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ORIGINAL ARTICLE – GYNECOLOGIC ONCOLOGY

Impact of Radical Hysterectomy Versus Simple Hysterectomy on Survival of Patients with Stage 2 Endometrial Cancer: A Meta-analysis

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ABSTRACT

Background. The strategy of radical surgery for stage 2 endometrial cancer (EC) remains controversial. This meta-analysis aimed to investigate the impact of radical hysterectomy (RH) versus simple hysterectomy (SH) on survival of patients with stage 2 EC.

Methods. A systematic review was conducted to identify studies comparing survival between RH and SH in International Federation of Gynecology and Obstetrics (FIGO) stage 2 EC patients by searching several databases to July 2018. Hazard ratios (HRs) with 95% confidence intervals (CIs) for overall survival and progression-free survival were pooled using Stata V.12.0.

Results. The study included 10 retrospective cohort studies enrolling 2866 patients. Patients who received RH did not show a significant survival benefit for either overall survival (pooled HR 0.92; 95% CI 0.72–1.16; $P = 0.484$) or progression-free survival (pooled HR 0.75; 95% CI 0.39–1.42; $P = 0.378$). The result remained consistent after it was balanced with possible impact from adjuvant radiotherapy (pooled HR 0.85; 95% CI 0.62–1.16; $P = 0.300$). In earlier studies that staged patients according to FIGO 1988, RH showed a 27% survival benefit (pooled HR 0.73; 95% CI 0.53–1.00; $P = 0.050$), whereas in newly published studies based on FIGO 2009 staging, it reversely showed increased risk of death (pooled HR 1.24; 95% CI 0.86–1.77; $P = 0.245$). However, no statistical significance was reached under either staging criterion.

Conclusions. Based on the results of this meta-analysis, RH does not significantly improve survival in stage 2 EC. The choice of RH remains controversial and should be considered carefully in clinical practice. More qualified studies are needed to determine the best treatment strategy for stage 2 EC.

Endometrial cancer (EC) is the most frequent gynecologic cancer in developed countries, and its incidence is ever rising in developing countries due to economic growth and lifestyle changes. In 2017, it was estimated that 61,380 new uterine cancer cases were diagnosed, and 10,920 women died of the disease in the United States, with EC accounting for approximately 97% of all uterine cancers.[1] According to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging, tumor that invades cervical stroma but does not extend beyond the uterus is defined as stage 2 EC and accounts for approximately 12% of the entire population.[2]

Historically, the surgical management of stage 2 EC has included a radical hysterectomy (RH) or modified radical hysterectomy (mRH) and pelvic lymph node dissection. Simple hysterectomy (SH) or so-called extrafascial hysterectomy has not been well accepted in routine clinical

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practice considering that cervical involvement may indicate a higher rate of parametrial invasion. However, the benefits of radical surgery for stage 2 EC were poorly supported by medical literature, especially in reports of large randomized control trials (RCTs).

The recommendations on this issue remain controversial in different guidelines. Although RH is recommended by the 2018 National Comprehensive Cancer Network (NCCN) guideline[1] as one of the surgical options, its candidates are unclear. Furthermore, it was not accepted as routine management by the European Society for Medical Oncology (ESMO) consensus conference in 2015.[3] Moreover, the value of RH also is doubted by the 2015 FIGO report.[4] Because radical surgery is associated with worse perioperative performance and more surgical morbidities, the life quality of these patients is seriously compromised. Therefore, the role of RH in stage 2 EC should be carefully evaluated on the basis of a systemic and comprehensive study of the existing literature. This meta-analysis aimed to investigate the impact of RH versus SH on survival for stage 2 EC patients.

MATERIALS AND METHODS

Search Strategy

Relevant studies were identified through systematic searches of the following databases to July 2018: PUBMED, MEDLINE, EMBASE, Cochrane Library, and Web of Science. The following terms were used:

> "endometrial neoplasm" or "endometrial cancer" or "endometrial carcinoma" and "radical" or "simple" or "total" or "extrafascial" or "hysterectomy."

Two investigators independently screened the search results for titles and abstracts. Reference lists of the relevant articles were manually searched to find potentially eligible papers.

Selection Criteria

The study included all observational and experimental studies that compared survival between RH and SH among FIGO stage 2 EC patients with surgical treatment and had sufficient data to obtain the hazard ratio (HR) with a 95% confidence interval (CI) for at least one of the quantitative survival outcomes, including overall survival (OS) and progression-free survival (PFS). We did not distinguish between mRH and RH (Piver–Rutledge classes 2 and 3).[5]

For staging, both FIGO 2009 and FIGO 1988 were allowed. We considered Kaplan–Meier curves or Cox proportional hazards regression models to calculate HR for survival comparison between groups. In case of two or more studies possibly including overlapping patients, we selected the one with higher quality or more detailed publication (see Supplementary Methods).

Data Extraction

Two investigators independently extracted data from the included studies using a standardized form (see Supplementary Methods). Hazard ratios were used directly if reported in the original study. When not provided, they were estimated from the data extracted from published Kaplan–Meier curves.[6]

Quality Assessment

The quality of the included studies was assessed independently by two reviewers according to the Newcastle–Ottawa Quality Assessment Scale (NOS) for cohort studies (see Supplementary Methods).[7]

Statistical Analysis

All statistical analyses were performed by Stata V.12.0 (Stata Corp, College Station, TX, USA), and two-sided *P* values lower than 0.05 were considered to be significant. Pooled measure was calculated with HR (with 95% CI) as a long-term outcome for survival analysis.[8] An HR lower than 1 indicated a survival benefit favoring the RH group. Statistical heterogeneity was assessed using the I^2 statistic and Q statistic.[9] A random-effect model was applied when significant heterogeneity existed (I^2 value $> 50\%$).[9] Otherwise, a fixed-effect model was used.

Subgroup analysis was performed to evaluate the impact of the 2009 FIGO stage updating on the results. Sensitivity analysis was performed by excluding the key studies. Publication bias was assessed by inspection of funnel plots, Egger test, and Begg test.

RESULTS

Study Identification and Selection

After systematic searches of electronic databases, screening of titles and abstracts, full-text reviews, and manual searches of references, 10 studies were included in the meta-analysis (Fig. 1). To avoid including patients repetitively from the same database, we excluded a Surveillance, Epidemiology, and End Results (SEER) study conducted by Wright et al.[10] that selected patients treated between 1988 and 2004, covering the periods of the other two SEER studies. We also excluded a study

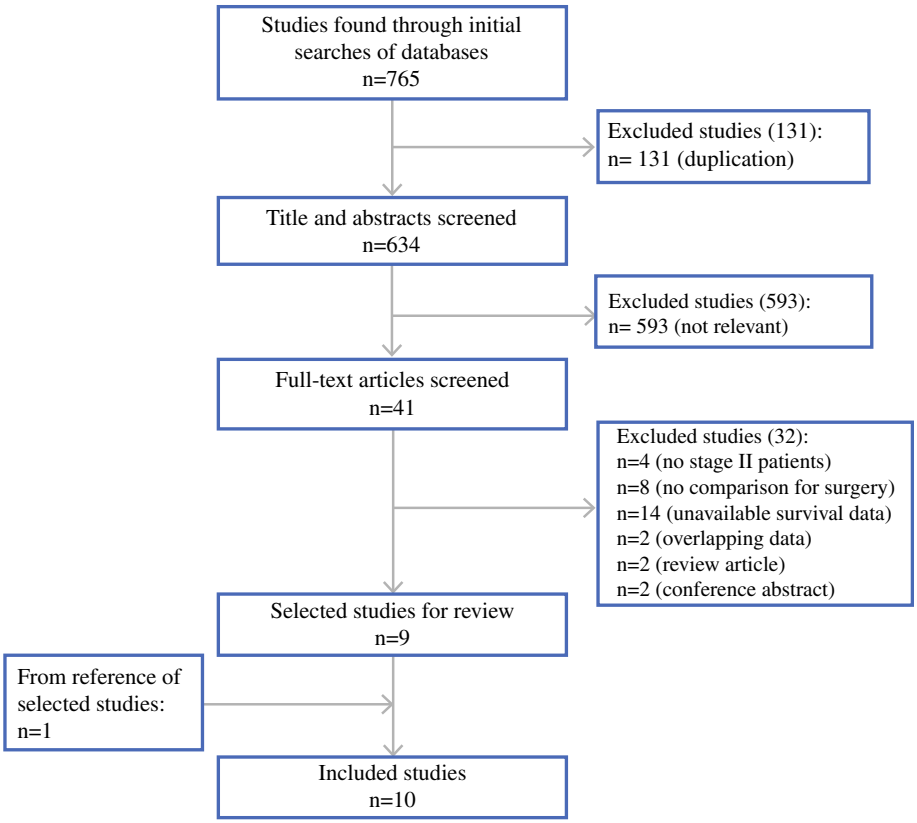

FIG. 1 Flow chart of studies identified, included, and excluded from the meta-analysis

conducted by Wojcieszynski et al.[11] using National Cancer Data Base (NCDB) data from 2004 to 2013, which may have included patients overlapping with the SEER study.[12]

Study Characteristics

The characteristics of the 10 included studies[13–22] are shown in Table 1. All were retrospective cohort studies. One of the studies was matched in a 2:1 ratio of SH to RH groups according to race, stage, tumor size, grade, region and lymphadenectomy practice.[20] In terms of staging criteria, three newly published studies identified surgical stage 2 patients according to FIGO 2009.[17,20,22] The remaining seven studies referred to FIGO 1988.[13–16,18,19,21] Two of these seven studies included some EC patients with suspected cervical involvement clinically that was not confirmed as a stage 2 disease postoperatively.[14,18]

In terms of grouping, three studies considered surgery type as well as adjuvant radiotherapy (ART).[13,14,16] The remaining seven studies grouped patients into SH and RH groups directly without stratification of ART.[15,17–22] Five of these seven studies showed significant difference between surgery groups.[15,17,18,20,21] Prognostic risk factors of EC such as histology, tumor grade, lymph-vascular invasion, deep myometrial invasion, and chemotherapy were taken into consideration, but most studies did not report concrete data between groups.

The included studies were published between 1993 and 2018. A total of 2866 patients were included, and the sample size ranged from 48 to 932 patients. The median follow-up time ranged from 26 to 120 months.

Quality Assessment of the Included Studies

According to the NOS for cohort studies, the median score of the included studies was 7.5 (Table S1). Five studies were graded as 9 or 8 (high quality), and the remaining five studies were graded as 7 or 6 (medium quality). The comparability of cohorts was variable among the studies, and little matching information was identified from the three studies published before 2001.[14,16,18]

Survival

Nine of the included studies reported the OS of the RH and SH surgery groups (Fig. 2). Cornelison et al.[16] grouped patients into four treatment groups according to surgery type and whether ART was received. Thus, two HRs were extracted respectively for comparison among patients who received surgery alone without ART and for comparison among those who received surgery plus ART.

TABLE 1 Study characteristics

Author	Country	Data source	Period	Sample size	Staging definition	Staging		Follow up (months)
Ayhan et al[13] (2004)	Turkey	Hacettepe University Hospital	1982–2000	48	FIGO 1988	2a	15	60 (24–108)
						2b	33	
Boente et al[14] (1993)	USA	Rush Medical College	1972–1988	138	FIGO 1988[a]	NA		82
Cohn et al[15] (2007)	USA	University of Ohio State, Duke, Alabama, Oklahoma, Washington and Mayo Clinic	1982–2004	162	FIGO 1988	2a	85	26 (1–186)
						2b	77	
Cornelison et al[16] (1999)	USA	SEER	1988–1994	932	FIGO 1988	2a	NA	60
						2b	NA	
Fu et al[17] (2018)	China	14 Hospitals of Taiwanese Gynecologic Oncology Group	1992–2013	246	FIGO 2009	2		78 (0.5–259)
Lemine et al[18] (1995)	Finland	Helsinki University Central Hospital	1970–1980	120	FIGO 1988[a]	NA		120
Orezzoli et al[19] (2009)	USA	Massachusetts General Hospital	1993–2003	81	FIGO 1988	2a	26	73 (5–210)
						2b	55	
Phelippeau et al[20] (2016)	France	SEER	1998–2012	819	FIGO 2009	2		37.0 (34.4–40.6)
Sartori et al[21] (2001)	Italy	University of Brescia, Pisa, Monza, Padova, and Torino	1980–1995	203	FIGO 1988	2a	111	112 (48–228)
						2b	92	
Takano et al[22] (2013)	Japan	7 Academic institutions of GOTIC of North Kanto	1995–2009	117	FIGO 2009	2		47

Author	Age (years)	Analyzed groups (no. of patients)	ART	Histology		Grade	
Ayhan et al[13] (2004)	55.8 (34–75)	Group 1 (27): SH plus ART	27[b]	E		1–2	40
		Group 2 (21): RH w/o ART				3	8
Boente et al[14] (1993)	63 (17–90)	Group 1 (68): SH plus ART	3	NA		NA	
		Group 2 (37): SH w/o ART					
		Group 3 (33): RH plus or w/o ART					
Cohn et al[15] (2007)	64 (34–89)	Group 1 (121): SH	32[b]	E	127	1	49
		Group 2 (39): RH		Others	35	2	68
						3	45
Cornelison et al[16] (1999)	NA	Group 1 (365): SH plus ART	634	E	751	1	240
		Group 2 (190): SH w/o ART		Others	181	2	396
		Group 3 (269): RH plus ART				3	257
		Group4(108): RH w/o ART					
Fu et al[17] (2018)	53.1 (42.5–63.7)	Group 1 (141): SH	166[b]	E		1	92
		Group 2 (108): RH				2	105
						3	46

TABLE 1 continued

Author	Age (years)	Analyzed groups (no. of patients)	ART	Histology		Grade	
Lemine et al[18] (1995)	63.5 (40–85)	Group 1 (60): SH	NA	NA		NA	
		Group 2 (60): RH					
Orezzoli et al[19] (2009)	NA	Group 1 (64): SH	67	E		NA	
		Group 2 (17): RH					
Phelippeau et al[20] (2016)	60.6 (58.3–61.9)	Group 1 (546): SH	502[b]	E		1	234
		Group 2 (273): RH				2	342
						3	210
Sartori et al[21] (2001)	59 (39–80)	Group 1 (135): SH	133[b]	E	155	1	67
		Group2 (68): RH		Others	48	2	70
						3	66
Takano et al[22] (2013)	NA	Group 1 (61): SH	23	NA		NA	
		Group 2 (56): RH					

FIGO, International Federation of Gynecology and Obstetrics; NA, not available; SEER, Surveillance, Epidemiology and End Results; GOTIC, Gynecologic Oncology Trial and Investigation Consortium; SH, simple hysterectomy; ART, adjuvant radiotherapy; E, endometrioid adenocarcinoma; RH, radical hysterectomy; w/o, without

[a]Clinical stage 2 endometrial cancer patients were included

[b]Significant difference between two surgery groups

For the pooled studies, the I^2 statistic was 33.7%, indicating low heterogeneity. Therefore, we used the fixed-effect model. The pooled HR of 0.92 (95% CI 0.72–1.16; $P = 0.484$) indicated that patients with RH did not show a significant OS benefit over those with SH.

Only three of the included studies reported on PFS. The pooled estimate (HR 0.75; 95% CI 0.39–1.42; $P = 0.378$) indicated that RH increased PFS compared with SH, but the result was not statistically significant (Fig. 2). The I^2 value was 0.0%, indicating little heterogeneity and use of the fixed-effect model.

To eliminate the possible impact of ART on survival, we dropped five studies with significant difference of ART between groups. Three studies with balanced ART and one study conducted by Cornelison et al.[16] with two HRs comparing patients who received surgery with and without ART, respectively, were included (Fig. 3). The pooled HR of 0.85 (95% CI 0.62–1.16; $P = 0.300$) also showed no significant difference in OS between groups, consistent with the result shown in Fig. 2. The I^2 value was 47.9%, indicating no significant heterogeneity and use of the fixed-effect model.

The implication of FIGO stage updating in 2009 was taken into consideration. Subgroup analysis (Fig. 4) showed that for patients staged 2 according to FIGO 1988, the pooled HR (0.73; 95% CI 0.53–1.00; $P = 0.050$) showed a 27% OS benefit of RH over SH. In contrast, when the pooled estimate in newly published studies included stage 2 EC patients under FIGO 2009, RH showed increased relative risk of death (HR 1.24; 95% CI 0.86–1.77; $P = 0.245$). The difference between subgroups was statistically significant, indicating inter-subgroup heterogeneity ($P = 0.030$). However, no significant difference in OS was reached under either staging criterion.

The impact of surgical approach (e.g., open vs laparoscopic) on survival of stage 2 EC patients was not considered in most of the included studies. Only five studies reported the exact surgical approach, with all the patients receiving open surgery.[13,14,18,19,21] Of the four studies reporting OS for stage 2 EC patients with open surgery,[13,14,19,21] the pooled HR (0.58; 95% CI 0.30–1.11; $P = 0.099$) indicated no significant difference in OS between the SH and RH groups.

Sensitivity Analysis

Boente et al.[14] included some EC patients with suspected cervical involvement clinically that was not confirmed to be stage 2 postoperatively. After the study was excluded, the pooled HR for OS comparison in studies including only surgical stage 2 patients was 0.93 (95% CI 0.73–1.18; $P = 0.526$).

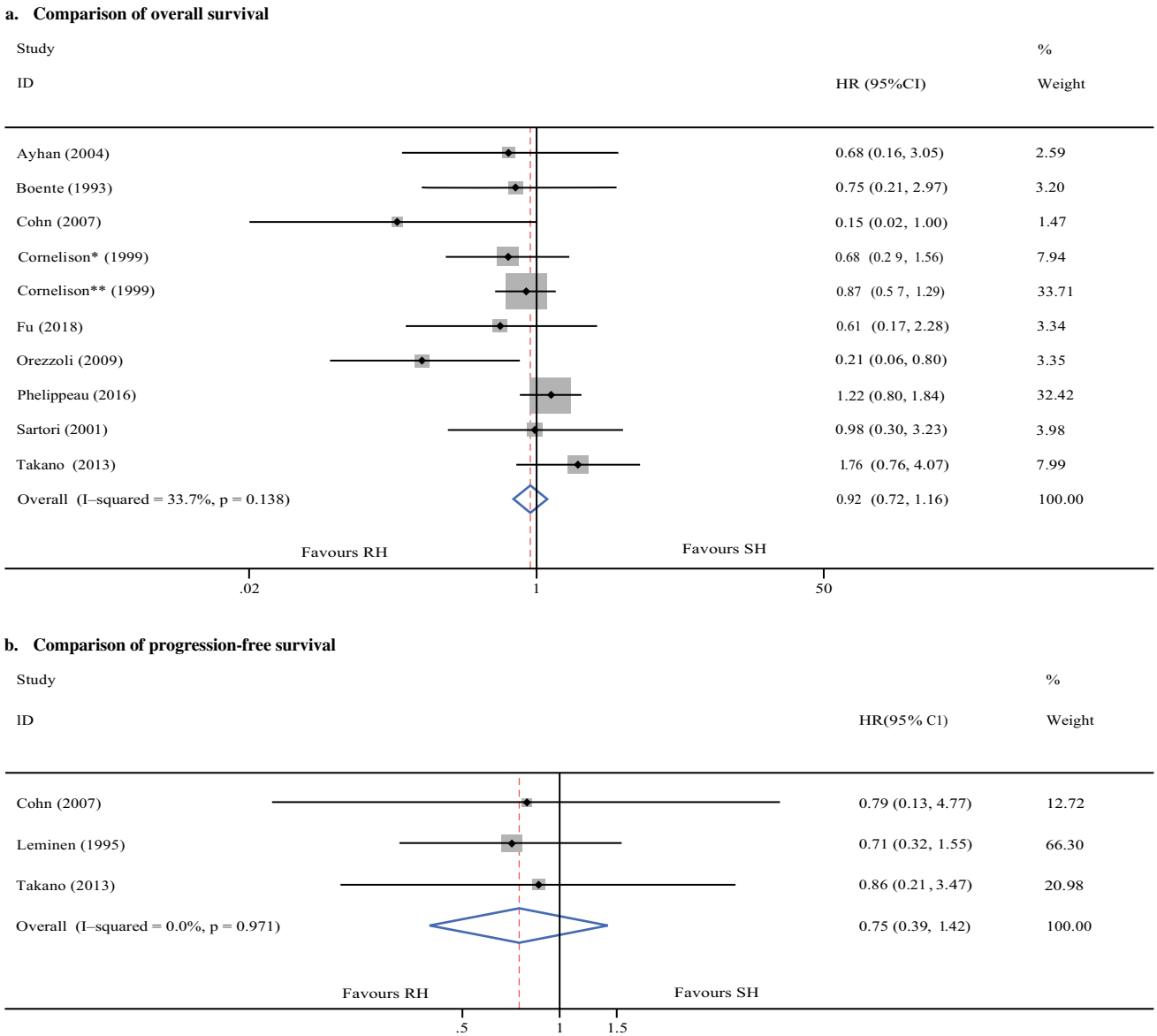

FIG. 2 Forest plot for comparison of survival between radical hysterectomy (RH) and simple hysterectomy (SH) for stage 2 endometrial cancer patients. **a** Overall survival. **b** Progression-free survival. *Comparison among patients who received surgery alone without adjuvant radiotherapy (ART). **Comparison among patients who received surgery plus ART

To avoid weighting of the result by several studies with large samples, we dropped the study conducted by Phelippeau and Koskas,[20] and RH showed an improved OS (HR 0.80; 95% CI 0.60–1.07; $P = 0.134$). After another study by Cornelison et al.[16] also was excluded, the findings still showed no significant difference in OS between groups (HR 0.76; 95% CI 0.48–1.21; $P = 0.245$).

As shown in Fig. 2, only one of the included studies reported a significant difference between two surgery groups. After the study[19] was excluded, the I^2 value dropped from 33.7% to 4.9%, and the pooled HR was 0.97 (95% CI 0.76–1.23; $P = 0.786$).

Publication Bias

The funnel plot of studies included in the OS comparison showed a symmetric distribution around the pooled estimate (Fig. S1). No significant publication bias was found in OS comparison (Egger test, $P = 0.079$; Begg test, $P = 0.152$) or PFS comparison (Egger test, $P = 0.387$; Begg test, $P = 1.000$).

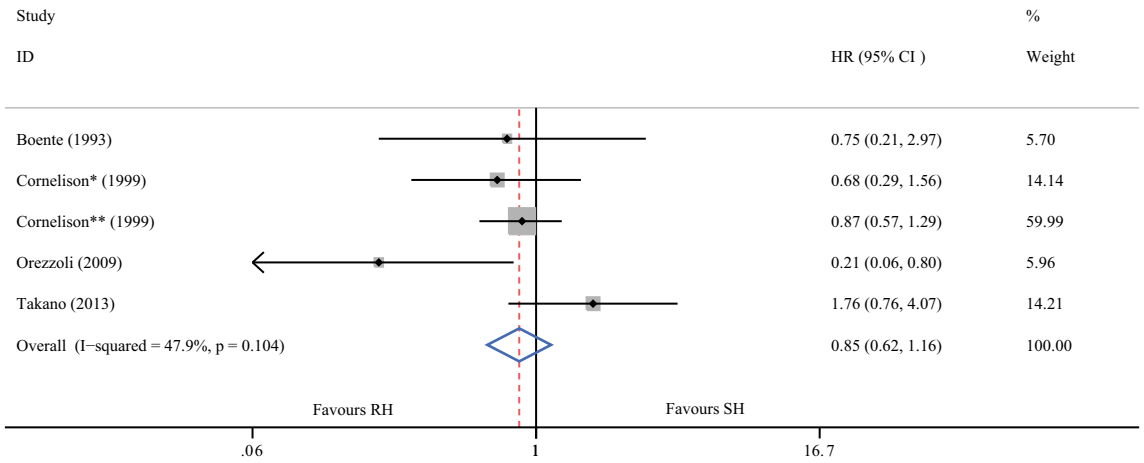

FIG. 3 Forest plot for comparison of overall survival with balanced adjuvant radiotherapy (ART). *Comparison among patients who received surgery alone without ART. **Comparison among patients who received surgery plus ART. RH, radical hysterectomy; SH, simple hysterectomy

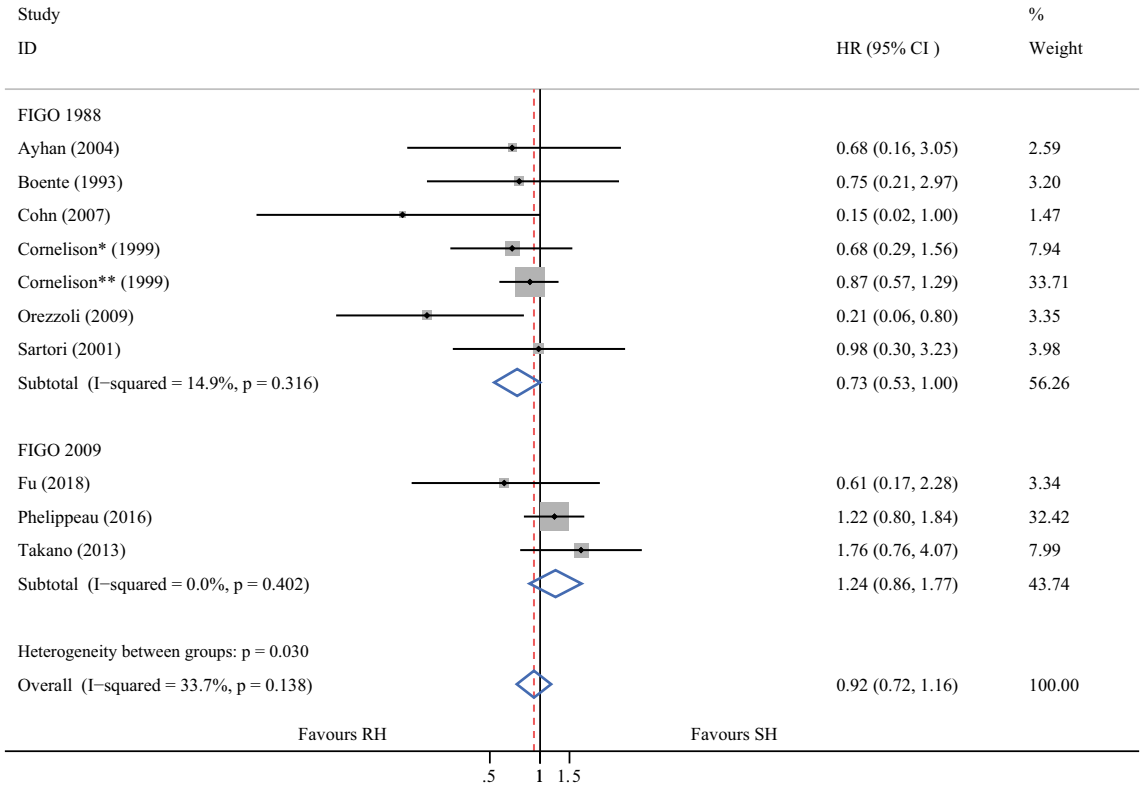

FIG. 4 Subgroup analysis of overall survival comparison according to different staging systems. *Comparison among patients who received surgery alone without adjuvant radiotherapy (ART). **Comparison among patients who received surgery plus ART. RH: radical hysterectomy; SH: simple hysterectomy

DISCUSSION

The treatment algorithm for operative stage 2 EC patients considers surgery as the preferred choice.[1] It usually refers to a staging surgery including hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy. Compared with SH, RH is more widely accepted in clinical practice to obtain broader parametrial margins.[23–25] However, previous studies have shown that patients who received RH had a significantly longer operative time, more blood loss, and a longer hospital stay;[17,22,26,27] In addition, RH is associated with more long-term morbidities such as voiding dysfunction, fistula formation, lymph

edema, and sexual dysfunction.[28] Therefore, the possible benefits of RH should be carefully weighed against the increased morbidity of the procedure compared with SH.

To date, no prospective study has compared the long-time survival between the two surgery types. Several retrospective studies have been published but have reported contradicting results.[15,19,20,22] Thus, the value of RH in stage 2 EC remains controversial. To our knowledge, no meta-analysis has been conducted previously to compare the long-time survival between RH and SH for stage 2 EC patients.

This meta-analysis showed that for stage 2 EC patients, neither RH nor mRH significantly improves OS (HR 0.92; 95% CI 0.72–1.16; $P = 0.484$) or PFS (HR 0.75; 95% CI 0.39–1.42; $P = 0.378$) compared with SH. Most of the included studies showed a slight survival benefit with RH. Only two recently published studies showed an OS benefit with SH. Notably, most of the studies were conducted before FIGO updating in 2009 and staged the patients according to FIGO 1988. Concerning updated FIGO staging, stage 2 includes only patients with cervical stromal invasion. Patients with uterine-confined disease and cervical mucosal involvement are no longer considered stage 2, which may have an impact on survival.

Theoretically, patients classified as stage 2 under the new criteria were more suitable for RH and showed greater survival benefit. However, subgroup analysis (Fig. 4) showed that RH for patients staged with FIGO 2009 may have decreased survival benefit compared with those staged before the FIGO updating.

To our knowledge, this paradoxical finding could be explained as follows. First, as medical imaging technology has been improved dramatically over the years, physicians have been able to get more staging information before surgery and thus tend to perform RH in more severe cases with poorer prognostic factors. Second, the advances in radiotherapy may lower the risk of locoregional recurrence resulting from insufficient parametrial margins in SH. Third, we could not exclude the fact that the better survival outcome of RH for patients staged before FIGO updating was related to selection bias among stage 2a and 2b patients. Furthermore, earlier published studies were mostly not based on multivariate analysis, and confounders were not well matched, resulting in lower quality.

Postoperative adjuvant therapy for early-stage EC has been mainly limited to radiotherapy.[1] The role of ART in the treatment of early-stage EC patients still is controversial. Previous studies have shown that ART improves pelvic control for some selected patients, which may improve PFS (but not OS) for EC patients.[29,30] Clinicians must consider the possible confounding effect of ART when evaluating the survival impact of surgical approach for stage 2 EC patients. In Fig. 3, the impact of ART could be considered as removed from the estimation because the included studies showed no significant difference in ART between the two surgery groups. The result (HR for OS, 0.85; 95% CI 0.62–1.16; $P = 0.300$) remained consistent with the roughly pooled estimate in Fig. 2a.

Notably, the type of hysterectomy also may affect postoperative ART, which is associated with significant short- and long-term morbidity. For the stage 2 EC patients in this study who had RH with a negative surgical margin and no evidence of extrauterine disease, ART could be avoided for some low- and intermediate-risk patients.[1] Experts may worry that the insufficient surgical margin of SH in these patients will cause unnecessary pelvic radiotherapy. However, the exact mode of ART (brachytherapy or external-beam pelvic radiotherapy or both) that the patients should accept plays a critical role and also has been controversial. Because most early-stage patients have recurrences in the vagina, many studies have noted that vaginal brachytherapy alone is reasonable, with excellent and equivalent vaginal and pelvic control rates and no difference in OS compared with external-beam pelvic radiotherapy plus brachytherapy for low- and intermediate-risk patients.[31–34] Additionally, for early-stage EC patients who received brachytherapy postoperatively, the life quality was not significantly compromised compared with those who received surgery alone.[35–38]

Recently, the unusual result of the Laparoscopic Approach to Cervical Cancer (LACC) trial demonstrated that minimally invasive surgery was associated with a lower rate of both DFS and OS for cervical cancer.[39] Therefore, the survival impact of minimally invasive surgery in malignant gynecologic surgery should be carefully evaluated. To date, two randomized phase 3 trials and one meta-analysis.[40–42] found no survival difference between the open and minimally invasive surgery groups of EC patients, yet the included cases all were stage 1, and corresponding studies of stage 2 EC are inaccessible currently. Theoretically, except for the common recurrence-related operative factors of minimally invasive surgery (e.g., use of an intrauterine manipulator, the laparoscopic opening of the vagina, and carbon dioxide insufflations) in both stages 1 and 2 EC, minimally invasive surgery in stage 2 EC may have a greater risk of tumor spread, considering that stage 2 EC has a common feature of cervical infiltration with cervical cancer.

In this meta-analysis, we tried to eliminate the influence of surgical approach (e.g., open vs laparoscopic) by analyzing studies with open surgery alone and found no survival advantage of RH in this group (HR for OS, 0.58; 95% CI 0.30–1.11; $P = 0.099$). Nevertheless, the survival impact of surgical approach on stage 2 EC remains unclear and deserves further investigation, especially well-designed RCTs with standardized tumor-free procedure.

During the past decades, the treatment method for EC with cervical involvement has been based on the belief that tumor extension of EC would behave similarly to cervical cancer.[43] The reported rate of parametrial involvement for EC patients is approximately 8% to 14%, most of which has occurred in stage 3 EC patients.[44–47] However, the reliability of cervical extension in predicting parametrial spread is poor. In EC patients with cervical involvement, the tumor originates in the corpus, then grows down to the cervical tissue and subsequently invades the stroma of the cervix. Because the tumor does not derive from the cervix as in cervical cancer, it has a lower possibility of parametrial metastasis. A Japanese retrospective study conducted by Watanabe et al.[45] reported that among 28 of 334 RH specimens with parametrial spread, only 10 had cervical involvement, whereas lymphovascular invasion was found in all cases with parametrial spread. These findings weakened the necessity of RH in EC, suggesting that the current surgical method of RH for stage 2 EC patients may be overtreatment.

A few inherent limitations of this study must be addressed. First, all the included studies were retrospective, lacked randomization, and were not very powerful. Only one of the included studies had a matched cohort, and in other studies, some of the important clinicopathologic parameters (e.g., age, body mass index [BMI], surgical approach, tumor volume, tumor grade, histology, lymph node metastasis, and chemotherapy) between groups were not adequately balanced due to limited data. This was a major confounder and limitation of our study. Each of these factors may significantly affect the adjuvant therapy and prognosis. Moreover, patients with more risk factors were more likely to receive RH instead of SH. Thus, the survival advantage of RH might have been underestimated. Readers should be aware of this when applying the conclusion of this meta-analysis. Second, the influence of staging migration weakened the strength of the conclusion in this meta-analysis.

In summary, our meta-analysis provided comprehensive clinical evidence to show that RH did not significantly improve survival for stage 2 EC patients compared with SH, irrespective of the administration of ART. The choice of RH should be considered carefully in clinical practice considering its long-term adverse effects. Given the limitation of our meta-analysis, the role of RH in the surgical management of stage 2 EC patients still is controversial, and more qualified studies, especially large RCTs, are needed to address this issue.

CONFLICT OF INTEREST The authhors declare that they have no conflict of interest.

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