Uptake and Outcomes of Intensity-Modulated Radiation Therapy for Uterine Cancer

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Abstract

Objective—While intensity-modulated radiation therapy (IMRT) allows more precise radiation planning, the technology is substantially more costly than conformal radiation and, to date, the benefits of IMRT for uterine cancer are not well defined. We examined the use of IMRT and its effect on late toxicity for uterine cancer.

Methods—Women with uterine cancer treated from 2001-2007 and registered in the SEER-Medicare database were examined. We investigated the extent and predictors of IMRT administration. The incidence of acute and late-radiation toxicities were compared for IMRT and conformal radiation.

Results—We identified a total of 3555 patients including 328 (9.2%) who received IMRT. Use of IMRT increased from 1.5% in 2001 to 23.2% in 2007. In a multivariable model, residence in the western U.S. and receipt of chemotherapy were associated with receipt of IMRT. Women who received IMRT had a higher rate of bowel obstruction (rate ratio=1.41; 95% CI, 1.03-1.93), but other late gastrointestinal and genitourinary toxicities as well as hip fracture rates were similar between the cohorts. After accounting for other characteristics, the cost of IMRT was $14,706 (95% CI, $12,073 to $17,339) greater than conformal radiation.

Conclusion—Use of IMRT for uterine cancer is increasing rapidly. IMRT was not associated with a reduction in radiation toxicity, but was more costly.

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Introduction

Despite a number of randomized clinical trials, the role of whole pelvic radiation for uterine cancer remains controversial.[1-3] For women with uterine-confined disease several studies have suggested that adjuvant external beam therapy reduces locoregional recurrences but does not improve overall survival.[1-3] For patients with tumor spread beyond the uterus, the role of radiation is evolving. While chemotherapy is now commonly used for advanced stage disease, pelvic radiotherapy is still often given in combination with cytotoxic therapy. [4, 5]

Traditionally, pelvic radiotherapy is delivered with a four-field box technique. While two-dimensional treatment plans were typically developed using fluoroscopy, three-dimensional conformal radiotherapy with computed tomography guided planning is now widely available.[6] Although conformal therapy provides excellent local tumor control, the normal anatomic structures of the pelvis are also at substantial risk for radiation toxicity. Both acute and late radiation toxicity of the small bowel, rectum, bladder and bone marrow are relatively common.[7]

To more precisely tailor radiation delivery, intensity-modulated radiation therapy (IMRT) has been developed. IMRT allows modulation of the radiation beam over its course to more precisely deliver radiotherapy to target tissues and spare nearby normal structures.[6, 8-11] The outcomes of IMRT compared to conformal therapy have been reported for a number of other tumor sites, but data describing pelvic IMRT for uterine cancer are limited.[8, 9, 12-18] Early studies have shown that IMRT reduces the radiation dose delivered to normal pelvic structures and suggest that IMRT is associated with lower rates of acute toxicity.[8, 9, 11-13, 19-23] Long-term toxicity data and the impact of IMRT on survival are largely lacking. Given the paucity of data describing pelvic IMRT for uterine cancer, we performed a population-based analysis to determine the uptake of IMRT, examine the effect of IMRT on late toxicity, and analyze the cost associated with IMRT compared to conformal pelvic radiotherapy for women with uterine cancer.

Methods

Data Source

We utilized the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. [24] SEER is a population-based cancer registry maintained by the National Cancer Institute that provides data on tumor characteristics, treatment, and survival, as well as demographic and selected census tract-level information. The Medicare database includes information on patients with Medicare part A (inpatient) and part B (outpatient) including diagnoses and billed claims. These two files are linked and provide data on initial services and follow-up. Exemption from the Columbia University Institutional Review Board was obtained. The SEER-Medicare database has been validated and utilized in a number of outcomes studies. [24-26]

Patient Selection

Women 65 years of age with primary tumors of the uterus diagnosed between January 1, 2001 and December 31, 2007 were analyzed. Only patients who received radiotherapy as defined below with a first claim within 18 months of diagnosis were included in the cohort. Each patient was classified as having received IMRT or conformal radiation using ICD-9 and CPT codes as previously described (Supplementary Table).[14, 15] We excluded patients with any radiation claims >6 months before the recorded diagnosis of uterine cancer as well as women with any claims for potential late radiation toxicities prior to initiation of radiation. We excluded patients who were enrolled in a non-Medicare health maintenance

organization because the billing claims for these patients are not submitted to Medicare for reimbursement.[27] Patients diagnosed at autopsy or by death certificate were also excluded and only patients who survived for more than 6 months after diagnosis were included in the analysis.

Patient Characteristics

Age at diagnosis was categorized into 5-year intervals. We recoded the SEER marital status variable as married, not married, and unknown. Socioeconomic status (SES) was generated from an aggregate score derived from education, poverty level, and income from the 2000 census tract data, as described previously.[28] Patients' scores were ranked on a scale of 1-5 with 1 being the lowest value. To estimate the prevalence of comorbid disease in our cohort, we used the Klabunde adaptation of the Charlson comorbidity index.[29, 30] Area of residence was categorized as metropolitan or nonmetropolitan. Tumor grade was grouped as well, moderately, or poorly differentiated or unknown.[31] The SEER registries in which patients were treated were categorized as: eastern (Connecticut, New Jersey), Midwestern (Detroit, Iowa, Utah, Atlanta, rural Georgia, Kentucky, Louisiana), and western (San Francisco, Hawaii, New Mexico, San Jose, Seattle, Los Angeles, greater California). Tumor histology was grouped as: endometrioid, serous, clear cell, carcinosarcoma, leiomyosarcoma, and other/unknown.[32] Performance of hysterectomy and lymphadenectomy, defined as removal of any lymph nodes, were recorded for each patient. Likewise, use of chemotherapy (any cytotoxic agent) and vaginal brachytherapy within 18 months of diagnosis was noted for each subject. Stage was recorded based on extent of disease and reported according to the 1988 FIGO classification system.

Outcomes

We examined late radiation toxicities reported with pelvic radiotherapy. Late radiation toxicity included radiation enteritis, bowel obstruction, other gastrointestinal complications (colonic stricture, vascular insufficiency of the bowel, rectovaginal fistula), genitourinary complications (radiation cystitis, genitourinary stricture, vesico-vaginal fistula), and hip fracture (Supplemental Table).

The cost of radiation was determined using Medicare reimbursement data for all claims associated with a code for conformal radiation or IMRT. Cost data was adjusted for inflation using the Prospective Pricing Index for part A claims and the Medicare Economic Index for part B claims and reported in 2010 dollars using previously described methodology.[33, 34] To adjust for geographic variation, we used the geographic adjustment factor for part A claims and the geographic practice cost index for part B claims.[33, 34] The total costs for all inpatient and outpatient claims associated with a billing code for radiation or IMRT were summed to report an aggregate, per patient radiation cost. Radiation cost data is reported as median costs with interquartile ranges.

Statistical Analysis

Clinical and demographic characteristics for women receiving conformal radiation therapy and IMRT were compared using χ^2 tests. Multivariabe logistic regression models were developed to examine predictors of IMRT use while controlling for other clinical variables. Results are reported as odds ratios with 95% confidence intervals (CI). [35] Given that cost data is not normally distributed, multivariable adjustment of costs based on the type of radiation administered were analyzed using quantile (median) regression methods.[36] This method directly estimates the adjusted median costs and 95% confidence intervals were derived based on bootstrap resampling methods. To estimate toxicities, we calculated the rate of each radiation-associated toxicity per 100 person-years of follow-up as previously described.[14] Follow-up was calculated as the time from the first radiation claim to the date

of last contact or death. Toxicity was compared between the conformal radiation therapy and IMRT groups using rate ratios with 95% confidence intervals.[14] The cumulative incidence of late radiation toxicity was further examined using Kaplan-Meier analyses. Separate analyses were reported for late gastrointestinal toxicity (gastrointestinal fistula or stricture), late genitourinary toxicity (genitourinary fistula, stricture, or radiation cystitis) and hip fracture. For each analysis the results were compared using the log-rank test. All analyses were conducted with SAS, version 9.13 (SAS Institute, Cary, NC). All statistical tests were two-sided.

Results

A total of 3555 patients with uterine cancer who received pelvic radiotherapy were identified. Overall, 3227 (90.8%) women received conformal radiation while 328 (9.2%) received IMRT (Table 1). Use of IMRT increased over time from 3.3% in 2002 to 23.2% by 2007 (Figure 1). IMRT was used for 9.0% of white women compared to 11.1% of black women (P=0.46) and in 9.4% of residents of metropolitan areas vs. 7.8% of those residing in non-metropolitan areas (P=0.35). Patients in the western U.S. were more likely to receive IMRT than women in the eastern and Midwestern regions (P<0.0001). Women who received chemotherapy (P<0.0001) and those who did not receive brachytherapy (P=0.006) were more likely to receive IMRT.

In a multivariable model, year of diagnosis remained the strongest predictor of IMRT use; compared to women treated in 2001 the odds ratio for receiving IMRT in 2007 was 15.26 (95% CI, 7.26-32.08) (Table 2). Compared to women in the eastern U.S., those in the Midwest (OR=1.74; 95% CI, 1.25-2.41) and those in the western U.S. (OR=2.23; 95% CI, 1.63-3.04) were more likely to receive IMRT. Patients who received chemotherapy were 74% more likely to have IMRT than those who did not receive chemotherapy.

Table 3 displays late radiation-related toxicities and toxicity rates per 100 person-years of follow-up. Compared to women who received conformal RT, those who received IMRT had a higher rate of bowel obstruction (rate ratio=1.41; 95% CI, 1.03-1.93). The rates of other late gastrointestinal toxicities were similar between the cohorts (Table 3). Likewise, there was no statistically significant difference in late genitourinary toxicity (RR=1.24; 95% CI, 0.85-1.81). The 100 person-year rate of hip fractures was 32.4 in women who received IMRT compared to 23.4 in those who received conformal therapy (rate ratio=1.38; 95% CI, 0.96-1.99).

A series of Kaplan-Meier analyses were performed to explore differences in the time to development of late radiation toxicity. There were no differences in the rates of gastrointestinal toxicity (P=0.66), genitourinary toxicity (P=0.46) or hip fracture (P=0.46) (Figure 2). The median cost of a course of conformal radiotherapy was $14,644 (IQR, $6226, $23,587) compared to $26,149 (IQR, $20,078, $38,642) for IMRT (P<0.0001). In a quantile regression model accounting for other patient, tumor, and treatment characteristics, the cost of IMRT remained $14,706 (95% CI, $12,073 to $17,339) greater than conformal radiation.

Discussion

Data describing the effectiveness of pelvic IMRT for uterine cancer is limited and predominately consists of small studies comparing IMRT to historical controls. Compared to conformal pelvic radiotherapy, IMRT appears to spare normal tissues and has been associated with lower rates of acute toxicity.[6, 8, 9, 11-13, 19, 23] One series noted gastrointestinal toxicity in 11% of women who received IMRT compared to 50% in those

who had whole pelvic radiation while a second study noted a reduction from 20% to 10% in grade 2 or greater genitourinary toxicity with IMRT.[9, 13] A recently reported phase II feasibility trial by the Radiation Therapy Oncology Group (RTOG) reported a non-significant 12% reduction in grade 2 bowel adverse events compared to historic controls and concluded that a phase III trial was warranted.[8]

Our findings are somewhat surprising in that we found little difference in the rates of late toxicity between the IMRT cohort compared to those who received conformal radiotherapy. One hypothesis for these findings is that the radiation dose delivered to surrounding tissues for those who received IMRT was greater than planned and expected. The difficulty in treatment planning for IMRT was demonstrated by the RTOG's feasibility trial in which 68% of the treatment plans delivered a higher than specified dose to the bladder, 76% of subjects received a higher than planned rectal dose and the femoral head constraints were exceeded in 33% of women.[8] Given that these results are from highly experienced centers it appears likely that field planning for IMRT, and probably outcome, are highly variable. Our data suggests that the potential benefits of IMRT for patients with uterine cancer have not yet been realized.

A number of studies have examined the uptake and utilization of IMRT for other tumor sites.[10, 14, 15, 37] From 2001 to 2005 use of IMRT for breast cancer increased from <1% to 11% and from 4% to 46% for patients with head and neck tumors.[15, 37] Perhaps most dramatically, use of IMRT for men with localized prostate cancer increased from 0.2% in 2000 to 96% by 2008.[14] Although prospective data for the effectiveness of IMRT for both breast and head and neck cancer have been reported, the data for prostate cancer is mainly derived from observational series.[16-18] Similar to our findings, many of these studies also identified significant regional variation in use of IMRT and hypothesized that these differences were due to differential Medicare reimbursement policies across regions.[10, 15, 37]

We were unable to demonstrate a decrease in late radiation toxicity with IMRT compared to conformal radiotherapy. Long-term analysis of women with stage I endometrial cancer who received whole pelvic radiation in the PORTEC trial noted 5-year actuarial toxicity rates of 20% for gastrointestinal side effects and 8% for genitourinary complications. Severe (grade 3 and 4) late toxicity was less common, and occurred in only 3% of patients. Notably, all of the severe late toxicities in the PORTEC study were gastrointestinal.[7] A number of treatment factors including field volume, daily fractionation, and use of brachytherapy as well as patient and tumor characteristics influence the incidence of radiation-related toxicity.[7] Given that adjuvant pelvic radiation for endometrial cancer is delivered to a large tissue volume and uses a relatively low dose of radiation (45-55 Gy), the potential toxicity benefits of IMRT for uterine cancer may be less significant than when pelvic radiotherapy is given for cervical cancer in which the total dose of radiation delivered (>80 Gy) is often much higher.

A major concern surrounding the use of IMRT is cost. For breast cancer, IMRT is more than twice as expensive as conformal therapy ($15,230 vs. $7179).[15] Our findings for uterine cancer were similar; compared to conformal therapy, the median cost for IMRT was nearly $12,000 greater. Given the substantial cost of IMRT, reimbursement appears to play an important role in allocation of the technology. Smith an colleagues noted that among Medicare beneficiaries with breast cancer, those women residing in regions with the most favorable reimbursement coverage were much more likely to receive IMRT than those patients who resided in regions with less favorable remuneration. Likewise, patients treated at freestanding radiation centers were more likely to receive IMRT than those managed at

hospital-associated centers.[15] We also identified substantial regional variation in use of IMRT that may have been influenced by reimbursement policies.

We recognize a number of important limitations in our analysis. Perhaps most importantly, we lack details on the actual delivery of radiation including the total dose delivered, fractionation schedule, and total treatment time. All of these parameters are known to influence toxicity and certainly warrant further study. Our study encompasses the years in which pelvic IMRT disseminated into practice. As with any new procedure, results might be expected to improve as physicians gain experience with the technique. The phase II RTOG trial demonstrates the difficulties with treatment planning for IMRT.[8] We recognize that not all toxicities may have been captured. To limit this bias we analyzed only major toxicities that were likely to generate a claim. Any underreporting of toxicities should have been balanced between the two groups. Finally, we are unable to record individual patient and physician preferences as well as subtle unmeasured patient and tumor characteristics that likely influenced both the allocation of treatment as well as outcomes.

In conclusion, our findings suggest that the use of IMRT has increased over time for women with uterine cancer undergoing pelvic radiotherapy. Despite the theoretic benefits of IMRT, we were unable to demonstrate a reduction in the rate of late radiation-related toxicities. Given the increased cost of IMRT, further randomized trials to examine the effectiveness and quality of treatment planning for women with uterine cancer undergoing pelvic radiotherapy are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Research Highlights

- Use of IMRT for uterine cancer is increasing rapidly.

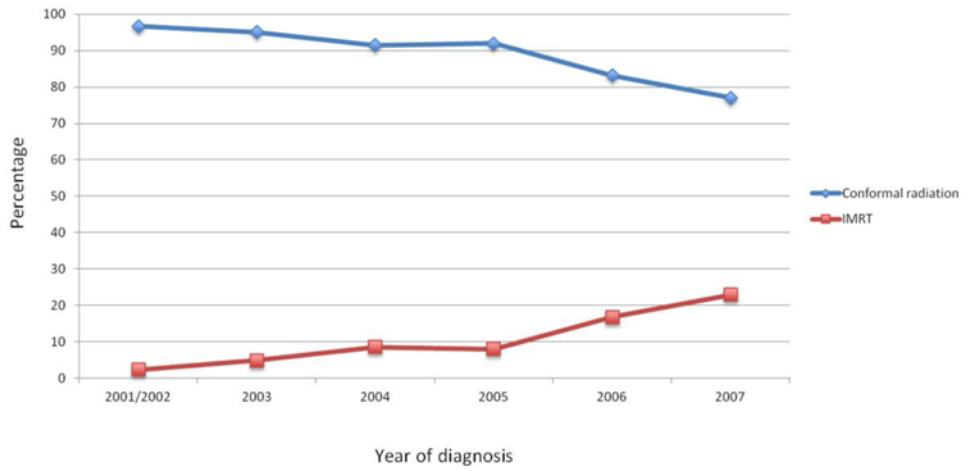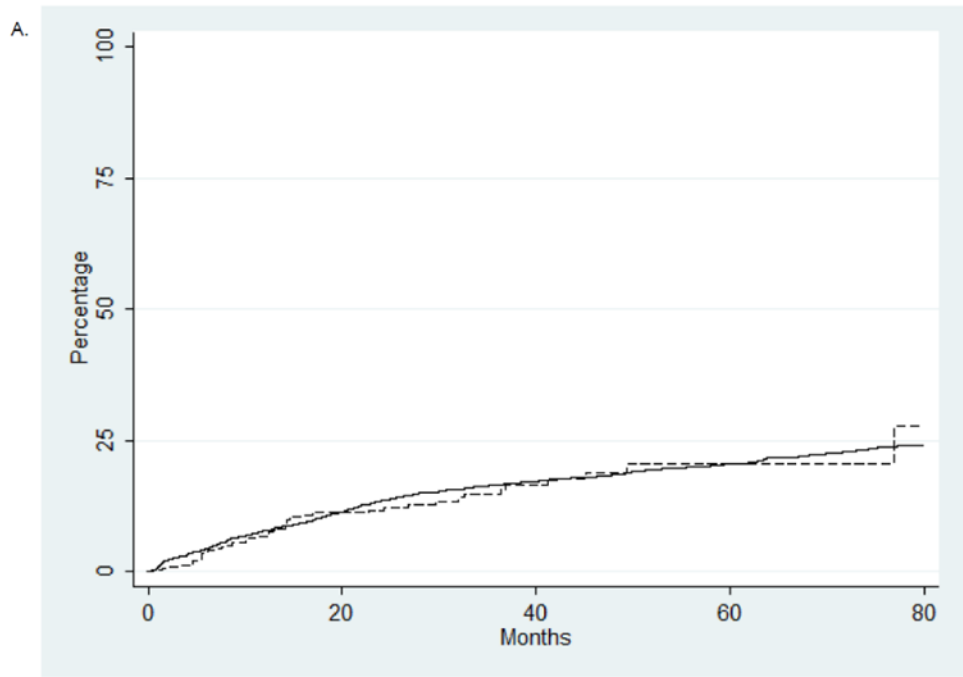- IMRT is not associated with a reduction in radiation toxicity, but was more costly.

Figure 1.
Pelvic radiotherapy stratified by year of treatment for women with uterine cancer.
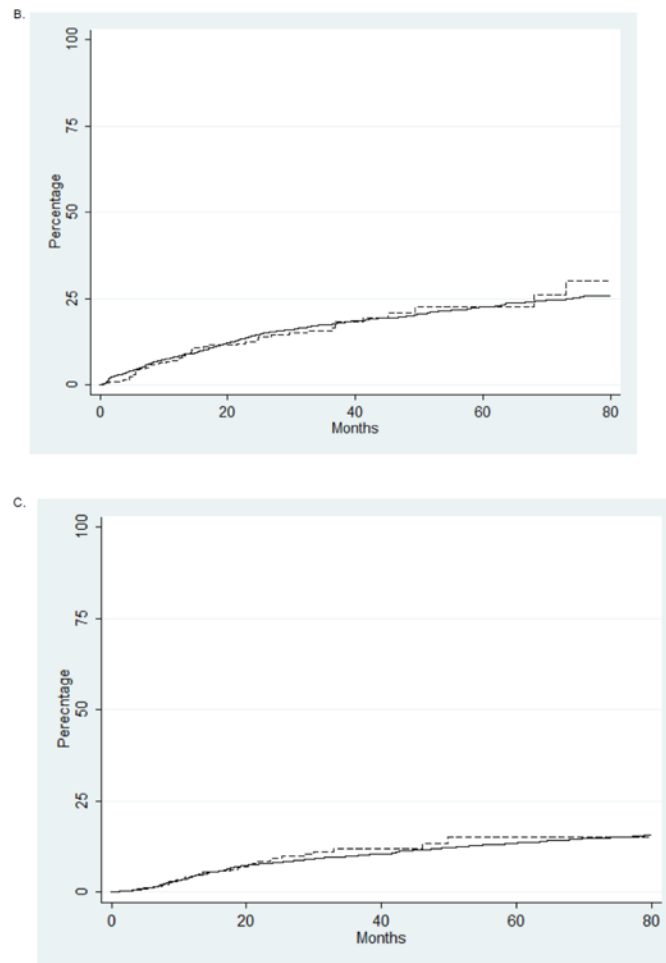
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Figure 2.
Kaplan-Meier analysis of late radiation toxicity stratified by type of radiation administered.
(A) Gastroinstestinal toxicity (P=0.66). B. Genitourinary toxicity (P=0.46). C. Hip fracture
(P=0.24).

Table 1

Clinical and demographic characteristics of the cohort stratified by radiation.

		Conformal radiation		IMRT		P-value
		N	(%)	N	(%)	
		3227	(90.8)	328	(9.2)	
Age (years)						0.13
	65-69	733	(90.2)	80	(9.8)	
	70-74	870	(91.3)	83	(8.7)	
	75-79	796	(92.3)	66	(7.7)	
	80	828	(89.3)	99	(10.7)	
Race						0.46
	White	2810	(91.0)	278	(9.0)	
	Black	248	(88.9)	31	(11.1)	
	Other/Hispanic/missing	169	(89.9)	19	(10.1)	
Year of diagnosis						<0.0001
	2001/2002	1036	(97.6)	25	(2.4)	
	2003	505	(95.1)	26	(4.9)	
	2004	460	(91.5)	43	(8.6)	
	2005	440	(91.9)	39	(8.1)	
	2006	422	(83.2)	85	(16.8)	
	2007	364	(76.8)	110	(23.2)	
Marital status						0.62
	Married	1385	(90.4)	147	(9.6)	
	Unmarried	1744	(91.2)	199	(8.8)	
	Unknown	98	(89.1)	12	(10.9)	
Area of residence						0.35
	Metropolitan	2931	(90.6)	303	(9.4)	
	Non-metropolitan	296	(92.2)	25	(7.8)	
SEER registry						<0.0001
	Eastern	1087	(94.7)	61	(5.3)	
	Midwest	1110	(90.7)	114	(9.3)	

	Conformal radiation		IMRT		P-value
	N	(%)	N	(%)	
West	1030	(87.1)	153	(12.9)	
Socioeconomic status					0.12
Lowest (first) quintile/unknown	390	(88.4)	51	(11.6)	
Second quintile	623	(89.0)	77	(11.0)	
Third quintile	762	(91.5)	71	(8.5)	
Fourth quintile	731	(92.0)	64	(8.1)	
Highest (fifth) quintile	721	(91.7)	65	(8.3)	
Comorbidity score					0.68
0	1577	(91.0)	156	(9.0)	
1	913	(91.0)	90	(9.0)	
2	737	(90.0)	82	(10.0)	
Tumor histology					0.65
Endometrioid	2207	(90.5)	233	(9.6)	
Serous/clear cell	340	(90.9)	34	(9.1)	
Carcinosarcoma/leiomyosarcoma	303	(91.0)	30	(9.0)	
Other/unknown	377	(92.4)	31	(7.6)	
Stage[1]					<0.0001
IA/IB	250	(88.0)	34	(12.0)	
IC	396	(89.8)	45	(10.2)	
INOS	815	(95.0)	43	(5.0)	
II	491	(92.0)	43	(8.1)	
III	695	(87.4)	100	(12.6)	
IV	339	(94.2)	21	(5.8)	
Unknown	241	(85.2)	42	(14.8)	
Tumor grade					0.47
1	526	(90.5)	55	(9.5)	
2	1004	(91.9)	89	(8.1)	
3	1255	(90.4)	133	(9.6)	
Unknown	442	(89.7)	51	(10.3)	
Hysterectomy					0.25

		Conformal radiation		IMRT		P-value
		N	(%)	N	(%)	
	No	474	(89.4)	56	(10.6)	
	Yes	2753	(91.0)	272	(9.0)	
Lymphadenectomy						0.31
	No	1223	(91.4)	115	(8.6)	
	Yes	2004	(90.4)	213	(9.6)	
Brachytherapy						0.006
	No	1593	(89.4)	188	(10.6)	
	Yes	1634	(92.1)	140	(7.9)	
Chemotherapy						<0.0001
	No	2306	(92.5)	187	(7.5)	
	Yes	921	(86.7)	141	(13.3)	
Location of radiation administration						<0.0001
	Hospital-based	52	(100)	-	-	
	Free standing	883	(87.4)	127	(12.6)	
	Combination	2292	(91.9)	201	(8.1)	

[1] FIGO (International Federation of Obstetrics and Gynecology) 1998 staging criteria.

SEER=Surveillance, Epidemiology, and End Results. IMRT=intensity-modulated radiation therapy.

Table 2

Multivariable logistic regression model of predictors of IMRT use.

	IMRT
Age (years)	
65-69	Referent
70-74	0.93 (0.68.1.27)
75-79	0.94 (0.67-1.31)
80	1.27 (0.92-1.75)
Race	
White	Referent
Black	1.07 (0.71-1.61)
Hispanic	0.28 (0.07-1.12)
Other	0.88 (0.53-1.46)
Year of diagnosis	
2001	Referent
2002	2.36 (1.02-5.47)[*]
2003	3.49 (1.58-7.72)[*]
2004	6.50 (2.98-14.19)[*]
2005	5.91 (2.69-12.98)[*]
2006	11.60 (5.48-24.58)[*]
2007	15.26 (7.26-32.08)[*]
Marital status	
Married	Referent
Unmarried	0.87 (0.69-1.10)
Unknown	1.23 (0.67-2.26)
Area of residence	
Non-metropolitan	Referent
Metropolitan	1.50 (0.97-2.33)
SEER registry	
Eastern	Referent
Midwest	1.74 (1.25-2.41)[*]
West	2.23 (1.63-3.04)[*]
Socioeconomic status	
Lowest (first) quintile	Referent
Second quintile	1.05 (0.73-1.52)
Third quintile	0.79 (0.54-1.15)
Fourth quintile	0.76 (0.51-1.14)
Highest (fifth) quintile	0.78 (0.52-1.16)
Comorbidity score	
0	Referent
1	0.95 (0.73-1.23)

	IMRT
2	1.06 (0.80-1.41)
Tumor histology	
Endometrioid	Referent
Serous	0.71 (0.46-1.10)
Clear cell	0.70 (0.32-1.52)
Carcinosarcoma	0.70 (0.44-1.11)
Leiomyosarcoma	0.61 (0.23-1.62)
Other/unknown	0.62 (0.42-0.92)[*]
Stage[1]	
IA	Referent
IB	0.91 (0.39-2.11)
IC	0.79 (0.35-1.78)
INOS	1.17 (0.50-2.70)
II	0.97 (0.43-2.18)
III	1.13 (0.52-2.46)
IV	0.68 (0.28-1.63)
Unknown	
Tumor grade	
1	Referent
2	0.85 (0.61-1.20)
3	0.89 (0.63-1.24)
Unknown	1.02 (0.67-1.54)
Hysterectomy	
No	Referent
Yes	0.93 (0.62-1.39)
Lymphadenectomy	
No	Referent
Yes	1.03 (0.76-1.39)
Brachytherapy	
No	Referent
Yes	0.82 (0.65-1.03)
Chemotherapy	
No	Referent
Yes	1.75 (1.36-2.25)[*]

FIGO (International Federation of Obstetrics and Gynecology) 1998 staging criteria.

SEER=Surveillance, Epidemiology, and End Results. IMRT=intensity-modulated radiation therapy.

[*] $P<0.005$

Table 3

Radiation-related toxicity stratified by type of radiation administered.

	Conformal Radiation					IMRT			IMRT vs. Conformal RT
	N	(%)	100 Person - Years	Rate	N	(%)	100 Person - Years	Rate	Rate ratio
Late toxicities									
Radiation enteritis	275	8.5%	11.55	23.8	19	5.8%	0.65	29.1	1.22 (0.77-1.94)
Bowel obstruction	494	15.3%	18.68	26.4	42	12.8%	1.12	37.3	1.41 (1.03-1.93)*
Other gastrointestinal complications	176	5.5%	7.18	24.5	12	3.7%	0.35	34.4	1.49 (0.78-2.52)
Genitourinary complication	271	8.4%	10.61	25.5	30	9.2%	0.95	31.7	1.24 (0.85-1.81)
Hip fracture	376	11.7%	16.06	23.4	32	9.8%	0.99	32.4	1.38 (0.96-1.99)

IMRT=intensity-modulated radiation therapy