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# Comparison of Survival Benefits of Combined Chemotherapy and Radiotherapy Versus Chemotherapy Alone for Uterine Serous Carcinoma

## *A Meta-analysis*

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**Objective:** To date, there is no convincing evidence comparing the impact of combined chemotherapy and radiotherapy with chemotherapy alone in postoperative uterine serous carcinoma (USC), which remains an unclear issue. We conducted a meta-analysis assessing the impact of combined chemotherapy and radiotherapy compared to chemotherapy alone on overall survival in postoperative USC.

**Methods:** A comprehensive search was performed in the databases of EMBASE, PubMed, Web of Science, and Cochrane Library from inception to March 2016. Studies comparing survival among patients who underwent combined chemotherapy and radiotherapy or chemotherapy alone after surgery for USC were included. Quality assessments were carried out by the Newcastle–Ottawa Scale. Hazard ratio (HR) for overall survival was extracted, and a random-effects model was used for pooled analysis. Publication bias was assessed using both funnel plot and the Egger regression test. Statistical analyses were performed using Stata version 13.0 software.

**Result:** Nine retrospective studies with relatively high quality containing 9354 patients were included for the final meta-analysis. The pooled results demonstrated that combined chemotherapy and radiotherapy significantly reduced the risk of death (HR, 0.72; $P < 0.0001$) compared to chemotherapy alone with a low heterogeneity ($I^2 = 21.0\%$, $P = 0.256$). Subgroup analyses indicated that calculating HR by unadjusted method may cause the heterogeneity among studies. Exploratory analyses showed that either patients with early stage disease (HR, 0.73; $P = 0.011$) or advanced stage disease (HR, 0.80; $P < 0.0001$) have survival benefits from combined chemotherapy and radiotherapy. No significant evidence of publication bias was found.

**Conclusions:** This is the first meta-analysis examining the role of combined chemotherapy and radiotherapy compared to chemotherapy alone in USC. Our results suggest the potential survival benefits of combined chemotherapy and radiotherapy. Further studies, preferably randomized clinical trials, are needed to confirm our results.

**Key Words:** Uterine serous carcinoma, Chemotherapy, Radiotherapy, Overall survival, Meta-analysis

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Uterine serous carcinoma (USC) [also known as uterine papillary serous carcinoma] is a rare and aggressive histological subtype of endometrial cancer. It constitutes less than 10% of all endometrial cancer, but accounts for more than 50% of all endometrial cancer relapses and deaths, with a 5-year overall survival (OS) rate of 18% to 27%.[1] As for molecular features, USC shares a high frequency of TP53 mutations and low frequency of PTEN mutations with serous ovarian carcinomas and basal-like breast carcinomas,[2] which may explain its aggressiveness.

Because of its aggressive behavior and its propensity for systemic spread, multimodality treatments were recommended. Treatment for USC begins with complete surgical staging with intent for cytoreduction to no residual disease, and systemic platinum/taxane-based chemotherapy considered as standard adjuvant therapy for patients with both early (I–II) and advanced (III–IV) stages.[1] Although some experts identified that combination of radiation and chemotherapy might provide best survival benefits for USC,[2] the question of whether combined chemotherapy and radiotherapy is associated with survival advantage still remains, due to the absence of convincing evidence.

Uterine serous carcinoma usually grouped with other histological subtypes of endometrial cancer in prospective trials because of its rarity, making it difficult to analyze this subtype separately; and subsequently, there is no currently ongoing randomized trial exclusively examining survival outcome for combined chemotherapy and radiotherapy compared to chemotherapy alone in patients with USC. Several retrospective studies on this topic have been reported mostly in recent years, involving both early and advanced stage cases.[3–11] Therefore, to further evaluate the role of combined chemotherapy with radiotherapy in postoperative patients and to help design future prospective study for this rare disease, we conducted a systematic review and meta-analysis focusing on the impact of combined chemotherapy and radiotherapy by comparing OS between patients who were treated with combined chemotherapy and radiotherapy and those with chemotherapy alone in USC only, excluding other subtypes of endometrial cancer, such as clear cell carcinoma and endometrioid carcinoma.

## METHOD

### Search Strategy

We performed a systematic literature review of published articles and unpublished abstracts, which compared survival outcome between patients receiving chemotherapy only and those receiving combined chemotherapy and radiotherapy for USC. We searched PubMed, Web of Science, EMBASE, and the Cochrane Library from inception to March 2016 by using the following keywords ["Uterine Papillary Serous Carcinoma" or "Uterine Serous Carcinoma" or "Endometrial Serous Adenocarcinoma"] AND ["Radiotherapy" or "Radiation" or "Intravaginal Radiation" or "Vaginal Brachytherapy"] AND ["Drug Therapy" or "Chemotherapy" or "Pharmacotherapy"].

### Study Selection

The studies included in the meta-analysis met the following inclusion criteria: (1) investigating patients who had a diagnosis of USC, and (2) including both patients who underwent postoperative chemotherapy alone and patients who underwent adjuvant chemotherapy in combination with radiotherapy. We excluded studies that (1) included other histological types of endometrial carcinoma together but did not separately describe the results of subgroup analysis limited to USC, and (2) did not provide sufficient data to acquire hazard ratio (HR) and its 95% confidence interval (CI) of combined chemotherapy and radiotherapy for OS.

### Data Extraction

Two authors independently extracted information from eligible studies using standardized forms. The following details were extracted: name of first author, publication year, and study period, country, and study design, number of patients, chemotherapy regimens, radiotherapy characteristics, follow-up duration, and International Federation of Gynecology and Obstetrics (FIGO) stage. Any discrepancies between the reviewers regarding the extraction of data were resolved by consensus.

### Quality Assessment

The risk of bias was assessed using the Newcastle–Ottawa Scale, including the following 3 factors: patient selection, comparability of the study groups, and assessment of outcomes.[12] Studies with scores greater-than over equal to 7 were considered as having a low risk of bias, scores of 4 to 6 as having a moderate risk of bias, and scores less than 4 as having a high risk of bias. We assessed that follow-up was adequate if the median or mean follow-up was in excess of 24 months.

### Statistical Analysis

The primary outcome is OS. The HR of undergoing combined chemotherapy and radiotherapy was used for pooled analysis. First, we directly extracted HR as well as its 95% CI from the text. We also calculated HR and 95% CI based on raw data using the methods of Tierney et al, when data were only available in the figures, we read the Kaplan–Meier curves by Engauge Digitiser version 7.2 and extracted the survival data to calculate HRs and its 95% CI according to Tierney et al.[13] In the absence of direct comparison

between combined chemotherapy and radiotherapy and chemotherapy only, adjusted indirect comparison was performed by using ITC software to obtain indirect data from available evidence.[14]

Pooled HR was calculated using the random-effects model via the inverse variance method and presented as forest plots. Heterogeneity among included studies was assessed using the Cochran Q test and the $I^2$ index, significant heterogeneity was denoted by a Cochran Q $P$ value of less than 0.05, and $I^2$ index of 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively.[15] We also performed subgroup analyses as the included studies had 2 types of data sources (national database or institutional data) and HRs were calculated in 2 methods (adjusted HR for other variables such as FIGO stage, or unadjusted HR for any interaction factors or only estimated from univariate Kaplan–Meier curve). In addition to subgroup analyses, further exploratory analyses were also performed for early (I–II) and advanced stage (III–IV) USC to investigate if the effect of combined chemotherapy and radiotherapy presents a difference between the 2 crowds, staging based on the 2009 FIGO staging system.[16] We applied a funnel plot as well as the Egger regression test to assess the possibility of publication bias. All statistical analyses were performed using Stata version 13.0 software (StataCorp LP, College Station, TX).

# RESULT

## Study Selection

We found 480 eligible studies including 162 duplicates in the initial search. Figure 1 outlines the selection process. A total of 9 studies were selected for the meta-analysis. There were 1 analysis using the National Cancer Database (NCDB), 1 using the Surveillance, Epidemiology, and End Results (SEER) database, and 7 institutional studies (4 from Unites States, 1 from Taiwan, and 2 from Australia). The characteristics of included studies are presented in Table 1. All 9 studies were retrospective analyses and overall research quality was relatively high as assessed by the Newcastle–Ottawa Scale; 9354 patients were included, 3609 patients received a combination of chemotherapy and radiotherapy, whereas 5745 patients received chemotherapy alone. Information about radiotherapy characteristics was unavailable in the NCDB analysis, chemotherapy regimens were unavailable in the

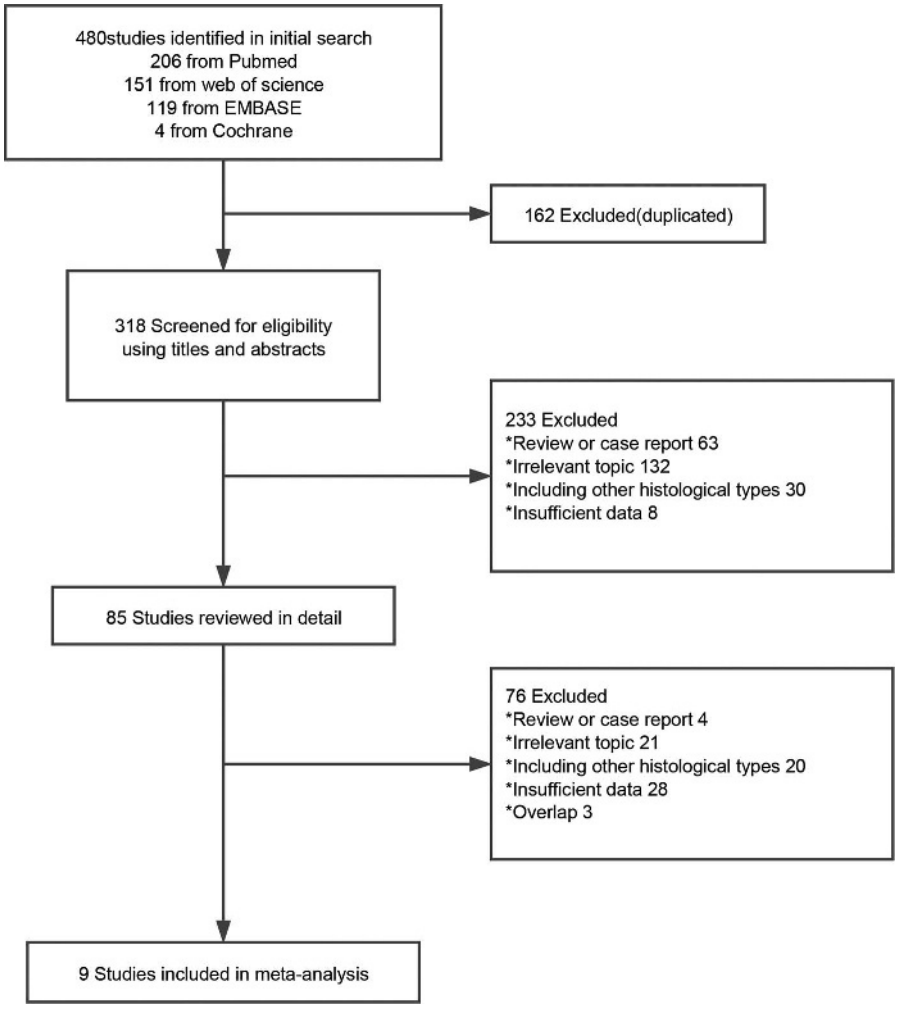


**FIGURE 1.** Study selection process.

**TABLE 1.** Characteristics of included studies

| Study | Data Sources (Country) | Study Period | Median Follow-up (Range) | Chemotherapy Regimens | Radiotherapy Characteristics | Stage | No. Patient | | NOS Score |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Chemotherapy | Chemoradiation | |
| Mahdi, 2016[3] | SEER (USA) | 2000–2009 | NA | NA | EBRT ± VBT | I–IV | 1272 | 566 | 7 |
| | | | | | | I–II | 288 | 153 | |
| | | | | | | III–IV | 892 | 353 | |
| Barrie, 2015[4] | Institution (USA) | 2001–2012 | NA | NA | VBT | I–II | 43 | 46 | 7 |
| Rauh-Hain, 2015[5] | NCDB (USA) | 2003–2011 | 52 | NA | NA | I–IV | 4290 | 2915 | 7 |
| | | | | | | I–II | 867 | 1221 | |
| | | | | | | III–IV | 2746 | 1347 | |
| Pol, 2015[6] | Institution (Australia) | 1996–2012 | 21 | Carboplatin | WPRT | I–IV | 13 | 10 | 7 |
| Lee, 2014[7] | Institution (USA) | 1980–2011 | 21 (2–140) | Platinum/ paclitaxel-based | EBRT ± VBT | IVB | 19 | 16 | 7 |
| Huang, 2014[8] | Institution (Taiwan) | 1991–2010 | 31 (2–208) | Platinum based (89%) | EBRT ± VBT | III–IV | 41 | 17 | 8 |
| Rauh-Hain, 2010[9] | Institution (USA) | 1995–2007 | 23 (1–142) | Platinum-based | EBRT ± VBT | IIIC–IV | 39 | 23 | 7 |
| Sood, 2003[10] | Institution (USA) | 1988–1998 | 19 (4–72) | Platinum/ paclitaxel-based | EBRT ± VBT | I–IV | 20 | 11 | 8 |
| Bancher-Todesca, 1998[11] | Institution (Australia) | 1988–1995 | 12 (8–68) | Platinum based | WPRT + VBT | I–IV | 8 | 5 | 8 |

EBRT, External beam radiation; NOS, Newcastle–Ottawa Scale; VBT, vaginal brachytherapy; WPRT, whole pelvic radiotherapy.

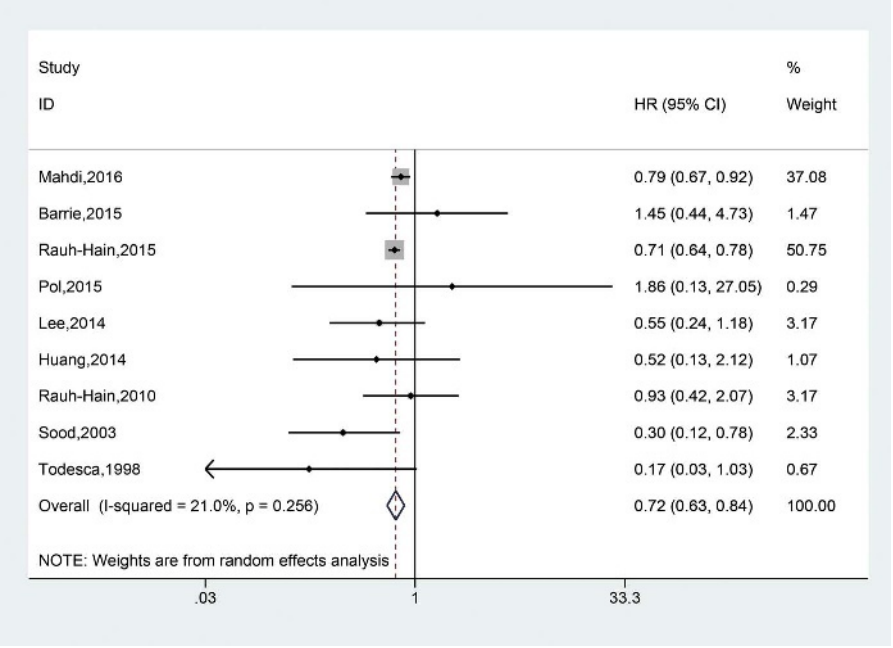


**FIGURE 2.** Forest plot of HRs for OS from the included studies comparing combined chemotherapy and radiotherapy with chemotherapy alone. The pooled effects were calculated with a random-effects model.

NCDB analysis and the SEER analysis, as well as in one institutional study.[5] Most of the known chemotherapy regimens are platinum or paclitaxel based. Radiotherapy of included studies is mostly based on external beam radiation, with or without vaginal brachytherapy, but one study investigated vaginal brachytherapy only.[5]

## Impact of Combined Chemotherapy and Radiotherapy Versus Chemotherapy

The pooled HR and 95% CI by comparing combined chemotherapy and radiotherapy versus chemotherapy alone was 0.72 [0.63–0.84], demonstrating that the risk of death was significantly reduced with combined chemotherapy and radiotherapy. There was a low heterogeneity in the OS result, with $I^2 = 21.0\%$ and $P = 0.256$ (Fig. 2).

Subgroup analysis by data sources showed that either patients from national database or from institutional data had a survival benefit for combined chemotherapy and radiotherapy; HR and 95% CI were 0.74 [0.67–0.81] in national database and 0.60 [0.36–0.99] in institutional data, both of them existed in a low heterogeneity within group (Fig. 3A). Subgroup analysis by HR calculation method indicated that effect of combined chemotherapy and radiotherapy would be obvious when HR was adjusted for known variables but inconspicuous when HR was calculated in an unadjusted way, for HR and 95% CI were 0.73 [0.67–0.79] with no significant evidence of heterogeneity ($I^2 = 0\%$, $P = 0.658$) in adjusted subgroup, but 0.57 [0.24–1.36] with heterogeneity ($I^2 = 59.1\%$, $P = 0.062$) in unadjusted subgroup (Fig. 3B). Calculated HR without adjusted for any confounding may contribute to the heterogeneity among all studies.

Exploratory analyses for comparisons of the effect of combined chemotherapy and radiotherapy in different stages of USC were also performed. In 2618 patients with early stages from 3 studies, 1420 underwent combined chemotherapy and radiotherapy, whereas 1198 underwent chemotherapy alone. Combined chemotherapy and radiotherapy was associated with improved OS [HR and 95% CI were 0.73 (0.58–0.93)] with a slight heterogeneity ($I^2 = 8.3\%$; $P = 0.336$) (Fig. 4A). As for advanced stage of USC, we extracted HR from 5 studies involving 5946 patients, 1756 of whom were in the combined chemotherapy and radiotherapy cohort and 3737 in chemotherapy cohort. The pooled HR and 95% CI were 0.80 [0.75–0.86] with no heterogeneity as $I^2 = 0\%$ and $P = 0.832$ (Fig. 4B).

## Publication Bias

Publication bias was assessed using the funnel plot with Egger regression test. No evidence of publication bias was identified in our meta-analysis [funnel plot, symmetrical (Fig. 5A); Egger test, $P = 0.591$ (Fig. 5B)].

# DISCUSSION

In this review and meta-analysis of 9 studies with relatively high research quality, we identified an increased OS for patients treated with combined chemotherapy and radiotherapy compared to those treated with chemotherapy alone. Exploratory analysis showed that patients with either early stage or advanced stage USC had survival benefit from combined chemotherapy and radiotherapy, whereas early stage seemed to have slightly lower HR of combined chemotherapy and radiotherapy than advanced cases. Subgroup analysis indicated that survival benefit of combined chemotherapy and radiotherapy would be more obvious and heterogeneity would be lower if HR was calculated in an adjusted way.

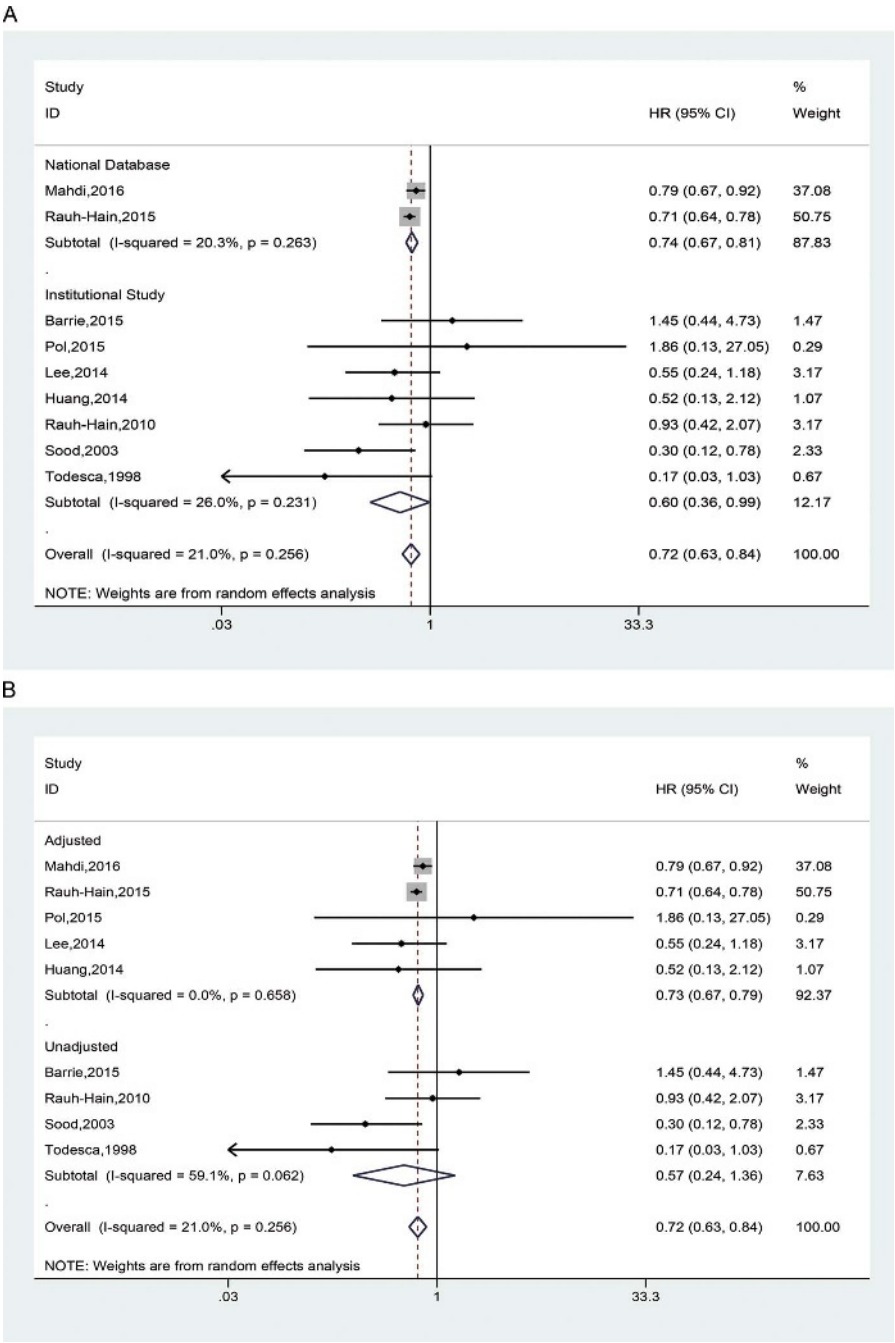


**FIGURE 3.** Subgroup analyses for OS according to data source (A) and HR calculation method (B). The pooled effects were calculated with a random-effects model.

We acknowledge several limitations of our meta-analysis, mostly because of the quality of included studies. All included studies are retrospective, due to the lack of randomized trials. Nonrandomized retrospective studies suffer from substantial selection biases that are difficult to adjust for; this may restrict our ability to detect accurate differences in survival outcomes. Nevertheless, we trusted that meta-analysis was a reliable alternative method when randomized trials were not reported in the past and near future (since there were no ongoing trials investigating the role of combined radiation to chemotherapy in USC). It is known that the meta-analysis consisting of high-quality randomized controlled trials (RCTs) served as the best medical evidence, but a well-conducted RCT is hard to operate in this topic due to its low incidence. It had been acknowledged that meta-analyses based on well-designed observational studies generally come to similar estimates with those based on RCT.[17] The studies included in our analysis were all performed in authoritative

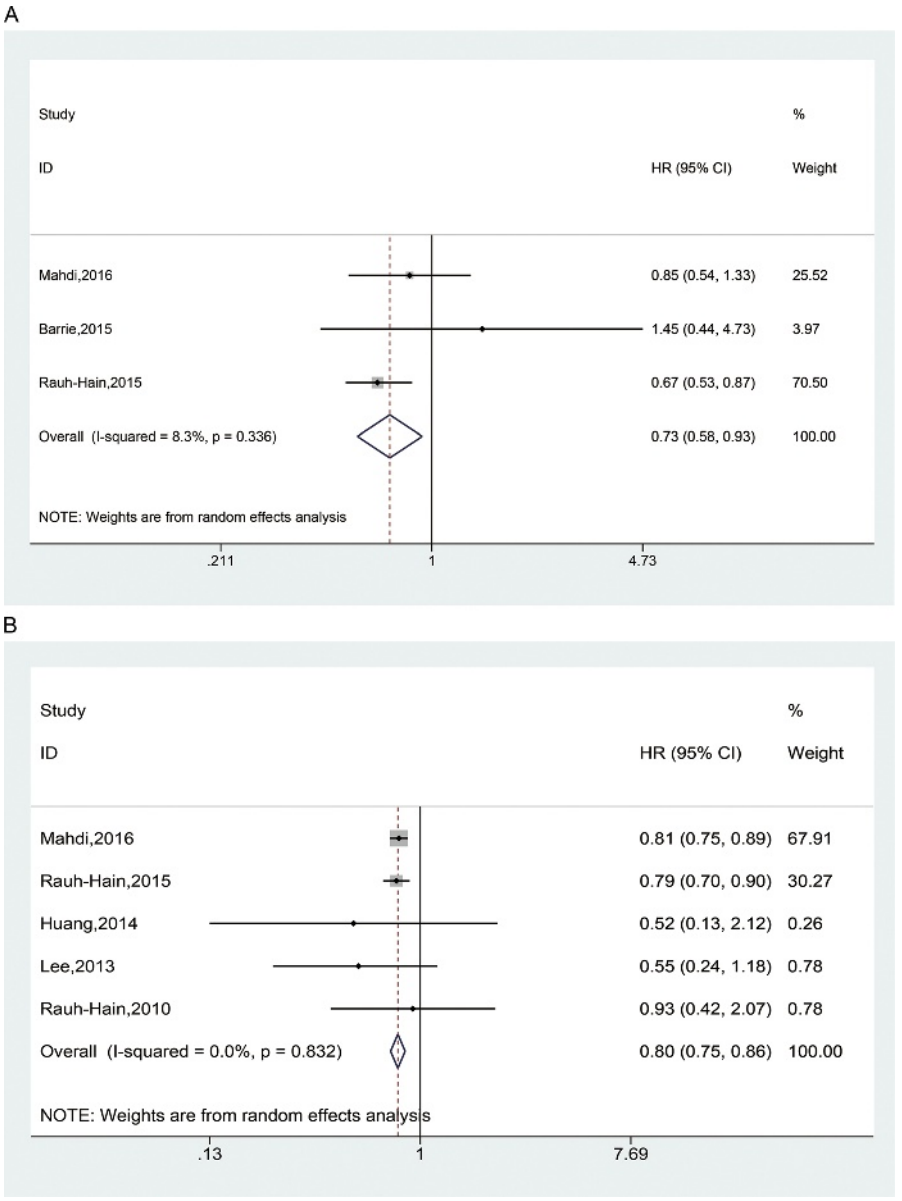


**FIGURE 4.** Forest plot of HRs for OS in patients with early stage disease (A) and advanced disease (B). The pooled effects were calculated with a random-effects model.

medical institutions with large patient volumes as well as experienced physicians and professional researchers. Hazard ratio estimates were mostly consistent, most of which were in the beneficial direction, and a very low heterogeneity among the studies probably caused by HR calculation. Relatively homogeneous treatments, platinum- or paclitaxel-based chemotherapy and external beam radiation with or without vaginal brachytherapy, were performed in most of our included studies. Therefore, our meta-analysis could be considered as reasonable and could provide more convincing evidence than each individual retrospective study.

To the best of our knowledge, this is the first meta-analysis focused on comparison of combined chemotherapy and radiotherapy versus chemotherapy in USC. A recently reported meta-analysis investigating the effect of radiotherapy combined chemotherapy versus radiotherapy alone in high-risk endometrial cancer, including USC and other histological type, indicated that advanced stage patients had survival benefits from radiotherapy combined chemotherapy whereas early stage patients had none.[18] Another related meta-analyses researched about sequential chemotherapy and radiotherapy for advanced endometrial cancer in the sandwich method, which did not investigate USC separately either.[19] These 2 analyses did not obviate the need for our meta-analysis, because we focused on different cohort and we are concerned about USC alone.

The currently ongoing Gynecologic Oncology Group 258 phase 3 study randomizes patients to radiation with

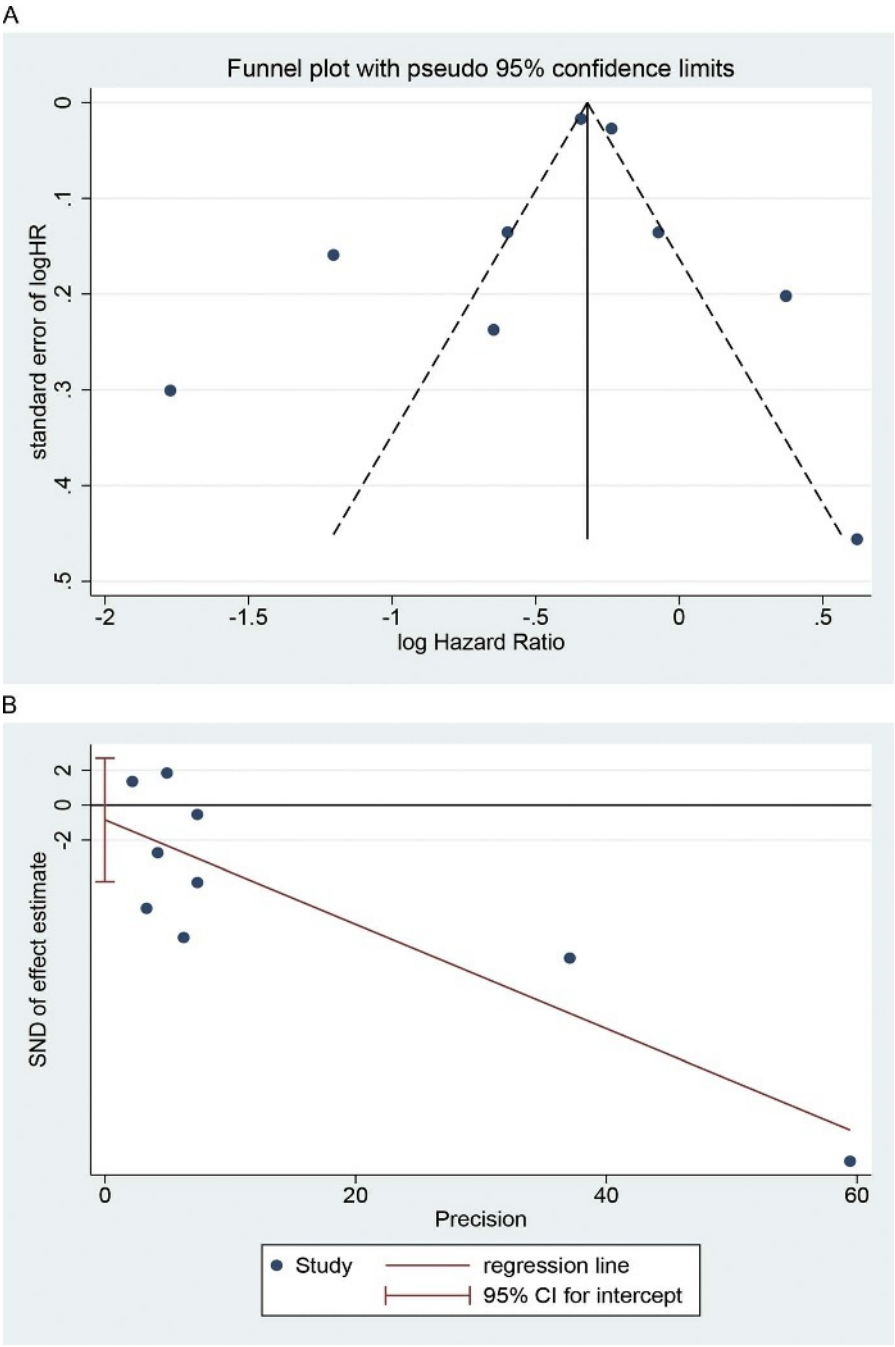


**FIGURE 5.** Publication bias in funnel plot (A) and Egger test (B).

concomitant and postradiation chemotherapy versus chemotherapy alone in endometrial cancers, which includes a proportion of USC and has not release any results yet. This trial may provide data to confirm or refute our analyses.

Most of our included studies investigated external beam radiation with or without vaginal brachytherapy, but one aimed on vaginal brachytherapy only. A reported trial, Gynecologic Oncology Group 249, released the results that there was no superiority in survival outcome of vaginal brachytherapy combined with chemotherapy to pelvic radiation therapy alone, with HR and 95% CI of 1.28 [0.689–2.36], in high-risk endometrial cancer including 15% USC.[20] We did not exclude this study for it contributed no significant heterogeneity, and another study from Taiwan included a proportion of vaginal brachytherapy cases as well, without discussing it separately. We conservatively think that radiation can add a survival benefit to concurrent chemotherapy, whereas the role of vaginal brachytherapy needs further discussion.

There are several limitations to this study. As described earlier, the pooled HR estimates from a limited number of

 

retrospective studies constituted the major weakness. An additional problem is that we used an indirect method to calculate HR as this was the only possible approach, although it has also been used in many other meta-analyses. Furthermore, the toxicity outcome was not evaluated in our analysis. And we failed to assess the separate estimates based on important covariates such as lymph node status, pure or mixed USC, and so on, which can lead to inaccuracies in our results.

## CONCLUSIONS

Our meta-analysis of retrospective studies demonstrates significant OS benefits, suggesting that using a combination of radiotherapy and chemotherapy rather than chemotherapy alone in patients with USC could be a promising option and could result in improvement of OS, although this study may not be extremely reliable due to inherent limitations. Additional trials, preferably randomized clinical trials, are needed for confirmation.

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