number R01CA145722 from the National Cancer Institute (NCI). NCI is not involved in the design or conduct of this study. The content is solely the responsibility of the authors and does not necessarily represent the official view of NCI or the National Institutes of Health.

Design, setting, and participants—We performed a population-based cohort study, using Medicare claims data linked to the Surveillance Epidemiology and End Results data. Competing risk models were used to evaluate the risks.

Measurements—GI toxicities requiring interventional procedures occurring at least 6 mo after cancer diagnosis.

Results and limitations—Among 41 737 patients in this study, 28 088 patients received radiation therapy. The most common GI toxicity was GI bleeding or ulceration. GI toxicity rates were 9.3 per 1000 person-years after three-dimensional conformal radiotherapy, 8.9 per 1000 person-years after intensity-modulated radiotherapy, 5.3 per 1000 person-years after brachytherapy alone, 20.1 per 1000 person-years after proton therapy, and 2.1 per 1000 person-years for conservative management patients. Radiation therapy is the most significant factor associated with an increased risk of GI toxicities (hazard ratio [HR]: 4.74; 95% confidence interval [CI], 3.97–5.66). Even after 5 yr, the radiation group continued to experience significantly higher rates of new GI toxicities than the conservative management group (HR: 3.01; 95% CI, 2.06–4.39). Because our cohort of patients were between 66 and 85 yr of age, these results may not be applicable to younger patients.

Conclusions—Patients treated with radiation therapy are more likely to have procedural interventions for GI toxicities than patients with conservative management, and the elevated risk persists beyond 5 yr.

Keywords

Prostate cancer; Radiation therapy; Late gastrointestinal toxicity; Medicare; Surveillance Epidemiology and End Results program

1. Introduction

Patients who choose to undergo prostate cancer therapy have several options, including radical prostatectomy, radiation therapy, and androgen-deprivation therapy (ADT). Similar to the other treatment modalities, radiation therapy carries risks of significant side effects. For example, a randomized controlled trial of radiation dose escalation (78 Gy vs 70 Gy) revealed that patients receiving the higher dose had incidences of grade 2 or 3 rectal toxicity of 19% and 7%, respectively [1]. Stone and Stock reported that brachytherapy conferred a risk of rectal bleeding of 24% in years 1–3 and a 2.8% risk of bleeding beyond 5 yr [2].

Further complicating the decision-making process is the fact that for most patients, prostate cancer is typically a slowly progressing disease that is diagnosed in older men, so conservative management is often appropriate. Understanding the potential side effects of various treatments is critical for decision making; however, data on long-term gastrointestinal (GI) toxicities following different radiation modalities are sparse. This population-based study investigates the long-term risk of GI toxicities that require intervention following radiation therapy for localized prostate cancer.

2. 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 sociodemographic data. The SEER cancer registry ascertainment rate exceeds 98% [3]. Multiple studies have verified the validity of the Medicare database [4–6]. The agreement between SEER and Medicare data with regard to radiation treatments for prostate cancer is 93% [7]. The study cohort consisted of patients 66–85 yr of age diagnosed with T1–T2

clinically localized prostate cancer between 1992 and 2005 ($n = 181\,171$) who were residents of the SEER regions. They must have enrolled in both Medicare Parts A and B for the 12 mo before cancer diagnosis. Exclusion criteria included having another cancer before prostate cancer ($n = 46\,522$), metastasis within 6 mo of cancer diagnosis ($n = 2725$), palliative radiation treatment within 12 mo of diagnosis ($n = 3342$), cryotherapy or radioisotope therapy ($n = 838$), repeated brachytherapy ($n = 104$), primary ADT not combined with radiotherapy ($n = 7119$) or radical prostatectomy ($n = 13\,060$) in the first 12 mo after diagnosis, unless surgery was used after radiation treatment. Also excluded were patients who had existing GI toxicity in the year before diagnosis ($n = 80$). Enrollment in a health maintenance organization (HMO), having private health insurance, or coverage through the Veterans Administration during the study period ($n = 65,644$) were also exclusion criteria because these health agencies have historically not been required to submit claims data to Medicare, resulting in incomplete medical records in the SEER-Medicare database for these patients [3].

Our final cohort consisted of 28 088 patients treated with radiation therapy and 13 649 patients who were conservatively managed (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 Current Procedural Terminology [CPT] codes in Addendum 1) within 1 yr of prostate cancer diagnosis. Radiation therapy was categorized as external-beam radiation therapy (EBRT), brachytherapy, or a combination (EBRT plus brachytherapy). Of the patients receiving EBRT, patients were subdivided into three-dimensional conformal radiotherapy (3D CRT), intensity-modulated radiotherapy (IMRT), or proton beam therapy. The 3D CRT was defined as only 3D CRT. IMRT was defined as IMRT only or the combination of 3D CRT and IMRT. Proton beam therapy was defined as protons only or protons combined with 3D CRT or IMRT.

In the United States, the Common Terminology Criteria for Adverse Events and Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) Late Radiation Morbidity Scoring Schema are common toxicity reporting systems [8,9]. To illustrate, the RTOG/EORTC scoring system for late small/large intestine toxicity defines grade 1 as mild diarrhea or cramping, bowel movement five times daily, slight rectal discharge or bleeding; grade 2 as moderate diarrhea and colic, bowel movement more than five times daily, excessive rectal mucus or intermittent bleeding; grade 3 as obstruction or bleeding requiring surgery; grade 4 as necrosis/perforation, fistula; and grade 5 as death directly related to radiation. To give an example of the relative frequency of these toxicities for a large series in the literature, Zelefsky et al reported on 743 patients treated with EBRT and found 14% with grade 1; 8%, grade 2; 0.8%, grade 3; and only one patient with grade 4 GI toxicity [10]. In this study, we chose to focus on late grade 3/4 toxicities that required intervention and could be reliably identified by using *International Classification of Diseases*, ninth revision (ICD-9) procedure codes or CPT codes. The toxicities were broadly categorized into GI bleeding/ulceration, fistula, stricture, and colostomy (ICD-9 and CPT codes are defined in Addendum 2 and available on request). We found that using procedure codes gave more consistent results than using ICD-9 diagnosis codes. Because our goal was to document late (rather than acute) toxicity, only GI toxicities that developed ≥ 6 mo after diagnosis were counted. Patients in the radiation group who received a second course of radiation treatment or patients in the conservative management group who received any radiation treatment were censored at the time of treatment.

We estimated the probability of any GI toxicity by using cumulative incidence [11,12]. Because we had two competing outcomes (death or GI toxicity), a competing risk Cox proportional hazards model was used to analyze the data, with time to either event as the response variable [12,13]. The Cox proportional hazards model for cause-specific hazard

was used to assess the effects of covariates on time to GI toxicity [12]. Hazard ratios (HRs) were also obtained in pairwise comparisons between radiation modalities (3D CRT, IMRT, protons, brachytherapy) and conservative management. To examine whether the elevated risk of GI toxicities persisted >5 yr in the radiation group versus the conservative management group, we examined the 20 114 men who survived at least 5 yr after cancer diagnosis and were still free of GI toxicities at the 5-yr point and compared the GI toxicity rate using a competing risk model. We performed the analysis using Stata v.8 (StataCorp, College Station, TX, USA) and SAS v.9.1 (SAS Institute, Cary, NC, USA).

3. Results

As shown in Table 1, the conservative management patients had higher comorbidity scores, were older, and were more likely to reside in a low-income area. Their cancers were more well differentiated, with lower T stage. With regard to radiation technique, of the 28 088 radiation patients, 19 063 patients were treated with EBRT, 5338 with brachytherapy monotherapy, and 3687 with a combination of EBRT and brachytherapy.

Table 2 summarizes the results for GI toxicity for the respective radiation modalities and conservative management. EBRT (8.8 per 1000 person-years) had a higher rate of GI toxicity than brachytherapy (5.3 per 1000 person-years). Conservative management, predictably, had the lowest rate (2.1 per 1000 person-years). Of the external-beam modalities, the rates of GI toxicities in descending order were protons (20.1 per 1000 person-years), 3D CRT (9.3 per 1000 person-years), and IMRT (8.9 per 1000 person-years). Of the late GI toxicities that were screened for, GI bleeding/ulceration was by far the most common.

Figure 1 compares the cumulative incidence of GI toxicities among patients treated with radiation therapy versus patients who were conservatively managed. At 10 yr the GI toxicity rate was 1.5% for conservative management versus 5.8% for radiation therapy. Figure 2 compares the cumulative incidence of GI toxicities for the various radiation therapy modalities and conservative management. Patients undergoing proton therapy and 3D CRT had the highest rates of GI toxicities; brachytherapy and IMRT offered the lowest rates among the radiation modalities. At 4 yr, the GI toxicity rates were protons (8.5%), 3D CRT (4.8%), combination therapy (3.5%), IMRT (3.3%), and brachytherapy (2.5%). Figure 3a and 3b demonstrate that the GI toxicity associated with proton therapy and IMRT decreased markedly as the year of diagnosis progressed.

As shown in Table 3, radiation therapy is the most significant factor associated with increased risk of GI toxicities (hazard ratio [HR]: 4.74; 95% confidence interval [CI], 3.97–5.66). To assess the long-term impact of radiation therapy, we examined those patients who had not developed any GI toxicity within the first 5 yr of diagnosis and compared the risk of GI toxicities after 5 yr. Patients receiving radiation therapy continued experiencing significantly higher rates of new GI toxicities than the conservative management group (HR: 3.01; 95% CI, 2.06–4.39; $p < 0.001$). However, the absolute difference was small: about 1% at 10 yr.

When considering pairwise comparisons (Table 4), all EBRT modalities had more GI toxicity than did conservative management. When compared with each other, IMRT had less GI toxicity than 3D CRT (HR: 0.67; 95% CI, 0.55–0.82) or protons (HR: 0.30; 95% CI, 0.19–0.47), and protons had higher GI toxicity than either 3D CRT (HR: 2.13; 95% CI, 1.45–3.13) or IMRT (HR: 3.32; 95% CI, 2.12–5.20).

4. Discussion

In this population-based study, we found that of the radiation modalities, brachytherapy (monotherapy) had the lowest rates of procedural intervention for late GI toxicity (5.3 per 1000 person-years). Somewhat surprising was that among the EBRT modalities, proton therapy had the highest rate of grade 3/4 toxicity, followed by 3D CRT and then IMRT (20.1, 9.3, and 8.9 per 1000 person-years, respectively). New technologies such as proton therapy and IMRT show substantial improvement over time, suggesting that experience with the technology may result in reduced risk of late toxicities.

That IMRT in recent years and brachytherapy offer relatively low rates of grade 3/4 toxicity is well borne out by the literature. Memorial Sloan-Kettering Cancer Center reported only a 1% risk of grade 3 GI toxicity in a cohort of prostate IMRT patients who were dose escalated to 81 Gy [14]. Gelblum and Potters reported a large series of 825 patients treated mostly with brachytherapy monotherapy and some with combined EBRT and brachytherapy. They reported a moderate amount of grade 2 rectal toxicity (6.6%) but very rare grade 3 toxicity (0.5%) [15]. Clinical decision making for prostate cancer is often extremely difficult. Unlike many other cancers, the decision to treat is often equivocal due to the relatively slow natural progression of prostate cancer and the typically advanced age of the patients. In this situation, where there is a clear option to manage conservatively rather than intervene, there is added emphasis to “do no harm.” This large population-based study demonstrates that IMRT and brachytherapy monotherapy are associated with very low levels of grade 3/4 GI toxicity and may offer an excellent risk–benefit ratio to patients and physicians struggling with these difficult choices. Because the theoretical advantage of proton therapy is reduced toxicity due to its particular dose deposition characteristics (the Bragg peak), it was somewhat surprising that protons were associated with the highest GI toxicity of the various radiation modalities. However, it must be pointed out that the sample size for the proton cohort was quite small because our study included patients diagnosed from 1992 to 2005, a period when proton therapy was in its relative infancy. In fact, our data showed a major decline in GI toxicity associated with protons over time (Fig. 3a). There have since been reports of favorable toxicity outcomes with proton therapy. Long-term follow-up of 1255 patients treated with proton plus photon therapy at Loma Linda University revealed late grade 3 and 4 GI toxicity of 1% and 0.2%, respectively [16]. A recent Japanese proton study reported 18%, 3%, and 0% grade 1, 2, and 3 late rectal toxicity, respectively [17].

This study has certain limitations. The results of retrospective SEER-Medicare studies depend largely on the accuracy of the ICD-9 and CPT codes used. In this case, we chose to focus on patients requiring procedural intervention because the accuracy of procedures is much higher than that of diagnosis codes alone. Another limitation is that our cohort of patients were between 66 and 85 yr of age, and so our results may not be completely applicable to younger patients. There are 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. Because HMO enrollees tend to be younger and healthier than their non-HMO counterparts, excluding them may bias this cohort toward an older population [3]. Finally, we have little data as to the specifics of treatment. For example, why did GI toxicity for protons decrease for patients diagnosed in 2004–2005? Was it due to improved equipment, a change in radiation dosage, or was there simply a learning curve to treating with protons?

5. Conclusions

There is a significantly elevated risk of GI toxicities following radiation therapy compared with conservative management, and this risk persists beyond 5 yr. Of the radiation modalities, IMRT in more recent years and brachytherapy monotherapy are associated with relatively low rates of late grade 3/4 GI toxicities and may be excellent choices in terms of optimizing the risk–benefit ratio. The choice of treatment modality is made all the more critical when one considers the advanced age of most prostate patients, the typically slow natural progression of prostate cancer, and the dramatic worsening of quality of life associated with serious GI toxicities. Somewhat surprisingly, proton therapy had the highest GI toxicity of the radiation modalities, although it was very time dependent, and by 2004–2005, GI toxicity associated with protons had decreased significantly. These data show the latest technology may not necessarily be superior to existing ones and that a substantial learning curve often exists for new interventions.

Acknowledgments

The authors acknowledge the efforts of the Applied Research Branch, Division of Cancer Prevention and Population Science, National Cancer Institute (NCI), the Office of Information Services, and the Office of Strategic Planning, Center for Medicare and Medicaid Services (CMS); Information Management Services (IMS), Inc., and the Surveillance Epidemiology and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

Funding/Support and role of the sponsor: This study was supported by NCI Challenge grant RC1CA145722, Robert Wood Johnson Foundation 60624, and CINJ Biometrics shared resource (NCI CA-72720-10).

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Fig. 1. Cumulative incidence estimates of any gastrointestinal (GI) toxicity by treatment group. Competing risk was computed by using cumulative incidence adjusting for death from any cause prior to any GI toxicity.

Fig. 2.

Cumulative incidence estimates of any gastrointestinal (GI) toxicity by radiation modality. Competing risk was computed by using cumulative incidence adjusting for death from any cause prior to any GI toxicity.

3D CRT = three-dimensional conformal radiotherapy; Brachy = brachytherapy; IMRT = intensity-modulated radiotherapy; Proton = proton beam therapy.

Fig. 3.

(a) Cumulative incidence estimates of any gastrointestinal (GI) toxicity by year of cancer diagnosis for proton-treated patients. Competing risk was computed by using cumulative incidence adjusting for death from any causes prior to any GI toxicity. (b) Cumulative incidence estimates of any GI toxicity by year of cancer diagnosis for patients treated with intensity-modulated radiotherapy. Competing risk was computed by using cumulative incidence adjusting for death from any causes before any GI toxicity.

Table 1Characteristics of the study cohort^a

Characteristics		Radiation therapy (<i>n</i> = 28 088), %	Conservative management (<i>n</i> = 13 649), %	<i>p</i> value (radiation vs conservative management)
Charlson comorbidity score	0	77	71	<0.001
	1	17	18	
	≥2	6	11	
Age group, yr	66–69	24	15	<0.001
	70–74	39	27	
	75–79	29	31	
	80+	8	27	
Diabetes	Yes	12	13	0.010
	No	88	87	
Myocardial infarction	Yes	2	3	<0.001
	No	98	97	
Peripheral disease	Yes	2	3	<0.001
	No	98	97	
Cancer grade	Well differentiated	5	20	<0.001
	Moderately differentiated	64	59	
	Poorly differentiated	29	15	
	Unknown	2	6	
Clinical stage at diagnosis	T1	52	65	<0.001
	T2	48	35	
Hormone within 1 yr	Yes	44	0	<0.001
	No	56	100	
Race	White	81	77	<0.001
	Black	11	13	
	Other	8	10	
SEER regions	North central	21	22	<0.001
	North east	24	15	
	West	40	51	
	South	15	12	
Poverty	Below poverty	11	21	<0.001
	Above poverty	89	79	
Year of cancer diagnosis	1992–1995	15	27	<0.001
	1996–2000	25	27	
	2001–2005	60	46	

SEER = Surveillance Epidemiology and End Results.

^aData are presented as column percentage. Race was self-determined by the patients. For cancer grade, Gleason score of 2–4, 5–7, and 8–10 corresponded to well-differentiated, moderately differentiated, and poorly differentiated disease, respectively. Clinical extension information provided by SEER was used to determine cancer stage (T1, T2). Charlsoncomorbidity score was derived from Medicare claims during the year before prostate cancer diagnosis by using a validated algorithm [18]. Chi-square test was used to assess the association between patient characteristics and any radiation therapy.

Table 2
Event rate of gastrointestinal toxicity by radiation therapy modalities and conservative management

	External-beam radiation					Events per person-year (rate per 1000)					Brachy plus EBRT (n = 3687)	Conservative management (n = 13 649)	p value
	All EBRT (n = 19 063)	3D CRT (n = 11 770)	IMRT ^a (n = 4645)	Protons (n = 337)	Unknown ^b (n = 2311)	Brachy only (n = 5338)							
Any GI toxicity	936/106 658 (8.8)	720/77 659 (9.3)	134/15 003 (8.9)	28/1390 (20.1)	54/12 606 (4.3)	137/25 672 (5.3)	148/19 654 (7.5)	145/70 564 (2.1)			<0.001 ^c / _{<0.001^d}		
GI bleeding	801/107 163 (7.5)	610/78 101 (7.8)	124/15 018 (8.3)	28/1390 (20.1)	39/12 655(3.1)	114/25 744 (4.4)	125/19 707 (6.3)	62/70 779 (0.9)			<0.001/<0.001		
GI fistula	32/109 998 (0.3)	25/80 429 (0.3)	NA	NA	NA	NA	NA	14/70 959 (0.2)			0.141/0.884		
GI stricture	49/109 860 (0.4)	39/80 307 (0.5)	NA	NA	NA	NA	NA	19/70 945 (0.3)			0.065/0.080		
GI colostomy	80/109 926 (0.7)	66/80 350 (0.8)	NA	NA	NA	15/26 089 (0.6)	14/20 158 (0.7)	60/70 878 (0.8)			0.436/0.353		

EBRT = external-beam radiation therapy; 3D CRT = three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; Protons = Proton beam therapy; Brachy = Brachytherapy; GI = gastrointestinal. NA = not available because Surveillance Epidemiology and End Results (SEER)-Medicare privacy rules prohibit disclosure of numbers <11 in any specific cell.

^aPatients treated with IMRT were diagnosed from 2001 to 2005. More than 70% of patients treated with IMRT were diagnosed in 2004 and 2005. The event rates were 11.4 per 1000 person-years (60 of 5244) for patients diagnosed before 2004, 9.9 per 1000 person-years (53 of 5353) for patients diagnosed in 2004, and 4.8 per 1000 person-years (21 of 4406) for patients diagnosed in 2005.

^bUnknown consists of unknown-type EBRT radiation therapy.

^cChi-square test used to assess the association between GI toxicity and any radiation therapy.

^dChi-square test used to assess the association of GI toxicity across different radiation modality groups (EBRT, Brachy only, Brachy plus EBRT).

Table 3

Regression on cause-specific hazard model including entire cohort (radiation and conservative management) for gastrointestinal toxicity^a

Characteristics	Hazard ratio for any GI toxicity (95% CI)
Radiation	
Conservative management	Ref
Radiation (all modalities)	4.74 (3.97–5.66)
Year of cancer diagnosis	
1992–1995	Ref
1996–2000	0.86 (0.82–0.90)
2001–2005	0.72 (0.69–0.77)
Charlson comorbidity status	
0	Ref
1	1.59 (1.52–1.66)
≥2	2.47 (2.34–2.62)
Age group, yr	
65–69	Ref
70–74	1.20 (1.13–1.27)
75–79	1.69 (1.60–1.79)
≥80	2.52 (2.36–2.68)
Clinical stage at diagnosis	
T1	Ref
T2	1.08 (1.04–1.12)
SEER regions	
North east	Ref
North central	1.01 (0.95–1.07)
South	1.03 (0.96–1.10)
West	0.94 (0.89–0.99)
Race	
White	Ref
Black	1.16 (1.09–1.22)
Other	0.76 (0.71–0.82)
Poverty	
Below poverty	Ref
Above poverty	0.78 (0.74–0.82)
Marital status	
Not married	Ref
Married	0.82 (0.79–0.85)

Characteristics	Hazard ratio for any GI toxicity (95% CI)
Cancer grade	
Well differentiated	Ref
Moderately differentiated	1.12 (1.06–1.18)
Poorly differentiated	1.45 (1.36–1.55)

SEER = Surveillance Epidemiology and End Results; CI = confidence interval; GI = gastrointestinal.

^a The hazard ratios were derived from competing risk model. Death before any GI toxicity was considered as a competing risk. Covariates included year of cancer diagnosis, comorbidity, age group, clinical stage at diagnosis, SEER regions, race, marital status, poverty, and cancer grade.

Table 4

Pairwise comparisons between radiation therapy modalities and conservative management for gastrointestinal toxicity^a

Comparison group	Hazard ratio for any GI toxicity (95% CI)
3D CRT vs conservative management	5.44 (4.52–6.54)
IMRT vs conservative management	4.33 (3.32–5.63)
Protons vs conservative management	13.7 (9.09–20.8)
Brachytherapy alone vs conservative management	3.62 (2.85–4.61)
IMRT vs 3D CRT	0.67 (0.55–0.82)
Protons vs 3D CRT	2.13 (1.45–3.13)
IMRT vs protons	0.30 (0.19–0.47)
IMRT vs brachytherapy alone	1.14 (0.89–1.48)
Brachytherapy alone vs 3D CRT	0.62 (0.51–0.75)
Protons vs IMRT	3.32 (2.12–5.20)

IMRT = intensity-modulated radiotherapy; 3D CRT = three-dimensional conformal radiotherapy; Protons = proton beam therapy; CI = confidence interval; GI = gastrointestinal.

^aThe hazard ratios were derived from competing risk model. Death before any GI toxicity was considered as a competing risk. Covariates included year of cancer diagnosis, comorbidity, age group, clinical stage at diagnosis, SEER regions, race, marital status, poverty, and cancer grade.

Addendum 1

Current Procedural Terminology codes for radiation therapy

Type of RT	Algorithm by CPT
Simple EBRT	77401 Radiation treatment, superficial or orthovoltage
	77402 Single port or parallel opposed, simple or no blocks, up to 5 MeV
	77403 6–10 MeV
	77404 11–19 MeV
	77406 ≥ 20 MeV
3D CRT	77407 RT two separate areas up to 5 MeV
	77408 6–10 MeV
	77409 11–19 MeV
	77411 20 MeV
	77412 RT three separate areas up to 5 MeV
	77413 6–10 MeV
	77414 11–19 MeV
	77416 20 MeV
IMRT	77418 IMRT (IMRT delivery)
Protons	77520 Proton simple without compensation
	77522 Proton simple with compensation
	77523 Proton intermediate
	77525 Proton complex
	77380 Proton beam delivery to single treatment area, single port, custom block
	77381 Proton beam treatment to one or two treatment areas, two or more ports, two or more custom blocks, two or more compensators
Brachytherapy	77776 Interstitial radiation source application simple
	77777 Interstitial radiation source application intermediate
	77778 Interstitial radiation source application complex
	77785 Remote afterloading high-dose rate radionuclide brachytherapy 1 channel
	77786 Remote afterloading high dose rate radionuclide brachytherapy 2–12 channels
	77787 Remote afterloading high-dose rate radionuclide brachytherapy >12 channels
	77799 Unlisted procedure, clinical brachytherapy
	9227 IMPL/INSERTION RADIOACTV ELEMENTS
	55860 Exposure of prostate any approach, for insertion of radioactive substance
	55862 Exposure of prostate any approach, for insertion of radioactive substance with lymph node biopsy
	55865 Exposure of prostate any approach, for insertion of radioactive substance with bilateral pelvic lymphadenopathy
	55859 Old code for transperineal placement of needles or catheters into prostate for interstitial radioelement application, with or without cystoscopy
	55875 Transperineal placement of needles or catheters into prostate for interstitial radioelement application, with or without cystoscopy
	C1715 Brachytherapy needle
	C1717 Brachytherapy source, nonstranded, high-dose rate iridium-192, per source

Type of RT	Algorithm by CPT
	C1719 Brachytherapy source, nonstranded, non-high-dose rate iridium-192, per source
	C1728 Catheter, brachytherapy seed administration
	C2634 Brachytherapy source, nonstranded, high activity, iodine-125, >1.01 mCi (NIST), per source
	C2635 Brachytherapy source, nonstranded, high activity, palladium-103, >2.2 mCi (NIST), per source
	C2636 Brachytherapy linear source, nonstranded, palladium
	C2638 Brachytherapy source, stranded, iodine
	C2639 Brachytherapy source, nonstranded, iodine
	C2640 Brachytherapy source, stranded, palladium
	C2641 Brachytherapy source, nonstranded, palladium

RT = radiotherapy; CPT = Current Procedural Terminology; EBRT = external-beam radiation therapy; 3D CRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; NIST = National Institute of Standards and Technology.

Addendum 2

Current Procedural Terminology and *International Classification of Diseases*, ninth revision (inpatient) codes algorithm for gastrointestinal toxicities

	CPT codes	ICD-9 (inpatient)
GI bleeding, ulceration	45317 Proctosigmoidoscopy, rigid, with control of bleeding (eg, injection, bipolar cautery, unipolar cautery, laser, heater probe, stapler, plasma coagulator) 45334 Flexible sigmoidoscopy with control of bleeding (eg, injection, bipolar cautery, unipolar cautery, laser, heater probe, stapler, plasma coagulator) 45382 Colonoscopy with control of bleeding (eg, injection, bipolar cautery, unipolar cautery, laser, heater probe, stapler, plasma coagulator) 46614 Anoscopy with control of bleeding (eg, injection, bipolar cautery, unipolar cautery, laser, heater probe, stapler, plasma coagulator)	48.31 Radical electrocoagulation of rectal lesion or tissue 48.32 Other electrocoagulation of rectal lesion or tissue
GI fistula	44660 Closure of enterovesical fistula without intestine or bladder resection 44661 Closure of enterovesical fistula with intestine or bladder resection 45800 Closure of rectovesical fistula 45805 Closure of rectovesical fistula with colostomy 45820 Closure of rectourethral fistula 45825 Closure of rectourethral fistula, with colostomy 46270 Surgical treatment of anal fistula, subcutaneous 46275 Surgical treatment of anal fistula, intersphincteric 46280 Surgical treatment of anal fistula transsphincteric, supra, extrasphincteric 46285 Surgical treatment of anal fistula, second stage 46288 Closure of anal fistula with rectal advancement flap 46706 Repair of anal fistula with fibrin glue 46707 Repair of anorectal fistula with plug 46710 Repair of ileoanal pouch fistula 46712 Repair of ileoanal pouch fistula, combined transperineal and transabdominal 46740 Repair of high imperforate anus with rectourethral or rectovaginal fistula 46742 Repair of high imperforate anus with rectourethral or rectovaginal fistula, combined transabdominal and sacroperineal approaches	48.73 Closure of other rectal fistula 48.93 Repair of perirectal fistula 49.1 Incision or excision of anal fistula 49.73 Closure of anal fistula 57.83 Repair of fistula involving bladder and intestine 57.83 Repair of fistula involving bladder and intestine
GI stricture	45150 Division of stricture of rectum 45303 Proctosigmoidoscopy, rigid, with dilation 45340 Sigmoidoscopy, flexible, with dilation by balloon, one or more strictures 45386 Colonoscopy, flexible, proximal to splenic flexure, with dilation by balloon, one or more strictures 45500 Proctoplasty for stenosis 45905 Dilation of anal sphincter under anesthesia other than local 45910 Dilation of rectal stricture under anesthesia other than local 46604 Anoscopy with dilation 46700 Anoplasty, plastic operation for stricture, adult	96.22 Dilation of rectum 96.23 Dilation of anal sphincter
GI colostomy	45563 Exploration, repair, presacral drainage for rectal injury with colostomy	46.1–46.14 Colostomy

CPT = Current Procedural Terminology; ICD-9 = *International Classification of Diseases*, ninth revision; GI = gastrointestinal.

Addendum 3

Common Terminology Criteria for Adverse Events v.4.0 toxicity grading for selected rectal toxicities^a

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rectal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Rectal ulceration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function (eg. altered dietary habits, vomiting, diarrhea)	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Rectal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Rectal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

GI = gastrointestinal; TPN = total parenteral nutrition; ADL = activities of daily living.

^a Full toxicity criteria available at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Addendum 4

RTOG/EORTC late radiation morbidity scoring schema^a

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Small/large intestine	Mild diarrhea Mild cramping Bowel movement five times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic Bowel movement more than five times daily Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/perforation fistula	Death directly related to radiation late effects

^a Full toxicity criteria available at <http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx>.

Zelesky et al reported on 743 patients treated with EBRT and found 14% with grade 1 GI toxicity, 8% with grade 2, 0.8% with grade 3, and only one patient with grade 4 GI toxicity [10].