

# WITHDRAWN: Outcomes in patients with early stage uterine clear cell carcinoma treated with chemotherapy and radiotherapy: A systematic review and meta-analysis

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## Research article

**Keywords:** uterus clear cell cancer, adjuvant therapy, chemotherapy, radiotherapy, overall survival, meta-analysis

**Posted Date:** September 9th, 2020

**DOI:** <https://doi.org/10.21203/rs.2.20417/v3>

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EDITORIAL NOTE:

The full text of this preprint has been withdrawn by the authors while they make corrections to the work. Therefore, the authors do not wish this work to be cited as a reference. Questions should be directed to the corresponding author.

# Abstract

**Background:** Uterine clear cell carcinoma (UCCC) is a rare histological type of endometrial cancer with poor prognosis and high risk of tumor relapse. Although adjuvant chemotherapy (CT) and/or radiotherapy (RT) are often recommended for early stage UCCC patients, the effectiveness of these treatment strategies remains unclear.

**Methods:** Systematic review and meta-analysis were applied to evaluate treatment-related outcomes of stage I-II UCCC patients. Search strategy was applied using electronic databases until June 1st, 2019. Inclusion criteria were retrospective, observational and prospective studies that reported outcome of UCCC patients receiving adjuvant therapy. Clinical endpoints like overall survival (OS) and progression-free survival (PFS) were evaluated. Data were extracted by two independent reviewers and a meta-analysis was performed.

**Results:** 12 articles with a total of 3845 patients were analyzed. Overall, adjuvant CT after surgery could improve 5 year-OS significantly compared to patients without CT (odds ratio (OR): 0.75, 95% confidence interval (CI): 0.58-0.95;  $p=0.02$ ). In comparison, RT could also improve OS in UCCC patients of early stage (OR: 0.61, 95% CI: 0.46-0.82;  $p=0.001$ ) compared to the patients without RT, in US and Europe patients. Lastly, when comparing the patients undergoing both CT and RT with those receiving CT or RT alone, no further improvement in OS was observed (OR: 0.95, 95% CI: 0.53-1.72;  $P=0.88$ ).

**Conclusions:** Either CT or RT after surgery could improve the OS of early stage of UCCC patients. However, combinatorial CT and RT treatment did not improve the OS compared with CT or RT treatment alone.

## 1. Background

Uterine clear cell carcinoma (UCCC), which accounts for 1% to 5% of endometrial cancers, is a highly aggressive cancer subtype that is frequently associated to poor prognosis and high tumor recurrence (1). Notably, up to 30% of UCCC patients demonstrated pelvic recurrence, whereas distant recurrence was found in up to 60% of these patients. Moreover, the 5-year overall survival (OS) for UCCC was approximately 60% compared to over 80% OS for other endometrial cancers (2). For early stage of pure UCCC, the 5-year OS rate were nearly 92% for Stage I, and 83% for Stage II.

Chemotherapy (CT) and/or radiotherapy (RT) are used as adjuvant treatment after complete surgery of endometrial cancer in order to improve patients' prognosis. Notably, as more aggressive histologic variants of malignant tumor, the latest National Comprehensive Cancer Network (NCCN) guideline of Uterine Neoplasms (Version 1. 2020) suggested different treatment strategies treated for UCCC and endometrioid adenocarcinoma. Up to present, there is no consensus concerning the specific treatment, particularly for stage I-II UCCC patients after primary treatment. The preferred adjuvant therapy is systemic therapy with vaginal brachytherapy, but the patients could also be treated by vaginal brachytherapy with or without external beam radiation therapy (EBRT) as recommended in NCCN guideline. Moreover, close monitoring prior to further treatment in patients of IA stage was also suggested. Recently, pooled analysis showed that application of adjuvant CT and RT in stage IA endometrial cancer with serous, clear cell or mixed histology was associated with better PFS compared to those from the observation group. Observation might benefit the patients only when there was adequate surgical staging (3). For patients with stage IB and II disease, different adjuvant therapies were recommended in the NCCN guidelines. Taken together, the best adjuvant therapy for early stage of UCCC remains unclear.

There is not enough data on the use of chemotherapy in early-stage clear cell cancers, although some clinical trials from Gynecologic Oncology Group (GOG) have investigated the effect of adjuvant therapy on UCCC (4). Furthermore, most retrospective studies often categorize both serous and clear cell subtypes as type II endometrial cancer, assuming that their clinical outcomes are same. Consequently, none of the individual studies could provide sufficient power for precise evaluation of the effect of adjuvant therapy in UCCC patients.

To our knowledge, the prognostic index of adjuvant therapy including progress free survival (PFS), disease free survival (DFS) or overall survival (OS) has not been systematically evaluated in early stage UCCC patients combining the data from all eligible previous studies. Therefore, in this meta-analysis, we aim to summarize and compare the impact of different adjuvant therapy regimens on prognostic value of early stage UCCC, thus providing practical implications for these disease.

## 2. Methods

To conduct systematic review and meta-analysis, electronic searches from Web of Science, PubMed and Medline were performed independently by two reviewers (X.Y. and J.C.) to identify all relevant studies that evaluated the efficacy of adjuvant therapy in early stage UCCC. The selection strategy for the database search is: (“adjuvant therapy” or “systemic therapy” or “chemotherapy” or “radiotherapy” AND “Uterine Clear Cell Carcinoma” or “UCCC” or “Endometrial Clear Cell Carcinoma”).

The search was concluded on June 1<sup>st</sup>, 2019, and was limited to publications written in English. Additional publications that were not identified during the electronic searches were selected manually. Publications in the forms of retrospective, observational and prospective randomized controlled trials were included, while publications like letters, case studies, or reviews were excluded. Uterine clear cell carcinoma were included regardless of whether they were pure uterine clear cell carcinoma or mixed uterine clear cell carcinoma. In addition, studies with unclear description of data on the outcomes of interests were also excluded from the analyses. Authors of identified studies were contacted for clarification on methods and outcomes when necessary. Disagreements between the two reviewers were resolved through discussion. All extracted data from the selected studies was arranged using a standard PRISMA data extraction form.

General characteristics of the extracted data included author names, year of publication, country, number and age of patients, different type of therapies and cases of different events based on 5-year OS and PFS. Different groups were compared. Here CT group means patients received chemotherapy while Not-CT group means patients received other therapy except chemotherapy (radiotherapy or observation). RT and Not-RT group means similarly the patients with radiotherapy or not. To ensure the completeness and accuracy of the extracted data, two reviewers (X.Y. and J.C.) extracted the data from the identified studies independently and then cross-checked their results. When discrepancies arose, the final decision was made through discussion. If the relevant data were not clear in a particular study, the corresponding author of the publication was contacted by email for further clarification.

The risk of bias was assessed by the reviewers in accordance to the Cochrane Handbook for Systematic Reviews of Interventions. The seven domains related to risk of bias that were evaluated for each trial included: (1) details of the randomization method, (2) concealment of treatment allocation, (3) masking of the participants and personnel, (4) blinding of the outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other bias. For each criterion, the risk of bias was rated as low, high, or unclear. Disagreement was resolved through discussion.

Data synthesis was performed using RevMan 5.3 (Cochrane Collaboration, London, UK). Continuous data were presented as mean value and standard deviation, and the weighted mean difference and 95% confidence interval (CI) were also calculated. Dichotomous data were expressed as odds ratios (ORs) with 95% CIs.  $p < 0.05$  was considered statistically significant. The heterogeneity in outcomes across all the trials was assessed using the  $\chi^2$  and  $I^2$  tests. An  $I^2$  value  $> 50\%$  was considered to indicate substantial heterogeneity, which prompted the use of a random-effect model for the subsequent analysis; otherwise, a fixed-effect model was applied. Meta-regression was applied when the heterogeneity was existed. Subgroup analysis was also performed to further meta-analysis when the study number is no smaller than 9. Publication bias was assessed by a funnel plot, in which the sample size was plotted on the Y-axis and the pooled OR on the X-axis. The presence of bias was considered when an asymmetrical plot was evidenced, whereas a symmetrical plot suggested no bias in the assessed publication. Begg's test and Egger's regression test for publication bias were calculated by Rstudio 1.2.1335 using package "Metafor".

## 3. Results

### 3.1. Eligible studies and their characteristics.

After initial search of the databases, we identified 59 potentially relevant reports from Pubmed and Medline (n=27) and Web of Science (n=32). After excluding repeated publications, a final 36 articles were examined. 14 articles were eliminated for analyses for the following reasons: (1) the reports were review or abstract (n=5), (2) non-English articles (n=1), (3) the reports were not related to adjuvant therapy in UCCC (n = 8). Full-text review were performed on 22 articles and 1 manually inquired articles. After carefully performing data extraction, an addition of 9 articles was removed from the analyses due to insufficient data. In the end, 12 articles were included in this meta-analysis (5-17) (**Supplemental Figure 1**).

### 3.2. Characteristics of the included studies

12 articles included consisted 3845 patients in total. The quality assessment and main characteristics of the included studies were summarized in **Table 1** and **Supplemental Figure 2** respectively. All studies selected were assessed to be in a good quality. The follow-up time of patients was more than 60 months to achieve the 5-year overall survival.

**Table 1. Basic characteristics of included studies.**

No	Author	Year	Clinical Trial	Nationality	Median age	Type of Adjuvant Treatment After OP	Total Patients	Type of patients
1	Creasman et al	2004	retrospective of the 25th Annual Report of FIGO published in 2001	Italy	NA	Observation/RT	59	26 Observation/33 RT
2	Thomas et al	2008	a retrospective review was conducted at 2 major gynecologic cancer centers between 1998 to 2004	US	64	Observation/Pelvic RT/VB	47	20 observation /27 RT
3	Rauh-Hain et al	2009	a retrospective review conducted at the Massachusetts General Hospital and Brigham and Women's Hospital between January, 1996 to January, 2007	US	64±7 for adjuvant therapy 70±8 for observation	RT/BRT/Pelvic RT and BRT	25	13 observation/12 RT
4	Hsu et al	2014	retrospective TGOG between 1991 to 2010	Chinese Taiwan	59.9±10.9 (33-86)	Observation/CT/RT	92	37 observation/22 CT/ 25 RT/ 8 CT+RT
5	Chang-Halpenny et al	2016	retrospective study at one single center from 1995 to 2012	US	65(35-84)	CT/RT/EBRT/VB	64	29 observation/6 CT/ 17 RT/ 12 CT+RT
6	Nguyen et al	2016	retrospective cohort study at 2 academic cancer centers from 2000 to 2014	Canada	65(45-96), mean 66.55±11.1	Observation/RT/CT	95	37 observation/2 CT/ 41 RT/ 15 CT+RT
7	Hong et al	2017	identified from the National Cancer Data Base from January, 1998 to December, 2012	US	68	CT/BRT/EBRT	with LND 1672	338 CT/ 1334 Not-CT
							without LND 307	41 CT/ 266 Not-CT
8	Mahdi et al	2016	retrospective review from SEER from 2000 to 2009	US	CT: 68 (30-87) CT+RT: 64 (34-85)	EBRT/CT	100	48 CT/52 CT+RT
9	Cetinkaya et al	2017	retrospective study at one single center from 2008 to 2014	Turkey	mean 64±9.8 (49-84)	Observation/ERT/BRT/CT	14	5 observation/4 CT/ 5 CT+RT
10	Sari et al	2017	retrospective study from 8 gynecologic oncology centers from January 1997 to November 2016	Turkey	63(42-84)	CT/BRT/EBRT	42	14 observation/8 CT/ 4 CT+RT/16 RT
11	Shinde et al	2018	identified from the National Cancer Database between 2004 and 2015	US	NA	CT/ERT/BRT	1246	RT 363/Not-RT 883
12	Armbruster et al	2019	a retrospective review conducted at the University of Texas MD Anderson	US	65.1(34-94)	Observation/CT/BRT/Pelvic RT	82	27 observation/9 CT/ 29 CT+RT/17 RT

Abbreviations: BRT: brachytherapy; CT: Chemotherapy; EBRT: external beam radiation therapy; ERT: external beam radiotherapy; LND: lymph node dissection; RT: Radiotherapy; VB: vaginal brachytherapy

### 3.3. Comparison of OS between CT and not-CT groups

In order to compare OS between patients receiving chemotherapy (CT group) and patients receiving other therapy except chemotherapy (not-CT group), 7 trials from 6 studies (Hsu et al 2014, Chang-Halpenny et al 2016, Nguyen et al 2017, Sari et al 2017, Hong et al 2017, Armbruster et al 2019) were included in the pooled analysis. Data extracted from 494 patients receiving CT and 1860 patients receiving not-CT were summarized. Pooled data revealed no difference in OS between the two groups ( $p=0.37$ ,  $I^2=7\%$ ). Consequently, a fixed-effect model was applied to estimate the overall outcomes. The OR of CT versus not-CT was 0.74 (95% CI: 0.58-0.95,  $p=0.02$ ), indicating a significant higher 5-year OS in CT group when compared to the not-CT group [Figure 1]. When comparing patients receiving CT versus those without any adjuvant therapy, the OR was 1.01 (95% CI: 0.39-2.58,  $p=0.99$ ), suggesting that OS was not significant between these groups [Supplement Figure 3].

### 3.4. Comparison of OS between RT and not-RT groups

For OS between patients receiving radiotherapy (RT group) and patients receiving other therapy except radiotherapy (not-RT group), 9 trials (Creasman et al 2004, Thomas et al 2007, Rauh-Hain et al 2009, Hsu et al 2014, Chang-Halpenny et al 2016, Nguyen et al 2017, Sari et al 2017, Shinde et al 2018, Armbruster et al 2019) were included in the pooled analysis. Extracted data from 619 patients receiving RT and 1133 patients receiving not-RT were summarized. Importantly, pooled data revealed significant difference between the OS of these two groups ( $p=0.02$ ,  $I^2=56\%$ ). So, a random-effect model was utilized to estimate the overall outcomes. Results revealed that OR of RT versus not-RT was 0.83 (95% CI: 0.47-1.46,  $p=0.52$ ), indicating no significant difference of overall survival between RT and not-RT groups [Figure 2]. Comparing OS for patients receiving RT with those without any adjuvant therapy, the OR was 0.94 (95% CI: 0.33- 2.65,  $p=0.90$ ) [Supplement Figure 4].

### 3.5. Comparison of OS between patients receiving CT plus RT and those with CT or RT alone

For OS comparison between patients receiving CT plus RT and those with CT or RT alone, 5 trials (Hsu et al 2014, Chang-Halpenny et al 2016, Sari et al 2017, Mahdi et al 2016, Armbruster et al 2019) were included in the pooled analysis, in which 105 patients receiving CT plus RT and 168 receiving CT or RT alone were analyzed. Pooled data revealed significant difference in OS between these two groups ( $p=0.51$ ,  $I^2=0\%$ ). Consequently, a fixed-effect model was applied to estimate the overall outcomes. The OR of CT plus RT versus CT or RT therapy alone was 0.95 (95% CI: 0.53-1.72,  $p=0.88$ ), indicating that the OS of these groups showed no significant difference [Figure 3]. For comparison of OS between patients receiving CT plus RT and those with no adjuvant therapy, 4 trials (Hsu et al 2014, Chang-Halpenny et al 2016, Sari et al 2017, Armbruster et al 2019) were included in the pooled analysis with extracted data from a total of 53 patients receiving CT plus RT and 107 receiving no adjuvant therapy. The OR of CT plus RT versus no adjuvant therapy groups was 1.07 (95% CI: 0.46-2.50,  $p=0.87$ ), indicating that there was no significant difference in OS between these groups using a fixed-effect model for overall outcome estimation [Supplemental Figure 5].

### 3.6. Comparison of PFS between CT and not-CT groups

In order to compare PFS between patients receiving CT and not-CT, 2 trials (Hsu et al 2014, Nguyen et al 2017) were included in the pooled analysis with 47 patients receiving CT and 140 receiving not-CT. Pooled data revealed no significant difference in PFS between these two groups ( $p=0.30$ ,  $I^2=7\%$ ), and therefore, a fixed-effect model was applied to estimate the PFS outcomes. The OR of CT versus not-CT was 0.44 (95%CI: 0.17-1.13,  $p= 0.09$ ), indicating that close to being statistically significant difference in PFS between CT and not-CT groups [Supplemental Figure 6].

### 3.7. Comparison of PFS between RT and not-RT groups

For PFS comparison between patients receiving RT and not-RT, 2 trials (Thomas et al 2007, Hsu et al 2014) were included in the pooled analysis. In particular, extracted data from 58 patients receiving RT and 79 receiving not-RT revealed statistically significant difference of PFS between these two groups ( $p=0.0004$ ,  $I^2=92\%$ ), and therefore, a random-effect model was applied to estimate the overall outcomes. The OR of RT versus not-RT was 1.18 (95%CI: 0.06-23.64,  $p=0.91$ ), indicating no significant difference of PFS between patients receiving RT and not-RT groups [Supplemental Figure 7].

### 3.8. Meta-regression and subgroup analyses

The heterogeneity issue between all included studies was addressed. We performed meta-regression analyses to explain expected heterogeneity in the comparison of OS between patients receiving RT and not-RT, ( $I^2=56\%$ ), by testing the effects of factors like sample size (case number >80 versus <80), nationality (Asia versus Europe and US) and publication year (before versus after 2010). Interestingly, the results indicated that difference in nationality contributed significantly to the overall heterogeneity ( $Z=0.04$ ,  $p=0.0466$ ) (Table 2). Therefore, subgroup analyses were performed. Data revealed that analyses on left 8 publications from Europe and US with a total number of 1660 patient indicated no heterogeneity ( $I^2=13\%$ ). The pooled data revealed OR of RT versus not-RT was 0.61 (95% CI: 0.46-0.82) and 5-year OS in RT group was significantly higher compared to the not-RT group using a fixed-effect model ( $p= 0.001$ ) (Supplemental Figure 8). Analysis on patients from Asia was not performed due to limited number of publication ( $n=1$ ) (Table 3).

Table 2. Meta-regression of factors in patients receiving Radiotherapy and Not-Radiotherapy.

Heterogeneity factors	Coefficient	SE	Z	P-value	95% CI (lower limit, upper limit)
No of patients	-0.004	0.640	1.00	0.996	0.17-5.88
Publication year	0.363	0.747	1.44	0.653	0.18-11.44
Nationality	-3.256	1.144	0.04	<b>0.0466</b>	0.00-0.92

Abbreviations: SE: standard effect; CI: confidence interval

Table 3. Subgroup analysis of factors in patients receiving Radiotherapy and Not-Radiotherapy.

Subgroup factors	criteria	No of Articles	Z	P value	I <sup>2</sup> %	OR
						95%CI
No of patients	<80	5	1.06	0.29	11	0.67 (0.33-1.40)
	>80	4	0.10	0.92	78	1.04 (0.43-2.55)
Publication year	before 2010	3	1.38	0.17	0	0.56 (0.25-1.27)
	after 2010	6	0.07	0.94	70	0.97 (0.45-2.09)
Nationality	Asia	1	2.68	0.007	Not applicable	9.12 (1.81-46.05)
	US+Europe	8	3.27	0.001	13	0.61 (0.46-0.82)

Abbreviations: OR: odds ratio; CI: confidence interval

### 3.9. Publication bias

In CT and not-CT groups, funnel plots formed a very distinctive symmetrical funnel shape with log ORs of the OS. These results implied that no publication bias was detected in the present study (Begg's test,  $p=0.07$ , Egger's test,  $p=0.62$ ) (**Supplemental Figure 9**). In RT and not-RT groups, no evidence of publication bias was detected as well (Begg's test,  $p=0.61$ , Egger's test,  $p=0.39$ ) (**Supplemental Figure 10**).

## 4. Discussion

UCCC, a relatively rare cancer of the endometrium, exhibits poor patients' prognosis even at early stage of the disease such as stage I-II. CT or RT has been applied as the adjuvant treatment after surgery to improve prognosis. However, it remains controversial of the effectiveness of CT or RT as the adjuvant therapy for early stage UCCC due to small number of cases reported in a limited few studies. Our study is the first meta-analysis, which aims to evaluate the effectiveness of adjuvant CT or RT on survival outcomes in stage I-II UCCC.

Our meta-analysis results have supported the notion that CT is beneficial for early stage, i.e. stage I-II UCCC. In particular, we found that patients receiving CT showed a significant higher 5 year-OS rate compared to those receiving not-CT ( $p=0.02$ ). This result was evidenced based on the pooled extracted data from 494 CT and 1860 not-CT patients without internal difference from a total of 7 trials ( $I^2 = 0\%$ ). Interestingly, in the study of Hsu *et al.*, 1 cases of death were reported from a total of 30 cases receiving adjuvant CT, while 9 death cases found from the 62 cases without receiving CT. According to the authors of this study, patients that did not receive adjuvant treatment tended to have lower risk of recurrence as evidenced by smaller tumor sizes and less myometrial invasion (6). In a study that consisted the largest study cohort, Hong *et al.* analyzed the nearly 2000 patients' data from the National Cancer Data Base (NCDB) and found that women undergoing hysterectomy, lymph node dissection (LND) and CT had the highest 5-year OS, followed by those with hysterectomy and LND without CT (13). The NCDB is a national cancer database that tracks over 1500 facilities in the United States. The data from NCDB are estimated to represent 70% of newly diagnosed cancer cases in the United States which is very reliable and value in this meta-analysis. Although Hong *et al.* has a heavy weight in the analysis, the results are very significant. Taken together, these results supported the use of CT in the treatment of early stage UCCC.

In the latest Randomized Trial of Radiation Therapy With or Without Chemotherapy for Endometrial Cancer (PORTEC-3), patients with serous or clear-cell cancers had an improvement in failure-free survival with the addition of CT, similar to those with endometrioid endometrial cancer (18). In addition, the Society of Gynecologic Oncology (SGO) has recommended the use of adjuvant treatment with CT for stage I-II UCCC patients (19). Together, all data has again confirmed the effectiveness of adjuvant CT in improving OS of the UCCC patients.

On the other hand, adjuvant RT has been applied for the treatment of early stage UCCC, a rationale inferred from the outcome data for women with uterine serous carcinoma and grade III endometrioid carcinoma (20). Application of

adjuvant RT in stage I-II patients remains as a controversial topic due to mixed patients' outcome obtained from different studies. Unlike papillary serous tumors, clear-cell carcinoma does not seem to have high propensity for abdomen. So, outcome data from certain trial opposed the routine use of whole-abdominal RT in patients (21). Consistent to these observation, our analyses revealed that OR of RT vs not-RT groups was 0.83 ( $p=0.52$ ), implying that the OS was not significantly different between RT and not-RT groups. Furthermore, Hsu *et al.* claimed that postoperative adjuvant RT was associated with poorer 5-year recurrence-free interval when compared to CT. Moreover, Chang-Halpenny *et al.* discovered poorer OS in patients treated with RT, by which the authors believed were due to the inclusion of a great proportion of patients with high-stage disease. Lastly, Hong *et al.* reported that women undergoing both hysterectomy and LND did not show improved survival rate with either brachytherapy or external beam RT. Taken together, these results may have led to the non-favorable recommendation of RT in early-stage UCCC patients.

Interestingly, our meta-regression analyses have identified nationality as the source of heterogeneity in the disparity of patients' treatment outcome. After excluding the study of Hsu *et al.* from analysis, we observed that  $I^2$  had reduced to 13% from 56% while the  $p$  value had changed to 0.001 (OR: 0.61, 95%CI: 0.46-0.82), indicating the superiority of RT in the corresponding US and Europe patients. Consistently, in the PORTEC-3 clinical trial, which involved collaborative efforts of multicenter worldwide, no difference in OS was observed between 29 UCCC patients receiving CT and 33 receiving RT, indicating that both CT and RT could yield favorable prognosis in patients (18). In addition, Desteli *et al.* also recommended vaginal brachytherapy for the treatment of UCCC (22). Lastly, Kim *et al.* conducted a large retrospective analysis of 451 UCCC and 882 UPSC (uterine papillary serous carcinoma) patients from the SEER database and found that the 5-year OS for RT and not-RT patients at stage IB were 76 % and 66% respectively ( $p=0.006$ ) whereas the 5-year OS for RT and not-RT patients at stage IC were 60.7% and 33.9% respectively ( $p=0.001$ ) (23). In short, all the evidences thus far have suggested adjuvant RT as a favorable treatment option for improving the survival of patients.

It is interesting to note that no survival improvement between patients receiving CT plus RT and CT or RT alone was observed in our meta-analysis ( $p=0.88$ ,  $I^2 = 0\%$ ). However, we could not exclude the possibility that the negative results might be due to limited available data, i.e. 273 patients from 5 individual studies. Notably, some studies have casted doubts on the efficacy of combinatorial treatment involving both CT and RT. In particular, Mahdi *et al.* found no statistical difference in OS between CT plus RT and CT only groups in stage I-II UCCC patients (5-year OS is 65% versus 67%,  $p=0.69$ ). In one GOG study, which involved retrospective analysis of 13 patients with stage I-II UCCC treated with whole abdominal radiotherapy, the 5-year PFS was 54%. Interestingly, treatment failures were often observed in patients receiving RT. Therefore, the authors concluded that adjuvant CT was necessary for the patients with radio-resistant cancers (24).

The prevalence of usage of CT and RT in UCCC is increasing in the recent years though controversies remain. With limited number of cases, Vogel *et al.* found a survival benefit in patients with stage IB to II disease with any form of adjuvant treatments including RT, CT or both (25). From the periods of 1998 to 2001 and 2005 to 2006, Xu *et al.* also found a declining use of observation (43.4 versus 41.7%) and RT alone (42.2 versus 27.1%) for stage I-II UCCC ( $p<0.001$ ) (26). In comparison, the increased use of CT and RT throughout the years was noted. Consequently, we have focused on the studies published from 2004 to 2019, with most of the studies published between 2016 and 2019, to ensure that our analyses capture the timely and representative CT and RT emerging era.

Chemotherapy and radiotherapy are also evaluated for toxicity in UCCC. In a PORTEC-3 trail published by de Bore *et al.*, common adverse events during the chemotherapy and radiotherapy in endometrial cancer were gastrointestinal

symptoms like diarrhea, ileus/obstruction, nausea or hematological disorders like febrile neutropenia or neuropathy like motor neuropathy sensory neuropathy (27). The study also mentioned the adverse events were higher in RT+CT group compared to CT group. One study (Chang-Halpenny et al, 2016) reported 11 experienced at least grade 2 peripheral neuropathy and 4 patients had grade 1 to 2 arthralgias from 18 patients receiving any chemotherapy. No grade 4 hematologic toxicities were reported. One patient stopped after a single cycle of carboplatin and paclitaxel due to headache, insomnia, and hallucinations. RT toxicity data were confirmed at 26 out of 29 patients. Two patients had incomplete EBRT course due to diarrhea (1 complicated by Clostridium difficile infection) and an additional patient developed radiation colitis and anemia requiring transfusions. No other acute grade 3 or 4 GI or GU radiation-related toxicities occurred. Following completion of treatment, 1 patient later developed small bowel obstruction requiring surgical exploration. Only mild side effects (dysuria, enterocolitis) were reported with VB and all completed treatment except for one who was found to progress at the cuff during treatment. Overall, toxicity appears acceptable, although risks exists with any adjuvant therapy.

Nevertheless, our study consists of several limitations. Firstly, we have only included 13 papers for analyses due to our strict inclusion criteria. In particular, certain studies that only had limited number of UCCC cases were omitted from our analyses. Secondly, we only selected OS and PFS as the indexes for prognostic analysis as most of the studies did not have survival data such as DFS (Disease-Free Survival), TTP (Time to Progression) or ORR (Objective Response Rate). Thirdly, the design of each individual study, such as the CT regimens and types of RT, was different, which might influence the final reporting of our meta-analysis. Lastly, in order to investigate the prognostic effects of CT or RT, multivariable COX regression of different clinical variables is necessary, however it is impossible for us to do this COX regression here because of limited data in each study.

## 5. Conclusion

As the first meta-analysis investigating the treatment of early stage of uterine clear cell carcinoma with nearly 4000 patients, we confirmed that either CT or RT as adjuvant therapy after surgery could improve the OS of early stage of UCCC patients. However, combinatorial CT and RT treatment did not improve the OS compared with CT or RT treatment alone. Our results support the administration of CT or RT for stage I-II UCCC patients. However, it remains to be elucidated how the treatments should be integrated into the adjuvant setting. Therefore, more prospective and randomized clinical trials with larger sample size should be performed in the future.

## Abbreviations

CT: chemotherapy; EBRT: external beam radiation therapy; GOG: Gynecologic Oncology Group; RT: radiotherapy; OS: overall survival; PFS: progression free survival; UCCC: Uterine Clear Cell Carcinoma; UPSC: uterine papillary serous carcinoma; OR: odds ratio; CI: confidence interval

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

## Availability of data and materials

Not applicable.

## Competing Interests

All authors declare no conflicts of interest.

## Funding

This work was supported by the National Natural Science Foundation of China (81802585 to X Yin; 81472426 to W Di), the grants from Shanghai Jiao Tong University School of Medicine (DLY201505 to W Di; YG2016MS51 to X Yin), Shanghai Municipal Commission of Health and Family Planning (2013ZYJB0202 and 15GWZK0701 to W Di), and the grant from Science and Technology Commission of Shanghai Municipality (16140904401 to X Yin). There was no role of funding agency in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

## Author contributions

Concept and design: J.C. and W.D. Data collection: J.C., Y.Z. and Y.X. Data and statistical analysis: J.C., Y.Z. and Y.X. Data interpretation: J.C., Y.X., and W.D. Drafting and revising the manuscript: J.C., G.Z., C.Z., C.W.C, D.C, Y.Z. and X.Y. Authors read and approved the manuscript

## Acknowledgments

Thanks all support from Department of Obstetrics and Gynecology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University. The authors are grateful to all staffs who contributed to this study.

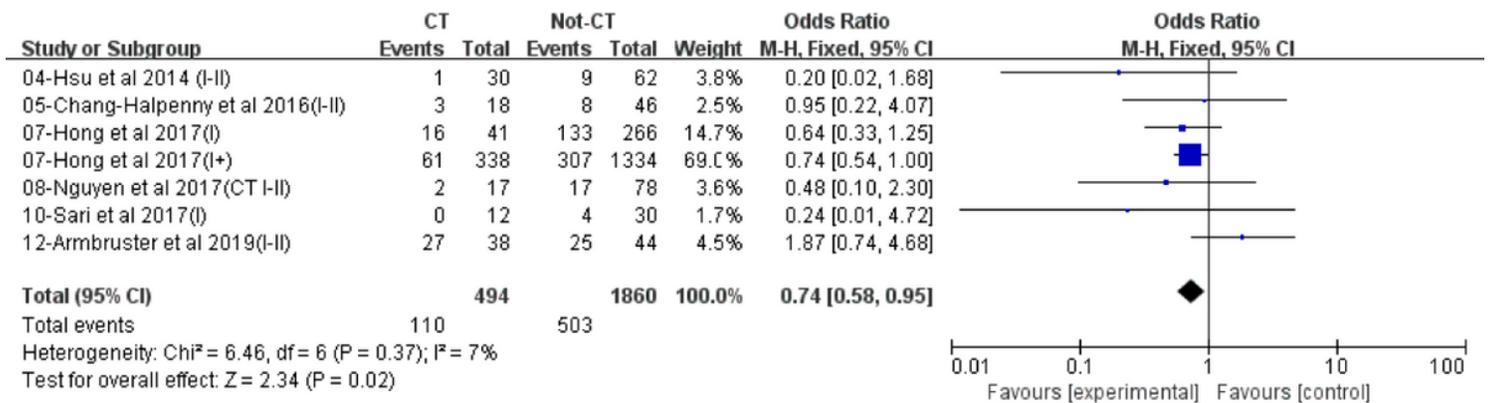
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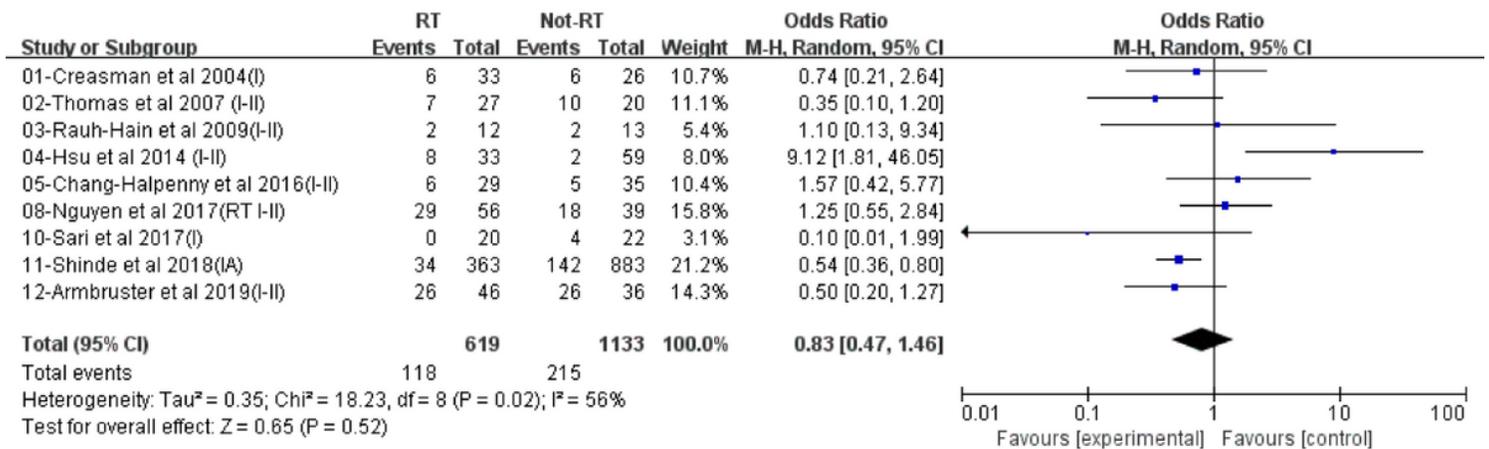
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## Figures



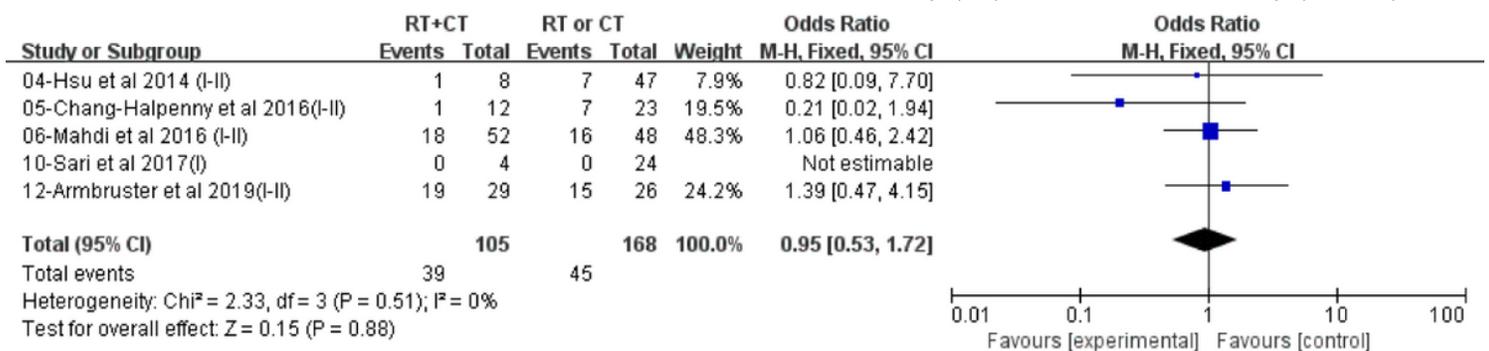
**Figure 1**

Pooled studies of overall survival between patients received Chemotherapy (CT) and not-chemotherapy (Not-CT).



**Figure 2**

Pooled studies of overall survival between patients received Radiotherapy (RT) and not-Radiotherapy (Not-RT).



**Figure 3**

Pooled studies of overall survival between patients received combinatorial radiotherapy and chemotherapy (RT+CT) and radiotherapy or radiotherapy (RT or CT) alone.

## Supplementary Files

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