Published in final edited form as:

J Geriatr Oncol. 2012 October 1; 3(4): 344–350. doi:10.1016/j.jgo.2012.06.005.

The effect of postoperative beam, implant, and combination radiation therapy on GI and bladder toxicities in female Medicare beneficiaries with stage I uterine cancer

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Abstract

Objective—Determine the risk of late gastrointestinal (GI) and bladder toxicities in women treated for Stage I uterine cancer with postoperative beam, implant, or combination radiation.

Methods—The Surveillance, Epidemiology, and End Results (SEER) tumor registry and Medicare claims were used to estimate the risk of developing late GI and bladder toxicities by type of radiation received. Bladder and GI diagnoses were identified 6–60 months after cancer diagnosis. Cox-proportional hazard models were used to estimate risk of any late GI or bladder toxicity due to type of radiation received.

Results—A total of 3,024 women with uterine cancer diagnosed from 1992–2005 were identified for analysis with a mean age of 73.9 (Standard Deviation (SD) $\pm$ 6.5). Bladder and GI toxicities occurred most frequently in the combination group, and least in the implant group. After controlling for demographic characteristics, tumor grade, diagnosis year, SEER region, comorbidities, prior GI and bladder diagnosis, and chemotherapy, women receiving implant radiation had a 21% absolute decrease in GI toxicities compared to women receiving combination radiation (Hazard Ratio (HR) 0.79, 95% confidence interval (CI) 0.68–0.92). No differences were observed between those receiving beam and combination in GI (HR 1.01 (0.89–1.14)) and bladder (HR 0.95 (0.80–1.11)) toxicities.

Conclusions—Older women receiving combined radiation had the highest rates of GI and bladder toxicities, while women receiving implant radiation alone had the lowest rates. When

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Conflict of Interest Statement

The authors disclose no actual or potential conflicts of interests including any financial, personal, commercial, or other relationships with other people or organizations that could inappropriately influence, or be perceived to influence, their work.

Authors Contributions

All authors significantly contributed to the manuscript. Specific contributions are as follows: Concept and design (Drs. Freeman, Hatch, Berenson, Asem and Samper-Ternent, Zhang and Kuo), Data collection (Drs. Zhang and Kuo), Analysis and interpretation of data (Dr. Asem, Freeman, Berenson, Dong, and Samper-Ternent), Manuscript writing (Dr. Samper-Ternent, Asem and Berenson) and approval (Drs. Samper-Ternent, Asem, Zhang, Kuo, Hatch, Freeman and Berenson).

selecting type of radiation for a patient, these toxicities should be considered. Counseling older women surviving cancer on late toxicities due to radiation must be a priority for physicians caring for them.

Keywords

uterine cancer; radiation therapy; late toxicities; SEER-Medicare database; older women

Introduction

Five year survival rates for women diagnosed with the International Federation of Gynecology and Obstetrics (FIGO) stage I uterine cancer are greater than 85%,⁽¹⁾ however, the optimal treatment is still controversial. In particular, the role of postoperative adjuvant treatments, such as radiation therapy, is not well defined.⁽²⁾ Trials have shown that in select patients with FIGO stage I disease with risk factors for distant spread, postoperative radiation therapy decreases local recurrences, but does not change survival.^(3;4) In contrast, a population based study reported that women receiving radiation have a survival advantage compared to those who do not.⁽⁵⁾ However, a similar population based study reported that there is no survival advantage for women receiving a combination of external beam radiation with brachytherapy compared to those receiving external beam radiation alone.⁽⁶⁾ Unfortunately most of these studies fail to include a significant number of older women, limiting the conclusions we can derive from these studies for this population group.⁽⁷⁾

Since the benefit of radiation therapy is controversial, evaluating the long term toxicities from radiation is important in deciding when and how it should be given. Careful consideration of factors that might worsen the prognosis after treatment, such as comorbid medical conditions and co-adjuvant chemotherapy, are usually not included in studies evaluating late toxicities. Additionally, counseling of patients undergoing cancer treatment is limited to data from studies focusing mostly on cancer related issues rather than quality of life issues. The gastrointestinal (GI) and genitourinary tracts are the most common sites of radiation toxicities.⁽⁸⁾ These toxicities can occur immediately, or years after treatment, and the related symptoms can significantly lower a patient's quality of life.^(9;10) These toxicities include diarrhea, frequent voiding, rectovaginal fistulas, radiation proctitis, and fecal leakage.^(11;12) Data available to counsel older patients on these and other effects of cancer treatment is limited. However, older patients experience more acute toxicities from radiation, putting them at higher risk for having late toxicities.⁽¹³⁾

Previous studies evaluating radiation toxicities are from retrospective chart reviews, clinical trials, and responses to questionnaires that usually include a limited number of older patients. Alternatively, population based studies provide a powerful way to evaluate long term toxicities in women treated with radiation therapy for uterine cancer. Population based studies offer the advantage of reducing selection bias because they include women treated across a broad range of settings, rather than only those treated in centers conducting clinical trials. Data from such studies is therefore more useful for counseling purposes. A previous population based study from our group reported that women receiving radiation therapy have higher rates of late GI and bladder toxicities than previously reported.⁽¹⁴⁾ The purpose of this study is to build on the previous study and use the Surveillance, Epidemiology, and End Results (SEER) database, along with Medicare claims, to compare the rates of GI and bladder toxicities among older women treated for AJCC1 stage I uterine cancer with three different types of postoperative radiation: 1) External beam delivers high energy x-rays or

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

photons to the anatomical treatment site typically using a machine called a linear accelerator, hereafter labeled “beam”; 2) Brachytherapy, is a treatment form of radiation using a source that is placed into or in close proximity to the area to be targeted, hereafter labeled “implant”; 3) Combination defined as radiation delivered using both beam and implant.(15) We defined the types of radiation based on SEER and Medicare codes as shown in Table 1. Medicare includes vulnerable populations of younger women (<65 years) with end stage renal disease and disabilities, as well as those 65 and older. Our study examines toxicities for all female beneficiaries to avoid selection bias.

Methods

The source of our data was the SEER tumor registry linked to Medicare claims. The SEER program of the National Cancer Institute routinely collects information regarding “patient demographics, primary tumor site, tumor morphology, and stage” along with vital statistics. (15) It collects information across broad geographic areas, covering approximately 28% of the population, and is considered to be representative of the US population as a whole.(15) The SEER-Medicare linked database connects the SEER subjects with their Medicare claims. We used linked data from 1992 to 2005 for women diagnosed with uterine cancer between 1973 and 2005. The data are de-identified prior to becoming public.

A total of 40,771 women who were diagnosed with AJCC stage I uterine cancer from 1992 to 2005 were identified in the SEER-Medicare database. First, women with cancer reported only on their autopsy or death certificate (11 cases), and women with multiple cancer sites (8,931 cases) were excluded. Next, to ensure that all medical claims were complete, women without both Medicare Part A and Part B, and women with an HMO with Medicare Part A between 1992 and 2005, were excluded (16,713 cases). In addition, women who either did not receive radiation therapy (11,184 cases) or who received an unclassified type of radiation (908 cases) were excluded. The final sample size was 3,024 women. Of these, 116 were under age 65, accounting for 3.8% of the total sample studied.

Data on patient characteristics, including age, race/ethnicity, marital status, education, SEER geographic region, residence, along with Medicaid eligibility and poverty as proxies for socioeconomic status, were analyzed on all eligible subjects. In addition, cancer characteristics including year of diagnosis, tumor grade, treatment with chemotherapy, and death status were extracted. Finally, patient comorbidities were quantified using the Charlson comorbidity index with Klabunde modification.(16;17)

Patients were defined as having radiation if they had a SEER code for postoperative radiation. To define radiation type, women were classified as having received implant (SEER code 2: radioactive implants, code 3: radioactive isotopes), beam (SEER code 1: beam radiation), or combination radiation therapy (codes 1 and 2) based on the SEER definition.

Bladder and GI diagnoses were identified from 6 to 60 months after the diagnosis of cancer using International Statistical Classification of Diseases and Related Health Problems-9 (ICD-9) and Current Procedural Terminology (CPT) codes. These included relevant GI and bladder diagnosis identified from inpatient, outpatient, or physician claims. Severe GI and bladder diagnosis were defined as those requiring hospitalization, need for an inpatient procedure, or need for surgical intervention. The details of how these outcomes were identified are described elsewhere.(14)

Comparisons of demographic characteristics and outcomes were made between patients receiving implant, beam, or combination radiation therapy. Chi-square tests were used to compare patients by cancer characteristics across all three radiation categories. The

percentage of patients diagnosed with GI or bladder toxicities, including severe toxicities, were calculated and compared using chi-square tests. Cox proportional hazard models were used to estimate the risk of any late GI or bladder toxicity due to the type of radiation received, and were adjusted for covariates. To determine if chemotherapy and the presence of one or more comorbidities modified the risk of GI and bladder toxicity, an interaction was performed between radiation type and chemotherapy as well as an interaction between radiation type and having a comorbidity. To present differences by radiation category, toxicity rates were defined as the failure rate estimated by the Kaplan Meier method and plotted against months from diagnosis. All statistical analyses were performed using SAS version 9.2 (SAS Institute, INC. Cary, NC). Approval was obtained from the University of Texas Medical Branch Institutional Review Board to conduct secondary data analysis using this dataset.

Results

Of a total of 3,024 women who were included for analysis, 22.9% received implant radiation, 54.2% received beam radiation, and 22.8% received combination radiation (Table 1). The mean age of the sample was 73.9 (SD $\pm$ 6.5). The majority of women who received radiation were diagnosed with grade 2–3 histologies, did not receive chemotherapy, and did not have any comorbidities.

Late GI and bladder toxicities occurred most frequently in the combination group, and the least frequently in the implant group (Table 2). There were significant differences in the number of GI, bladder, and severe GI toxicities by radiation type ($p < 0.05$). Severe bladder toxicities occurred in less than 1% of patients, and were not significantly different across all radiation types ($p = 0.57$). No significant differences were observed in the percentage of women with any GI and any bladder toxicities ($p < 0.07$).

The rates of GI and bladder toxicities over time calculated using the Kaplan Meier method are shown in Figures 1 and 2. Separate lines are used for each radiation type. Patients were censored at loss of coverage, at death prior to 60 months, at the end of the study period (12/31/2006) or at 60 months of complete follow-up. Patients receiving combination radiation therapy had higher rates of GI and bladder toxicities over time, while women who received implant radiation had the lowest frequency of GI and bladder toxicities over time.

Women receiving implant radiation and beam radiation were less likely to experience GI toxicities compared to women receiving a combination of both (Table 3). After controlling for year of diagnosis, age, grade, race, Medicaid eligibility, poverty, education, SEER region, comorbidities, prior GI and bladder diagnosis, and chemotherapy, women receiving implant radiation had an absolute decrease in GI toxicities of 21% compared to women receiving combination (Hazard Ratio 0.79, 95% Confidence Interval: 0.68–0.92). There were no significant differences in GI toxicities when comparing women receiving beam to those receiving combination. There were also no significant differences in bladder toxicities between the three groups when adjusting for covariables.

Even though the largest difference in GI toxicities was observed between combination and implant radiation, additional analysis were conducted to better understand the difference in risk between beam and implant radiation. After controlling for all covariates, beam radiation was still related to lower toxicity risk compared to combination but a statistically significant higher risk of toxicity compared to implant radiation (HR 1.27, 95% CI 1.12–1.46).

In multivariable analysis, the risk of late GI and bladder toxicities was higher for women receiving chemotherapy in addition to radiation (HR 1.36, 95% CI 1.22–1.51 and HR 1.60, 95% CI 1.38–1.84; respectively). However, the effect of chemotherapy and comorbidities on

the risk of GI and bladder toxicities across radiation types was not significantly different. For both GI and bladder toxicities, the interaction of chemotherapy and implant radiation, as well as the interaction of chemotherapy and beam radiation were not significant. Furthermore, for both GI and bladder toxicities, the interaction between the presence of one or more comorbidities and implant radiation, as well as the interaction between the presence of one or more comorbidities and beam radiation were not significant.

Discussion

In summary, women with AJCC stage I uterine cancer in this database who received postoperative combination radiation therapy had significantly higher rates of GI and bladder toxicities, while women receiving implant radiation had the lowest. However, the rates of severe GI toxicity we observed are higher than previously reported.(4;18;19) In this study, 6.9% of patients who received implant radiation experienced severe GI toxicity. In contrast, a previous trial reported that less than 1% of patients receiving vaginal brachytherapy experienced grade 3 or 4 GI toxicity.(4) Similarly, 10.5% of women who received beam radiation in this study experienced severe GI toxicity compared to previous studies which reported rates of grade 3 or 4 toxicities between 2% and 4.7%.(4;19) Finally, we observed that 9.3% of women in the combination group experienced severe GI toxicities compared to 2.8% which has been previously reported.(18)

These differences between rates in our study compared to prior studies could be a result of differences in defining toxicities. Previous studies used either the French-Italian glossary or the European Organization for Research and Treatment of Cancer - Radiation Therapy Oncology Group (EORTC-RTOG) scale, both of which offer standardized definitions of toxicities.(20) Conversely, our study, used ICD-9 and CPT codes. As a result, certain procedures which we classified as related to a toxicity may have been performed for other reasons, especially taking into account the mean age of women included. For example, a colonoscopy may have been performed as part of a diagnostic or screening evaluation. Despite the differences in methodologies, our sample is a more accurate reflection of what older survivors living in the United States experience compared to women studied in clinical trials and therefore provides better information for counseling purposes.

The incidence of late GI and bladder toxicities before initiation of radiation treatment is an issue that could partially explain the higher rates we reported. If women have symptoms that can be mistaken with late toxicities before the treatments start then higher rates would be reported. However, we explored this possibility and concluded this was not an issue in our analyses. Any GI toxicity occurring within 6 months of first radiation occurred in 22.3% of women included in our analyses, no statistically significant difference was observed by radiation type for this rate ($p=0.85$). For any bladder toxicity, the rate was 14.8% and differences by radiation type were also not statistically significant ($p=0.62$).

This study also elucidates the toxicity profile associated with different types of radiation among older female survivors of stage I uterine cancer. This is in agreement with previous studies which showed that women given postoperative external beam radiation have more bowel symptoms than those who receive vaginal brachytherapy.(9) Further, other side effects and toxicities, such as developing additional malignancies, are higher in patients treated with external beam or combination radiation compared to vaginal brachytherapy.(21) Thus, these findings further support the conclusions of other investigators that if survival is not affected, and if radiation therapy is going to be given, vaginal implant radiation alone should be considered to minimize the negative impact on the survivor's quality of life.(3;4) Furthermore, women need counseling on the potential late toxicities derived from radiation treatment given that they are more prevalent than previously reported.

There are some limitations to this study. First, specific details of treatment including the dose of radiation, the exact type of radiation (such as conventional 2D external beam or 3D conformal external beam), or the presence of lymphadenectomy during surgery are not known. These are variables which impact the rates of radiation toxicity.(22;23) Second, there is a possibility that the rates of toxicities may have been underestimated in instances when subjects had symptoms that were not listed as a diagnosis in the claims. Alternatively, the rates of toxicities may be overestimated as some diagnostic procedures may have been used to evaluate a potential toxicity, even if one is not found. Third, guidelines for radiation treatment of uterine cancer changed in the time period analyzed (1992–2005). However, analysis of the year of diagnosis, which serves as a proxy for year of treatment, showed no significant effect or toxicity rates by year. Fourth, we excluded 908 women from the analysis because the type of radiation received was not documented. However, toxicity rates for this group were similar to those reported on Table 2 (52.8% for GI toxicities and 30.9% for bladder toxicities).

Despite these limitations, we are able to conclude that women treated with combination radiation therapy are at higher risk for GI and bladder toxicities compared to women treated with implant radiation alone. We also conclude that the rates of toxicities in all groups are higher than previously reported. These toxicities are known to have a negative impact on the quality of life of survivors.(9–11) In our study almost 30% of women receiving radiation had 1 or more comorbid medical conditions as show by the Charlson Index. Clinical trials usually exclude participants with several medical conditions. Our findings are a better reflection of what older women that survive uterine cancer face and help inform clinicians of how survivorship plans must be designed. Because survival for women with stage I uterine cancer is high,(1) goals of treatment should include minimizing long term toxicities. Therefore, clinicians taking care of women with uterine cancer should weigh the risks of the toxicities with the benefits of decreased local recurrences. Clinicians can ultimately use this information to help counsel patients with uterine cancer being treated with postoperative radiation to help create better and more accurate survivorship plans.

Acknowledgments

This study was supported by a grant (5R01CA133069-03) from the National Cancer Institute (PI J. Freeman). Infrastructure support was provided by the Sealy Center on Aging at the University of Texas Medical Branch. Dr. Samper-Ternent is also supported in part by the Health Resources and Services Administration, the National Center for Advancing Translational Sciences (NCATS), and the National Institute on Disability and Rehabilitation Research (grants UB4HP19213-01, UL1TR000071, H133P110012) Dr. Mohammed was a postdoctoral fellow supported by a National Research Service Award in women's reproductive health (T32HD0551563, PI is Dr. Berenson) funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Dr. Berenson is supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development through a Midcareer Investigator Award in Patient-Oriented Research Award (K24HD043659, PI Berenson). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Eunice Kennedy Shriver National Institute of Child Health and Human Development nor the National Institutes of Health. Some findings of this study were presented at the 2011 Society of Gynecologic Investigation Annual Meeting.

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.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

The collection of the California cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract N01-PC-35136 awarded to the Northern California Cancer Center, contract N01-PC-35139 awarded to the University of Southern California, and contract N02-PC-15105 awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement #U55/CCR921930-02 awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the

author(s) and endorsement by the State of California, Department of Public Health the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred. The authors acknowledge the efforts of the Applied Research Program, NCI; the Office of Research, Development and Information, 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.

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Figure 1. GI toxicity rate over time estimated by Kaplan Meier method

Patients were censored at loss of coverage, death prior to 60 months, end of follow-up period (12/31/2006) or 60 months of complete follow up. Toxicity rates were defined as the failure rate estimated by Kaplan Meier method and plotted against months from diagnosis.

Figure 2. Bladder toxicity rate over time estimated by Kaplan Meier method

Patients were censored at loss of coverage, death prior to 60 months, end of follow-up period (12/31/2006) or 60 months of complete follow up. Toxicity rates were defined as the failure rate estimated by Kaplan Meier method and plotted against months from diagnosis.

Table 1

SEER and Medicare codes used to define the three radiation groups

	Beam	Implant	Combination
SEER codes	20–32, 40–43	50–55, 60–62	80, 85 and any combination of Beam + Implant
HCPCS Codes	77402–77416, 77418, G0243, G0173, G0251, G0339, G0340	77761–77784, 77799	Combination of Beam + Implant

Codes found in the outpatient claim and carrier claim were used. Code included in outpatient claim was used as primary source and carrier claim was used as secondary source of information.

Table 2

Characteristics of women with stage I uterine cancer receiving each type of radiation

	Type of radiation			
	Total 3,024	Implant 694	Beam 1,640	combination 690
Age group (years)				
< 65	116	4.6%	3.2%	4.5%
65–69	745	27.7%	22.7%	26.1%
70–74	889	24.9%	29.2%	34.3%
75–79	756	24.2%	27.1%	20.7%
80+	518	18.6%	17.7%	14.3%
Grade				
Grade 1	593	22.0%	19.7%	17.0%
Grade 2	1,133	39.0%	37.8%	35.1%
Grade 3	821	22.0%	27.9%	30.6%
Grade 4	169	3.9%	6.5%	5.2%
Unknown	308	13.0%	8.2%	12.2%
Race/ethnicity				
White	2,679	92.1%	87.6%	87.5%
Black	163	3.7%	5.6%	6.5%
Hispanic	104	2.2%	3.8%	3.9%
Other	78	2.0%	3.0%	2.0%
Received chemotherapy				
No	2,258	75.4%	75.5%	71.9%
Yes	766	24.6%	24.5%	28.1%
Charlson Comorbidity index				
HZ=0	2,163	70.2%	71.6%	72.6%
HZ=1	597	20.9%	18.9%	20.6%
HZ=2	167	5.3%	6.2%	4.2%
HZ 3	97	3.6%	3.3%	2.6%

Table 3

Frequency of GI or bladder toxicities by radiation type

Toxicity 6–60 months	Type of Radiation			P value
	Implant n=694	Beam n=1,640	Combination n=690	
GI (%)	50.4	56.9	59.9	0.001
Bladder (%)	28.4	29.8	34.1	0.05
Any GI and any Bladder	19.9	21.3	24.8	0.07
Severe * GI (%)	6.9	10.5	9.3	0.03
Severe * BL (%)	<1	<1	<1	0.57

* Severe is defined as requiring hospitalization, need for inpatient procedure, or surgical intervention. GI = Gastrointestinal Toxicities. BL = Bladder Toxicities

Table 4

Risk of developing any GI or bladder toxicity by radiation type

Type of radiation	Any GI unadjusted	Any GI adjusted*	Any bladder unadjusted	Any bladder adjusted*
	HR (95% CI)**	HR (95% CI)	HR (95% CI)	HR (95% CI)
Combination	1	1	1	1
Implant	0.75 (0.65–0.86)	0.79 (0.68–0.92)	0.79 (0.65–0.95)	0.91 (0.75–1.11)
Beam	0.94 (0.84–1.06)	1.01 (0.89–1.14)	0.87 (0.74–1.02)	0.95 (0.80–1.11)

* Adjusted for year of diagnosis, age, stage, grade, race, marital status, Medicaid eligibility, educational level, treatment with surgery, chemotherapy, Charlson comorbidity index, SEER region, having a GI or bladder diagnosis prior to cancer diagnosis, and having an early GI or bladder diagnosis.

** HR = Hazard Ratio (95 % Confidence Interval)