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ORIGINAL REPORT

Comparative Effectiveness of Minimally Invasive Hysterectomy for Endometrial Cancer

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ABSTRACT

Purpose
Despite the potential benefits of minimally invasive hysterectomy for uterine cancer, population-level data describing the procedure's safety in unselected patients are lacking. We examined the use of minimally invasive surgery and the association between the route of the procedure and long-term survival.

Methods
We used the SEER-Medicare database to identify women with stage I-III uterine cancer who underwent hysterectomy from 2006 to 2011. Patients who underwent abdominal hysterectomy were compared with those who had minimally invasive hysterectomy (laparoscopic and robot-assisted). Perioperative morbidity, use of adjuvant therapy, and long-term survival were examined after propensity score balancing.

Results
We identified 6,304 patients, including 4,139 (65.7%) who underwent abdominal hysterectomy and 2,165 (34.3%) who underwent minimally invasive hysterectomy; performance of minimally invasive hysterectomy increased from 9.3% in 2006 to 61.7% in 2011. Robot-assisted procedures accounted for 62.3% of the minimally invasive operations. Compared with women who underwent abdominal hysterectomy, minimally invasive hysterectomy was associated with a lower overall complication rate (22.7% *v* 39.7%; $P < .001$), and lower perioperative mortality (0.6% *v* 1.1%), but these women were more likely to receive adjuvant pelvic radiotherapy (34.3% *v* 31.3%) and brachytherapy (33.6% *v* 31.0%; $P < .05$). The complication rate was higher after robot-assisted hysterectomy compared with laparoscopic hysterectomy (23.7% *v* 19.5%; $P = .03$). There was no association between the use of minimally invasive hysterectomy and either overall (HR, 0.89; 95% CI, 0.75 to 1.04) or cancer-specific (HR, 0.83; 95% CI, 0.59 to 1.16) mortality.

Conclusion
Minimally invasive hysterectomy does not appear to compromise long-term survival for women with endometrial cancer.

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INTRODUCTION

Surgical management remains the cornerstone of treatment for most women with endometrial cancer. The majority of patients diagnosed with uterine cancer undergo hysterectomy, often in combination with salpingo-oophorectomy and sometimes lymphadenectomy. Traditionally, the procedure was most commonly performed through a midline laparotomy and is associated with substantial perioperative morbidity and mortality.[1,2]

Laparoscopic hysterectomy was first described in the early 1990s. Compared with laparotomy, laparoscopy has been associated with decreased perioperative morbidity and an earlier return to normal functioning for gynecologic cancer surgery.[3] By the mid-2000s, robot-assisted hysterectomy also began to diffuse into clinical practice.[4,5] Similar to laparoscopy, robot-assisted hysterectomy appears to have a favorable morbidity profile compared with laparotomy. Despite the potential benefits of these procedures, prior studies have reported that uptake of minimally invasive surgery (MIS) in gynecology has been slow.[4,6]

In addition to short-term complications, long-term outcomes and survival are an important concern for patients with cancer. In addition to the technical challenges of the surgery, the potential risks of minimally invasive hysterectomy for patients with cancer include metastases to the port sites and disruption of the uterus at the time of surgery. Although a large trial by the Gynecologic Oncology Group was unable to demonstrate that minimally invasive hysterectomy was not inferior to laparotomy, other small studies have suggested that the procedure is safe.[7-13]

Despite the potential benefits of minimally invasive hysterectomy for uterine cancer, population-level data describing the safety of the procedure in unselected patients are largely lacking. We performed a population-based analysis to compare minimally invasive with abdominal hysterectomy for uterine cancer. We specifically examined trends in the use of MIS, as well as the association between the route of the procedure and long-term survival.

METHODS

Data Source

The SEER-Medicare database was used for analysis.[14-16] SEER is a population-based tumor registry developed by the National Cancer Institute (NCI). SEER captures data on time of diagnosis, tumor histology, location, stage, treatment, and survival, as well as demographic and selected census tract-level information. The Medicare database captures data on patients with Medicare Part A (inpatient) and Part B (outpatient), including billed claims, services, and diagnoses. These two files are linked and provide data on initial services and all follow-up care. Exemption from the Columbia University Institutional Review Board was obtained.

Cohort Selection

Women 65 years of age or older with stage I-III uterine cancer who underwent hysterectomy from 2006 to 2011 were included in the analysis. Patients with endometrioid, serous, and carcinosarcoma histology were included. Women who received chemotherapy or radiation prior to hysterectomy, patients enrolled in a non-Medicare health maintenance organization, those receiving Medicare for a reason other than age, and patients with other primary cancers were excluded.

Patients were initially classified as having undergone an abdominal (open) hysterectomy or minimally invasive hysterectomy based on the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) and Current Procedural Terminology coding. Patients with billing codes for both an abdominal and minimally invasive hysterectomy were categorized as having undergone an abdominal hysterectomy. Billing codes for robot-assisted surgery were introduced in October 2008. Given the availability of this coding, we further stratified women treated between 2009 and 2011 as having undergone either a laparoscopic or robot-assisted hysterectomy. For each subject, we noted the performance of concurrent lymphadenectomy.

Patient Characteristics

Age at the time of diagnosis was stratified into 5-year intervals, and race was recorded as white, black, and other. The marital status of each patient was recorded as married, unmarried, and unknown. An aggregate socioeconomic status (SES) score was calculated from education, poverty level, and income data from the 2000 census tract data, as previously reported by Du et al.[17] Patient scores were ranked on a scale of 1 through 5 by use of a formula that incorporated education, poverty, and income weighted equally, with 1 being the lowest value. Comorbid medical diseases were assessed using the Klabunde adaptation of the Charlson comorbidity index (ie, the Klabunde–Charlson index).[18,19] Medicare claims were examined for diagnostic codes of the International Classification of Disease, Ninth Revision. Each condition was weighted, and patients were assigned a score that was based on the Klabunde-Charlson index.[19] Area of residence was categorized as metropolitan or nonmetropolitan, and the SEER registries were grouped as East, West, and Midwest.

Hospital characteristics analyzed included hospital teaching status (yes or no), NCI Cancer Center designation (yes or no), and hospital bed size ($<$ 200, 200-400, 401-600, $>$ 600). Procedural volume was assessed as mean annual procedural volume, calculated as the mean number of procedures performed per year for years in which a hospital performed at least one operation.[20] Separate volume estimates were tabulated for abdominal, minimally invasive, laparoscopic, and robotically assisted hysterectomy. Stage was captured using the American Joint Committee on Cancer staging criteria and converted to the current International Federation of Gynecology and Obstetrics staging system for uterine cancer, and tumor grade was grouped as moderately or poorly differentiated or unknown.

Outcomes

The primary outcome of the analysis was long-term survival. Cancer-specific and overall survival were assessed for each surgical group. In addition, perioperative morbidity and mortality were analyzed. Perioperative complications were categorized based on a previously described system: (1) intraoperative complications (bladder injury, ureteral injury, intestinal injury, vascular injury, and other operative injury); (2) surgical site complications (wound complications, abscess, hemorrhage, bowel obstruction, ileus); and (3) medical complications (venous thromboembolism, myocardial infarction, cardiopulmonary arrest, renal failure, respiratory failure, stroke, bacteremia/sepsis, shock, and pneumonia).[4,5] A composite score of any of these complications was also examined.

Transfusion during the hospitalization was measured. Perioperative mortality was defined as death within 30 days of the procedure. Use of adjuvant vaginal brachytherapy, whole pelvic radiation, and chemotherapy during the 6-month period after surgery was noted for each subject.

Statistical Analyses

Frequency distributions between categorical variables were compared using χ^2 tests. The association between demographic, clinical, and oncologic characteristics and use of minimally invasive or robot-assisted hysterectomy was estimated using multivariable random effects logistic regression models accounting for hospital-level clustering.

The inverse probability of treatment weighting (IPTW) approach based on propensity score was used to balance the observed confounders between treatments. Separate models were developed to compare the abdominal versus minimally invasive hysterectomy cohort and the laparoscopic versus robot-assisted cohorts.

The propensity score is the predicted probability of treatment, minimally invasive or robot-assisted hysterectomy, in the current analysis.[21-23] To calculate the propensity score, we fit a logistic regression model that included all of the clinical, oncologic, and hospital characteristics and two-way interaction terms with a *P* value of less than .15 for the use of minimally invasive hysterectomy and a *P* value of less than .05 for the use of robot-assisted hysterectomy to allow model convergence. The predicted probability (the propensity score) was estimated for each patient and ranged from 0 to 1. The weighting assumptions of the IPTW approach assigned patients who underwent the treatment of interest a weight of 1/propensity score and those who did not undergo the treatment of interest a weight of 1/(1-propensity score).[21,24] To reduce the bias from extreme weights, a stabilization technique that multiplies the treatment and comparison weights by a constant and a trimming technique that trims the stabilized weights within a specified range ($\leq$ 10) were applied.[25]

After IPTW, we assessed the balance of measured confounders between treatments via a weighted regression approach, in which each covariate was regressed on the treatment variable. The clinically unimportant differences between treatment groups were determined by a threshold value of less than 0.2 for all coefficients in the weighted regression model.[26]

After propensity score balancing, morbidity, mortality, and subsequent treatment were compared between groups. The effect of route of hysterectomy on overall mortality and cancer-specific mortality was evaluated using Cox proportional hazards models. Survival was also examined using Kaplan-Meier analyses and compared with log rank tests. All analyses were conducted with SAS, version 9.4 (SAS Institute, Cary, NC). All statistical tests were two-sided. A *P* value of less than .05 was considered statistically significant.

RESULTS

A total of 6,304 patients, including 4,139 (65.7%) women who underwent abdominal hysterectomy and 2,165 (34.3%) who underwent minimally invasive hysterectomy, were identified. Performance of minimally invasive hysterectomy increased from 9.3% (95% CI, 7.6% to 11.0%) in 2006 to 61.7% (95% CI, 58.7% to 64.8%) in 2011 (Fig 1A). Among those women who underwent a minimally invasive operation, robot-assisted hysterectomy accounted for 61.8% (95% CI, 57.3% to 66.3%) of the procedures in 2009, 63.4% (95% CI, 59.3% to 67.4%) of the procedures in 2010, and 61.7% (95% CI, 57.8% to 65.6%) of the procedures in 2011 (Fig 1B).

Table 1 displays the characteristics of women who underwent abdominal versus minimally invasive (laparoscopic or robot-assisted)

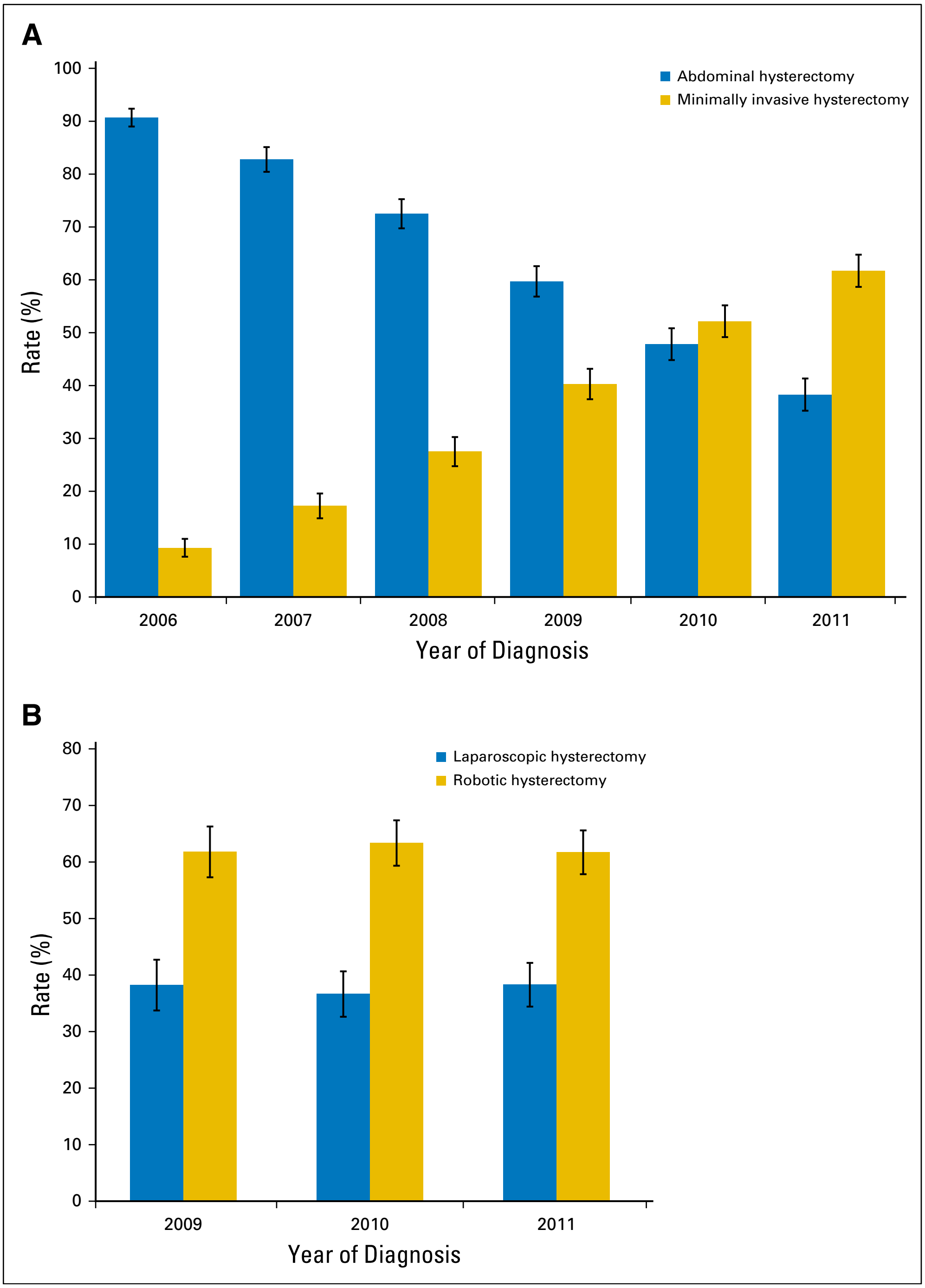

Fig 1. (A) Trends in the use of minimally invasive and abdominal hysterectomy (2006-2011; $P < .001$). (B) Trends in the use of robot-assisted and laparoscopic hysterectomy (2009-2011; $P = .94$).

Table 1. Clinical and Demographic Characteristics of the Cohort Comparing Minimally Invasive and Abdominal Hysterectomy

	Unadjusted					Inverse Probability of Treatment Weighting*				
	Abdominal Hysterectomy (N = 4,139)		MIS Hysterectomy (N = 2,165)			Abdominal Hysterectomy (N = 4,762)		MIS Hysterectomy (N = 3,100)		
Characteristic	No.	(%)	No.	(%)	P†	No.	(%)	No.	(%)	P‡
Year of diagnosis					< .001					.01
2006	1,032	(24.9)	106	(4.9)		877	(18.4)	402	(13.0)	
2007	826	(20.0)	172	(7.9)		768	(16.1)	495	(16.0)	
2008	730	(17.6)	277	(12.8)		789	(16.6)	489	(15.8)	
2009	667	(16.1)	450	(20.8)		837	(17.6)	595	(19.2)	
2010	508	(12.3)	554	(25.6)		764	(16.1)	569	(18.4)	
2011	376	(9.1)	606	(28.0)		727	(15.3)	550	(17.8)	
Age, years					.01					.91
< 65-69	1,151	(27.8)	648	(29.9)		1,353	(28.4)	904	(29.2)	
70-74	1,176	(28.4)	6535	(30.2)		1,401	(29.4)	928	(29.9)	
75-79	873	(21.1)	450	(20.8)		986	(20.7)	619	(20.0)	
≥ 80	939	(22.7)	414	(19.1)		1,022	(21.5)	649	(20.9)	
Race/ethnicity					.001					.29
White	3,608	(87.2)	1,951	(90.1)		4,201	(88.2)	2,787	(89.9)	
Black	288	(7.0)	109	(5.0)		296	(6.2)	167	(5.4)	
Other	243	(5.9)	105	(4.9)		265	(5.6)	146	(4.7)	
Marital status	.	.			.002					.61
Married	1,859	(44.9)	1,055	(48.7)		2,185	(45.9)	1,395	(45.0)	
Unmarried	2,148	(51.9)	1,026	(47.4)		2,411	(50.6)	1,610	(51.9)	
Other	132	(3.2)	84	(3.9)		166	(3.5)	95	(3.1)	
Residence					< .001					.39
Metropolitan	3,381	(81.7)	1,920	(88.7)		3,984	(83.7)	2,633	(84.9)	
Nonmetropolitan	758	(18.3)	245	(11.3)		778	(16.3)	467	(15.1)	
Socioeconomic status					< .001					.38
Lowest (first) quintile	1,109	(26.8)	421	(19.5)		1,186	(24.9)	710	(22.9)	
Second quintile	1,030	(24.9)	463	(21.4)		1,133	(23.8)	725	(23.4)	
Third quintile	692	(16.7)	358	(16.5)		792	(16.6)	493	(15.9)	
Fourth quintile	918	(22.2)	606	(28.0)		1,126	(23.7)	778	(25.1)	
Highest (fifth) quintile	390	(9.4)	317	(14.6)		525	(11.0)	394	(12.7)	
Registry area					< .001					.16
East	959	(23.2)	566	(26.1)		1,164	(24.5)	763	(24.6)	
Midwest	1,485	(35.9)	546	(25.2)		1,513	(31.8)	889	(28.7)	
West	1,695	(41.0)	1,053	(48.6)		2,084	(43.8)	1,447	(46.7)	
Comorbidity score					< .001					.76
0	2,252	(54.4)	1,329	(61.4)		2,686	(56.4)	1,754	(56.6)	
1	1,184	(28.6)	548	(25.3)		1,315	(27.6)	879	(28.4)	
≥ 2	703	(17.0)	288	(13.3)		761	(16.0)	467	(15.1)	
Grade					< .001					.43
1	1,369	(33.1)	841	(38.9)		1,665	(35.0)	1,165	(37.6)	
2	1,331	(32.2)	660	(30.5)		1,521	(31.9)	980	(31.6)	
3	1,008	(24.4)	398	(18.4)		1,049	(22.0)	632	(20.4)	
Unknown	431	(10.4)	266	(12.3)		528	(11.1)	324	(10.5)	
Tumor stage					< .001					.37
IA	2,037	(49.2)	1,193	(55.1)		2,410	(50.6)	1,670	(53.9)	
IB	859	(20.8)	424	(19.6)		986	(20.7)	603	(19.4)	
INOS	138	(3.3)	69	(3.2)		165	(3.5)	102	(3.3)	
II	436	(10.5)	162	(7.5)		463	(9.7)	258	(8.3)	
III	669	(16.2)	317	(14.6)		737	(15.5)	467	(15.1)	
Lymphadenectomy					.40					.64
No	1,227	(29.6)	620	(28.6)		1,405	(29.5)	939	(30.3)	
Yes	2,912	(70.4)	1,545	(71.4)		3,357	(70.5)	2,161	(69.7)	
Histology					< .001					.003
Endometrioid	3,654	(88.3)	1,961	(90.6)		4,259	(89.4)	2,829	(91.3)	
Carcinosarcoma	151	(3.7)	39	(1.8)		133	(2.8)	40	(1.3)	
Serous	334	(8.1)	165	(7.6)		370	(7.8)	231	(7.5)	
Teaching hospital					< .001					.06
No	1,363	(32.9)	727	(33.6)		1,588	(33.3)	1,054	(34.0)	
Yes	2,567	(62.0)	1,201	(55.5)		2,855	(60.0)	1,790	(57.7)	
Unknown	209	(5.1)	237	(11.0)		319	(6.7)	256	(8.3)	

(continued on following page)

Table 1. Clinical and Demographic Characteristics of the Cohort Comparing Minimally Invasive and Abdominal Hysterectomy (continued)

	Unadjusted					Inverse Probability of Treatment Weighting*				
	Abdominal Hysterectomy (N = 4,139)		MIS Hysterectomy (N = 2,165)			Abdominal Hysterectomy (N = 4,762)		MIS Hysterectomy (N = 3,100)		
Characteristic	No.	(%)	No.	(%)	P†	No.	(%)	No.	(%)	P‡
NCI center					< .001					
No	3,701	(89.4)	1,857	(85.8)		4,178	(87.7)	2,726	(88.0)	.98
Yes	367	(8.9)	243	(11.2)		475	(10.0)	303	(9.8)	
Unknown	71	(1.7)	65	(3.0)		108	(2.3)	70	(2.3)	
Hospital beds					< .001					.69
< 200	563	(13.6)	182	(8.4)		556	(11.7)	341	(11.0)	
200-400	1,182	(28.6)	528	(24.4)		1,322	(27.8)	820	(26.5)	
401-600	1,486	(35.9)	908	(41.9)		1,788	(37.6)	1,242	(40.1)	
> 600	837	(20.2)	480	(22.2)		988	(20.8)	624	(20.1)	
Unknown	71	(1.7)	67	(3.1)		108	(2.3)	72	(2.3)	
Hospital volume					< .001					.37
Median (IQR)	4.2	(2.2-9.7)	5.7	(3.0-9.8)		4.6	(2.4-9.7)	5.2	(2.3-9.7)	

Abbreviations: IQR, interquartile range; MIS, minimally invasive surgery; NCI, National Cancer Institute.
*Frequency numbers were rounded to integers based on weight.
†*P* values were derived from χ^2 tests.
‡*P* values were derived from weighted surveylogistic model.

hysterectomy. After propensity score balancing, treatment in a more recent year and endometrioid histology remained associated with performance of MIS hysterectomy ($P < .05$ for both). After propensity score balancing, among women who underwent a minimally invasive hysterectomy, hospital teaching status and treatment at a NCI-designated cancer center remained associated with performance of robot-assisted compared with laparoscopic hysterectomy ($P < .05$ for both; Table A1, online only).

In a multivariable model of the entire cohort, more recent year of diagnosis, higher SES, treatment at a larger hospital, and treatment at an intermediate-volume hospital were associated with minimally invasive hysterectomy ($P < .05$ for all; Table 2). In contrast, patients treated in the Midwest and who had more comorbidities, higher tumor grade, higher stage, and carcinosarcomas were less likely to undergo a minimally invasive hysterectomy ($P < .05$ for all). When limited to women who underwent a minimally invasive hysterectomy, patients treated at an NCI-designated cancer center and at larger hospitals were more likely to undergo a robot-assisted procedure, whereas older women were less likely to have a robotically assisted procedure ($P < .05$ for all).

After propensity score balancing, minimally invasive hysterectomy was associated with a lower overall complication rate compared with abdominal hysterectomy (22.7% *v* 39.7%; odds ratio [OR], 0.46; 95% CI, 0.41 to 0.51) and lower rates of surgical site complications (OR, 0.32; 95% CI, 0.28 to 0.37), medical complications (OR, 0.56; 95% CI, 0.50 to 0.63), transfusions (OR, 0.44; 95% CI, 0.35 to 0.56), and perioperative mortality (OR, 0.57; 95% CI, 0.34 to 0.95). Women who underwent minimally invasive hysterectomy were more likely to receive adjuvant pelvic radiotherapy compared with women who underwent abdominal hysterectomy (34.3% *v* 31.3%; OR, 1.14; 95% CI, 1.04 to 1.26) and brachytherapy (33.6% *v* 31.0%; OR, 1.13; 95% CI, 1.03 to 1.24). Receipt of adjuvant chemotherapy was similar between the groups ($P = .81$)

The overall rate of complications was 23.7% in women who underwent robot-assisted hysterectomy compared with 19.5% after laparoscopic hysterectomy (OR, 1.28; 95% CI, 1.03 to 1.59; Table 3). There were no differences in the rates of intraoperative complications (OR, 0.84; 95% CI, 0.53 to 1.33), surgical site complications (OR, 1.26; 95% CI, 0.92 to 1.72), or transfusions (OR, 0.84; 95% CI, 0.51 to 1.39), whereas the rate of medical complications was higher after robotically assisted hysterectomy (14.1% *v* 10.0%; OR, 1.48; 95% CI, 1.12 to 1.96). There were no statistically significant differences in the rate of use of adjuvant therapy between laparoscopic and robot-assisted hysterectomy.

There was no significant association between the use of minimally invasive hysterectomy and either overall (HR, 0.89; 95% CI, 0.75 to 1.04) or cancer-specific (HR, 0.83; 95% CI, 0.59 to 1.16) mortality (Table 4). The results were similar after adjustment for adjuvant therapy and when the cohort was limited to patients with stage I tumors. Similarly, there was no statistically significant difference in either overall (HR, 1.00; 95% CI, 0.72 to 1.41) or cancer-specific (HR, 1.53; 95% CI, 0.76 to 3.05) mortality for robotic compared with laparoscopic hysterectomy or in any of the sensitivity analyses. Likewise, there was no difference in survival in any of the Kaplan-Meier analyses (Fig 2).

DISCUSSION

Our findings suggest that long-term survival is similar after minimally invasive and abdominal hysterectomy in women with endometrial cancer. Although minimally invasive hysterectomy is associated with decreased morbidity, the procedure was also associated with increased use of adjuvant radiation compared with abdominal hysterectomy. There was no difference in survival between robot-assisted and laparoscopic hysterectomy; however,

Table 2. Multivariable Models of Predictors of Minimally Invasive and Robot-Assisted Hysterectomy

Predictor	Minimally Invasive Hysterectomy (*v* Abdominal Hysterectomy) OR (95% CI)	Robot-Assisted Hysterectomy (*v* Laparoscopic Hysterectomy) OR (95% CI)
Year of diagnosis		
2006	Referent	—
2007	2.19 (1.60 to 2.98)*	—
2008	4.84 (3.59 to 6.53)*	—
2009	10.50 (7.81 to 14.11)*	Referent
2010	19.25 (14.08 to 26.33)*	1.24 (0.82 to 1.87)
2011	33.66 (24.60 to 46.06)*	1.08 (0.73 to 1.58)
Age, years		
< 65-69	Referent	Referent
70-74	1.04 (0.86 to 1.26)	0.80 (0.54 to 1.19)
75-79	1.11 (0.90 to 1.38)	0.77 (0.50 to 1.19)
≥ 80	0.91 (0.73 to 1.13)	0.59 (0.37 to 0.95)†
Race/ethnicity		
White	Referent	Referent
Black	0.73 (0.52 to 1.03)	1.30 (0.66 to 2.57)
Other	0.72 (0.51 to 1.02)	0.81 (0.40 to 1.65)
Marital status		
Married	Referent	Referent
Unmarried	0.90 (0.77 to 1.05)	1.34 (0.97 to 1.86)
Other	1.07 (0.69 to 1.65)	1.61 (0.71 to 3.65)
Residence		
Metropolitan	Referent	Referent
Nonmetropolitan	0.97 (0.74 to 1.28)	1.86 (0.93 to 3.70)
Socioeconomic status		
Lowest (first) quintile	Referent	Referent
Second quintile	1.19 (0.94 to 1.50)	0.71 (0.42 to 1.21)
Third quintile	1.31 (1.01 to 1.70)†	1.04 (0.59 to 1.82)
Fourth quintile	1.47 (1.15 to 1.88)†	0.81 (0.49 to 1.36)
Highest (fifth) quintile	1.47 (1.09 to 1.98)†	0.73 (0.40 to 1.31)
Registry area		
East	Referent	Referent
Midwest	0.45 (0.25 to 0.82)†	2.78 (0.90 to 8.62)
West	1.03 (0.58 to 1.85)	0.43 (0.15 to 1.23)
Comorbidity score		
0	Referent	Referent
1	0.77 (0.65 to 0.92)†	0.82 (0.57 to 1.18)
≥ 2	0.52 (0.42 to 0.65)*	1.27 (0.80 to 2.03)
Grade		
1	Referent	Referent
2	0.84 (0.70 to 1.02)	0.90 (0.62 to 1.32)
3	0.62 (0.49 to 0.78)*	1.05 (0.64 to 1.71)
Unknown	0.79 (0.60 to 1.03)	0.84 (0.50 to 1.42)
Tumor stage		
IA	Referent	Referent
IB	0.99 (0.81 to 1.21)	1.00 (0.66 to 1.50)
INOS	1.23 (0.80 to 1.92)	0.87 (0.35 to 2.15)
II	0.70 (0.54 to 0.92)†	1.17 (0.64 to 2.14)
III	0.68 (0.54 to 0.85)†	1.15 (0.73 to 1.81)
Lymphadenectomy		
No	Referent	Referent
Yes	0.89 (0.74 to 1.07)	2.05 (1.41 to 2.98)†
Histology		
Endometrioid	Referent	Referent
Carcinosarcoma	0.34 (0.20 to 0.56)*	1.07 (0.38 to 3.04)
Serous	1.08 (0.81 to 1.45)	1.79 (0.94 to 3.39)
Teaching hospital		
No	Referent	Referent
Yes	1.03 (0.70 to 1.52)	1.31 (0.57 to 3.00)
Unknown	1.24 (0.81 to 1.89)	1.83 (0.75 to 4.47)
NCI center		
No	Referent	Referent
Yes	0.93 (0.48 to 1.81)	5.61 (1.36 to 23.16)†
Unknown	NA	NA
Hospital beds		
< 200	Referent	Referent
200-400	1.36 (0.82 to 2.25)	7.29 (2.01 to 26.45)†
401-600	2.93 (1.56 to 5.49)†	3.90 (0.92 to 16.47)
> 600	4.05 (2.03 to 8.11)*	8.11 (1.77 to 37.25)†
Unknown	NA	NA
Hospital volume		
Low	Referent	Referent
Intermediate	1.80 (1.07 to 3.03)†	1.83 (0.74 to 4.53)
High	1.38 (0.63 to 3.05)	0.99 (0.29 to 3.38)
Unknown	NA	NA

Abbreviations: NA, Not applicable for the colinearity between hospital factors; OR, odds ratio.
*$P < .001$.
†$P < .05$.

robotically assisted hysterectomy was associated with a small, but statistically significant, increased risk of complications.

We noted a marked increase in the use of MIS for uterine cancer between 2006 and 2011. In a previous analysis of the same data set, our group found that only 8.5% of hysterectomies for uterine cancer were performed minimally invasively in 2005.[6] In the current study, we found that the use of minimally invasive hysterectomy increased by more than six-fold, from 9% in 2006 to 62% in 2011. In the later years of the study, robot-assisted procedures accounted for approximately two thirds of the minimally invasive operations. During the time frame of the study, robotic technology diffused widely into gynecologic practice and likely contributed to the increased use of minimally invasive techniques for uterine cancer.[4]

An important benefit of MIS is lower rates of perioperative morbidity. Prior studies comparing laparoscopic hysterectomy with laparotomy for endometrial cancer have consistently shown lower complication rates and shorter hospitalizations.[12,27,28] Furthermore, MIS appears to be associated with improved quality of life during the perioperative period.[9,29] Our data are consistent with these findings. Compared with laparotomy, women who underwent minimally invasive hysterectomy were 60% less likely to experience a complication.

We noted a slightly higher complication rate for robot-assisted hysterectomy compared with laparoscopic hysterectomy. Importantly, the higher perioperative morbidity rate with robotically assisted surgery was not due to intraoperative injuries or surgical site complications, but rather, postoperative medical complications. Specifically, the rates of respiratory and renal failure as well as bacteremia were higher after robot-assisted surgery. Prior studies have reported substantially longer operative times with robot-assisted hysterectomy, which may in part explain the morbidity profile we identified.[30,31] Higher pulmonary morbidity was also reported in a prior study in which the pneumonia rate after robotically assisted hysterectomy was more than double that found after laparoscopy.[32] These data may also

Table 3. Comparison of Morbidity and Mortality for Patients Who Underwent Minimally Invasive Compared With Abdominal Hysterectomy and Robotically Assisted Compared With Laparoscopic Hysterectomy After Adjusting for Observed Confounders Using Inverse Probability of Treatment Weighting

	Inverse Probability of Treatment Weighting						Inverse Probability of Treatment Weighting					
	Abdominal Hysterectomy (N = 4,762)		MIS Hysterectomy (N = 3,100)			MIS Versus Abdominal Hysterectomy	Laparoscopic Hysterectomy (N = 821)		Robotic-Assisted Hysterectomy (N = 1,157)			Robot-Assisted Versus Laparoscopic Hysterectomy
	No.	(%)	No.	(%)	*P*	OR (95% CI)*	No.	(%)	No.	(%)	*P*	OR (95% CI)
Any complication	1,861	(39.1)	703	(22.7)	< .001	0.46 (0.41 to 0.51)	160	(19.5)	274	(23.7)	0.03	1.28 (1.03 to 1.59)
Intraoperative complications	289	(6.1)	179	(5.8)	.59	0.95 (0.78 to 1.15)	52	(6.3)	60	(5.2)	0.29	0.84 (0.53 to 1.33)
Surgical site complications	1,102	(23.1)	272	(8.8)	< .001	0.32 (0.28 to 0.37)	67	(8.2)	117	(10.1)	0.15	1.26 (0.92 to 1.72)
Medical complications	1,094	(23)	444	(14.3)	< .001	0.56 (0.50 to 0.63)	82	(10)	164	(14.1)	0.01	1.48 (1.12 to 1.96)
Transfusion	321	(6.7)	96	(3.1)	< .001	0.44 (0.35 to 0.56)	29	(3.5)	34	(3.0)	0.49	0.84 (0.51 to 1.39)
Perioperative death	53	(1.1)	20	(0.6)	.03	0.57 (0.34 to 0.95)	*	*	*	*	0.09	0.14 (0.01 to 1.39)
Discharge status					< .001						< .001	
Home	4,193	(88.1)	2,812	(90.7)			629	(76.6)	1,107	(95.6)		
Nursing home	506	(10.6)	147	(4.7)			46	(5.6)	50	(4.3)		
Dead	*	*	*	*			*	*	*	*		
Unknown	*	*	*	*			*	*	*	*		
Adjuvant therapy												
Brachytherapy	1,475	(31.0)	1,042	(33.6)	.01	1.13 (1.03 to 1.24)	244	(29.8)	391	(33.8)	.06	1.21 (0.99 to 1.46)
Pelvic radiotherapy	1,492	(31.3)	1,062	(34.3)	.01	1.14 (1.04 to 1.26)	249	(30.3)	395	(34.1)	.07	1.19 (0.99 to 1.48)
Chemotherapy	637	(13.4)	421	(13.6)	.81	1.02 (0.89 to 1.16)	141	(17.2)	210	(18.1)	.58	1.07 (0.84 to 1.35)

Abbreviation: OR, odds ratio.
*Suppressed due to small cell size.

Table 4. Adjusted Mortality Based on Route of Hysterectomy

Route of hysterectomy	Cancer-Specific Mortality HR (95% CI)	Overall Mortality HR (95% CI)
Minimally invasive versus abdominal hysterectomy		
Base model		
Abdominal hysterectomy	Referent	Referent
Minimally invasive hysterectomy	0.83 (0.59 to 1.16)	0.89 (0.75 to 1.04)
Adjusted for adjuvant therapy		
Abdominal hysterectomy	Referent	Referent
Minimally invasive hysterectomy	0.81 (0.58 to 1.14)	0.88 (0.75 to 1.04)
Stage I base model		
Abdominal hysterectomy	Referent	Referent
Minimally invasive hysterectomy	1.01 (0.58 to 1.73)	0.98 (0.78 to 1.21)
Stage I adjusted for adjuvant therapy		
Abdominal hysterectomy	Referent	Referent
Minimally invasive hysterectomy	0.97 (0.56 to 1.67)	1.01 (0.77 to 1.19)
Robot-assisted *v* laparoscopic hysterectomy		
Base model		
Laparoscopic	Referent	Referent
Robot-assisted	1.53 (0.76 to 3.05)	1.00 (0.72 to 1.41)
Adjusted for adjuvant therapy		
Laparoscopic	Referent	Referent
Robot-assisted	1.45 (0.73 to 2.918)	0.97 (0.69 to 1.37)
Stage I base model		
Laparoscopic	Referent	Referent
Robot-assisted	1.47 (0.43 to 5.08)	0.92 (0.57 to 1.49)
Stage I adjusted for adjuvant therapy		
Laparoscopic	Referent	Referent
Robot-assisted	1.38 (0.39 to 4.82)	0.92 (0.57 to 1.49)

NOTE. Comparison of propensity score balanced groups and adjusted for adjuvant therapy (radiation, brachytherapy, chemotherapy).

suggest that some higher risk patients who would previously have undergone laparotomy are undergoing less morbid, MIS with robotic assistance. Although we did not specifically analyze cost, prior studies have suggested that robot-assisted surgery is more costly than laparoscopy.[4,5,33]

Encouragingly, we found no difference in survival between laparotomy and MIS for endometrial cancer. In the Gynecologic Oncology Group's LAP2 trial, 2,616 women with apparent stage I-II endometrial cancer were randomly assigned to either laparotomy or laparoscopy. Although the study did not meet the protocol-specified definition of noninferiority, survival was similar between the two arms, and the findings were largely interpreted to indicate that MIS is safe for endometrial cancer.[7] Other smaller prospective series have reported similar outcomes comparing laparoscopy and laparotomy.[8-13] Although data comparing survival for robot-assisted hysterectomy with other modalities of hysterectomy are more limited, institutional studies have generally reported equivalent outcomes.[34-37] Importantly, the 95% CI for MIS compared with abdominal hysterectomy in our primary survival analysis ranged from 0.75 to 1.04, suggesting that MIS hysterectomy is unlikely to be inferior to an abdominal procedure. Furthermore, our findings of equivalent survival across the modalities of hysterectomy were similar in a wide range of sensitivity analyses.

We identified an increased use of adjuvant radiation, both whole pelvic radiation and brachytherapy, in women who underwent minimally invasive hysterectomy. The need for additional cancer-directed therapy has been used as a surrogate for surgical outcomes and quality for other procedures, such as prostatectomy, a disease process that similarly has favorable survival and high cure rates.[38] The mechanism underlying the need for increased use of adjuvant therapy after minimally invasive hysterectomy remains unclear, particularly as patients who had a minimally invasive procedure had somewhat more favorable tumor prognostic factors, even after propensity score balancing. Particularly for women with large uteri, manipulation at the time of surgery or disruption or spillage of tumor from the uterine cavity may prompt use of radiation. This phenomenon warrants further investigation and careful monitoring.

Like prior studies, we noted a number of disparities in the allocation of treatment of women with endometrial cancer.[39] Minimally invasive hysterectomy was more commonly used in patients with higher SES and in larger hospitals. This is in accord with other studies of hysterectomy for both benign and oncologic indications that have shown significant disparities in the use of newer procedures.[4,5] Not surprisingly, women with higher stage tumors and more aggressive histologic subtypes were less likely to undergo a minimally invasive operation.

Although our study benefits from the inclusion of a large sample of patients, we recognize a number of important limitations. First, claims data undercaptures complications. To mitigate this bias, we chose to include only major perioperative complications. Although any undercapture of complications should be balanced across the groups, we recognize that we cannot measure minor complications with the current study design. Second, our analysis is limited to elderly Medicare beneficiaries and may not be generalizable to all women. However, the SEER-Medicare dataset represents a unique resource to examine long-term survival linked to detailed tumor

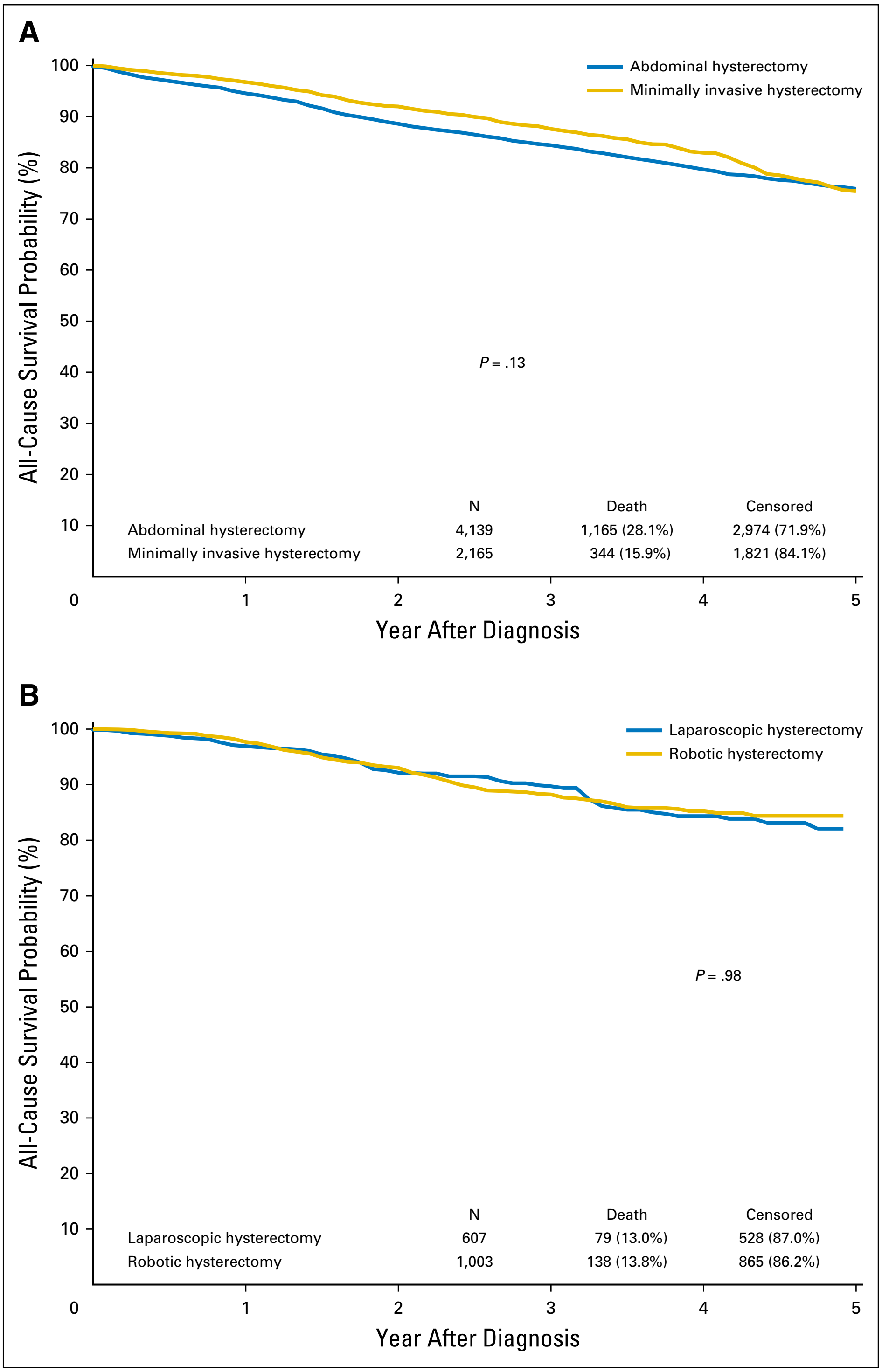

Fig 2. (A) Kaplan-Meier analysis of overall survival for abdominal versus minimally invasive hysterectomy (*P* = .13). (B) Kaplan-Meier analysis of overall survival for laparoscopic versus robot-assisted hysterectomy (*P* = .98).

data. Third, given that survival is favorable for early-stage endometrial cancer, our analysis is not powered to detect small differences in survival between groups. As discussed previously, this is an intrinsic limitation of studies of endometrial cancer and highlights the importance of including other outcomes metrics, such as complications and patient-reported outcomes in comparative effectiveness studies. Lastly, as with any study of administrative data, we cannot capture individual patient and physician preferences that undoubtedly influenced treatment decision making.

In sum, these data suggest that the use of minimally invasive hysterectomy for uterine cancer has increased rapidly since 2007 and now accounts for more than 60% of operations for the disease. Importantly, the procedure is associated with long-term survival that is comparable to abdominal hysterectomy and a favorable morbidity profile.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Comparative Effectiveness of Minimally Invasive Hysterectomy for Endometrial Cancer

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Appendix

Table A1. Clinical and Demographic Characteristics of Women Who Underwent Laparoscopic or Robot-Assisted Hysterectomy

	Unadjusted					Inverse Probability of Treatment Weighting*				
	Laparoscopic Hysterectomy (N = 607)		Robot-Assisted Hysterectomy (N = 1,003)			Laparoscopic Hysterectomy (N = 821)		Robot-Assisted Hysterectomy (N = 1,157)		
Characteristic	No.	(%)	No.	(%)	P†	No.	(%)	No.	(%)	P‡
Year of diagnosis					.82					.61
2009	172	(28.3)	278	(27.7)		220	(26.8)	318	(27.5)	
2010	203	(33.4)	351	(35.0)		264	(32.2)	400	(34.6)	
2011	232	(38.2)	374	(37.3)		337	(41.0)	439	(38.0)	
Age, years					.31					.83
< 65-69	167	(27.5)	312	(31.1)		238	(28.9)	353	(30.5)	
70-74	192	(31.6)	298	(29.7)		268	(32.6)	345	(29.9)	
75-79	122	(20.1)	211	(21.0)		164	(20.0)	245	(21.2)	
≥ 80	126	(20.8)	182	(18.2)		152	(18.5)	214	(18.5)	
Race/ethnicity					.44					.56
White	544	(89.6)	897	(89.4)		740	(90.1)	1,021	(88.2)	
Black	28	(4.6)	58	(5.8)		45	(5.5)	72	(6.2)	
Other	35	(5.8)	48	(4.8)		37	(4.5)	65	(5.6)	
Marital status					.21					.70
Married	308	(50.7)	465	(46.4)		418	(51.0)	559	(48.3)	
Unmarried	274	(45.1)	488	(48.7)		371	(45.2)	548	(47.3)	
Other	25	(4.1)	50	(5.0)		32	(3.9)	51	(4.4)	
Residence					< .001					.43
Metropolitan	565	(93.1)	857	(85.4)		741	(90.2)	1,020	(88.1)	
Nonmetropolitan	42	(6.9)	146	(14.6)		80	(9.8)	137	(11.9)	
Socioeconomic status					.001					.59
Lowest (first) quintile	110	(18.1)	207	(20.6)		141	(17.2)	223	(19.3)	
Second quintile	120	(19.8)	219	(21.8)		180	(21.9)	238	(20.6)	
Third quintile	83	(13.7)	173	(17.3)		118	(14.4)	192	(16.6)	
Fourth quintile	175	(28.8)	289	(28.8)		253	(30.8)	349	(30.2)	
Highest (fifth) quintile	119	(19.6)	115	(11.5)		129	(15.7)	154	(13.3)	
Registry area					< .001					.17
East	153	(25.2)	273	(27.2)		224	(27.3)	314	(27.1)	
Midwest	125	(20.6)	319	(31.8)		190	(23.1)	330	(28.5)	
West	329	(54.2)	411	(41.0)		407	(49.6)	513	(44.4)	
Comorbidity score					.49					.59
0	360	(59.3)	605	(60.3)		518	(63.0)	696	(60.1)	
1	164	(27)	247	(24.6)		201	(24.5)	296	(25.6)	
≥ 2	83	(13.7)	151	(15.1)		102	(12.5)	166	(14.3)	
Grade					.04					.83
1	245	(40.4)	346	(34.5)		300	(36.5)	418	(36.1)	
2	184	(30.3)	297	(29.6)		241	(29.4)	343	(29.7)	
3	102	(16.8)	207	(20.6)		175	(21.3)	228	(19.7)	
Unknown	76	(12.5)	153	(15.3)		105	(12.8)	168	(14.6)	
Tumor stage					.40					.51
IA	338	(55.7)	532	(53.0)		462	(56.2)	631	(54.5)	
IB	119	(19.6)	188	(18.7)		169	(20.6)	211	(18.2)	
INOS	21	(3.5)	33	(3.3)		19	(2.3)	37	(3.2)	
II	47	(7.7)	77	(7.7)		60	(7.3)	88	(7.6)	
III	82	(13.5)	173	(17.3)		111	(13.5)	191	(16.5)	

(continued on following page)

Table A1. Clinical and Demographic Characteristics of Women Who Underwent Laparoscopic or Robot-Assisted Hysterectomy (continued)

	Unadjusted					Inverse Probability of Treatment Weighting*				
	Laparoscopic Hysterectomy (N = 607)		Robot-Assisted Hysterectomy (N = 1,003)			Laparoscopic Hysterectomy (N = 821)		Robot-Assisted Hysterectomy (N = 1,157)		
Characteristic	No.	(%)	No.	(%)	*P*†	No.	(%)	No.	(%)	*P*‡
Lymphadenectomy					< .001					.41
No	220	(36.2)	231	(23.0)		236	(28.7)	306	(26.4)	
Yes	387	(63.8)	772	(77.0)		586	(71.3)	852	(73.6)	
Histology					.10					.32
Endometrioid	557	(91.8)	887	(88.4)		752	(91.6)	1,030	(89.0)	
Carcinosarcoma	12	(2.0)	25	(2.5)		13	(1.6)	27	(2.3)	
Serous	38	(6.3)	91	(9.1)		56	(6.9)	100	(8.7)	
Teaching hospital					< .001					.0037
No	233	(38.4)	275	(27.4)		283	(34.4)	347	(30.0)	
Yes	298	(49.1)	594	(59.2)		453	(55.1)	620	(53.6)	
Unknown	76	(12.5)	134	(13.4)		86	(10.4)	190	(16.4)	
NCI center					< .001					.024
No	547	(90.1)	813	(81.1)		728	(88.6)	957	(82.7)	
Yes	41	(6.8)	152	(15.2)		72	(8.8)	146	(12.6)	
Unknown	19	(3.1)	38	(3.8)		21	(2.6)	54	(4.7)	
Hospital beds					< .001					.43
< 200	55	(9.1)	49	(4.9)		45	(5.5)	61	(5.3)	
200-400	129	(21.3)	269	(26.8)		218	(26.5)	286	(24.7)	
401-600	295	(48.6)	370	(36.9)		350	(42.6)	472	(40.8)	
> 600	107	(17.6)	277	(27.6)		185	(22.6)	284	(24.5)	
Unknown	21	(3.5)	38	(3.8)		24	(2.9)	54	(4.7)	
Hospital volume										
Median (IQR)	5.8	(3-10.0)	5.5	(3.3-9.7)	.01	6	(3.3-10.0)	5.7	(3.3-9.7)	.78

*Frequency numbers were rounded to integers based on weight.
†*P* values were derived from χ^2 tests.
‡*P* values were derived from weighted surveylogistic model.