

## Original Article



# Impact of adjuvant hysterectomy on prognosis in patients with locally advanced cervical cancer treated with concurrent chemoradiotherapy: a meta-analysis

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## ABSTRACT

**Objective:** Few data exist regarding adjuvant hysterectomy (AH) in locally advanced cervical cancer (LACC) patients treated with chemoradiotherapy. We investigated the effect of AH on prognosis in LACC patients, through meta-analysis.

**Methods:** EMBASE and MEDLINE databases and the Cochrane Library were searched for published studies comparing LACC patients who received AH after chemoradiotherapy with those who did not, through April 2016. Endpoints were mortality and recurrence rates. For pooled estimates of the effect of AH on mortality/recurrence, random- or fixed-effects meta-analytical models were used.

**Results:** Two randomized trials and six observational studies (AH following chemoradiotherapy, 630 patients; chemoradiotherapy, 585 patients) met our search criteria. Fixed-effects model-based meta-analysis indicated no significant difference in mortality between the groups (odds ratio [OR]=1.01; 95% confidence interval [CI]=0.58–1.78;  $p=0.968$ ) with low cross-study heterogeneity ( $p=0.73$  and  $I^2=0.0$ ). This pattern was observed in subgroup analysis for study design, radiation type, response after chemoradiotherapy, and hysterectomy type. The pooled OR for AH and recurrence was 0.59 (95% CI=0.44–0.79;  $p<0.05$ ) with low cross-study heterogeneity ( $p=0.29$  and  $I^2=17.8$ ), favoring the AH group. However, this pattern was not observed in the subgroup analysis for the randomized trials. There was no evidence of publication bias.

**Conclusion:** In this meta-analysis, AH following chemoradiotherapy did not improve survival in patients with LACC, although it seemed to reduce the risk of recurrence. Concerning the significant morbidity of AH after chemoradiotherapy, routine use of AH should be avoided.

**Keywords:** Cervical Neoplasms; Hysterectomy; Chemoradiotherapy; Prognosis; Meta-Analysis

## INTRODUCTION

Since cytological screening was introduced, the incidence of cervical cancer has decreased remarkably. However, in 2012, there were approximately 528,000 new cases and 266,000 cervical cancer-associated deaths worldwide [1]. In Korea, it is the most common female

**Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

**Author Contributions**

Conceptualization: S.S.H.; Data curation: S.S.H., K.S.N., C.S.H., K.J.E., L.S.J.; Formal analysis: S.S.H., K.S.N.; Funding acquisition: S.S.H., K.S.N.; Investigation: S.S.H., K.S.N., C.S.H., K.J.E., L.S.J.; Methodology: S.S.H., K.S.N., L.S.J.; Resources: S.S.H., K.S.N., C.S.H., K.J.E., L.S.J.; Software: S.S.H., K.S.N., C.S.H., K.J.E., L.S.J.; Supervision: S.S.H., K.S.N.; Validation: S.S.H., K.S.N.; Visualization: S.S.H.; Writing - original draft: S.S.H., K.S.N., C.S.H., K.J.E., L.S.J.; Writing - review & editing: S.S.H., K.S.N., C.S.H., K.J.E., L.S.J.

genital malignancy, and in 2013, the age-standardized incidence rate was 9.5 cases per 100,000 women [2,3].

Based on five phase III randomized control trials demonstrating that concurrent chemoradiotherapy (CCRT) improves survival outcome in patients with locally advanced cervical cancer (LACC) [4], CCRT is accepted as the standard treatment for these patients [5,6]; however, the 5-year overall survival remains approximately 70%. Investigators have evaluated whether adjuvant hysterectomy (AH) after CCRT contributes to any survival benefit. One randomized controlled trial (RCT) by the Gynecologic Oncology Group (GOG) investigated the role of AH after radiotherapy (without concomitant chemotherapy) in this patient population [7]. Nonetheless, in the era of CCRT, there is still conflicting evidence regarding the therapeutic role of AH in LACC.

The current meta-analysis quantified the effects of AH on survival outcome in LACC patients treated with CCRT. This will help both physicians and LACC patients to balance the risks and benefits of AH after CCRT.

## MATERIALS AND METHODS

### 1. Literature search

A systematic review and meta-analysis were performed using previously described reporting guidelines [8-10]. The EMBASE and MEDLINE databases, and Cochrane Central Register for Controlled Trials database were searched up to April 2016, irrespective of language. Pre-publication papers were also included. The search strategy is described in the **Supplementary Data 1**. Titles and abstracts were checked to identify potentially eligible studies. The full texts were then reviewed in detail. References were manually screened to find additional studies. Two authors (S.S.H. and L.S.J.) independently carried out all searches.

### 2. Eligibility criteria

Inclusion criteria for this meta-analysis were as follows: 1) RCT or prospective/retrospective cohort or case-control study; 2) participants receiving primary CCRT for LACC (stage IB2 to IVA); 3) AH following CCRT (CCRT+AH), as intervention; 4) CCRT without AH (CCRT), as comparison; and 5) outcomes of mortality or recurrence rates measured via relative risks (RRs), odds ratios (ORs), or hazard ratios (HRs) with 95% confidence intervals (CIs) (or sufficient data for calculation). For studies with duplicated data, the most recent or instructive study was selected. Single-arm cohort studies or case reports were excluded.

### 3. Data extraction

The following data were extracted from each study: first author; publication year; study design, location, and period; age; sample size; tumor stage; histology; radiotherapy details (dose, duration, external beam radiotherapy [EBRT], intracavitary brachytherapy [ICBT]); concomitant chemotherapy details (regimen, dose, duration); AH details (simple or radical); time interval from CCRT completion to AH; disease status after CCRT, follow-up duration; recurrence; death from disease; adverse events related to treatment; and variables controlled for in the analysis. For response after CCRT, a good response was defined as a decrease in tumor volume  $\geq 50\%$  on magnetic resonance imaging (MRI) on completion of CCRT [11,12]. Each study was systematically reviewed for features that may introduce bias, similarity of risk factors for prognosis, and similarity of follow-up durations, between the CCRT+AH group

and the CCRT group. Three authors (S.S.H., L.S.J., and K.S.N.) independently extracted data; discrepancies were jointly reviewed until consensus was reached.

#### 4. Quality assessment

For non-randomized studies (NRSs), the quality of each study was evaluated using the nine-star Newcastle-Ottawa scale (NOS) in three categories: selection, comparability, and exposure (case-control studies) or outcomes (cohort studies) [13]. Based on quality assessment standards from previous meta-analyses [14], a study with five or more stars was defined as high quality in the present meta-analysis. To evaluate the study quality for RCTs, the following features were assessed: randomization procedure, estimation of sample size, blinding and allocation concealment, loss to follow-up, dropout and intention-to-treat analysis [15]. Study quality was quantified using the Jadad/Oxford quality scoring system [16]. Three authors (S.S.H., L.S.J., and K.S.N.) independently evaluated study quality; discrepancies were jointly reviewed until consensus was reached.

#### 5. Data generation and analysis

The primary endpoint was the mortality rate. The secondary endpoints were the total, local, and distant recurrence rates. The OR and 95% CI for the mortality or recurrence rates for the CCRT+AH and CCRT groups were calculated from the original data of each study. Cross-study heterogeneity was examined using the Cochran Q test and the  $I^2$  statistic [17,18]. If either the Q test ( $p < 0.1$ ) [17] or the  $I^2$  statistic ( $> 50\%$ ) [18] indicated substantial heterogeneity between studies, a random-effects model was used (DerSimonian-Laird method) to estimate the combined OR; [19] otherwise, a fixed-effects model (Mantel-Haenszel method) was used. Subgroup analyses according to study design (RCT or NRS), type of radiation (ICBT following EBRT or EBRT only), residual tumor after CCRT (residual or no residual), response after CCRT (good response or not), and type of AH (simple hysterectomy [SH] or radical hysterectomy [RH]) were carried out.

Sensitivity analysis was conducted by withdrawing 1 study at a time from the meta-analysis to evaluate its effect on the pooled OR [10]. Publication bias was determined using the fail-safe N test [20] and the Begg-Mazumdar rank correlation test [21,22]. Comprehensive Meta-Analysis version 2.0 (Biostat, Englewood, NJ, USA) was used for all statistical tests. A 2-sided  $p$  value  $< 0.05$  was considered significant. The statistician (K.S.N.) contributed the present meta-analysis.

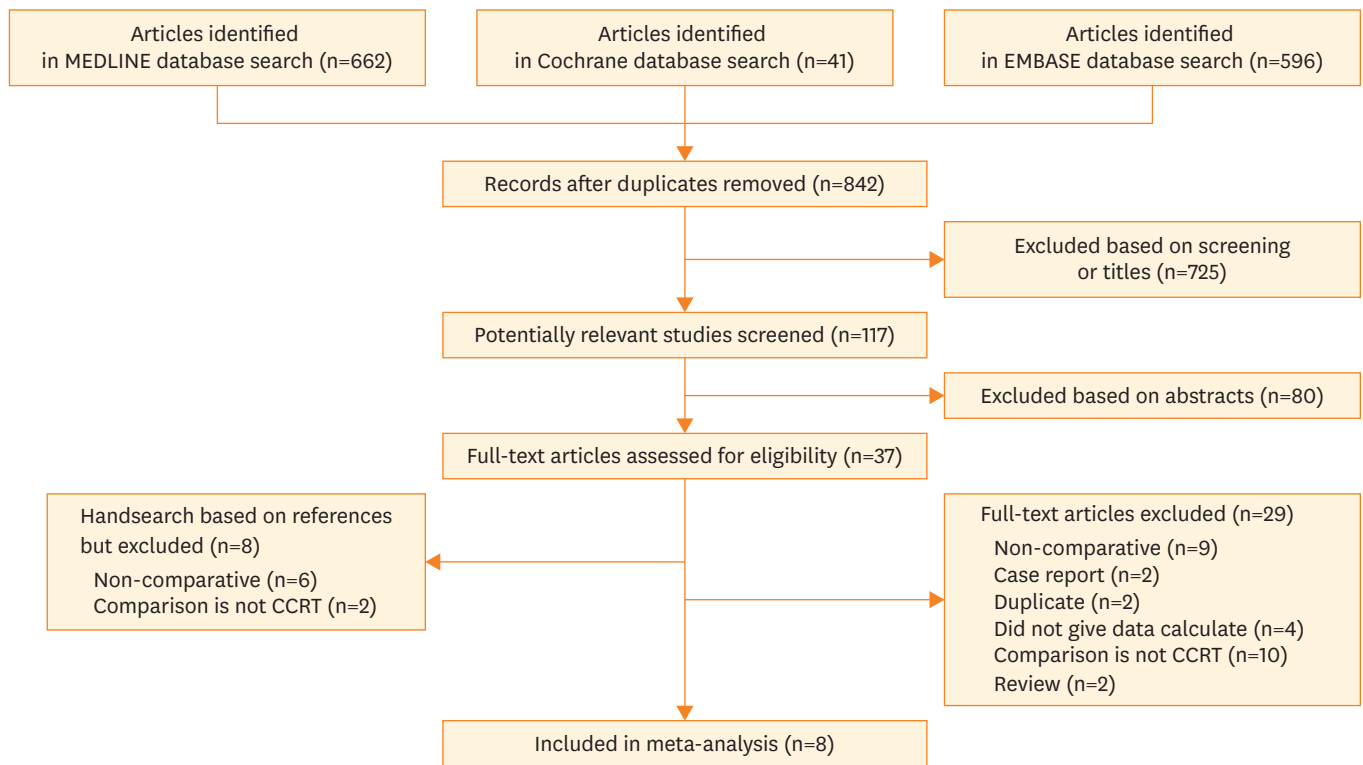
## RESULTS

### 1. Literature search

From 842 records, 38 papers were identified for detailed full-texts review. Finally, eight studies were included in the meta-analysis [11,12,23-28]. The literature search process is depicted in **Fig. 1**. **Supplementary Table 1** shows the excluded studies with reasons for exclusion.

### 2. Study characteristics

**Table 1** lists the study characteristics. Eight papers, published between 2008 and 2014, involved 630 LACC patients who received AH after CCRT and 585 who did not receive AH after CCRT. Two were RCTs [25,26] and 6 were NRSs [11,12,23,24,27,28]. The studies were conducted in France [12,25,27], Mexico [24,26], China [11,28], and the US [23]. For the RCTs, the quality score was 3 on the Jadad/Oxford quality scoring system (**Supplementary Table 2**). For the



**Fig. 1.** Flow diagram of the literature search process. CCRT, concurrent chemoradiotherapy.

NRSs, the quality scores were 6 or 7 (**Supplementary Table 3**). All included NRSs received three stars and 2 stars for selection and exposure, respectively. One study received one star for comparability because of one controlled confounder (e.g., disease status after CCRT); 5 studies received two stars because they satisfied additional comparability criteria.

The median ages in the CCRT+AH group and CCRT group were 47 and 48 years, respectively, with median follow-up periods of 88 and 90 months, respectively. All studies, except 1 [12], reported similar histology distributions (squamous and non-squamous) between CCRT+AH and CCRT groups. All patients received concomitant cisplatin-based chemotherapy. In 5 studies, patients received a concomitant weekly single cisplatin regimen [11,12,23-25], whereas the other studies featured combination cisplatin regimens [26-28]. The median EBRT dose was 48.3 Gy (range, 40–55 Gy). ICBT following EBRT was administered to both groups in all studies, except for 2 in which the CCRT+AH group did not receive ICBT [11,26]. The time interval from CCRT completion to AH ranged from 2 to 12 weeks. One study included only patients that achieved complete response after CCRT [25] and 2 studies included only patients that achieved a good response (decrease in tumor volume  $\geq 50\%$ ) after CCRT [11,12]. The other 5 studies included all patients who did not show progressive disease after CCRT completion [23,24,26-28]. The type of AH was SH in 1 study [23], RH in 3 [11,24,26], and a mixture of AH and RH in 4 [12,25,27,28].

### 3. Meta-analysis of the impact of AH on survival

Five studies compared CCRT+AH with CCRT in terms of survival with a combined total of 60 deaths (33/208 patients with CCRT+AH vs. 27/178 patients with CCRT). No significant

**Table 1.** Characteristics of studies included in the meta-analysis

Study/ design	Location/ study period	Median age (yr)	Stage (No.)	Histology (No.)	LN metastasis (No.)	Median follow-up period (mo)	CCRT details			AH details		Adjusted variables*		
							Median dose of EBRT (Gy)	Median dose of ICBT (Gy)	Median duration of CCRT (day)	Concomitant chemotherapy regimen	Median time interval from completion to AH (wk)		Disease status at timing of AH	Type of AH
Wang et al. [11] / Retrospective case-control study	China/ 2004-2011	NR	IIB: 119 IIB: 121 Non-SCC: 5	SCC: 112 Non-SCC: 7 SCC: 116 Non-SCC: 5	13	36	40-50	28-35 <sup>§</sup>	60 <sup>†</sup>	Weekly cisplatin (40 mg/m <sup>2</sup> )	2-3	Only good responders <sup>!</sup>	RH: 119 RH: 119	b, c, f, g
Sun et al. [28] / Retrospective case-control study	China/ 1992-2012	NR	IIB: 90 III: 101 IVA: 1 IIB: 84 III: 100 IVA: 2	SCC: 149 Non-SCC: 43 SCC: 140 Non-SCC: 47	18	190 <sup>†</sup>	45-50	45-55	NR	Weekly cisplatin (40 mg/m <sup>2</sup> ) + 5-fluorouracil (500 mg/m <sup>2</sup> )	10-12	All <sup>†</sup>	SH: 99 RH: 72	b, c, g
Chereau et al. [27] / Retrospective case-control study	France/ 2002-2012	49 <sup>*</sup>	IB2: 15 IIA: 4 IIB: 27 IB2: 4 IIA: 5 IIB: 25	SCC: 39 Non-SCC: 7 SCC: 29 Non-SCC: 5	9	31	40-55	20	NR	Triweekly 5-fluorouracil infusion (750 mg/m <sup>2</sup> /day) + cisplatin (20-25 mg/m <sup>2</sup> /day) on days 1, 2, 4, and 5.	6	All <sup>†</sup>	SH: 32 RH: 14	c, d, g
Cetina et al. [24] / RCT	Mexico/ 2004-2009	NR	IB2: 18 IIA: 11 IIB: 82 IB2: 18 IIA: 12 IIB: 70	SCC: 100 Non-SCC: 11 SCC: 83 Non-SCC: 17	NR	36 <sup>*</sup>	50.4	30-35 <sup>§</sup>	47	Weekly cisplatin (40 mg/m <sup>2</sup> ) + gemcitabine (125 mg/m <sup>2</sup> )	4-6	All <sup>†</sup>	RH: 86	a, b, c, d, g
Morice et al. [25] / RCT	France/ 2003-2006	45	IB2: 16 II: 15 IB2: 15 II: 15	SCC: 28 Non-SCC: 3 SCC: 24 Non-SCC: 6	9	46	45-50	15	51	Weekly cisplatin (40 mg/m <sup>2</sup> )	6-8	Only complete responders	SH or RH: 31	a, b, c, e, f, g
Lèguevaque et al. [12] / Retrospective case-control study	France/ 1998-2006	51 <sup>*</sup>	IB2: 22 II: 71 III: 12 IVA: 3	SCC: 95 Non-SCC: 16	18	NR	45	35	NR	Weekly cisplatin (40 mg/m <sup>2</sup> )	5-7	Only good responders <sup>!</sup>	SH or RH: 67	f
Cetina et al. [26] / Retrospective matched-control study	Mexico/ 1999-2003	45	IB2: 9 IIA: 4 IIB: 27 IB2: 9 IIA: 4 IIB: 27	SCC: 28 Non-SCC: 12 SCC: 28 Non-SCC: 12	NR	26	50	35	40	Weekly cisplatin (40 mg/m <sup>2</sup> )	<7	All <sup>†</sup>	RH: 40	a, b, c, d, g
Darus et al. [23] / Retrospective case-control study	US/ 1994-2004	41 <sup>*</sup>	IB2: 24 IB2: 31	SCC: 16 Non-SCC: 8 SCC: 23 Non-SCC: 7	NR	47	45	45	<56	Weekly cisplatin (40 mg/m <sup>2</sup> )	6	All <sup>†</sup>	SH-24	a, b, d, g

(continued to the next page)

**Table 1.** (Continued) Characteristics of studies included in the meta-analysis

Study/ design	Location/ study period	Treatment	Recurrence (No.)	Death of disease (No.)	Median age (yr)	Stage (No.)	Histology (No.)	LN metastasis (No.)	Median follow-up period (mo)	CCRT details			AH details		Adjusted variables*
										Median dose of EBRT (Gy)	Median dose of ICBT (Gy)	Median duration of CCRT (day)	Concomitant chemotherapy regimen	Median time interval from CCRT completion to AH (wk)	
RCTs combined	CCRT+AH (n=142)	II: 108 Non-SCC: 14	21	4 of 31	45†	IB2: 34 II: 108	SCC: 128 Non-SCC: 14	9 of 31 (29%)	38†	50.0†	28.6†				
Non- randomized observational studies combined	CCRT+AH (n=488)	II: 176 Non-SCC: 77	75	28 of 177	47†	IB2: 48 II: 176	SCC: 344 Non-SCC: 77	40 of 232 (17%)	105†	46.6†	39.4†				
All combined	CCRT+AH (n=630)	II: 284 Non-SCC: 94	96	33 of 208	47†	IB2: 92 II: 284	SCC: 468 Non-SCC: 94	49 of 263 (19%)	88†	47.3†	37.0†				

AH, adjuvant hysterectomy; CCRT, concurrent chemoradiotherapy; EBRT, external beam radiotherapy; ICBT, intracavitary brachytherapy; LN, lymph node; MRI, magnetic resonance imaging; NR, not reported; RCT, randomized controlled trial; RH, radical hysterectomy; SCC, squamous cell carcinoma; SH, simple hysterectomy.

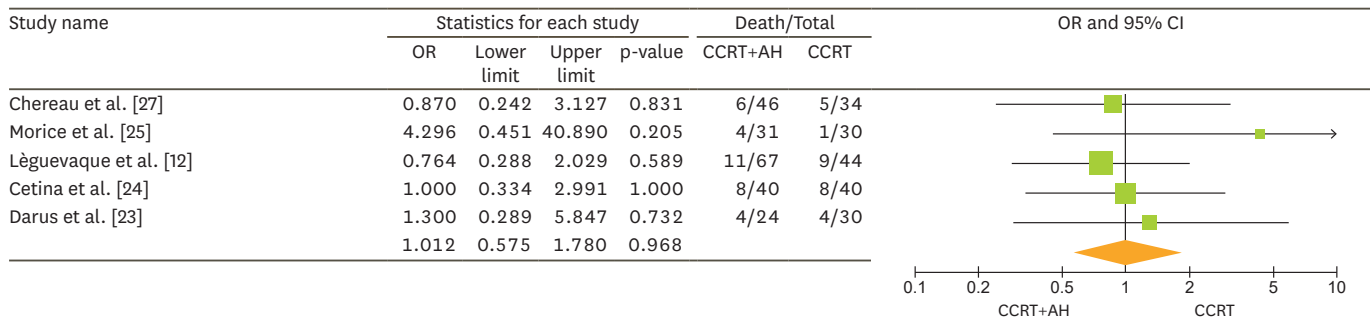
\*Mean; †weighted average; ‡median duration of chemoradiation in the group with no AH; §brachytherapy was not performed for the AH group; ¶good response was defined as a decrease in tumor volume of at least 50% according to MRI on completion of CCRT; †all patients who did not show progressive disease after CCRT completion; \*\*adjusted variables are as follow: age (a); stage (b); histology (c); initial tumor size (d); pelvic LN metastasis (e); disease status after CCRT (f); median follow-up period (g).

**Adjuvant hysterectomy in cervical cancer**

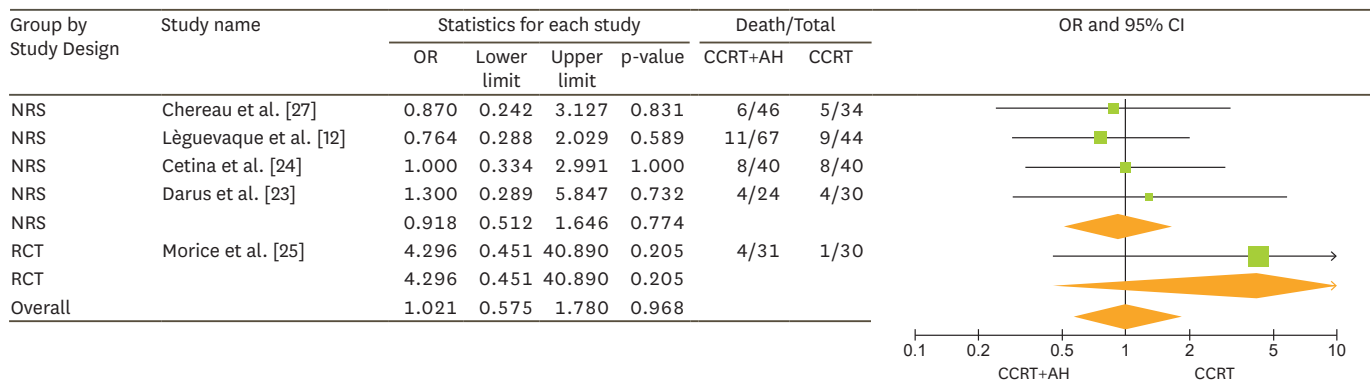
difference in the mortality rate was observed between the 2 groups (OR=1.01; 95% CI=0.58–1.78; p=0.968) with low cross-study heterogeneity (p=0.73 and I<sup>2</sup>=0.0) (**Fig. 2A**).

In the sensitivity analysis, no study significantly influenced the pooled OR for AH and mortality (**Supplementary Fig. 1A**). No publication bias was found; the funnel plot was symmetrical (**Supplementary Fig. 2A**).

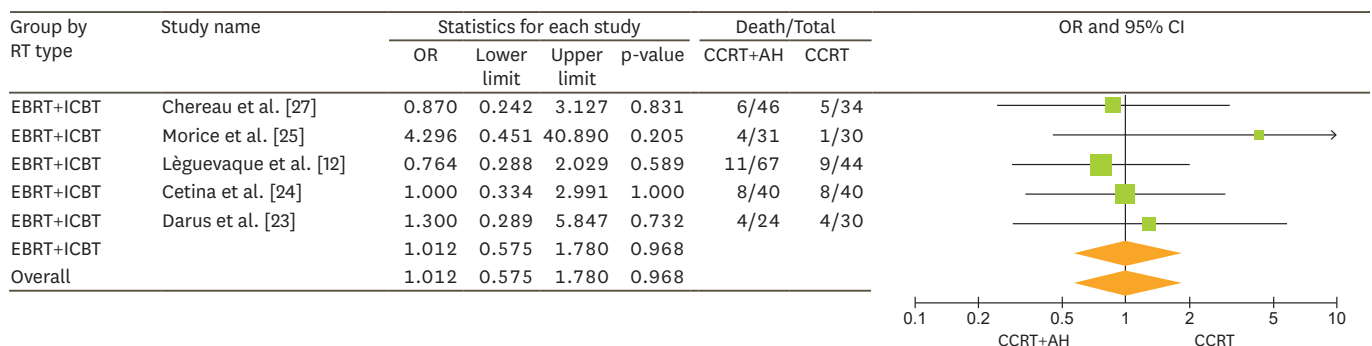
**A**



**B**



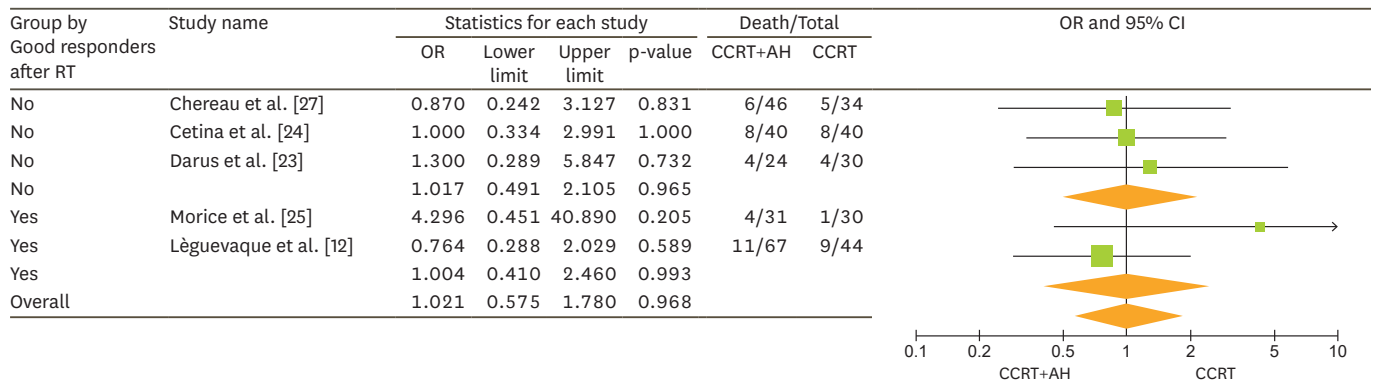
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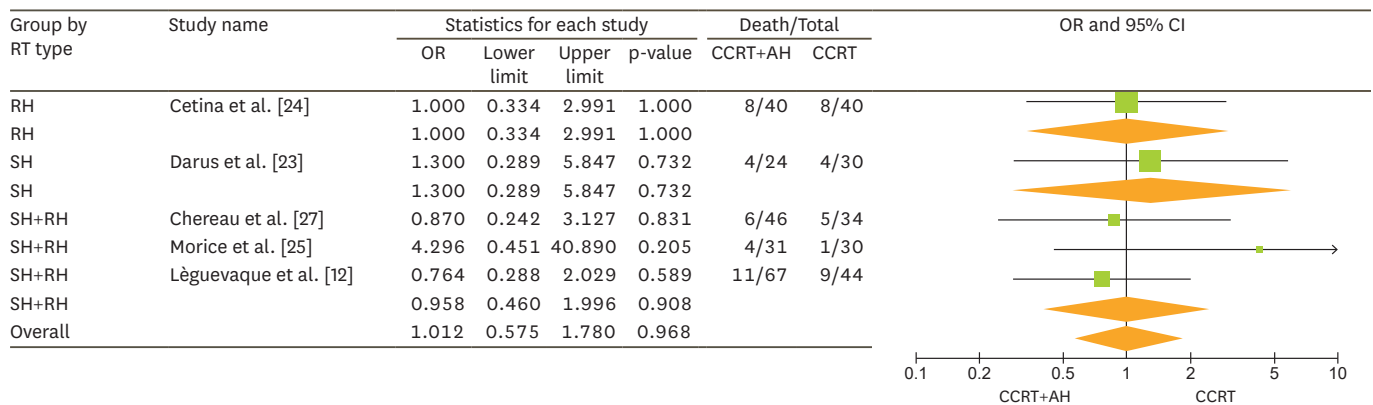
**Fig. 2.** (A) ORs for the risk of mortality in each study and all studies combined; AH following CCRT was compared with CCRT alone in a meta-analysis based on the fixed-effects model. Low cross-study heterogeneity was observed (p=0.73, I<sup>2</sup>=0.0). The association between AH and mortality in subgroup meta-analyses is shown according to (B) study design, (C) type of radiation, (D) response after CCRT, and (E) type of hysterectomy. The size of each square is proportional to the sample size in each study, and the horizontal line through the square indicates the 95% CI for that study. For the pooled analysis, the diamond indicates the pooled value, and the right and left ends of the diamond indicate the 95% CI for the analysis. AH, adjuvant hysterectomy; CCRT, concurrent chemoradiotherapy; CI, confidence interval; EBRT, external beam radiation; ICBT, intracavitary brachytherapy; NRS, non-randomized study; OR, odds ratio; RCT, randomized controlled trial; RH, radical hysterectomy; SH, simple hysterectomy. (continued to the next page)

**Adjuvant hysterectomy in cervical cancer**

**D**



**E**



**Fig. 2.** (Continued) (A) ORs for the risk of mortality in each study and all studies combined; AH following CCRT was compared with CCRT alone in a meta-analysis based on the fixed-effects model. Low cross-study heterogeneity was observed ( $p=0.73$ ,  $I^2=0.0$ ). The association between AH and mortality in subgroup meta-analyses is shown according to (B) study design, (C) type of radiation, (D) response after CCRT, and (E) type of hysterectomy. The size of each square is proportional to the sample size in each study, and the horizontal line through the square indicates the 95% CI for that study. For the pooled analysis, the diamond indicates the pooled value, and the right and left ends of the diamond indicate the 95% CI for the analysis. AH, adjuvant hysterectomy; CCRT, concurrent chemoradiotherapy; CI, confidence interval; EBRT, external beam radiation; ICBT, intracavitary brachytherapy; NRS, non-randomized study; OR, odds ratio; RCT, randomized controlled trial; RH, radical hysterectomy; SH, simple hysterectomy.

**4. AH and mortality risk in subgroup meta-analyses**

**Fig. 2B** illustrates the ORs for AH and mortality for each study and the pooled ORs for study design (NRS or RCT). Only 1 RCT was included (61 patients); the OR was 4.30 (95% CI=0.45–40.9;  $p=0.205$ ). There were 4 NRS studies (325 patients); the pooled OR was 0.92 (95% CI=0.51–1.65;  $p=0.774$ ) ( $p=0.95$  and  $I^2=0.0$ ), indicating no significant difference in mortality rate between the groups.

**Fig. 2C** shows the pooled ORs for mortality according to radiation type (ICBT following EBRT or EBRT only). ICBT following EBRT was performed for both CCRT+AH and CCRT groups in all five studies. The pooled OR was 1.01 (95% CI=0.58–1.78;  $p=0.968$ ) with low cross-study heterogeneity ( $p=0.73$  and  $I^2=0.0$ ).

**Fig. 2D** shows the pooled ORs for mortality according to response after CCRT. In the 2 studies with good responders or complete responders after CCRT [12,25], no significant difference in mortality was found between the CCRT+AH and CCRT groups (OR=1.00; 95% CI=0.41–2.46;  $p=0.993$ ) ( $p=0.17$  and  $I^2=47.4$ ). In the remaining studies, no significant difference in mortality was found between the 2 groups (OR=1.02; 95% CI=0.49–2.10;  $p=0.965$ ) ( $p=0.92$  and  $I^2=0.0$ ).



**Fig. 2E** shows the pooled ORs for mortality according to AH type. In three studies featuring a mixture of SH and RH [12,25,27], there was no significant difference in mortality between the groups (OR=0.96; 95% CI=0.46–2.00;  $p=0.908$ ) ( $p=0.38$  and  $I^2=0.0$ ). There was 1 study each for RH (OR=1.00; 95% CI=0.33–2.99;  $p>0.99$ ) [24] and SH (OR=1.30; 95% CI=0.29–5.85;  $p=0.732$ ) [23].

### 5. Meta-analysis of the impact of AH on recurrence

The eight studies comprised a total of 1,215 patients with a combined total of 229 recurrences (96/630 patients with CCRT+AH vs. 133/585 patients with CCRT). The pooled OR for AH and any recurrence was 0.59 (95% CI=0.44–0.79;  $p<0.05$ ) with low cross-study heterogeneity ( $p=0.29$  and  $I^2=17.8$ ), favoring the CCRT+AH group (**Fig. 3A**). No publication bias was found ( $p=0.11$ ); the funnel plot was symmetrical (**Supplementary Fig. 2B**). Seven studies, assessing 837 patients, reported on local recurrence (**Fig. 4A**). The results favored the CCRT+AH group (OR=0.56; 95% CI=0.33–0.96;  $p=0.034$ ) with low cross-study heterogeneity ( $p=0.96$  and  $I^2=0.0$ ). No publication bias was found ( $p=0.23$ ); the funnel plot was symmetrical (**Supplementary Fig. 2C**). Seven studies, assessing 837 patients, reported on distant recurrence (**Fig. 4B**). There was no significant difference for distant recurrence between the 2 groups (OR=0.88; 95% CI=0.54–1.45;  $p=0.621$ ) with low cross-study heterogeneity ( $p=0.51$  and  $I^2=0.0$ ). No publication bias was found ( $p=0.13$ ); the funnel plot was symmetrical (**Supplementary Fig. 2D**).

The study by Sun et al. [28] significantly affected the pooled OR for AH and recurrence. When this study was excluded, no significant difference in recurrence was observed between the groups (OR=0.71; 95% CI=0.49–1.03;  $p=0.072$ ) (**Supplementary Fig. 1B**).

### 6. AH and the risk of recurrence in subgroup meta-analyses

**Fig. 3B** illustrates the ORs for AH and recurrence for each study and the pooled ORs according to the type of study design. Two RCTs were conducted, with a total of 272 patients. A total of 39 recurrences (21/141 with CCRT+AH) were observed in the RCTs. There was no significant difference in recurrence between the CCRT+AH and CCRT groups (OR=1.05; 95% CI=0.52–2.11;  $p=0.889$ ). There were 6 NRSs, with a total of 943 patients and a combined total of 190 recurrences (75/488 CCRT+AH). The pooled OR for observational studies was 0.52 (95% CI=0.37–0.72;  $p<0.05$ ) ( $p=0.80$  and  $I^2=0.0$ ) favoring CCRT+AH.

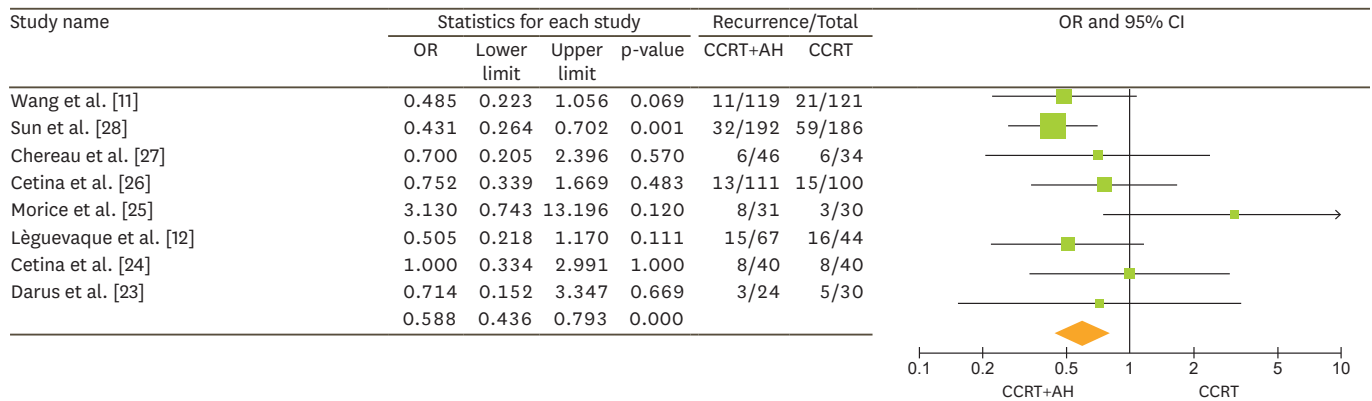
**Fig. 3C** shows the pooled ORs for recurrence according to radiation type. In the two studies in which the CCRT+AH group did not receive ICBT after EBRT [11,26], there was no significant difference in recurrence between the groups (OR=0.60; 95% CI=0.34–1.05;  $p=0.073$ ) with low cross-study heterogeneity ( $p=0.44$  and  $I^2=0.0$ ). However, the pooled OR for the remaining studies in which ICBT was administered to both groups after EBRT was 0.58 (95% CI=0.41–0.83;  $p<0.05$ ) ( $p=0.11$  and  $I^2=31.9$ ), favoring CCRT+AH.

**Fig. 3D** illustrates the pooled ORs for AH and recurrence according to response after CCRT. In the two studies of good responders or complete responders after CCRT [11,12,25], there was no significant difference in recurrence between groups (OR=0.64; 95% CI=0.37–1.08;  $p=0.094$ ) with substantial cross-study heterogeneity ( $p=0.07$  and  $I^2=63.4$ ). However, the pooled OR for the remaining studies was 0.57 (95% CI=0.40–0.81;  $p<0.05$ ) with low cross-study heterogeneity ( $p=0.57$  and  $I^2=0.0$ ), thus favoring AH.

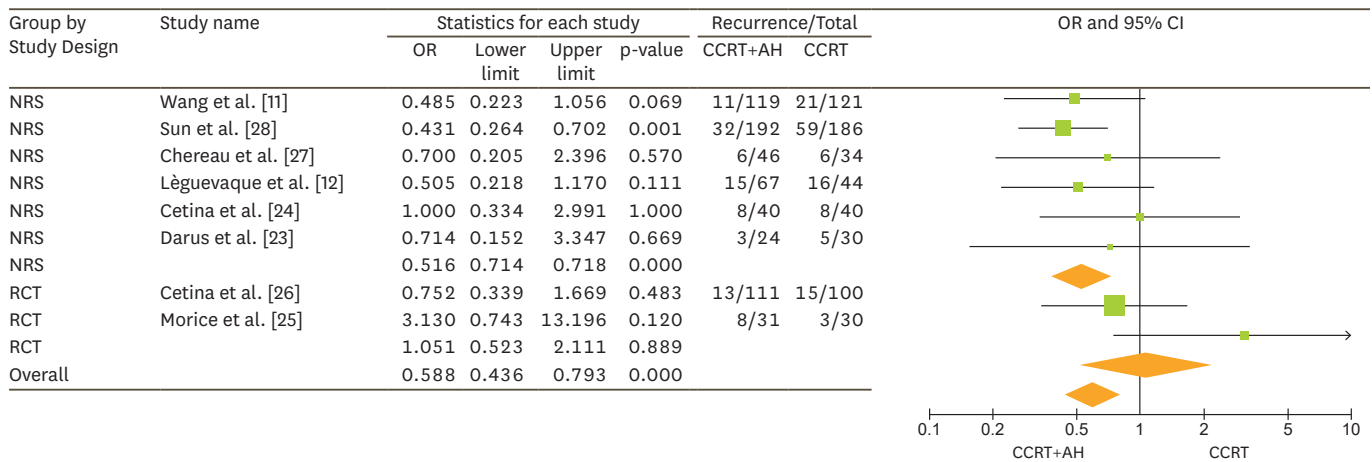
**Fig. 3E** shows the pooled ORs according to AH type. RH did not lead to a significant decrease in the risk of recurrence (OR=0.67; 95% CI=0.41–1.10;  $p=0.110$ ) ( $p=0.53$  and  $I^2=0.0$ ). For SH, only 1 study was reported (OR=0.71; 95% CI=0.15–3.35;  $p=0.669$ ) [23].

**Adjuvant hysterectomy in cervical cancer**

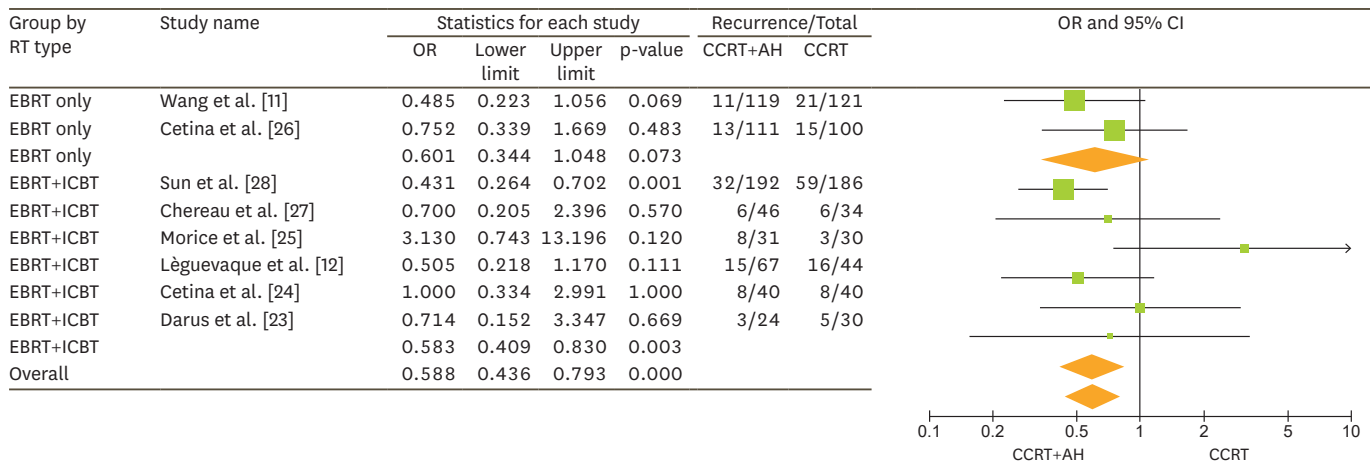
**A**



**B**



**C**

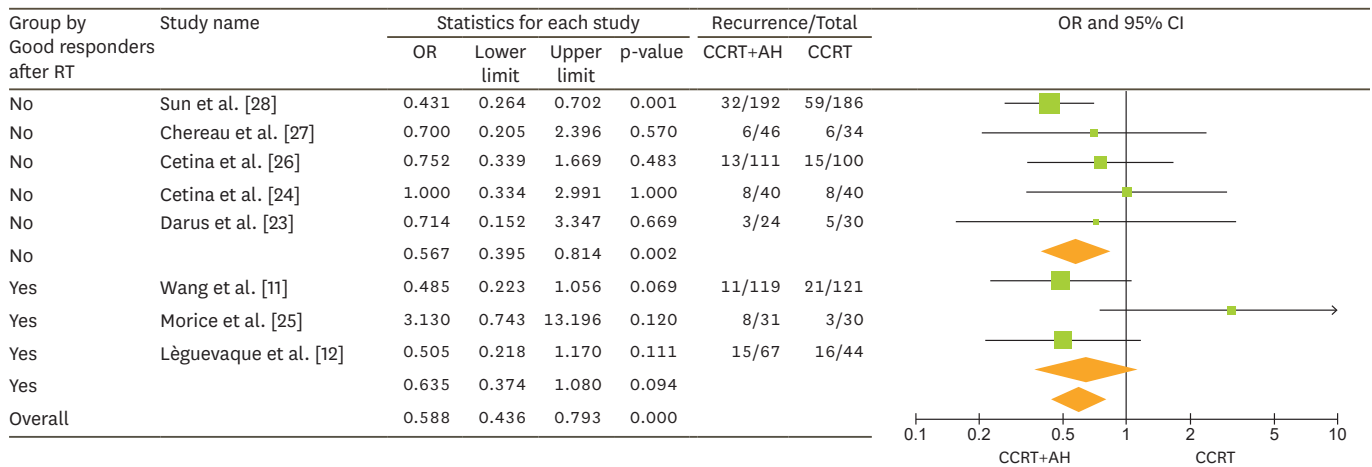


**Fig. 3.** (A) ORs for the risk of any recurrence in each study and all studies combined; AH following CCRT was compared with CCRT alone in a meta-analysis based on the fixed-effects model. Low cross-study heterogeneity was observed ( $p=0.29$ ,  $I^2=17.8$ ). The association between AH and recurrence in subgroup meta-analyses is shown according to (B) study design, (C) type of radiation, (D) response after CCRT, and (E) type of hysterectomy.

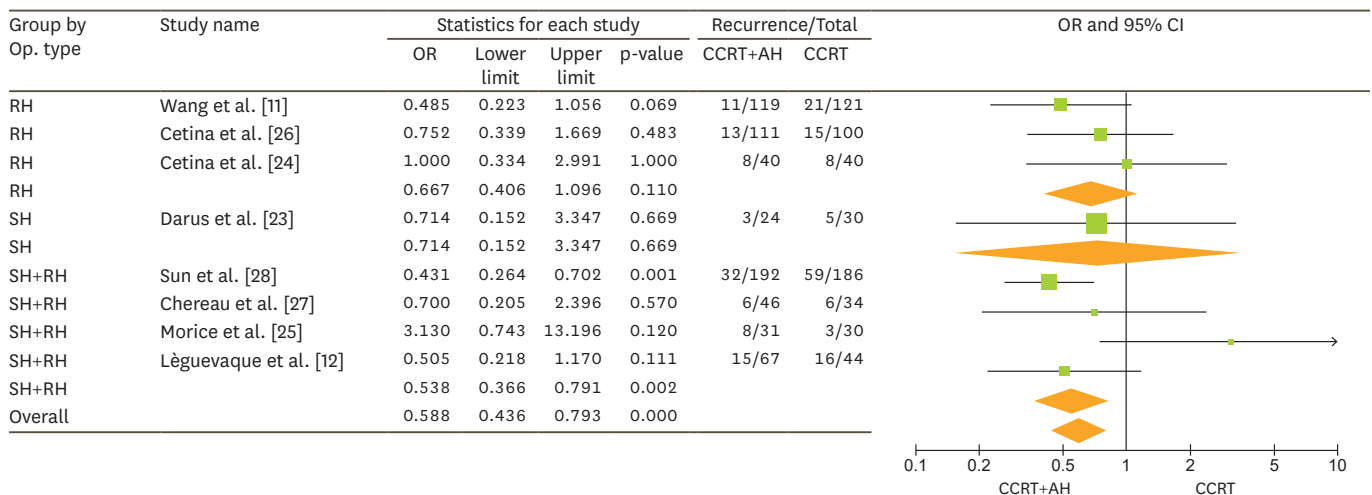
AH, adjuvant hysterectomy; CCRT, concurrent chemoradiotherapy; CI, confidence interval; EBRT, external beam radiotherapy; ICBT, intracavitary brachytherapy; NRS, non-randomized study; OR, odds ratio; RCT, randomized controlled trial; RH, radical hysterectomy; SH, simple hysterectomy. (continued to the next page)

**Adjuvant hysterectomy in cervical cancer**

**D**



**E**



**Fig. 3.** (Continued) (A) ORs for the risk of any recurrence in each study and all studies combined; AH following CCRT was compared with CCRT alone in a meta-analysis based on the fixed-effects model. Low cross-study heterogeneity was observed ( $p=0.29$ ,  $I^2=17.8$ ). The association between AH and recurrence in subgroup meta-analyses is shown according to (B) study design, (C) type of radiation, (D) response after CCRT, and (E) type of hysterectomy. AH, adjuvant hysterectomy; CCRT, concurrent chemoradiotherapy; CI, confidence interval; EBRT, external beam radiotherapy; ICBT, intracavitary brachytherapy; NRS, non-randomized study; OR, odds ratio; RCT, randomized controlled trial; RH, radical hysterectomy; SH, simple hysterectomy.

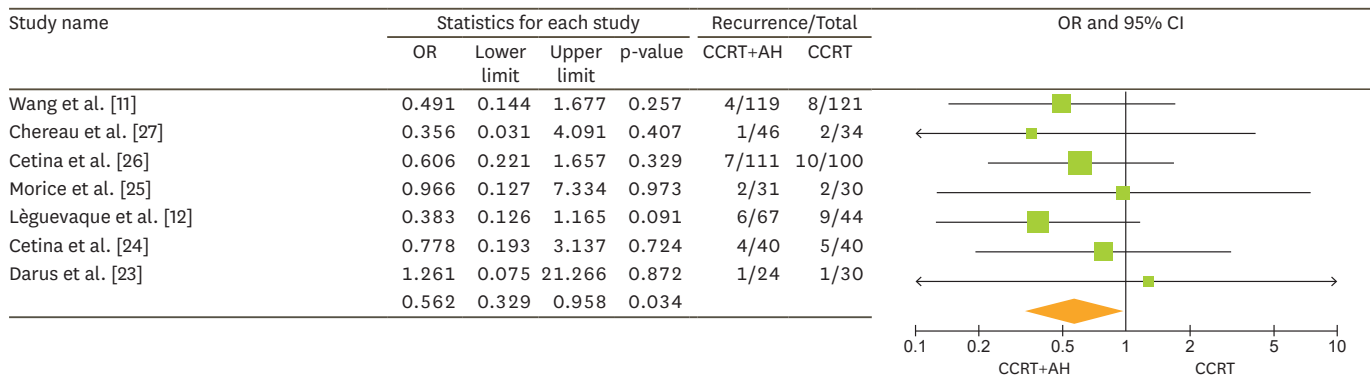
**7. Grade 3 and higher adverse events**

Data regarding postoperative complications were available for three studies [24,26,28] (Table 2). Of those, Sun et al. [28] reported postoperative complications of grade 2 or higher, whereas the other 2 reported complications of grade 3 or higher [24,26]. Only the RCT by Cetina et al. [26] clearly gave information according to intraoperative, early, and late postoperative complications after AH. The pooled incidence of grade 3 or higher postoperative complications was 26.5% (95% CI=19.5%–33.5%).

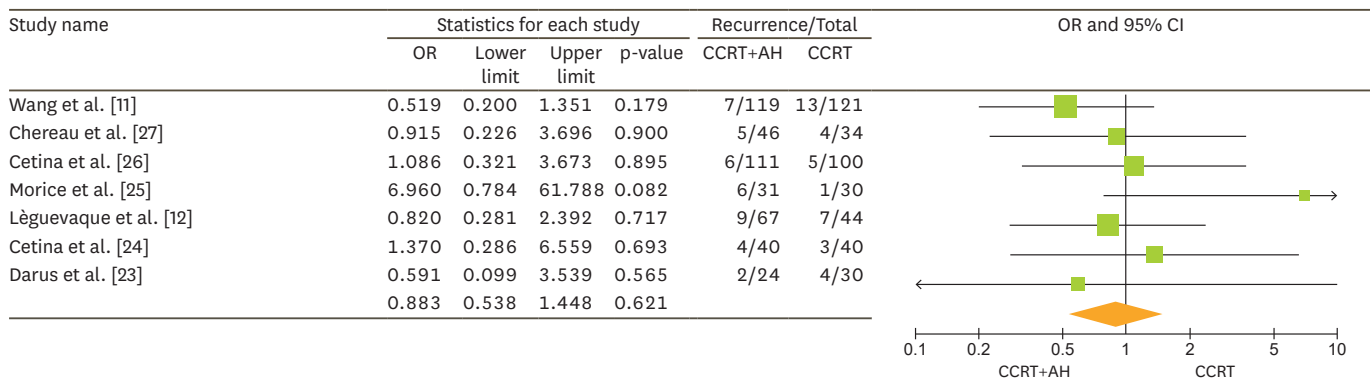
Data on late toxicity were available for four studies [11,23,24,26] (Table 2). The most common grade 3 or higher adverse event was small/large bowel toxicity in both groups. There were no significant differences in incidence of grade 3 or higher late toxicities between the 2 groups (5.2%, 95% CI=2.6%–7.7% vs. 4.4%, 95% CI=2.1%–6.8%; 2-proportion z-test,  $p=0.68$ ).

**Adjuvant hysterectomy in cervical cancer**

**A**



**B**



**Fig. 4.** (A) ORs for the risk of local recurrence in each study and all studies combined; AH following CCRT was compared with CCRT alone in a meta-analysis based on the fixed-effects model. Low cross-study heterogeneity was observed ( $p=0.96$ ,  $I^2=0.0$ ). (B) ORs for the risk of distant recurrence in each study and all studies combined; AH following CCRT was compared with CCRT alone in a meta-analysis based on the fixed-effects model. Low cross-study heterogeneity was observed ( $p=0.51$ ,  $I^2=0.0$ ).

AH, adjuvant hysterectomy; CCRT, concurrent chemoradiotherapy; CI, confidence interval; OR, odds ratio.

**DISCUSSION**

In the current meta-analysis, AH after CCRT in LACC patients had no benefit in terms of survival, compared with no AH after CCRT. This pattern was consistently observed in the subgroup analyses of study design, radiation type, response after CCRT, and type of hysterectomy, although AH was associated with a reduced recurrence rate.

AH following radiotherapy has been utilized based on the concept that it may improve local control, and positively affect survival in patients with LACC. In the GOG-71 trial, 256 LACC patients treated with radiation without concomitant chemotherapy were randomly assigned to AH after radiation (n=132) or radiation only (n=124) [7]. There was no difference in survival between the two arms, although the 5-year local relapse rate was lower in the AH arm (14% vs. 27%). At the present time, the standard treatment for LACC is platinum-based CCRT, since CCRT offers improvement in overall survival as well as local and distant control [4]. Therefore, studies without concomitant chemotherapy are rarely clinically valid. It is important to examine the published data regarding the role of AH in the era of CCRT. In this regard, our meta-analysis is timely and appropriate.

**Adjuvant hysterectomy in cervical cancer**
**Table 2.** Severe adverse events associated with treatment\*

Symptom	Cetina et al. [26]		Cetina et al. [24]		Darus et al. [23]		Wang et al. [11]		Sun et al. [28]		All combined	
	CCRT (n=100)	CCRT+AH (n=111)	CCRT (n=40)	CCRT+AH (n=40)	CCRT (n=30)	CCRT+AH (n=24)	CCRT (n=121)	CCRT+AH (n=119)	CCRT (n=186)	CCRT+AH (n=192)	CCRT	CCRT+AH
<b>Intraoperative complications</b>												
Vascular	NA	3 (2.7)	NA	0	NA	NR	NA	NR	NA	2 (1.0) <sup>†</sup>	NA	5 (1.5)
Urethral tear	NA	1 (0.9)	NA	0	NA	NR	NA	NR	NA	0	NA	1 (0.3)
Ureter section	NA	2 (1.8)	NA	0	NA	NR	NA	NR	NA	0	NA	2 (0.6)
<b>Early postoperative complications</b>												
Bleeding	NA	9 (9.0)	NA	0	NA	NR	NA	NR	NA	0	NA	9 (2.6)
Local infection	NA	2 (1.8)	NA	3 (7.5)	NA	NR	NA	NR	NA	0	NA	5 (1.5)
<b>Late postoperative complications</b>												
Local infection	NA	6 (5.4)	NA	0	NA	NR	NA	NR	NA	5 (2.6) <sup>†</sup>	NA	11 (3.2)
Systemic infection	NA	1 (0.9)	NA	0	NA	NR	NA	NR	NA	1 (0.5) <sup>†</sup>	NA	2 (0.6)
Lymphocyst	NA	3 (2.7)	NA	5 (12.5)	NA	NR	NA	NR	NA	15 (7.8) <sup>†</sup>	NA	23 (6.7)
Urinary	NA	0	NA	5 (12.5)	NA	NR	NA	NR	NA	7 (3.6) <sup>†</sup>	NA	12 (3.5)
Gastrointestinal	NA	0	NA	0	NA	NR	NA	NR	NA	2 (1.0) <sup>†</sup>	NA	2 (0.6)
Total events	NA	27 (24.3)	NA	13 (32.5)	NA	NR	NA	NR	NA	32 (16.7) <sup>†</sup>	NA	72 (21.0)
<b>Late toxicity</b>												
Small/Large intestine	4 (4)	2 (1.8)	2 (5)	0	2 (6.7)	2 (8.3)	0	1 (0.8)	NR	NR	8 (2.7)	5 (1.7)
Bladder	3 (3)	0	3 (7.5)	2 (5)	0	1 (4.2)	0	0	NR	NR	6 (2.1)	3 (1.0)
Kidney	0	0	0	0	0	0	1 (0.8)	5 (4.2)	NR	NR	1 (0.3)	5 (1.7)
Total events, n (%)	7 (7)	2 (1.8)	5 (12.5)	2 (5)	2 (6.7)	3 (12.5)	1 (0.8)	6 (5.0)	NR	NR	15 (5.2)	13 (4.4)

Date shown are number (%).

AH, adjuvant hysterectomy; CCRT, concurrent chemoradiotherapy; NA, not applicable; NR, not reported.

\*Toxicity assessment was performed according to Radiation Therapy Oncology Group toxicity criteria and the Chassigne grading system; <sup>†</sup>grade 2 or more.

In terms of recurrence, the results of the study design subgroups differ; estimates from the NRSs implied that AH prevented recurrence, whereas those from the RCTs did not. One possible explanation is that inherent design features of NRSs may lead to selection bias. Although prognostic variables such as age, stage, histology, and tumor size were evenly distributed between the two groups in the NRSs, patients with distant metastasis or progressive disease during/after CCRT would have not undergone AH. The lymph node (LN) metastasis rate in the CCRT group (31%) was higher than that of the CCRT+AH group (17%) in 3 NRSs that reported the nodal metastasis rate [11,12,24], whereas there was no difference in LN metastasis rate in the RCTs [25]. This implies that patients with a more favorable prognosis may receive AH in NRSs. In addition, after sensitivity analysis, the overall association between AH and recurrence was significantly influenced by the study by Sun et al. [28]. Furthermore, the control groups in the 6 NRSs had a higher recurrence rate (115/455, 25%) compared with the RCTs (18/130, 14%). As seen in **Table 1**, baseline risk factors of recurrence differed between the control groups; compared with the RCTs, the NRS control groups had more stage III/IVA disease (0% vs. 34%) and LN metastasis (29% vs. 36%). These selection bias features may have influenced the high rate of recurrence in the NRS control groups, and the results should be interpreted with caution.

Clinicians' concern of AH after CCRT is for cases with residual disease after CCRT. Some experts believe that AH may be effective in patients with persistent residual disease after CCRT [29-31]. Houvenaeghel et al. [30] reported that AH may improve prognosis in LACC patients with macroscopic residual disease after CCRT, allowing a 3-year survival rate of 64.9%. Meanwhile, Azria et al. [32] have reported that the therapeutic effect of AH was disappointing in their small series of 10 patients who developed bulky (>2 cm) residual disease after CCRT for LACC, because LN metastasis was frequent in these patients. Recently, Kim et al. [33] reported the disease course in 53 patients with residual disease using MRI 3 months after CCRT for LACC [33]. In their analysis, 60% of patients with residual tumors did not show further

progression without any treatment, especially in cases of residual tumors sized  $\leq 2$  cm. In this context, the true therapeutic effect of AH should be tested in cases of residual disease. However, in our meta-analysis, there was no eligible study that was comprised exclusively of patients with residual disease. Instead, we performed subgroup analysis according to response after CCRT; AH was not associated with recurrence and mortality in two studies that exclusively included good responders and in one study that exclusively included patients with complete response after CCRT. This supports the current guidelines that do not recommend AH for patients who achieve a complete response [5,6]. Well-designed clinical trials aimed at patients with residual disease after CCRT are needed to elucidate the therapeutic impact of AH.

Although most studies implemented EBRT followed by ICBT for CCRT+AH and CCRT groups, the CCRT+AH group did not receive ICBT in two studies [11,26]. Subgroup analysis of these 2 studies revealed that AH was not associated with recurrence. However, AH reduced the risk of recurrence in the remaining six studies. ICBT, which is typically combined with EBRT, is a critical component of radiotherapy for LACC [34]; total doses for ICBT and EBRT of  $\geq 80$ –85 Gy to point A are currently recommended [34]. In this regard, the CCRT+AH group that did not undergo ICBT received less radiotherapy than the CCRT group in two studies [11,26]. This may result in biased estimation of the effect of AH. Accordingly, future studies of the oncologic outcomes according to radiotherapy in patients undergoing AH are needed.

Our meta-analysis included 2 RCTs. RCTs overcome numerous weaknesses associated with NRSs and provide the best available data regarding the effect of AH in LACC patients. In the trial by Morice et al. [25], only patients with macroscopic and radiological complete response after CCRT were enrolled. This meant that AH could be assessed between subgroups with similar prognostic factors. However, the trial was closed prematurely due to insufficient accrual; it only included 61 patients. Another RCT by Cetina et al. [26] included 211 patients, but the experimental arm did not receive ICBT. It aimed to demonstrate that RH after EBRT was associated with a greater survival benefit in LACC patients compared with EBRT followed by ICBT. Thus, the RCTs in the current meta-analysis might have had suboptimal power owing to insufficient enrollment or different study designs.

Postoperative complications are a major concern of AH after CCRT and must be balanced against the potential benefits of treatment. According to the present analysis, the pooled incidence of grade 3 and higher postoperative adverse events was 26.5%, which is mainly attributable to the RCT by Cetina et al. [26]. In a recent retrospective analysis of 362 LACC patients undergoing AH after CCRT, grade 3–4 adverse events occurred in 21(5.8%) patients [35]. This difference may be explained by the inherent limitations of a retrospective design [36]. In addition, complication rates depend on the radicality of the surgery, accompanying procedures, residual tumor, time interval from CCRT completion to AH, and the skill of the surgeons [26,35]. Indeed, the toxicity of radiotherapy can be exacerbated by other treatment modalities, such as surgery and chemotherapy. Compared with radiation alone, acute hematologic and gastrointestinal toxicity was higher with CCRT in LACC patients [4]. In general, radiation causes tissue to swell and become fibrotic. Thus, AH can be difficult to perform because the potential for healing and the quality of the tissues are negatively influenced by the preceding CCRT [37]. The use of advanced radiotherapy techniques such as intensity modulated radiotherapy (IMRT) can reduce toxicity compared with conventional radiotherapy. There are recent studies indicating IMRT results in lower grade 3 toxicity [38]. Unfortunately, advanced radiotherapy techniques were not considered in this study due to lack of data. Thus, future studies are needed to evaluate the role of AH in patients receiving advanced radiotherapy techniques.

Our meta-analysis had some limitations and the results should be interpreted with caution. First, most studies were observational. This feature may impede the comprehensive reporting of any confounding factors. Second, the studies were conducted in different institutions with presumably varying protocols and surgical expertise. Third, this meta-analysis was performed at a study level, rather than a patient level, and other risk factors such as initial tumor size, stage, nodal metastasis, or residual disease after CCRT could not be considered. Therefore, the effect of AH according to these features could not be analyzed. Fourth, although two RCTs are included in this study, they are underpowered due to aforementioned reasons. Finally, the heterogeneity of the mortality rate associated with RCTs is significant. The differences in sample size, stage, details of CCRT or AH, and other factors between the two RCTs in our analysis may be responsible for the high heterogeneity. A random-effects model was used to minimize, but not eliminate, this.

In conclusion, AH following CCRT does not improve survival in patients with LACC, although it seems to reduce the risk of recurrence. Concerning the significant morbidity associated with AH after CCRT, routine use of AH following CCRT should be avoided. AH may be considered in cases with residual disease after CCRT. However, the exact therapeutic role of AH in this population remains unclear. Further clinical trials with regard to AH for this subgroup are warranted. A multicenter randomized trial by the Korean Gynecologic Oncology Group is under development to address this issue.

## SUPPLEMENTARY MATERIALS

### Supplementary Data 1

The search strategy

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### Supplementary Table 1

Excluded studies with reasons

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### Supplementary Table 2

Jadad score for the risk of bias and quality assessment of RCTs

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### Supplementary Table 3

NOS for the risk of bias and quality assessment of NRSs

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### Supplementary Fig. 1

Sensitivity analysis in which 1 study at a time was omitted and the pooled OR for all remaining studies was calculated. (A) Mortality rate and (B) recurrence rate.

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### Supplementary Fig. 2

Funnel plots for identifying publication bias in the meta-analysis of (A) mortality (n=5), (B) recurrence (n=8), (C) local recurrence (n=7), and (D) distant recurrence (n=7). The Begg-Mazumdar rank correlation test indicates no evidence of publication bias in (A-D) (p=0.09, 0.11, 0.23, and 0.13, respectively).

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