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Comparison of survival and perioperative outcomes following simple and radical hysterectomy for stage II endometrial cancer: a single-institution, retrospective, matched-pair analysis

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Abstract

Objective: We aimed to compare the survival and perioperative outcomes of patients with stage II endometrial cancer (EC) undergoing simple hysterectomy (SH) or radical hysterectomy (RH), to validate the various guidelines.

Methods: A total of 155 consecutive patients diagnosed with stage II EC from 2000 to 2014 were reviewed. We identified 40 pairs of patients (40 SH and 40 RH) who were matched in terms of age, pathological type, and lymphovascular space invasion status using matched-pair analysis. Patient data were collected from medical records and outcomes were determined by telephone follow-up.

Results: Among the 80 patients in the two groups, seven died from tumor recurrence. However, cancer-related survival rates were not significantly different between the SH and RH groups. The 3-year cancer-related survival rates in the SH and RH groups were 94.97% and 92.53%, and the 5-year survival rates were 92.40% and 90.03%, respectively. Regarding perioperative outcomes,

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the SH group had significantly less intraoperative bleeding and a significantly shorter catheter-indwelling time than the RH group.
Conclusions: SH provides similar survival outcomes and a superior perioperative quality of life compared with RH in patients with stage II EC.

Keywords
Endometrial cancer, simple hysterectomy, radical hysterectomy, survival, quality of life, postoperative complication

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Introduction

Endometrial cancer (EC) is the second most prevalent gynecological malignancy in China according to the National Central Cancer Registry of China, with a 5-year prevalence rate of 31.6 per 100,000 women.[1] Current treatment strategies for EC are based on the International Federation of Gynecologists and Obstetricians (FIGO) staging system. The 1988 FIGO staging system defined stage II EC as EC with cervical mucosal and stromal involvement; however, the 2009 revised staging criteria indicated that stage II EC should only include patients with cervical stromal invasion.[2] Radical hysterectomy (RH) with bilateral salpingo-oophorectomy (BSO) is recommended for patients with stage II EC on the basis of the 2014 European Society for Medical Oncology (EMSO) and National Comprehensive Cancer Network (NCCN) guidelines.[3–5] However, recently published NCCN guidelines for uterine neoplasms in 2018 recommend both simple hysterectomy (SH) and RH for operable patients with cervical involvement, together with BSO, cytology (peritoneal lavage), and lymph node dissection if indicated.[6] In addition, the latest ESMO guidelines do not recommend RH for the management of stage II EC, and the recommendation is for EC up to grade B.[7]

RH refers to excision of the uterus with the parametrium (i.e., round, broad, cardinal, and uterosacral ligaments) and the upper one-third to one-half of the vagina. However, stage II EC does not invade the parametrium or vagina. Furthermore, RH is associated with a high postoperative incidence of sexual dysfunction, significant blood loss, bladder and bowel dysfunction, and fistula formation.[8,9] Nevertheless, several clinical studies have demonstrated the benefits of RH compared with SH in patients with stage II EC, and showed that RH or modified RH might improve overall survival compared with SH.[10–12] However, other studies have provided contradictory results, and showed that SH provided comparable survival outcomes to RH in patients with FIGO stage II EC.[13–15] Therefore, despite changes in the guidelines, the need for more invasive surgical methods for stage II EC remains controversial.

We aimed to address this controversy and the validity of the changes in the guidelines by examining previous articles published over several decades, and by comparing the survival and perioperative outcomes of matched patients with stage II EC who underwent SH or RH at the Obstetrics and Gynecology Hospital of Fudan University.

Materials and methods

Study selection for literature review

We screened studies investigating survival outcomes of patients with stage II EC treated with SH or RH worldwide over several decades. We performed a MEDLINE search with the keywords *simple hysterectomy, radical hysterectomy, stage II endometrial cancer*, and *survival*. We also further searched the reference lists of relevant publications to identify missed studies.

Study participants

A total of 1171 patients were diagnosed with EC and operated on at the Obstetrics and Gynecology Hospital of Fudan University from 2000 to 2014. Patients with pathological stage II EC according to the FIGO 2009 guidelines were included in the study. Patients with only cervical glandular invasion and patients who were lost to follow-up were excluded. The remaining patients were divided into an RH and SH group, matched according to age, pathological type, and lymphovascular space invasion (LVSI) using a case-matching method. BSO, lymphadenectomy, omentum resection, and appendectomy were performed as appropriate. Patients were under observation or received subsequent therapy, including chemotherapy, radiotherapy, or endocrine therapy, if necessary. Demographic, surgical, pathological, and postoperative outcome data were extracted from the resident admission notes, discharge records, surgical records, pathology reports, progress notes, and nursing records in the medical archives of the Obstetrics and Gynecology Hospital of Fudan University. Information on patient outcomes was obtained by telephone follow-up at specified intervals. The study was approved by the ethics committee of the Obstetrics and Gynecology Hospital of Fudan University. All enrolled patients provided written informed consent.

Surgical methods

SH involved complete removal of the uterus and cervix, with or without BSO, and RH involved additional resection of the lateral parametrium and ventral parametrium. RH was further classified into four types according to the range of parametrial resection, based on criteria published in 2011.[16] All types of RH, except type 4, met the study inclusion criteria.

Performance of lymphadenectomy associated with SH or RH, as well as omentum resection, was decided based on pre- and perioperative findings.

Statistical analysis

Categorical and numerical demographic, surgical, pathological, and postoperative variables in the SH and RH groups were analyzed and compared using χ^2 and t-tests. $P < 0.10$ or $P < 0.05$ was considered to indicate statistical significance.

The main outcome was cancer-related survival, with death as an event. Survival was compared using the log-rank test and Kaplan–Meier analysis. Multivariate analysis was carried out by Cox proportional hazards regression.

Results

Previous studies of survival following SH and RH for stage II EC

A search of the MEDLINE database for studies of patients with stage II EC treated with SH or RH identified 11 relevant articles published from 1993 to 2017. Three articles were based on data from the Surveillance, Epidemiology, and End Result (SEER) database, and the other eight were retrospective studies from America, Italy, Turkey,

and Japan. There was thus a lack of data from China in relation to survival after SH and RH among patients with stage II EC. All four studies conducted before 2011 showed that survival after RH was superior to that after SH, while all five studies conducted after 2009 showed similar survival after RH and SH (Table 1). These results suggest that the survival advantage of RH in patients with stage II EC gradually disappeared, and the procedure may have resulted in more serious perioperative complications. In addition, studies from America and Italy found that survival after RH was superior to that after SH, while studies from Turkey and Japan found similar survival after RH and SH (Table 1). The conclusions regarding the relative outcomes of RH and SH may thus be affected by both geographic region and study period.

Table 1. Summary of previous articles comparing survival of patients with stage II endometrial cancer following SH or RH.

Author	Publication year	Study period	Region	Sample size	Survival (SH vs RH)
Boente et al.[26]	1993	1972–1988	USA	202	RH superior to SH (77% vs 86%) 5 year-related OS
Cornelison et al.[12]	1999	1988–1994	SEER database	932	RH superior to SH (84% vs 92.96%) 5 year-related OS
Mariani et al.[27]	2001	1984–1993	Italy	82	RH superior to SH (68% vs 76%) 5 year-related OS
Sartori et al.[10]	2001	1980–1995	Italy	203	RH superior to SH (79% vs 94%) 5 year-related OS
Ayhan et al.[28]	2004	1982–2000	Turkey	48	RH equal to SH (83% vs 90%) 5 year-related OS
Cohn et al.[11]	2007	1982–2004	USA	162	RH superior to SH (81% vs 88%) 5 year-related OS
Wright et al.[29]	2009	1988–2004	SEER database	1577	RH equal to SH (79% vs 82%) 5 year-related OS
Miyamoto et al.[30]	2016	1990–2009	Japan	247	RH equal to SH
Phelippeau and Koskas[15]	2016	1998–2012	SEER database	819	RH equal to SH (88.7% vs 94.1%) 3 year-related OS
Takano et al.[13]	2013	1995–2009	Japan	300	RH equal to SH (84% vs 83.6%) 5 year-related OS
Ozgul et al.[14]	2018	2002–2015	Turkey	250	RH equal to SH (83% vs 89%) 5 year-related OS

SH: simple hysterectomy, RH: radical hysterectomy, OS: overall survival.

Patient characteristics

Among 1171 patients diagnosed with EC and operated on from 2000 to 2014, 155 women aged 23 to 77 years were diagnosed with stage II EC according to final pathology reports during the same period. Of these 155 patients, 56 had undergone SH and 99 had undergone RH. Sixteen of these 155 patients died of tumor recurrence but no patients died of other causes during the follow-up period. We excluded 30 patients who were lost to follow-up (11 SH and 19 RH). Following case-matching, 80 patients (40 SH and 40 RH) were therefore included in our final study (Figure 1). The demographic, surgical, and pathological characteristics of the patients are presented in Table 2.

The groups were comparable with regard to age, pathological type, pathological grade, tumor size, depth of myometrial invasion, depth of cervical stromal invasion, LVSI, hypertension, diabetes, surgical pathway, postoperative therapy, lymphadenectomy, and omentum resection.

Three patients (3/40, 7.5%) in the SH group had recurrence, including one in the pelvis, one in the liver, and one in the liver, pelvis, and intestines. Four patients (4/40, 10%) in the RH group had recurrence, including one in the vaginal cuff, two in the pelvis, and one with distant metastasis in the liver.

Survival of patients with stage II EC

The relationships between demographic, surgical, and pathological factors and overall survival were assessed by Kaplan–Meier analysis, which identified primary tumor pathological type ($P = 0.069$), LVSI ($P = 0.063$), surgical pathway ($P = 0.059$), and lymphadenectomy ($P = 0.041$) as significant predictors of overall survival (Table 3). These significant prognostic factors ($P < 0.100$) in the Kaplan–Meier analysis were then analyzed using a Cox

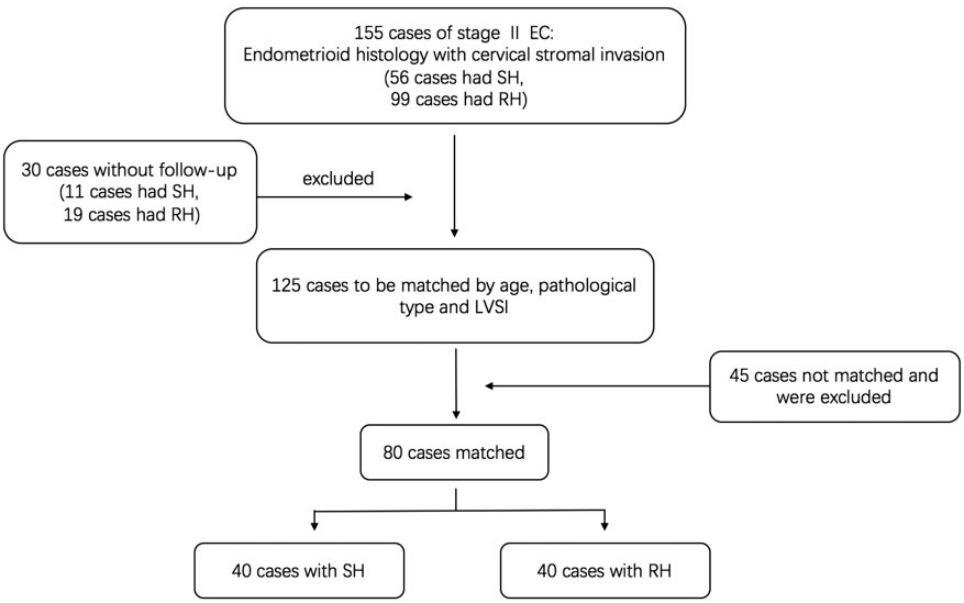

Figure 1. Flowchart of case selection in matched-pair analysis. A case-matched method was used to obtain two homogeneous groups according to age, pathological type, and LVSI. EC: endometrial cancer, SH: simple hysterectomy, RH: radical hysterectomy, LVSI: lymphovascular space invasion.

Table 2. Patient demographic, surgical, and pathological characteristics.

	Simple hysterectomy	Radical hysterectomy	χ^2 *P* value
Age (years)	52.75 ± 9.32	52.80 ± 9.44	0.981
Pathological type			
Endometrioid adenocarcinoma	30	29	0.800
Other type*	10	11	
Grade (among endometrioid adenocarcinomas)			
1	18	9	0.072
2	10	15	
3	2	5	
Tumor size according to final pathologic record			
<2 cm	16	8	0.137
2–5 cm	17	21	
>5 cm	7	11	
Myometrial invasion depth			
<1/2	27	26	0.813
≥1/2	13	14	
Cervical stromal invasion depth			
<1/2	33	28	0.293
≥1/2	7	12	
LVSI			
No	32	28	0.302
Yes	8	12	
Hypertension			
No	31	33	0.576
Yes	9	7	
Diabetes			
No	33	34	0.762
Yes	7	6	
Surgical pathway			
Laparotomy	21	23	0.186
Laparoscopic surgery	19	17	
Lymphadenectomy			
No	6	2	0.136
Yes	34	38	
Omentum resection			
No	36	38	0.396
Yes	4	2	
Postsurgical treatment			
Observation	16	16	0.506
Chemotherapy	17	17	
Chemotherapy+radiotherapy	7	5	
Endocrine therapy	0	2	

*Serous carcinoma, mucinous adenocarcinoma, clear cell adenocarcinoma, and mixed cell adenocarcinoma. LVSI: lymphovascular space invasion.

Table 3. Prognostic indicators in patients with stage II endometrial cancer.

Risk factor	Cases	Deaths	Cancer-related survival rate	χ^2	*P*
Age (years)					
<60	58	5	91.4%	0.005	0.945
≥60	22	2	90.9%		
Grade (among endometrioid adenocarcinomas)					
1	27	1	96.3%	1.333	0.513
2	25	1	96.0%		
3	7	1	85.7%		
Pathological type					
Endometrioid adenocarcinoma	59	3	94.9%	3.306	0.069
Other*	21	4	81.0%		
Tumor size					
<2 cm	24	2	91.7%	2.436	0.296
2–5 cm	38	5	86.8%		
>5 cm	18	0	100.0%		
Myometrial invasion deep					
<1/2	53	3	94.3%	1.715	0.190
≥1/2	27	4	85.2%		
Cervical invasion deep					
<1/2	61	6	90.2%	0.350	0.554
≥1/2	19	1	94.7%		
LVSI					
Yes	20	4	80.0%	3.454	0.063
No	60	3	95.0%		
Surgical method					
Simple hysterectomy	40	3	92.5%	0.090	0.764
Radical hysterectomy	40	4	90.0%		
Surgical pathway					
Laparotomy	44	6	86.4%	3.564	0.059
Laparoscopic	36	1	97.2%		
Lymphadenectomy					
Yes	72	5	93.1%	4.186	0.041
No	8	2	75.0%		
Omentum resection					
Yes	6	1	83.3%	0.567	0.451
No	74	6	91.9%		
Postsurgical treatment					
Observation	32	1	96.9%	3.464	0.325
Chemotherapy	34	5	85.3%		
Chemotherapy + radiotherapy	12	1	91.7%		
Endocrine therapy	2	0	100.0%		

*Serous carcinoma, mucinous adenocarcinoma, clear cell adenocarcinoma, and mixed cell adenocarcinoma. LVSI: lymphovascular space invasion.

Table 4. Multivariate analysis of demographic, surgical, and pathological factors.

Risk factor	Hazard ratio (95% CI)	*P* value
Pathological type (endometrioid adenocarcinoma compared withother types*)	0.521 (0.102–2.669)	0.434
LVSI (no compared with yes)	0.337 (0.068–1.672)	0.183
Surgical pathway (laparotomy compared with laparoscopic surgery)	4.122 (0.418–40.669)	0.225
Lymphadenectomy (no compared with yes)	1.700 (0.289–9.997)	0.557

*Serous carcinoma, mucinous adenocarcinoma, clear cell adenocarcinoma, and mixed cell adenocarcinoma. CI, confidence interval, LVSI: lymphovascular space invasion.

proportional hazards model. However, after removing confounding factors, no factor had any significant effect on survival of patients with stage II EC (Table 4).

Furthermore, there was no significant difference in cancer-related survival rates between the SH and RH groups (Table 3). The 3-year cancer-related survival rates in the SH and RH groups were 94.97% and 92.53%, and the 5-year cancer-related survival rates were 92.40% and 90.03%, respectively. There were no significant differences in cancer-related survival rates between the two groups (Figure 2).

Perioperative outcomes of SH and RH

In terms of choosing the optimal surgical method for stage II EC, we examined perioperative outcomes and quality of life, in addition to cancer-related survival rates (Table 5). SH was associated with significantly less intraoperative bleeding (mean ± standard deviation: 325.0 ± 307.7 mL vs 625.0 ± 581.4 mL, respectively, $P = 0.010$) and a shorter catheter-indwelling time compared with RH (4.8 ± 3.5 days vs 11.5 ± 3.9 days, $P < 0.001$). However, there was no significant difference in the length of hospital stay after surgery, hospitalization cost, therapeutic time with antibiotics, or total number of postoperative complications between the two groups.

Moreover, 12.5% (5/40) of patients in the SH group had postoperative complications (postoperative morbidity, n = 3; incision infection, n = 1; pelvic abscess, n = 15), compared with 10.0% (4/40) in the RH group (intestinal obstruction, n = 1; postoperative morbidity, n = 1; *Escherichia coli* infection, n = 1; uroschesis and urinary tract infection, n = 1). There was no significant difference in complication rates between the two groups, but there were more types of complications after RH compared with SH.

Discussion

Although most women diagnosed with EC present with early-stage disease confined to the uterus, metastatic disease is identified in a significant percentage after comprehensive staging surgery,[17] suggesting the need for more radical and thorough surgery in patients with stage II EC. Previous editions of the NCCN and EMSO guidelines recommended RH for clinical stage II EC with suspected gross cervical involvement. However, given the high incidence of sexual dysfunction and poor quality of life following RH, we investigated the possibility of replacing RH with SH in patients with stage II EC.

Several studies found that RH was associated with increased disease-free and

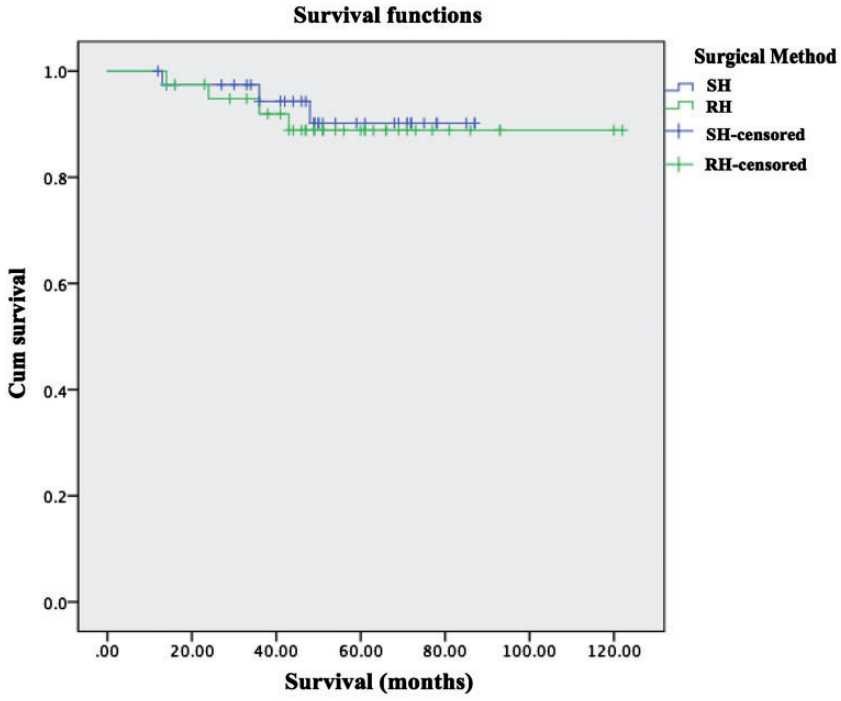

Figure 2. Cancer-related survival curve according to hysterectomy type. There were no significant differences in survival between the SH and RH groups. The 3-year cancer-related survival rates in the SH and RH groups were 94.97% and 92.53% and the 5-year cancer-related survival rates were 92.40% and 90.03%, respectively. SH: simple hysterectomy, RH: radical hysterectomy, Cum survival: cumulative survival, censored: patients lost to follow-up and patients who survived until the end of the study.

Table 5. Comparison of perioperative situations in patients undergoing simple hysterectomy and radical hysterectomy.

	Simple hysterectomy	Radical hysterectomy	*P* value	χ^2
Length of postoperative hospital stay	13.5 ± 4.6	15.4 ± 4.8	0.060	
Hospitalization costs	22428.1 ± 7654.9	22428.1 ± 12562.0	0.516	
Hospitalization costs (after 2008)	23115.2 ± 9134.8	27151.1 ± 11432.3	0.283	
Intraoperative bleeding	325.0 ± 307.7	625.0 ± 581.4	0.010	
Therapeutic time of antibiotics	3.4 ± 1.5	3.9 ± 2.0	0.259	
Time of indwelling catheter	4.8 ± 3.5	11.5 ± 3.9	<0.001	
Postoperative complications	5	4	0.724	0.125

overall survival. For example, Sartori et al.[10] conducted a retrospective trial of 135 SH and 68 RH procedures for stage II EC and showed that the 5-year (94% vs 79%) and 10-year (94% vs 74%) survival rates were higher in the RH compared with the SH group. Likewise, Cohn et al.[11] studied 162 patients with surgical stage II EC and found a significantly better 5-year disease-free survival rate in

patients undergoing RH compared with extrafascial hysterectomy (94% vs 76%). In a larger sample size, Cornelison et al.[12] based their results on the SEER database, which included 932 patients with stage II EC, and showed that RH was associated with better survival than SH (92.96% vs 84.36%), but there was no significant survival difference between patients with and without radiation in either surgical group.

However, the above-mentioned studies were performed almost 10 years ago, prior to the development of the FIGO 2009 staging system. They therefore included patients with both endocervical glandular involvement (1988 FIGO stage IIA) and cervical stromal invasion (1988 FIGO stage IIB). In addition, the prevalence of laparoscopy and improvements in surgical equipment, environment, and technology may also have increased survival after hysterectomy. Although several studies found no significant improvement in overall survival among patients with EC after laparoscopy compared with laparotomy, [18,19] some reports indicated that the morbidity of hysterectomy has decreased over recent decades.[20–22] Averette et al.[21] demonstrated a continuing trend towards decreasing morbidity and mortality rates after RH in the published literature. Likewise, Benjamin et al.[22] reported significant reductions in blood loss, blood transfusions, and hospital stay after hysterectomy between the periods 1980 to 1993 and 1991 to 1993. In addition, advancements in pathological diagnosis and radiological technologies enable the discovery of small parametrial infiltrations in more patients, resulting in more extensive surgeries and thorough treatments and thus decreasing the incidence of misdiagnosed stage II EC and allowing patients to undergo non-radical surgeries.

Several recent studies have shown conflicting results. For example, Takano et al.[13] reported on 300 patients with stage II EC who underwent RH, modified hysterectomy, or SH, and indicated that the type of hysterectomy was not a prognostic factor in patients with EC and gross cervical involvement, though perioperative and late adverse events were more frequent in patients treated with RH. Similarly, Ozgul et al.[14] conducted a multicenter, retrospective trial in Turkey including 250 patients with stage II EC, of whom 199 underwent SH and the remaining 51 underwent RH. They found that age was the only independent risk factor for overall survival, and the type of hysterectomy had no effect on either disease-free or overall survival. Phelippeau et al.[15] analyzed the data for 2886 patients with type 1 FIGO stage II EC from the SEER database. After one-to-two matching, 273 patients who underwent RH and 546 who received SH were included in the statistical analysis, which found no significant difference in 3-year cancer-related survival rates between the two groups (88.7% and 94.1%, respectively).

In the current study, we aimed to determine the survival and perioperative outcomes in patients with stage II EC according to the 2009 FIGO staging system, treated with different types of hysterectomy. We used a case-matched method to avoid any effects of population heterogeneity between the SH and RH groups on the final results. Our results showed that hysterectomy type had no impact on overall survival, although RH could lead to more intraoperative bleeding, a longer catheter-indwelling time, and more complex postoperative complications.

Parametrectomy is the most challenging part of an RH. It is responsible for postoperative urological dysfunction associated with autonomic nerve injury, and the interval before recovery of spontaneous voiding depends on the amount of parametrium removed. This accounts for why patients undergoing RH need a longer catheter-indwelling time than patients who

undergo SH.[23,24] As shown in the current and previous studies, RH can also lead to significant blood loss and more complex postoperative complications, which in turn prolong hospital stay. [9,13] Furthermore, RH is associated with a high incidence of sexual dysfunction, which may severely reduce the patient's quality of life.[8] Indeed, some patients in the current study complained of an unsatisfactory sex life during their telephone follow-up calls.

The above results suggest that reducing the universality of surgery in patients with stage II EC may not only decrease perioperative complications, but may also improve patient quality of life.

The current study had some limitations. We included patients diagnosed with stage II EC from 2000 to 2014, and this long time span may thus have introduced differences in relation to the operative methods, given that perioperative effects were related to the operation environment and technique of the surgeon. In addition, 30 patients were lost to follow-up, which would unavoidably cause some bias. Furthermore, the case-matched method meant that the sample size was relatively small, and investigations in a larger sample could enhance the credibility of these results. Finally, it should be noted that a *P*-value >0.05 does not necessarily indicate a lack of any difference, and we should learn to embrace uncertainty.[25] Thus although our results were most compatible with a lack of any important difference between SH and RH in terms of survival outcomes in patients with stage II EC, it is not possible to make definitive decisions based solely on the *P*-value.

Conclusions

The results of the current retrospective study suggest that SH has similar survival outcomes to RH in patients with FIGO stage II EC. Furthermore, RH may be associated with more intraoperative bleeding, a longer catheter-indwelling time, and more complex postoperative complications than SH. Further prospective studies with large sample sizes are needed to confirm the outcomes of these two surgical procedures in patients with stage II EC.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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