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Late GI and Bladder Toxicities after Radiation for Uterine Cancer

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Abstract

Objective—To determine the impact of radiation treatment for corpus uteri cancer on the development of late gastrointestinal (GI) and bladder toxicities in older women.

Methods—We used a linked database of the *Surveillance, Epidemiology and End Results* (SEER) *program* tumor registry records and *Medicare* claims to estimate the risk of late radiation toxicities in a population based sample of 23,591 women diagnosed with corpus uteri cancer from 1992–2005. Gastrointestinal (GI) and bladder diagnoses were included up to 60 months after diagnosis. Cox proportional hazard models were used to estimate risk of any late GI or bladder diagnosis with or without hospitalization, due to radiation.

Results—Women treated with radiation had an absolute increase in late GI toxicities of 7.7% and an absolute increase in late bladder toxicities of 3.9%. Most toxicities were not severe. Only 10% of irradiated women with a lower GI diagnosis and less than 1% of irradiated women with a bladder diagnosis, required hospitalization. In the multivariable analysis, advancing age, having chemotherapy, higher comorbidities and prior or early GI and bladder diagnoses were predictive of late toxicities among irradiated women.

Conclusions—Late GI toxicities are more common than previously reported. It is important to analyze late toxicities in population based samples of women with uterine cancer. The results of this and future analyses can be used to identify areas where development of “Survivorship Plans” will remind and encourage women to report symptoms related to potential toxicities.

Keywords

Late toxicities; radiation; uterine cancer; older women; SEER-Medicare database

Introduction

Uterine cancer is the fourth most common cancer affecting women in the United States (US) [1]. The incidence for uterine cancer has been calculated to be 23.3 per 100,000 women [1]. There are two main histological types of uterine cancer: endometrial carcinoma and

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sarcomas. Sarcomas only represent 5% of all the uterine cancers [2]. Survival rates for uterine cancer overall are high, with a 5-year relative survival rate of about 90% reported for women diagnosed between 1992 and 2001 [3]. Assessment of late side effects related to definitive uterine cancer therapies is very important due to the potential for long-term survival.

Radiotherapy (either brachytherapy or external pelvis radiation) is an integral part of post-operative adjuvant therapy for most patients with high risk features [4,5]. Other adjuvant therapies like hormonal therapy and chemotherapy are individualized and mostly recommended for more advanced stages or patients with metastases [4].

The gastrointestinal (GI) tract and the urinary bladder are the most common sites of toxicities after radiotherapy [6]. Those toxicities occurring after six months have been labeled late toxicities. Late toxicities affect the quality of life of patients and cause concerns among physicians caring for these patients [7,8]. Studies have reported that the rates of severe (RTOG/EORTC grades 3 and 4 late radiation morbidity score) GI and bladder toxicities after radiation for endometrial cancer are about 8% [6]. Rates of less severe GI and bladder symptoms however may be significantly higher and require further study [9,10].

Multimodality therapy of postoperative radiation has been shown to improve disease-free survival with a concurrent increase in GI and bladder toxicity profiles [11,12]. Enhancement in radiation treatment, planning and delivery, has demonstrated a reduction in potential toxicity to organs at risk [10,13]. Tumor directed targeted therapy with consideration of dose and fractionation are strategies to reduce toxicity and some investigators advocate the use of medications as radioprotectants as well [10,14,15].

Most reports on the frequency and risks of toxicities related to radiotherapy come from clinical trials, case reports and single institution studies. This body of data is representative only of a highly selected group of women and is subject to bias, has a short follow-up interval of the subjects and includes a small number of older women. Population based data is a powerful source of information that can help us determine the prevalence and severity of late toxicities among older women after radiotherapy for uterine cancer. Our study analyzes the incidence of GI and bladder toxicities after radiation therapy in a population-based sample of older women diagnosed with uterine cancer.

Methods

Data Source

The source of data for this study is the SEER-Medicare linked database. The SEER program is a national population based tumor registry that gathers information on incidence of cancer cases. Medicare is the largest health insurer covering 97% of adults over 65 years of age in the US. A link between eligible SEER subjects and their Medicare claims has been established through an agreement between the National Cancer Institute and the Centers for Medicare and Medicaid Services [16]. Persons with cancer diagnosed between 1973 and 2005 have been linked and their complete Medicare claims are available between 1991 and 2005. The match rate of persons aged 65 and older with a cancer diagnosis in SEER was 93% when compared to their Medicare enrollment records. Claims data for this study are available in separate files for hospital services (Medicare Provider Analysis and Review File (MEDPAR)), physician and medical services (Carrier File), and outpatient services (Hospital Outpatient Standard Analytic File (OUTSAF)).

Population

Our study population includes women in the SEER-Medicare database with uterine cancer diagnosis over the period 1992-2005. A total of 59,420 women were identified. To ensure complete information, cancer cases identified from autopsy reports or death certificates alone (132 cases), and women with multiple cancer sites (11,309 cases) were excluded. Women without Medicare part A and part B between 1992-2005 (5,779 cases) and women enrolled in an HMO and women with only Medicare part A over the period 1992-2005 (5,267 cases) were also excluded. The radiation category included women with beam radiation, brachytherapy or combination of both. This resulted in a total sample of 23,591 women.

Demographic characteristics, dates of diagnosis, and disease extension were obtained from the SEER-Medicare PEDSF file for all patients. Socioeconomic status was indirectly measured by Medicaid eligibility [17]. Comorbidity scores were calculated using the Klabunde modification of the Charlson index based on claims data in the year prior to uterine cancer diagnosis [18,19].

Treatment

Radiation was defined as receiving beam radiation, radioactive implants or a combination of both based on SEER database codes 1-6, or having a Medicare radiation claim 1-6 months after diagnosis of uterine cancer. The specific International Classification of Diseases, 9th revision (ICD-9-CM) codes and Healthcare Common Procedure Coding System (HCPCS) codes used to identify claims were: V580, V661, V671, or procedure codes 9221-9229, or HCPCS codes 77401-77499 and 77750-77799.

Adjuvant treatment with chemotherapy and surgery were used as covariates. Chemotherapy was defined using ICD-9CM DX codes V58.1, V66.2, V67.2 or ICD-9-CM procedure codes 992.5 or HCPCS codes 96400-96549, J9000-J9999, Q0083-Q0085, or revenue center codes 0331, 0332, 0335. Surgery was defined using SEER site specific surgery codes 20,30,35,40,50,60,70,61-64,71,72,80-82.

Study Outcomes

GI and bladder diagnoses were included from 6 to 60 months after diagnosis. These diagnoses were defined by selected ICD-9 and Current Procedural Terminology (CPT) codes. A complete list of codes included in this study is provided in Table 1. We classified diagnoses as follows: 1) "Any gastrointestinal or bladder diagnosis," defined as relevant GI or bladder diagnoses identified on inpatient (MEDPAR file), outpatient (Outpatient file), or physician (Carrier file) claims; 2) "hospitalizations," defined as GI or bladder diagnoses serious enough to require hospitalization (MEDPAR file); and 3) "procedures," defined as GI or bladder procedures or surgical interventions (MEDPAR, Outpatient, and Carrier file). For "any diagnosis" and "procedures," all relevant claims were included, regardless of ICD-9-CM diagnosis position. For "hospitalizations," only diagnosis in the first or second positions were examined.

Statistical Analyses

Patient characteristics were compared between women who had radiation therapy (n=8,006) and those who did not have radiation (n= 15,585) using chi-square test for categorical variables and student t-test for continuous variables. Adjusted time-to-event curves were estimated from stratified Cox Proportional Hazard Models (n=23, 591). The Cox models created were then used to analyze predictors of GI and bladder toxicities in women who received radiation (n=8,006) and included radiation (yes vs. no), age, tumor stage¹, tumor

grade, ethnicity, Medicaid eligibility, chemotherapy, surgery, comorbidity index, and diagnosis year.

Using only the group of women diagnosed with uterine cancer between 1992-2002 who had complete 60 month follow-up information (n=8,797), we plotted the percentage of patients with any GI or bladder diagnosis for each month starting 12 months prior to uterine cancer diagnosis through 60 months after diagnosis. Diagnoses were divided in two categories due to the clear differences in the frequency of diagnoses around the time of radiation treatment compared to the frequency of late diagnosis. These categories are consistent with known patterns of toxicity related to radiation [7]. Diagnoses occurring within 6 months of first radiation were labeled “early toxicities” and those occurring between 6 and 60 months after initial radiation were labeled “late toxicities”. Data were plotted and resulting curves were compared with General Linear Model repeated ANOVA in the 6-60 month time period to determine significant differences by treatment group and time.

In order to identify differences by type of GI or bladder diagnosis and type of GI or bladder procedures over time, chi-square tests were used to compare women who received radiation to women who did not receive radiation. All p-values were two-sided. Statistical analyses were performed using the SAS software version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Of the total number of women with uterine cancer included in this study, 8,006 (33.9%) received radiation. As shown in Table 2, women who received radiation were older, were more likely to have uterine cancer diagnosed at more advanced stages, and also were more likely to have poor cancer differentiation (grades 3 and 4).

Figure 1 shows the percentage of women who had lower GI or bladder diagnoses for each month, starting 12 months before diagnosis and extending to 60 months after uterine cancer diagnosis. Separate curves were depicted for those patients who underwent radiation and those who did not. There were increases in early toxicities for both groups around the time of the cancer diagnosis (Figures 1 a and b). The trend was higher for GI toxicities, approximately 6 months after diagnosis and remained elevated ($p<.0001$). Late GI toxicities appear to peak around 12 to 24 months after diagnosis. The trend for bladder toxicities is less pronounced but still significant ($p<.0001$).

We then determined the percentage of women with specific lower GI and bladder diagnoses from one year before diagnosis until five years after radiation. For these analyses, we limited the patient population to the 8,797 women who had complete follow-up for 5 years (Table 3). Overall, no important differences in toxicity rates were observed prior to uterine cancer diagnosis. Most early GI toxicities were significantly higher for the radiation group compared to the no radiation group. Conversely, no significant differences in early bladder toxicities were observed between the two groups. Women treated with radiation had an absolute increase in late GI toxicities of 7.7% and an absolute increase in late bladder toxicities of 3.9%.

The most common late GI toxicity was inflammation such as colitis and diarrhea; rates were 7.6% higher among irradiated women (42.2% of irradiated women vs. 34.6% of non-irradiated women) (Table 3). The most common bladder toxicities were hemorrhage and incontinence; hematuria rates were 1.6% higher among irradiated women compared to those

¹The SEER-Medicare database has Medicare claims starting in 1991. For this reason staging for cancer is based on the AJCC 1988 staging system.

non-irradiated and incontinence rates were 3.5% higher. A total of 10.1% of irradiated women experienced lower GI toxicities serious enough to require hospitalization over the 5-year period, compared to 5.2% of women who did not receive radiation. For bladder toxicities the percentage was considerably lower; less than 1% of women who received radiation required hospitalization for late bladder toxicities.

When medical procedures were examined, the rate of diagnostic endoscopies was 7% higher in irradiated women and the difference was statistically significant ($p<.0001$) (Table 3). Also, the percentage of patients who required lower GI surgical procedures was significantly higher in women who received radiation compared to women who did not receive radiation (3.1% vs. 2.1%, $p=0.003$). Two fifths of irradiated women had a lower GI endoscopy over the five years after cancer diagnosis and one tenth of irradiated women had a cystoscopy. A 2.8% increase in risk of having bladder surgical procedures was also observed and the difference was significant ($p<.0001$).

Hazard ratios (HR) of late GI and bladder toxicities were obtained for the entire sample ($n=23,591$). Two models were created for each toxicity type. For late GI toxicities the HR was 1.38 with a 95% confidence interval (95% CI) between 1.33 and 1.43. After adjusting for all sociodemographic covariates, comorbidities and concomitant treatments (surgery and chemotherapy), the magnitude of the HR decreased but remained statistically significant (HR 1.31, 95% CI 1.26-1.36). Similarly, for late bladder toxicities, the unadjusted ratio was HR 1.22, 95% CI 1.16-1.27 and after controlling for all covariates the magnitude decreased but remained statistically significant (HR 1.13, 95% CI 1.08-1.19). We additionally analyzed the interaction between radiation and all covariates for GI and bladder toxicity in the complete sample and the interaction between grade 4 vs. 1 and radiation (parameter estimate 0.28; $p=.005$) was the only significant one at the 0.05 level. This results can be observed in Figure 2.

Adjusted time to event curves using the total population of women diagnosed with uterine cancer ($n=23,591$) are depicted in Figure 2a for GI toxicities and in Figure 2b for bladder. Figure 2a depicts the adjusted curve for women with GI toxicities. Women receiving radiation had higher toxicity rates compared to women who did not receive radiation. Five years after initial treatment, irradiated women had 8.1% higher risk of late GI toxicities compared to non irradiated women (Absolute Risk [AR] 0.081; 95% Confidence Interval [95% CI] 0.065-0.098). Figure 2b depicts the adjusted curve for women with bladder toxicities. Similarly, irradiated women had higher toxicity rates. The absolute risk for bladder toxicities was 3.5% for irradiated women compared to non irradiated women (AR 0.035; 95% CI 0.019-0.051).

Table 4 shows the odds associated with developing any GI and bladder diagnosis among women receiving radiation. Multivariable analyses found that women with advancing age, those who had chemotherapy, those with higher comorbidities, those with GI or bladder diagnoses 12 months prior to cancer diagnosis and women with early GI or bladder toxicities had statistically significant with higher risk of both GI and bladder late toxicities. Higher tumor grade only increased the risk for GI late toxicities while being Medicaid eligible only increased the risk of late bladder toxicities. Having surgery decreased the risk of late bladder toxicities.

Discussion

In this study we evaluated lower GI and bladder toxicity after radiation therapy for uterine cancer. Among the women who received radiation, an absolute increase in late GI toxicities and bladder toxicities was observed. Inflammation was the most common GI toxicity.

Incontinence and hematuria were the most common bladder toxicities. Differences in late GI toxicities were significantly higher for women in the radiation group and this trend remained over time. Conversely, differences in late bladder toxicities were significantly higher for irradiated women but the trend did not hold over time. Diagnostic procedures, particularly endoscopies and cystoscopies, were also elevated among women treated with radiation. Despite these rates, most toxicities appear to have been mild to moderate since only 10% of irradiated women required hospital admission for a lower GI diagnosis and less than 1% of irradiated women required hospital admission for a bladder diagnosis. In the multivariable analysis, advancing age, having chemotherapy, higher comorbidities and prior or early GI and bladder diagnoses were predictive of late toxicities among irradiated women.

The rates of GI and bladder late toxicities reported in our study are comparable to previous studies [12,20,21]. For example, in a multi-center clinical trial performed in the Netherlands, 691 women with stage I endometrial cancer were evaluated and 5-year rates of late GI, urinary tract, vagina and bone complications were reported in 26% of women who received radiation compared to 4% of women who did not receive radiation [12], a 22% absolute increase in late toxicities. When the rates were estimated by complication site (i.e. GI and bladder), the GI rates were 20% and the bladder rates were 8% over the same time period [12]. Few other studies have evaluated toxicity at 5-years of follow-up [11,12]. Despite these rates, identification of late toxicities was based on the French-Italian glossary, a very broad and general classification for complications related to radiation therapy[22]. Thus, rates of complications reported in our study are probably an overestimation and are not specific.

Direct comparisons of results obtained from patient surveys and toxicities assessed by medical claims pose limitations because they measure different aspects of GI and bladder toxicities, in addition to comparing patient-reported symptoms with physician reported diagnoses. Our approach using claims-based data may ascertain more mild toxicities, or toxicities that are relevant for the physician but not necessarily bothersome for the patients, especially if physicians have incentives to register all diagnoses, regardless of how minor they are. Despite these limitations, the use of claims data provides advantages over other data sets. Toxicities are registered precisely over time and it is likely that additional transient symptoms are captured. In addition, claims data allow us to compare baseline rates of GI and bladder diagnoses between the irradiated and non-irradiated women, allowing calculation of absolute risk.

Previous literature has discussed radiation treatment parameters for uterine cancer including optimal doses and volume [5,10,13,21]. Less attention has been directed towards individual characteristics that predispose women to treatment toxicity. In our study, individual characteristics such as older age and higher comorbidities increase the risk of both GI and bladder toxicities. Other individual factors, such as GI and bladder diagnosis 12 months before cancer, and early toxicities were also associated with higher risk of late toxicities. Conversely, education decreased the risk of both GI and bladder diagnoses. Thus, despite the increased risk of toxicities due to advancing age, age alone cannot be considered a contraindication to radiation therapy or other types of cancer treatment[10,23].

Previous studies have also reported an increased survival and reduction in recurrence of cancer with increased acute toxicity in women treated for some types of uterine cancer with concomitant radiation therapy and chemotherapy [24]. They also report that the prevalence rates of late toxicities are unclear. Our data adds to this literature by finding that chemotherapy increases the prevalence of late GI and bladder toxicities in our cohort of women. Future analyses need to identify other factors that can influence toxicities related to

chemotherapy, determine prevalence rates and establish potential mechanisms to explain late toxicity rates in older women with dual therapy.

Our study has some limitations. First, we determined diagnoses consistent with toxicity using Medicare claims. Our rates of diagnoses are likely to underestimate all toxicities and some women may have toxicities not included through billing codes. Second, few details regarding radiation treatment were available. Radiation fields and applied doses are important predictors of late toxicities that were not available. Third, this study probably covered a period during which some improvements to treatment planning were implemented. Despite this, no significant decrease in toxicity over time was observed in the unadjusted or adjusted analyses. Fourth, there could be a bias when including some diagnostic procedures to identify late toxicities. Nevertheless, identification of differences in number of procedures performed by treatment group is an important indicator of healthcare provision. Finally, grouping beam and brachytherapy might influence the results obtained. This approach is likely to underestimate the effect of radiation on late toxicities.

In conclusion, our data show that there are many women who develop GI and bladder late toxicities following radiation therapy for uterine cancer. Older women, women who receive chemotherapy and those with a higher comorbidity burden were at higher risk of developing both GI and bladder toxicities after radiation. The severity of both types of toxicities, however, appeared to be low. Given that radiotherapy is currently one of the cornerstones of treatment for uterine cancer, it is important to have better information on the long-term effects of radiation therapy. Even if most toxicities described are not serious enough to result in hospitalization, they significantly reduce quality of life in women who survive cancer. The heterogeneity of the aging process highlights the importance of considering a variety of individual factors when determining outcomes from radiation therapy in women with uterine cancer.

Conflict of Interest Statement

The authors disclose no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within 24 months of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

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Figure 1.

Percentage of patients with a Medicare claim for (A) gastrointestinal (GI) late toxicities and (B) bladder late toxicities, for every month between 12 months before and 60 months after cancer diagnosis, stratified by radiation treatment (n=8,797)

(A) Between radiation group effect: F value=151.6, $p<.0001$ Time*radiation effect: F value=1.98, $p<.0001$

(B) Between radiation group effect: F value=20.56, $p<.0001$ Time*radiation effect: F value=1.30, $p=.07$

Figure 2. Adjusted¹ time-to-event curves for (A) time until any late gastrointestinal (GI) toxicity and (B) time until any late bladder toxicity, stratified by radiation group (n=23,591)

¹Curves were adjusted by age, AJCC stage, grade, ethnicity, marital status, Medicaid eligible, education, chemotherapy treatment, surgery, comorbidities, SEER region, diagnoses 12 months before initial radiation and early toxicities.

Table 1

GI and bladder diagnoses and procedure ICD-9 and CPT codes used for study

GI Diagnoses	ICD-9 codes
Ischemia	557.0, 557.1
Inflammation	558.1, 558.2, 787.91, 562.0, 562.1, 555.1
Hemorrhage	578.1, 578.9, 569.3
Stricture or obstruction	569.2, 560.8, 560.9
Ulcers and perforations	569.82, 569.83, 569.41
Fistulas	565, 619.0, 619.1, 619.2, 619.9, 537.4, 569.81, 596.1
GI Procedures	ICD-9 and CPT codes
Endoscopies	45.21, 45.23, 45.24, 48.21, 48.23, 49.21. 44360, 44366, 44376, 44385, 45300-45345, 45355-45387, 46600-46615
Surgical interventions or procedures	45.00, 45.03, 45.7, 45.8, 46.1, 46.2, 46.75, 48.5, 48.9, 48.7, 49.71. 44140-44160, 44204-44212, 45110-45123, 46.76, 47.92, 49.73, 49.1, 48.73, 48.93, 70.72-70.74. 45000, 45005, 45020, 45800, 45805, 45820, 45825, 46.80, 46.81, 96.22, 96.23. 45500, 45905, 45910, 46700
Bladder Diagnoses	ICD-9 codes
Cystitis	595.1, 595.2, 595.3, 595.82, 595.9
Incontinence	788.2, 788.30, 788.31, 788.34, 788.37, 788.38
Hemorrhage	596.7, 599.7
Obstruction	599.6
Fistulas	619.0, 619.1, 596.1, 596.2
Bladder Procedures	ICD-9 and CPT codes
Cystoscopies	57.32, 57.33. 52000, 52001, 52005, 52007
Surgical interventions or procedures	57.6, 57.7, 57.81, 57.85, 57.87, 57.91, 57.92. 51725-51798, 51520, 51525, 51530, 51535, 51550, 51555, 51565, 51570, 51575, 51580, 51585, 51590, 51595, 51596, 51800, 51820, 51960, 51980, 52204, 52214, 52260, 52310, 52315, 53400, 53405, 57.0, 57.1, 57.41, 58.5, 58.6. 51600, 51605, 51610, 51700, 51701-51703, 51736, 51741, 51795, 51797, 51798, 56.84, 57.83, 57.84, 58.43. 44660, 44661, 51900, 51920, 51925, 57320, 57330

GI = Gastrointestinal; ICD-9 = International Classification of Diseases, 9th version; CPT = Current Procedural Terminology

Table 2

Patient characteristics by radiation status

	n = 23,591	Radiation (%) n=8,006	No Radiation (%) n=15,585	p-value
Age group				
≤ 64	1,493	5.1	7.0	
65-69	4,926	21.8	20.4	
70-74	5,887	26.8	24.0	
75-79	5,225	23.3	21.6	
80+	6,060	23.0	27.1	<0.0001
Race group				
White	20,161	84.6	85.9	
Black	1,765	8.2	7.1	
Hispanic	917	4.1	3.8	
Other	748	3.1	3.2	0.0087
Marriage status				
All others	14,031	58.4	60.0	
Married	9,560	41.6	40.0	0.0191
Medicaid Eligible				
Yes	5,143	20.8	22.3	0.0067
AJCC Stage				
Stage 0/I*	15,433	51.4	72.6	
Stage II	2,017	16.2	4.6	
Stage III	2,147	17.1	5.0	
Stage IV	2,351	10.3	9.8	<0.0001
Grade				
grade1	7,265	17.2	37.7	
grade2	6,993	32.5	28.2	
grade3	5,116	6.6	4.2	
grade4	1,173	12.4	13.2	<0.0001
Acute Myocardial Infarction				
Yes	224	0.9	1.0	0.8852
Diabetes				
Yes	4,499	20.1	18.5	0.0032
Peripheral Vascular Disease				
Yes	539	2.2	2.3	0.4662
Chemotherapy				
Yes	5,642	29.8	20.9	<0.0001
Cancer directed surgery				
Had surgery	20,648	86.9	87.9	0.0365
Comorbidity Index				
0	15,624	66.3	66.2	
1	4,940	21.1	20.9	

	n = 23,591	Radiation (%) n=8,006	No Radiation (%) n=15,585	<i>p-value</i>
2	1,835	7.5	7.9	
≥ 3	1,192	5.1	5.0	0.7182

AJCC = American Joint Committee on Cancer ; GI = Gastrointestinal; SEER = Surveillance, Epidemiology and End Results (SEER) Program; The SEER-Medicare database has Medicare claims starting in 1991. For this reason staging for cancer is based on the AJCC 1988 staging system.

* Stage 0 and I were combined due to confidentiality issues related to the small number of women in stage 0 in our sample; in the combined stage 0/I group, only 2.1% of women belong to stage 0.

Table 3

Percentages of the 8,797 women with 60 months of complete follow-up who had GI and bladder diagnoses, hospitalizations and procedures.

GI Diagnosis	Before Dx Toxicity (12 months before)		Early Toxicity (1-6 months)		Late Toxicity (6-60 months)	
	Count	%	Count	%	Count	%
<i>Any GI toxicity</i>						
<i>Ischemia</i>	Radiation	381	14.0	595	21.9	1653
	No Radiation	968	15.9	1062	17.5	3224
	<i>p</i>		0.0208		<0.0001	
						<0.0001
<i>Inflammation</i>	Radiation	<11	<1.0*	<11	46	1.7
	No Radiation	<11	<1.0*	22	53	0.9
	<i>p</i>		0.6870		0.0165	0.0008
<i>Hemorrhage</i>	Radiation	159	5.8	341	12.5	1148
	No Radiation	457	7.5	512	8.4	2104
	<i>p</i>		0.0044		<0.0001	
						<0.0001
<i>Stricture/Obstruction</i>	Radiation	162	6	133	4.9	857
	No Radiation	394	6.5	300	4.9	1405
	<i>p</i>		0.3473		0.9251	<0.0001
<i>Ulcers/Perforations</i>	Radiation	23	0.8	107	3.9	336
	No Radiation	31	0.5	208	3.4	373
	<i>p</i>		0.0626		0.2331	<0.0001
<i>Fistula</i>	Radiation	<11	<1.0*	<11	55	2
	No Radiation	<11	<1.0*	22	71	1.2
	<i>p</i>		0.1521		0.8198	0.0018
<i>Fistula</i>	Radiation	<11	<1.0*	14	67	2.5
	No Radiation	17	0.3	38	87	1.4

GI Diagnosis	Before Dx Toxicity (12 months before)		Early Toxicity (1-6 months)		Late Toxicity (6-60 months)		
	Count	%	Count	%	Count	%	
GI Hospitalization (Include all primary Dx codes only for those hospitalized)	<i>p</i>	0.4909		0.5317		0.0007	
	Radiation	14	0.5	54	2.0	274	10.1
	No Radiation	29	0.5	56	0.9	315	5.2
	<i>p</i>	0.8157		<0.0001		<0.0001	
GI Procedures							
	Endoscopies						
	Radiation	203	7.5	219	8.1	1148	42.2
	No Radiation	562	9.2	409	6.7	2143	35.3
	<i>p</i>	0.0060		0.0261		<0.0001	
Surgical Procedures							
	Radiation	<11	<1.0*	13	0.5	85	3.1
	No Radiation	11	0.2	49	0.8	116	2.1
	<i>p</i>	0.6440		0.0888		0.0029	
Bladder Diagnosis	Before Dx toxicity (12 months before)		Early Toxicity (1-6 months)		Later toxicity (6-60 months)		
	Count	%	Count	%	Count	%	
Any Bladder toxicity	Radiation	366	13.5	388	14.3	974	35.8
	No Radiation	813	13.4	941	15.5	1941	31.9
	<i>p</i>		0.9214		0.1398		0.0004
Cystitis	Radiation	86	3.2	67	2.5	271	10
	No Radiation	178	2.9	142	2.3	448	7.4
	<i>p</i>		0.5544		0.7187		<0.0001
Incontinence	Radiation	65	2.4	125	4.6	470	17.3
	No Radiation	200	3.3	388	6.4	953	15.7
	<i>p</i>		0.0223		0.0009		0.0601
Hemorrhage							

Bladder Diagnosis	Before Dx toxicity (12 months before)		Early Toxicity (1-6 months)		Later toxicity (6-60 months)			
	Count	%	Count	%	Count	%		
Obstruction	Radiation	248	9.1	128	4.7	471	17.3	
	No Radiation	455	7.5	261	4.3	836	13.8	
	<i>p</i>		0.0092		0.3862		<0.0001	
	Radiation	<11	<1.0*	12	0.4	24	0.9	
	No Radiation	<11	<1.0*	11	0.2	40	0.7	
Fistula	<i>p</i>		0.2850		0.0272		0.2529	
	Radiation	<11	<1.0*	<11	<1.0*	18	0.7	
	No Radiation	<11	<1.0*	21	0.3	24	0.4	
	<i>p</i>		0.5342		0.3274		0.0934	
	Bladder Hospitalization (Include all primary Dx codes only for those hospitalized)	Radiation	<11	<1.0*	<11	<1.0*	15	0.6
No Radiation		<11	<1.0*	<11	<1.0*	18	0.3	
<i>p</i>			0.4089		0.4089		0.0703	
Bladder Procedures		Radiation	112	4.1	108	4.0	277	10.2
		No Radiation	194	3.2	252	4.1	430	7.1
	<i>p</i>		0.0286		0.6999		<0.0001	
	Surgical Procedures	Radiation	41	1.5	67	2.5	272	10.0
		No Radiation	93	1.5	208	3.4	438	7.2
<i>p</i>			0.9351		0.0168		<0.0001	

GI = Gastrointestinal; Dx = Diagnosis

The SEER-Medicare database has Medicare claims starting in 1991. For this reason staging for cancer is based on the 1988 AJCC staging system

* Due to confidentiality issues, counts with less than 11 women are presented as "<11" and the corresponding percentages are reported as "<1%".

Table 4

Multivariate analysis of factors associated with any late GI and bladder diagnosis or hospitalization with a late GI and bladder diagnosis in 8,006 women treated with primary radiation therapy.

	Any late GI diagnosis adjusted HR (95% CI)	Any late bladder diagnosis adjusted HR (95% CI)
Age (every 10 year increase)	1.04 (1.00-1.09)	1.08 (1.02-1.14)
Ethnicity		
White	1.00	1.00
Black	0.93 (0.81-1.06)	0.93 (0.78-1.11)
Hispanic	0.93 (0.79-1.09)	1.03 (0.83-1.27)
Other	0.87 (0.70-1.07)	0.88 (0.66-1.15)
AJCC Stage		
Stage 0	1.00	1.00
Stage I	0.91 (0.29-2.84)	0.22 (0.08-0.61)
Stage II	0.99 (0.32-3.09)	0.26 (0.10-0.71)
Stage III	1.03 (0.33-3.22)	0.26 (0.09-0.70)
Stage IV	1.25 (0.40-3.92)	0.34 (0.13-0.94)
Tumor Grade		
Grade1	1.00	1.00
Grade2	0.94 (0.86-1.02)	0.88 (0.78-0.98)
Grade3	1.04 (0.95-1.14)	0.95 (0.85-1.08)
Grade4	1.24 (1.07-1.43)	1.06 (0.88-1.29)
Medicaid eligible (yes)	0.97 (0.89-1.06)	1.27 (1.14-1.41)
Chemotherapy (yes)	1.35 (1.26-1.44)	1.45 (1.32-1.58)
Surgery group (yes)	0.92 (0.82-1.04)	0.74 (0.64-0.86)
Charlson Comorbidity Index		
0	1.00	1.00
1	1.14 (1.05-1.23)	1.19 (1.07-1.31)
2	1.21 (1.07-1.36)	1.17 (0.99-1.37)
3	1.36 (1.17-1.57)	1.32 (1.09-1.60)
Had previous GI diagnosis (12 months prior)	1.41 (1.31-1.53)	
Had early GI diagnosis (0-6 months after)	1.45 (1.35-1.55)	
Had previous bladder diagnosis (12 months prior)		1.51 (1.36-1.67)
Had early bladder diagnosis (0-6 months after)		1.75 (1.59-1.93)

Models also adjusted for education, marital status, SEER region, unknown stage and grade and year of diagnosis.

GI= Gastrointestinal; HR = Hazard Ratios; AJCC = American Joint Committee on Cancer; SEER = Surveillance, Epidemiology and End Results (SEER) Program; The SEER-Medicare database has Medicare claims starting in 1991. For this reason staging for cancer is based on the 1988 staging system