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A Society of Gynecologic Oncology Evidence-based Review (and Recommendations)

Effect of adjuvant therapy on the risk of recurrence in early-stage leiomyosarcoma: A meta-analysis

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HIGHLIGHTS

- This meta-analysis included 747 early uLMS cases from 12 studies.
- Neither AC nor AR reduced recurrence in surgically treated patients with early uLMS.
- This was consistently observed in the subgroup analysis of gemcitabine/docetaxel regimen.

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ABSTRACT

Objectives. To assess the effect of adjuvant chemotherapy (AC) or radiotherapy (AR) on the risk of recurrence in surgically treated patients with early-stage uterine leiomyosarcoma (uLMS).

Methods. We searched the PubMed, EMBASE, and MEDLINE, and Cochrane databases for publications up to March 2019, which compared patients with early-stage uLMS who received AC or AR with those who did not. The primary endpoint was recurrence rate. Random- or fixed-effects models were used for pooled estimates of the effect of adjuvant treatments on recurrence rates. Subgroup analyses were conducted based on study design, surgical staging, AC regimen (gemcitabine/docetaxel regimen), and type of AR.

Results. Three randomized trials and 9 observational studies (9 studies for AC vs. observation, $n = 496$; 9 studies for AR vs. observation, $n = 425$) were included. The meta-analysis indicated that AC did not decrease the risk of recurrence compared with observation (odds ratio [OR] = 0.65, 95% confidence interval [CI] = 0.37–1.15, $P = 0.14$; $P = 0.09$ and $I^2 = 42.1$). Similarly, AR did not decrease the risk of recurrence compared with observation (OR = 1.11, 95% CI = 0.56–2.21, $P = 0.76$; $P = 0.10$ and $I^2 = 40.4$). Meta-regression analyses revealed no significant association between median follow-up time and recurrence. In subgroup analyses (study design, surgical staging, gemcitabine/docetaxel regimen, type of AR), neither AC nor AR decreased the risk of recurrence significantly.

Conclusion. AC, including gemcitabine/docetaxel regimen, or AR did not reduce the recurrence rate in patients with early-stage uLMS.

Contents

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1. Introduction

Uterine leiomyosarcoma (uLMS) is a rare gynecological cancer that accounts for 1% of all uterine corpus cancers [1,2]. Only 25%–50% cases are diagnosed preoperatively; unfortunately, imaging studies and endometrial biopsy are not reliable for preoperative diagnosis of uLMS [3]. In most cases, uLMS is confirmed based on histologic examination following hysterectomy or myomectomy. Surgical removal is the mainstay for uLMS treatment; however, the survival outcome is not satisfactory. Even for early-stage uLMS, the recurrence rate has been reported to be 53%–71% [1]. Adjuvant chemotherapy (AC) or radiotherapy (AR) has been proposed after surgical resection in patients with early-stage uLMS to improve oncological outcomes. However, the effect of adjuvant therapy on the prognosis of uLMS remains uncertain.

In 2017, the Korean Gynecologic Oncology Group (KGOG) conducted a survey among the members of KGOG to investigate the clinical management of uLMS in Korea. Overall, 42.3% of the respondents recommended AC or AR following surgery for stage I uLMS [4]. The survey findings reflect the concern of physicians regarding the poor prognosis of uLMS and uncertainty of the role of adjuvant therapy for early-stage uLMS. A previous meta-analysis reported that the role of AC is unclear. However, the sample size was relatively small (including 360 patients), and most patients included in this analysis received AC with agents besides the gemcitabine/docetaxel combination regimen, which is recommended in recent clinical practice [5]. Since the publication of the first meta-analysis, more evidence has accumulated regarding this issue [6–9], which justifies the updated review. Therefore, we executed a systematic review and a meta-analysis to investigate the effect of AC/AR on the risk of recurrence in surgically treated patients with early-stage uLMS.

2. Methods

2.1. Literature search

A systematic review and a meta-analysis were conducted using previously described reporting guidelines and publications [10–12]. We searched PubMed, EMBASE, MEDLINE, and Cochrane Central Register for Controlled Trials databases up to March 2019, irrespective of the language. Pre-publication studies were also included. The detailed search strategy is described in Appendix S1.

2.2. Eligibility criteria and study selection

Titles and abstracts were checked to identify potentially eligible studies. The full texts were then reviewed in detail. References were manually screened to identify additional studies. Two authors (S.H. Chae and S.H. Shim) independently performed all searches. The inclusion criteria for this meta-analysis were as follows: (1) a randomized controlled trial (RCT), prospective/retrospective cohort study, nested case-control study, or population-based case-control study; (2) participants diagnosed as International Federation of Gynecology and Obstetrics (FIGO) stage I or II uLMS and confirmed by pathology after surgery; (3) observation following surgery as a comparison; (4) AC/AR including concurrent chemoradiotherapy (CCRT) following surgery as an intervention; and (5) outcomes of recurrence rates measured as 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 and case reports were excluded.

2.3. Data extraction

The following data were extracted from each study: first author; publication year; study design, location, and period; age of the patient; sample size; tumor stage; histology; AC details (regimen, dose, cycle); AR details [dose, external beam radiotherapy (EBRT), intracavitary brachytherapy (ICBT)]; and recurrence rates. Each study was systematically reviewed for features that could introduce bias, including similarity in risk factors for prognosis and similarity in follow-up durations between the observation and AC/AR groups. Two authors (S.H. Chae and S.H. Shim) independently extracted data, and discrepancies were jointly reviewed until consensus was reached.

2.4. Quality assessment

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

2.5. Data generation and analysis

The primary endpoint was the total recurrence rate of uLMS. The secondary endpoints were the local and distant recurrence rates. Because not all of the included studies provided the HRs calculated by a time-to-event analysis, ORs and 95% CIs for the recurrence rates of the observation and AC/AR groups were calculated from the original data of each study. We also conducted meta-regression analyses to examine the impact of follow-up time on study effect estimates. Cross-study heterogeneity was examined using the Cochran Q test and the I^2 statistic [17,18]. Q test $P < 0.1$ [17] or I^2 statistic >50% [18] indicated substantial heterogeneity among studies. If substantial heterogeneity between studies were observed, 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 were planned a priori and were performed according to the study design (NRS or RCT), complete surgical staging (CSS; Yes or No), AC regimen (gemcitabine/docetaxel regimens or non-gemcitabine/docetaxel regimens), and type of radiation (EBRT only or EBRT+ICBT). Sensitivity analysis was conducted by withdrawing one study at a time from the meta-analysis to evaluate its effect on the pooled OR. Publication bias was determined using the Begg-Mazumdar rank correlation [20] and fail-safe N [21] tests. All analyses were performed using Comprehensive MetaAnalysis version 2.0 (Biostat, Englewood, NJ, USA) by a medical statistician (M.S. Chang). A two-sided P value <0.05 was considered significant.

3. Results

3.1. Literature search

From 790 records, 37 publications were selected based on their titles. Abstracts were reviewed, and 28 publications were identified for detailed full-text review. Finally, 12 publications were included in the meta-analysis [6,8,9,22–30]. Fig. 1 depicts the literature search process. Excluded studies and the reasons for exclusion are shown in Table S1.

3.2. Study characteristics

Table 1 shows the characteristics of the 12 included studies. These studies were published between 1985 and 2018 and included a total of 747 patients, of whom 363 were observed after surgery, 224 received AC, and 160 received AR. Three studies were RCTs [9,26,28] and 9 were NRSs [6,8,22–25,27,29,30]. Seven studies were conducted in the US [6,8,9,23,26,27,29], one in Taiwan [30], one in Korea [24], one in Italy [6], one in the UK [28], and one in Germany [22]. The quality score was 3 for RCTs (Jadad/Oxford quality scoring system, Table S2) except for the study by Omura et al. For NRSs, the quality score was 7 (Table S3). All included NRSs received three stars for selection.

Details of the AC regimen and AR for each study are shown in Table 1. Four studies clearly stated the number of patients for whom complete CSS was performed [23,24,26,29]. The median age was 54 years, with a median follow-up period of 51.9 months. Five studies included only stage I uLMS [6,9,24,27,30]. One study reported the tumor grade [30].

3.3. Meta-analysis of the effect of AC after surgery on the recurrence rates

Nine studies compared the recurrence rate after surgery in the observation and AC groups [8,9,23–27,29,30]. Overall, 496 patients had early-stage uLMS, and recurrence was observed in 260 (52.4%) patients (149/272 patients receiving no adjuvant therapy vs. 111/224 patients receiving AC). No significant difference in total recurrence rates was observed between the observation and AC groups (OR = 0.65, 95% CI = 0.37–1.15, $P = 0.14$); the cross-study heterogeneity was high ($P = 0.09$ and $I^2 = 42.1$; Fig. 2A). The P value of the meta-regression analysis between the effect estimates (OR) and follow-up time was 0.77, indicating that median follow-up time did not contribute to the large heterogeneity of the effect estimates (Fig. S1). In the sensitivity analysis, no study significantly influenced the pooled OR for AC and recurrence (Table S4). The funnel plot for publication bias was asymmetric (Fig. 2B). However, the quantified tests for a publication bias indicated that the observed overall effect was robust ($P = 0.12$, Begg-Mazumdar rank correlation test).

Four studies compared the local recurrence rates in the observation and AC groups [9,25,26,29]; no significant difference was observed between the groups (OR = 1.01, 95% CI = 0.54–1.89, $P = 0.97$; $P = 0.37$ and $I^2 = 4.8$; Fig. 2C). The P value of the meta-regression analysis between the effect estimates (OR) and follow-up time was 0.36, indicating that median follow-up time did not contribute to the large heterogeneity of the effect estimates (Fig. S1). The funnel plot for a publication bias was asymmetric (Fig. 2D). However, the other quantified tests for a publication bias indicated that the observed overall effect was robust ($P = 0.09$, Begg-Mazumdar rank correlation test).

Distant recurrence was indicated in six studies [9,24–27,29]. There was no significant difference between the AC and observation groups with respect to distant recurrence rates (OR = 0.68, 95% CI = 0.29–1.60, $P = 0.38$; $P = 0.053$ and $I^2 = 54.2$; Fig. 2E). The P value of the meta-regression analysis between the effect estimates (OR) and follow-up time was 0.89, indicating that median follow-up time did not contribute to the large heterogeneity of the effect estimates (Fig. S1). There was no evidence of a publication bias ($P = 0.70$, Begg–Mazumdar rank correlation test). The funnel plot for a publication bias was symmetric (Fig. 2F).

3.4. Meta-analysis of the effect of AR after surgery on recurrence rates

Nine studies compared the recurrence rates after surgery in the observation and AR groups [6,22–26,28–30]. Overall, 425 patients were included, and recurrence was observed in 243 (57.2%) patients (146/265

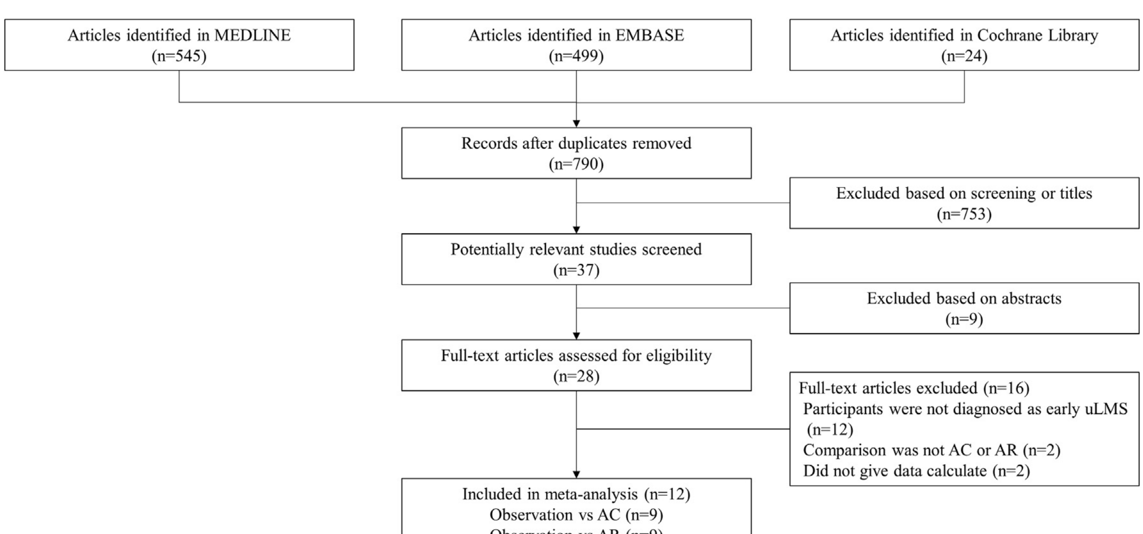


Fig. 1. Flow diagram of the literature search process. uLMS, uterine leiomyosarcoma; AC, adjuvant chemotherapy; AR, adjuvant radiotherapy.

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

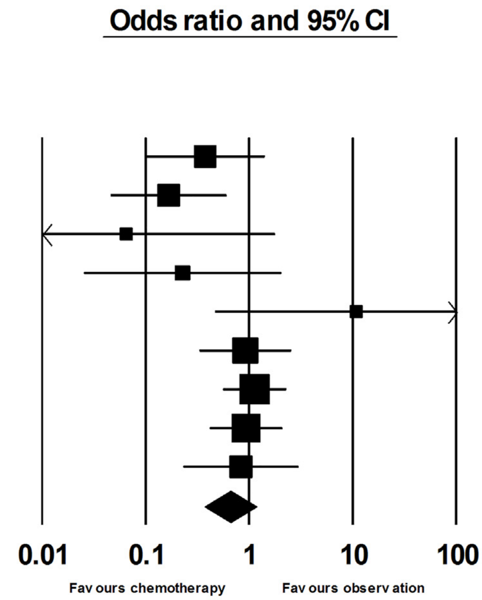
Author (year)	Country	Type of study design	Study period	Median age (range)	Number of observation	Number of adjuvant therapy	Complete surgical staging	Included stage	Median follow up duration (months)	AC regimen	Details of AR
Omura et al. (1985)	US	RCT	1973–1982	58	20	AC: 17 AR: 11	Yes	I and II	64	Adriamycin (60 mg/m^2, every 3 weeks)	
Hornback et al. (1986)	US	NRS	1973–1982	NA	19	AC: 27 AR: 11	Obs: 19 AC: 18 AR: 11	I and II	NA[a]	Doxorubicine (60 mg/m^2, every 3 weeks)	EBRT, 40Gy ICBT, 20Gy
Piver et al. (1988)	US	NRS	1973–1979	NA	3	AC: 7	NA	I: 10	35.5	Doxorubicine (50 mg/m^2 or 75 mg/m^2 every 4 weeks) CYVADIC (Vincristine sulfate 1 mg/m^2 on day 1 and 5; Adriamycin 40 mg/m^2, Cyclophosphamide 400 mg/m^2 on day 2; Dacarbazine 200 mg/m^2 days 1–5 every 4 weeks)	
Hoffmann et al. (1996)	Germany	NRS	1958–1994	55	4	AR: 6	NA	I: 9 II: 1	29		EBRT, 45-60Gy ICBT, 21Gy
Wu et al. (2006)	Taiwan	NRS	1984–2003	47 (26–85)	31	AC: 9 AR: 1	Yes	I: 41	47	Cisplatin/Ifosfamide: 4 Cisplatin/Adriamycin alternating with Cisplatin/Ifosfamide: 3 Cisplatin/Adriamycin/Cyclophosphamide: 2 Cisplatin/Adriamycin/Epirubicin: 4 Liposomal doxorubicin: 2 Vincristine/Adriamycin/Cyclophosphamide: 1	
Reed et al. (2008)	UK	RCT	1988–2001		49	AR: 50	Yes	I and II	81.6		EBRT, 50.47Gy
Kim et al. (2009)	Korea	NRS	1994–2007	46 (32–63)	8	AC: 8 AR: 7	Yes	I: 23	29	Cisplatin/Adriamycin Cisplatin/Adriamycin/Ifosfamide	
Ricci et al. (2013)	US	NRS	1990–2010	55.4	34	AC: 39 AR: 35	Obs: 14 AC: 16 AR: 11	I: 94 II: 14	41.8	Doxorubicine/Cisplatin: 9 Gemcitabine/Docetaxel: 23 (Gemcitabine 900 mg/m2 on day 1 and 8, Docetaxel 75 mg/m^2 on day 8 every 3 weeks) Ifosfamide or Doxorubicin: 5 Topotecan: 2 Cisplatin/Ifosfamide: 1	EBRT (45-54Gy) or combination of EBRT and ICBT
Mancari et al. (2014)	Italy	NRS	1946–2011	51 (21–74)	62	AC: 64 AR: 14	NA	I: 125 II: 15	63	Doxorubicine/Ifosfamide: 54 (Ifosfamide 2 g/m^2/day on days 1–5, Doxorubicn 25 mg/m^2/day on days 1–3 every 3 weeks) Gemcitabine/Docetaxel: 4 (Gemcitabine 900 mg/m^2 on day 1 and 8, Docetaxel 75 mg/m^2 on day 8 every 3 weeks) Doxorubicin/Dacarbazine: 2	EBRT, 50.4Gy
Magnuson et al. (2015)	US	NRS	1969–2012	55 (35–75)	38	AR: 25	Yes	I: 63	45.6		EBRT, 45-51Gy
Littell et al. (2017)	US	NRS	2006–2013	54 (48–60)	77	AC: 33	NA	I: 110	40.5	Gemcitabine/Docetaxel: 31 (Gemcitabine 900 mg/m^2 on day 1 and 8, Docetaxel 75 mg/m^2 on day 8 every 3 weeks) Gemcitabine/Docetaxel/Doxorubicin: 2 (Gemcitabine 900 mg/m^2 on days 1 and 8, Docetaxel 75 mg/m^2 on day 8 every3 weeks for cycles 1–4, Doxorubicin 60 mg/m^2 every 3 weeks for cycles 5–8)	
Hensley et al. (2018)	US	RCT	2012–2016	NA	18	AC: 20	Obs: 18 AC: 20	I: 38	19.1	Gemcitabine/Docetaxel/Doxorubicin: 20 (Gemcitabine 900 mg/m^2 on days 1 and 8, Docetaxel 75 mg/m^2 on day 8 every3 weeks for cycles 1–4, Doxorubicin 60 mg/m^2 every 3 weeks for cycles 5–8)	
RCTs combined					87	AC: 37 AR: 61	Yes	I and II			
NRSs combined					276	AC: 187 AR: 99		I and II			
All combined					363	AC: 224 AR: 160		I and II			

Obs, Observation; AC, Adjuvant chemotherapy; AR, Adjuvant radiotherapy; NA, not applicable; NRS, non-randomized study; RCT, randomized controlled trial; EBRT, external beam radiation therapy; CYVADIC, combination chemotherapy of cyclophosphamide, vincristine, doxorubicin and dacarbazine; ICBT, intracavitary brachytherapy.

[a] Minimum follow-up of 24 months.

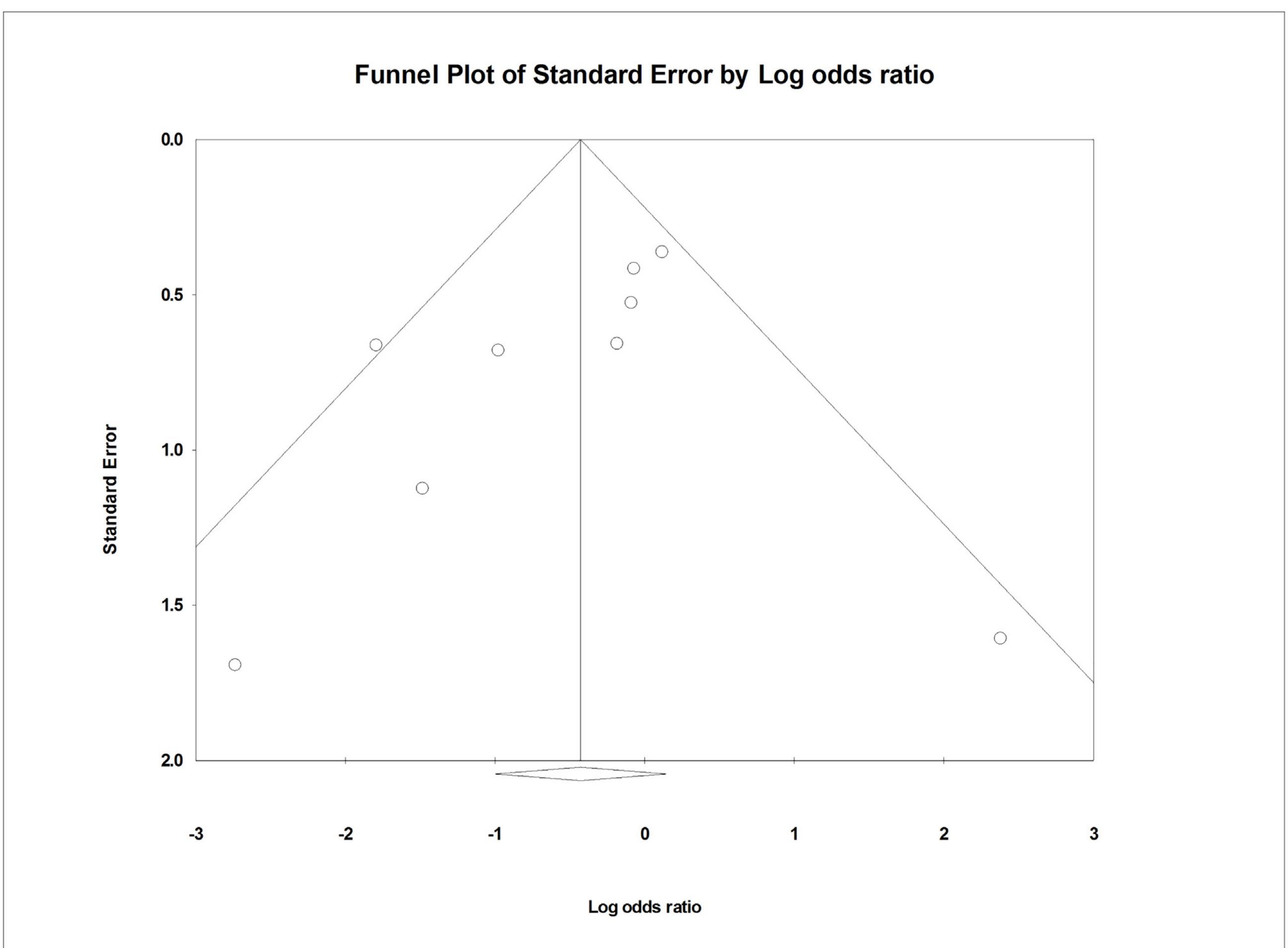
(A)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Omura , 1985	0.377	0.099	1.430	-1.435	0.151
Hornback, 1986	0.167	0.045	0.612	-2.700	0.007
Piver, 1988	0.065	0.002	1.794	-1.615	0.106
Wu , 2006	0.227	0.025	2.062	-1.317	0.188
Kim, 2009	10.818	0.463	252.789	1.481	0.139
Ricci, 2013	0.916	0.326	2.574	-0.166	0.868
Mancari, 2014	1.127	0.553	2.296	0.328	0.743
Littell, 2017	0.933	0.412	2.111	-0.167	0.868
Hensley, 2018	0.833	0.229	3.028	-0.277	0.782
	0.652	0.368	1.154	-1.470	0.142

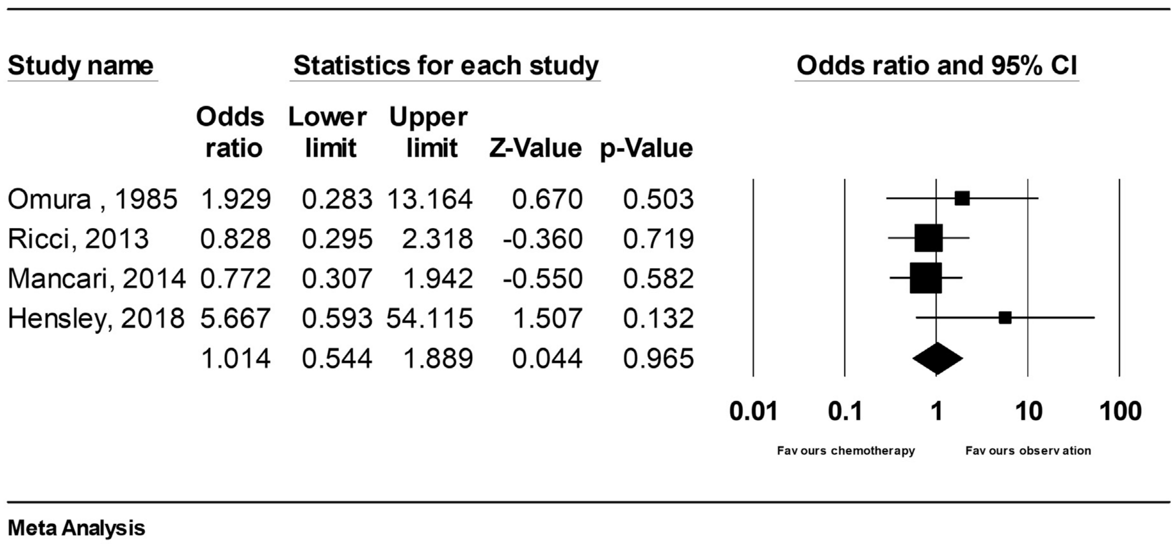


Meta Analysis

(B)



(C)



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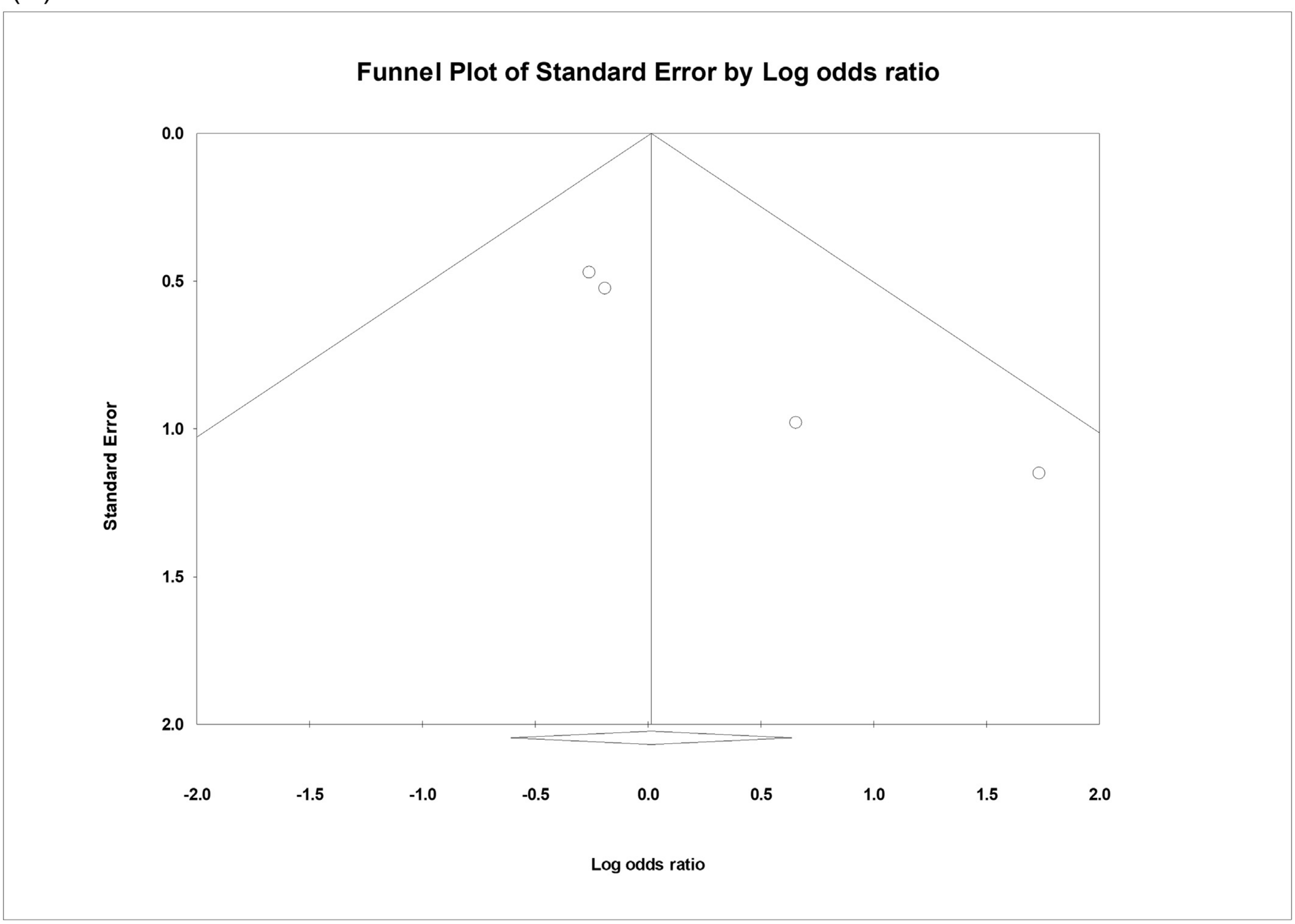


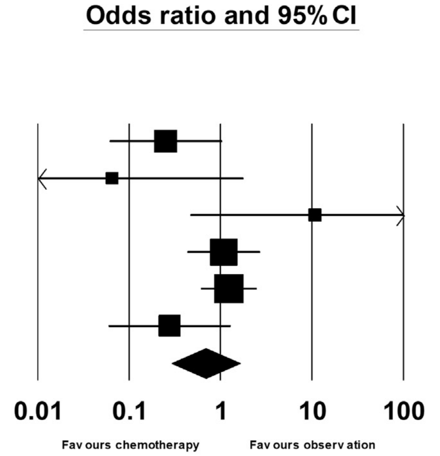
patients receiving no adjuvant therapy vs. 97/160 patients receiving AR). No significant difference in total recurrence rates was observed between the observation and AR groups (OR = 1.11, 95% CI = 0.56–2.21, $P = 0.76$); the cross-study heterogeneity was high ($P = 0.10$ and $I^2 = 40.4$; Fig. 3A). The P value of the meta-regression analysis between the effect estimates (OR) and follow-up time was 0.27, indicating that median follow-up time did not contribute to the large heterogeneity of the effect estimates (Fig. S2). In the sensitivity analysis, no study significantly influenced the pooled OR for AR and recurrence (Table S5). There was no evidence of a publication bias ($P = 0.75$, Begg–Mazumdar rank correlation test). The funnel plot for a publication bias was symmetric (Fig. 3B).

Six studies compared the local recurrence rates between the observation and AR groups [6,25,26,28–30]; no significant difference

(E)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Omura , 1985	0.252	0.061	1.047	-1.897	0.058
Piver, 1988	0.065	0.002	1.794	-1.615	0.106
Kim, 2009	10.818	0.463	252.789	1.481	0.139
Ricci, 2013	1.086	0.431	2.737	0.174	0.862
Mancari, 2014	1.231	0.605	2.507	0.574	0.566
Hensley, 2018	0.277	0.059	1.307	-1.621	0.105
	0.680	0.289	1.599	-0.884	0.377

Statistics for each study



Meta Analysis

(F)

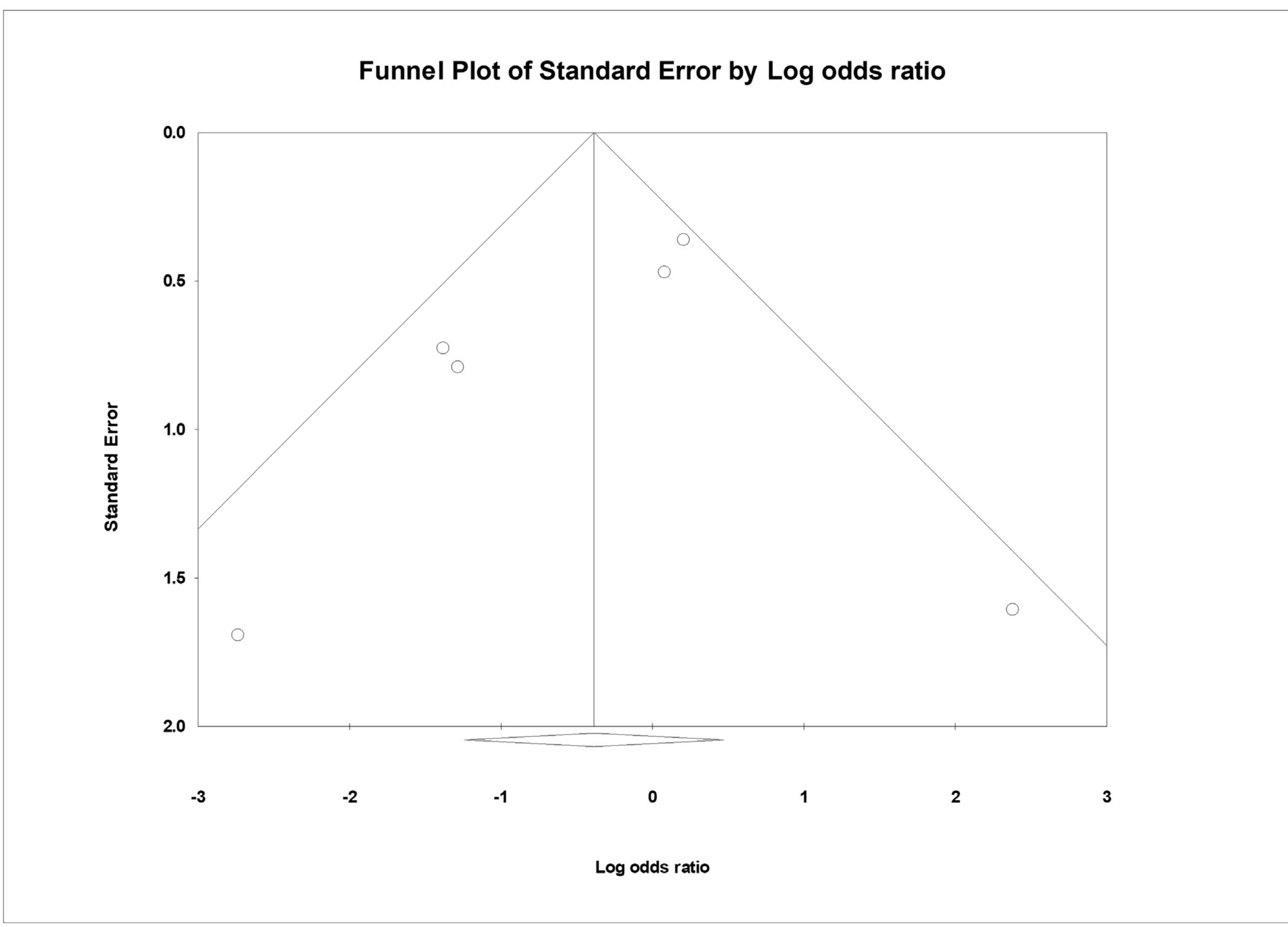
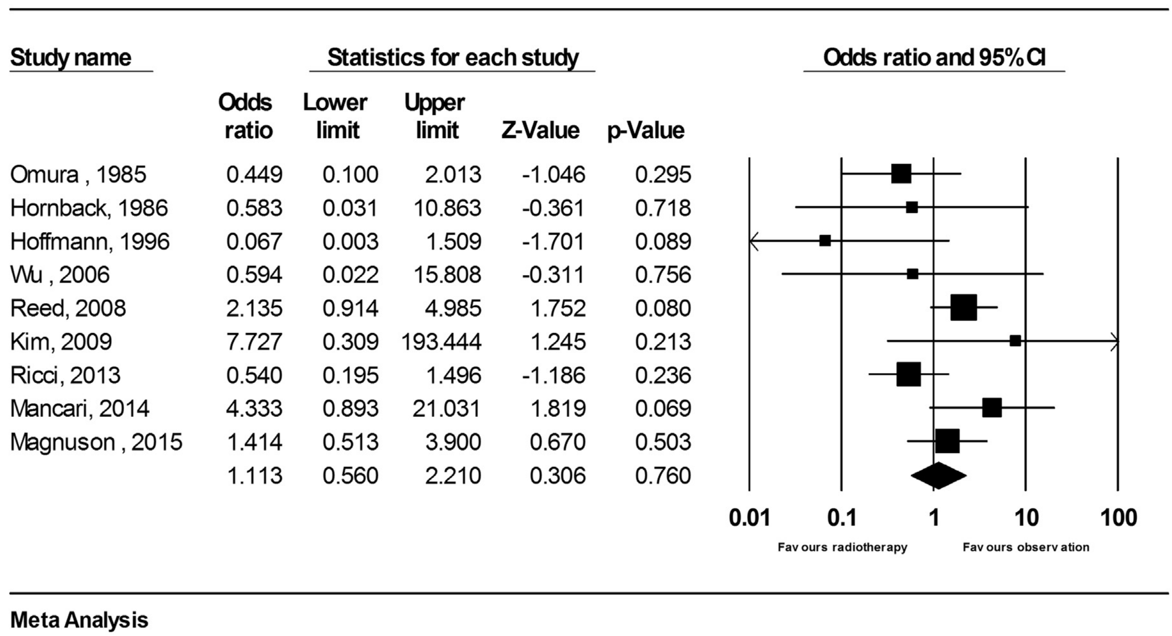


Fig. 2. (A) Odds ratios (ORs) for the risk of any recurrence in each study and all studies combined; adjuvant chemotherapy was compared with observation following surgery in a meta-analysis based on the random-effects model. (B) Funnel plots for identifying publication bias in the meta-analysis of any recurrence ($n = 9$). The Begg-Mazumdar rank correlation test indicates no evidence of publication bias ($P = 0.12$). (C) ORs for the risk of local recurrence in each study and all studies combined based on the fixed-effects model. (D) Funnel plots for identifying publication bias in the meta-analysis of local recurrence ($n = 4$). The Begg-Mazumdar rank correlation test indicates no evidence of publication bias ($P = 0.09$). (E) ORs for the risk of distant recurrence in each study and all studies combined based on the random-effects model. (F) Funnel plots for identifying publication bias in the meta-analysis of distant recurrence ($n = 6$). The Begg-Mazumdar rank correlation test indicates no evidence of publication bias ($P = 0.70$).

(A)


Study name
Statistics for each study
Odds ratio and 95% CI
Odds ratio
Lower limit
Upper limit
Z-Value
p-Value
Omura , 1985 0.449 0.100 2.013 -1.046 0.295
Hornback, 1986 0.583 0.031 10.863 -0.361 0.718
Hoffmann, 1996 0.067 0.003 1.509 -1.701 0.089
Wu , 2006 0.594 0.022 15.808 -0.311 0.756
Reed, 2008 2.135 0.914 4.985 1.752 0.080
Kim, 2009 7.727 0.309 193.444 1.245 0.213
Ricci, 2013 0.540 0.195 1.496 -1.186 0.236
Mancari, 2014 4.333 0.893 21.031 1.819 0.069
Magnuson , 2015 1.414 0.513 3.900 0.670 0.503
1.113 0.560 2.210 0.306 0.760
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10
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Fav ours radiotherapy
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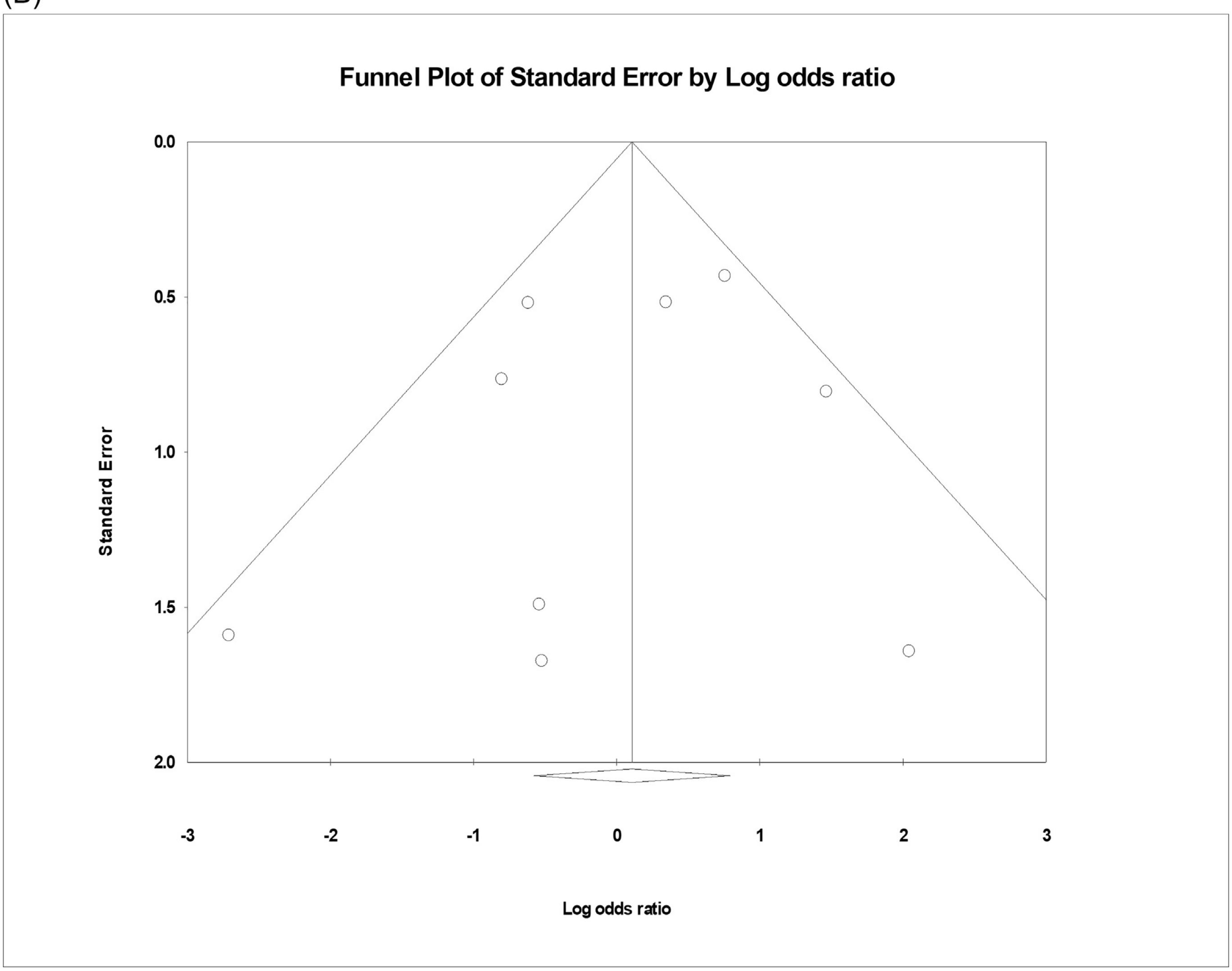
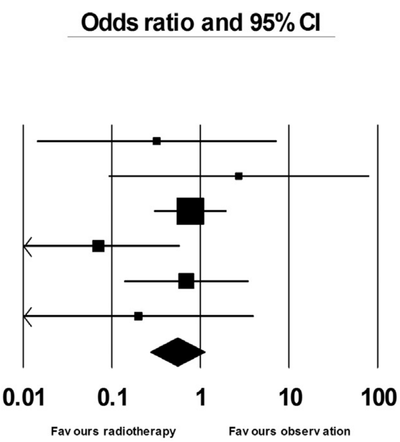
Meta Analysis

(B)


Funnel Plot of Standard Error by Log odds ratio
0.0
0.5
1.0
1.5
2.0
Standard Error
-3
-2
-1
0
1
2
3
Log odds ratio

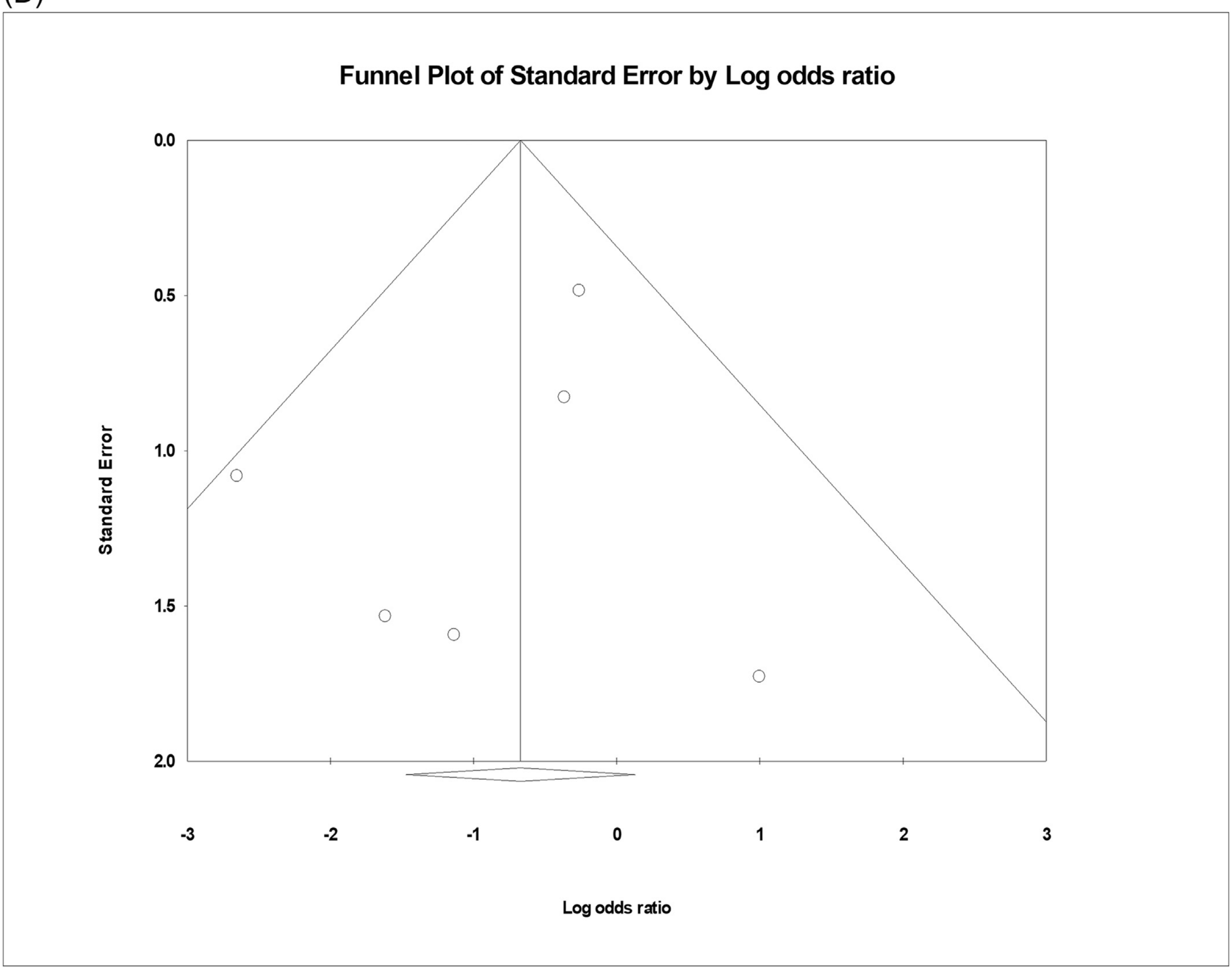
(C)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Omura , 1985	0.322	0.014	7.318	-0.711	0.477
Wu , 2006	2.714	0.092	80.334	0.578	0.563
Reed, 2008	0.771	0.298	1.995	-0.537	0.592
Ricci, 2013	0.071	0.008	0.589	-2.450	0.014
Mancari, 2014	0.694	0.137	3.524	-0.440	0.660
Magnuson , 2015	0.199	0.010	4.021	-1.053	0.292
	0.544	0.268	1.101	-1.692	0.091



Meta Analysis

(D)

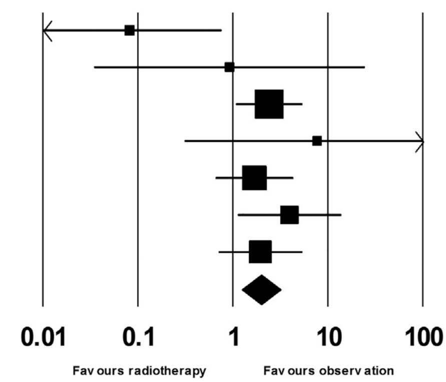


was observed (OR = 0.54, 95% CI = 0.27–1.10, $P = 0.09$; $P = 0.35$ and $I^2 = 10.2$; Fig. 3C). The P value of the meta-regression analysis between the effect estimates (OR) and follow-up time was 0.13, indicating that median follow-up time did not contribute to the large heterogeneity of the effect estimates (Fig. S2). There was no evidence of a publication bias ($P = 0.85$, Begg–Mazumdar rank

(E)

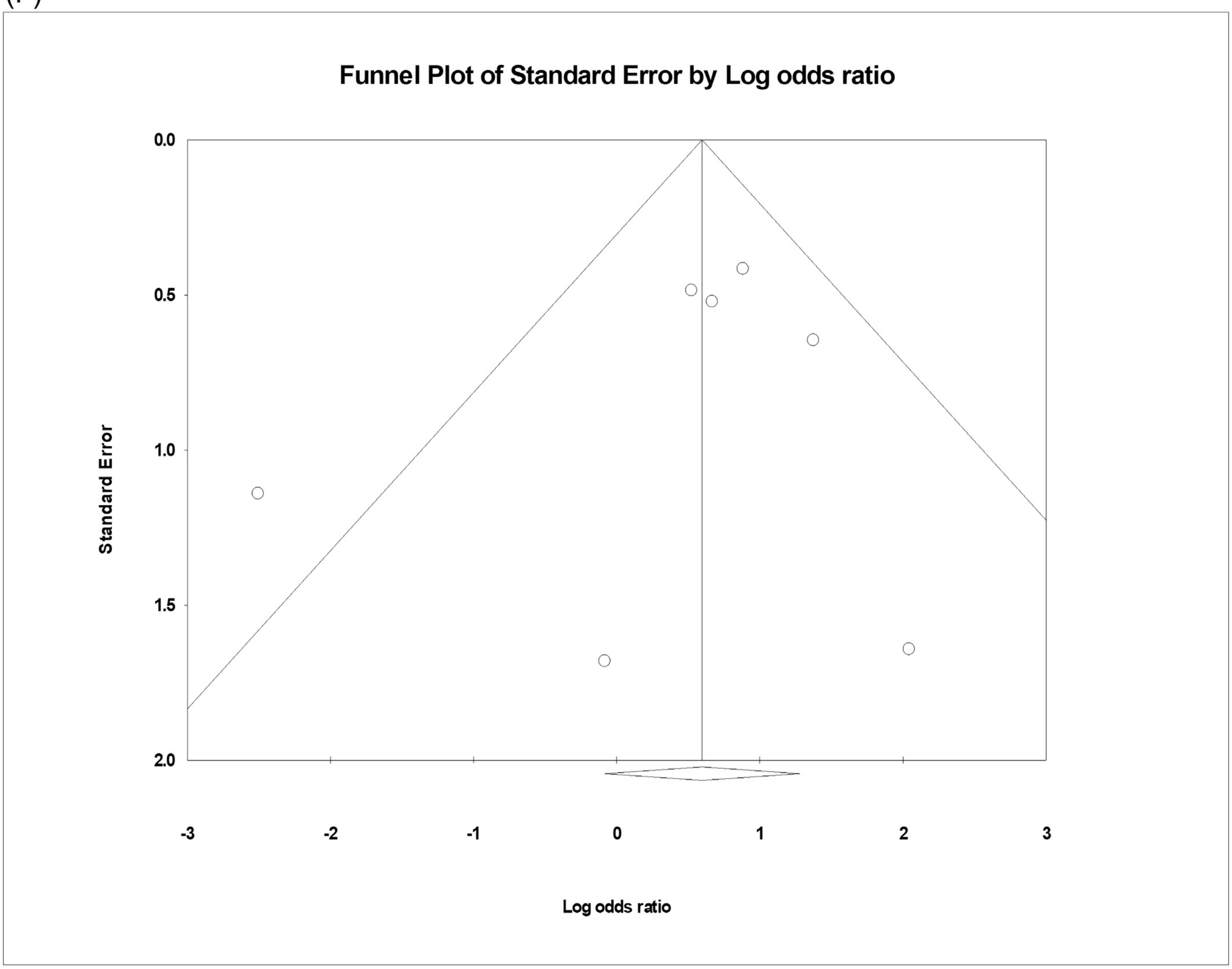
Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Omura , 1985	0.082	0.009	0.766	-2.194	0.028
Wu , 2006	0.922	0.034	24.870	-0.049	0.961
Reed, 2008	2.421	1.071	5.475	2.124	0.034
Kim, 2009	7.727	0.309	193.444	1.245	0.213
Ricci, 2013	1.689	0.652	4.376	1.079	0.281
Mancari, 2014	3.958	1.115	14.055	2.128	0.033
Magnuson , 2015	1.952	0.702	5.429	1.281	0.200
	1.966	1.232	3.139	2.833	0.005

Odds ratio and 95% CI



Meta Analysis

(F)



correlation test). The funnel plot for a publication bias was symmetric (Fig. 3D).

Seven studies compared the distant recurrence rates between the observation and AR groups [6,24–26,28–30]. AR did not decrease the risk of distant recurrence (OR = 1.97, 95% CI = 1.23–3.14, $P < 0.05$; $P = 0.12$ and $I^2 = 41.1$; Fig. 3E). The *P* value of the meta-regression analysis between the effect estimates (OR) and follow-up time was 0.85, indicating that median follow-up time did not contribute to the large heterogeneity of the effect estimates (Fig. S2). There was no evidence of a publication bias ($P = 0.76$, Begg–Mazumdar rank correlation test). The funnel plot for a publication bias was symmetric (Fig. 3F).

3.5. AC and risk of recurrence in subgroup meta-analysis

Table 2 shows the subgroup analyses comparing the recurrence rates after surgery in the observation and AC groups. Subgroup analysis was performed for the study design. Two RCTs [9,26] and seven NRS [8,23–25,27,29,30] were included in this subgroup analysis. No significant difference in the total recurrence rate was observed between the observation and AC groups in the RCT subgroup analysis (OR = 0.57, 95% CI = 0.23–1.44 $P = 0.23$) and in the NRS subgroup analysis (OR = 0.66, 95% CI = 0.32–1.37, $P = 0.27$).

CSS was performed in seven studies [9,23–26,29,30]. No significant difference in total recurrence rates was observed between the observation and AC groups in the CSS subgroup analysis (OR = 0.64, 95% CI = 0.32–1.28, $P = 0.21$).

Subgroup analysis based on the AC regimen was performed. Three studies [8,9,29] used the gemcitabine/docetaxel combination regimen and other six studies [18,23,24,26,27,30] used non gemcitabine/docetaxel regimens. There was no significant difference in the total recurrence rate between the observation and AC groups in the gemcitabine/docetaxel subgroup analysis (OR = 0.91, 95% CI = 0.51–1.61, $P = 0.74$).

3.6. AR and risk of recurrence in subgroup meta-analysis

Table 3 shows the subgroup analyses comparing the recurrence rates after surgery in the observation and AR groups. Subgroup analysis was performed for the study design. Two RCTs [26,28] were included in this subgroup analysis. No significant difference in total recurrence rates was observed between the observation and AR groups in the RCT subgroup analysis (OR = 1.11, 95% CI = 0.25–5.02, $P = 0.89$) and in NRS subgroup analysis (OR = 1.05, 95% CI: 0.58–1.92, $P = 0.87$).

CSS was performed in eight studies [6,23–26,28–30]. No significant difference in the total recurrence rate was observed between the observation and AR groups in the CSS subgroup analysis (OR = 1.28, 95% CI = 0.80–2.01, $P = 0.30$).

Subgroup analysis was performed based on the use of ICBT. In three studies in which the AR group received a combination of EFRT and ICBT [6,22,23,25,28,29], no significant difference in the recurrence rates was observed between the two groups (OR = 0.45; 95% CI = 0.18–1.14; $P = 0.09$).

4. Discussion

This study reviewed the evidence on adjuvant therapy (AC and AR) in early-stage uLMS patients using meta-analysis. The result indicates that neither AC nor AR reduces total/local/distant recurrence rates of early-stage uLMS compared with observation after surgery. This finding was further corroborated by the subgroup analyses based on AC regimen, study design, CSS, and radiation type.

In majority of the studies, the number of enrolled patients was not large enough to sufficiently elucidate the effect of AC/AR on the prognosis of early-stage uLMS. In 2016, Bogani et al. has conducted a meta-analysis regarding the effect of AC in patients with early stage uLMS [5]. The meta-analysis of 360 patients indicated that AC did not improve disease-free survival in comparison to observation, or radiotherapy, although the sample size was relatively small and the effect of AC with the gemcitabine/docetaxel combination regimen was not analyzed. Compared with a previous meta-analysis [5], the present meta-analysis included 747 patients with four additional studies; these included a recently published RCT [9]. Moreover, we identified three studies [8,9,29] that provided more information on the role of the widely used gemcitabine/docetaxel combination regimen. Additionally, pooled estimates of the effect of AR on recurrence compared with observation was evaluated in the present study. Therefore, this meta-analysis provides evidence that AC/AR is not effective in patients with early-stage uLMS.

In the present study, the subgroup analysis based on study design showed no significant difference in the recurrence rates between the observation and AC/AR groups. The rarity of uLMS poses a challenge for designing prospective trials; there is a lack of RCTs that might provide information on stage I/II uLMS treatment. Regarding the role of AC, the GOG 277 phase III trial was recently reported [9]. GOG 277 was designed to assess whether adjuvant gemcitabine/docetaxel combination regimen followed by doxorubicin could improve survival outcomes compared with observation in patients with completely resected early-stage uLMS. This phase III RCT was expected to overcome the limitations of the previously reported NRS and provide the most relevant data on the effect of AC on early-stage uLMS. Unfortunately, because of the accrual futility, the study ended prematurely. Although the sample size ($n = 38$) was smaller than expected and statistical robustness was not accomplished, the overall survival rate in the AC group was 34.3 months (95% CI = 25.3–43.3 months). This was not superior to the overall survival rate in the observation group, which was 46.4 months (95% CI = 43.6–49.1 months).

Regarding the role of AR, the EORTC 55874 study should be considered. This was a phase III RCT comparing pelvic recurrence rate between the observation and AR groups in surgically treated patients with stage I/II uterine sarcoma. Of 224 patients, 99 had uLMS, while more than half of the patients were diagnosed with other histological types of uterine sarcoma (92 carcinosarcoma and 30 endometrial stromal sarcoma). The progression-free survival and overall survival rates in the uLMS cohort was not significantly different. In addition, no improvement in the local control rate was observed in the uLMS cohort receiving AR, which was also confirmed in our study. uLMS is more likely to have an early hematogenous spread [31]. Therefore, local pelvic radiotherapy is less beneficial in patients with uLMS than those with other histological types of uterine sarcoma [32].

Various chemotherapeutic regimens have been considered, given the high risk of distant relapse posed by uLMS. Of these, gemcitabine/docetaxel combination regimen shows an overall response rate of 27%–35.8% in patients with metastatic uLMS [33,34] and is considered the standard-of-care for these patients. In a single arm phase II study, treatment of patients with early-stage uLMS with adjuvant gemcitabine/docetaxel combination regimen followed by doxorubicin resulted in a 2-year disease-free survival rate of 78%, which exceeded historic expectations [35]. Of 46 evaluable patients, recurrence was observed in 12 (26%) patients at a median duration of 12.6 months. Subsequently, the implementation of gemcitabine/docetaxel combination regimen as AC for early-stage uLMS has increased significantly from

Fig. 3. (A) Odds ratios (ORs) for the risk of any recurrence in each study and all studies combined; adjuvant radiotherapy was compared with observation following surgery in a meta-analysis based on the random-effects model. (B) Funnel plots for identifying publication bias in the meta-analysis of any recurrence (n = 9). The Begg-Mazumdar rank correlation test indicates no evidence of publication bias ($P = 0.75$). (C) ORs for the risk of local recurrence in each study and all studies combined based on the fixed-effects model. (D) Funnel plots for identifying publication bias in the meta-analysis of local recurrence (n = 6). The Begg-Mazumdar rank correlation test indicates no evidence of publication bias ($P = 0.85$). (E) ORs for the risk of distant recurrence in each study and all studies combined based on the fixed-effects model. (F) Funnel plots for identifying publication bias in the meta-analysis of distant recurrence ($n = 7$). The Begg-Mazumdar rank correlation test indicates no evidence of publication bias ($P = 0.76$).

Table 2
Subgroup analysis comparing observation versus adjuvant chemotherapy for recurrence.

	Number of studies	Observation	AC patients (n)	OR (95% CI) for mortality	*P* value	Study heterogeneity	
						I^2	*P* value, Cochran Q
Study design							
RCT	2	38	37	0.57 (0.23–1.44)	0.23	0%	0.40
NRS	7	234	187	0.66 (0.32–1.37)	0.27	53%	0.05
Complete surgical staging							
Yes	7	192	184	0.64 (0.32–1.28)	0.21	48%	0.13
No	2	80	40	0.41 (0.04–4.57)	0.47	57%	0.13
AC regimen							
Gemcitabine/Docetaxel regimens	3	129	93	0.91 (0.51–1.61)	0.74	0%	0.99
Not Gemcitabine/Docetaxel regimens	6	143	132	0.46 (0.16–1.34)	0.16	61%	0.02

AC, adjuvant chemotherapy; RCT, Randomized controlled trial; NRS, non-randomized study; EBRT, external beam radiotherapy; ICBT, intracavitary brachytherapy; OR, odds ratio; NA, not applicable.

6.5% in 2006–2008 to 46.9% in 2009–2013 [8]. However, subsequent GOG 277 trial did not show the superior survival outcome with AC, although ultimately not powered to be statistically robust. Littell et al. had recently reported that the adjuvant gemcitabine/docetaxel group ($n = 33$) had no benefit of disease-free and overall survival for patients with stage I uLMS compared with observation ($n = 77$) [8]. This study is the largest series evaluating the therapeutic effect of adjuvant gemcitabine/docetaxel combination regimen for early-stage uLMS and reported similar result as our meta-analysis. In the present study, there was no significant difference in the recurrence rates between the observation and AC groups in the gemcitabine/docetaxel subgroup analysis. Thus, the data from the GOG 277 trial and the data from the present analysis support the recommendation for observation of patients with surgically treated early-stage uLMS.

Although the study by Seagle et al. was not included in the present meta-analysis [7], it requires mentioning. This recently published retrospective cohort study is the largest on uLMS ($n = 7445$) to use the US National Cancer Database (NCDB) from 1998 to 2013. In propensity score–matched cohort analyses, chemotherapy is associated with 8.5-month increased survival of women with metastatic uLMS ($n = 492$, event time ratio = 1.66; 95% CI, 1.46–1.90; $P < 0.001$), whereas adjuvant chemotherapy was not associated with increased survival among patients with stage I uLMS ($n = 622$, event time ratio = 0.91, 95% CI = 0.78–1.05, $P = 0.18$). Although the NCDB did not provide data on recurrence, considering that recurrence is a surrogate of survival, the results from the NCDB analysis are in the same context as the present meta-analysis and support the recommendation of observing patients with surgically treated early-stage uLMS.

The possible explanations for why the routine adjuvant therapy does not improve early-stage uLMS are as follows: (1) "use of the wrong drug" and (2) "treating the wrong patients" [36]. To overcome the first issue, we need to identify agents that are more effective than gemcitabine/docetaxel regimen, which has been tested in patients with early-stage uLMS. Other agents proposed to date have low objective response rates in uLMS, for example pazopanib 11% [37], trabectedin 10% [38]; and olaratumab was proven ineffective in the phase III ANNOUNCE trial [39]. To treat the appropriate population that could benefit from adjuvant therapy, it is essential to find reliable biomarkers to identify the highest risk group. So far, unfortunately, clinicopathological variables are not elucidated to predict the response to adjuvant therapy in early-stage uLMS [8]. In metastatic leiomyosarcoma, O^6-methylguanine DNA methyltransferase expression and dual PI3K/mTOR pathway have been suggested as potential predictive biomarkers [40,41]. Thus, further research is necessary to improve our understanding of the molecular pathway responsible for aggressive behavior of the disease and to discover predictive biomarkers, which can identify cohort benefit from adjuvant therapy in early-stage uLMS.

Our meta-analysis had several limitations. First, majority of the included studies were NRSs. Thus, the study may not provide a comprehensive review of the potential confounding variables. Although we endeavored to perform subgroup analyses to adjust for several potential confounders, not all of them could be controlled. Second, the individual studies were performed in various clinical settings with different practice protocols. Third, the present meta-analysis was not conducted at patient level and thus, other known prognostic factors such as tumor grade, mitosis, tumor size, and tumor morcellation were not considered. Therefore, the effect of adjuvant therapy according to these factors could not be analyzed. Fourth, because not all of the studies provided HRs that were calculated by a time-to-event analysis, the pooled estimates for risk of recurrence was evaluated by ORs. Thus, we conducted meta-regression analyses to examine the impact of follow-up time on study effect estimates and demonstrated that the median follow-up time of the included studies was not associated with the heterogeneity of our study. Finally, cross-study heterogeneity was observed. As a result of subgroup analysis, study design, details of AC/AR regimen, surgical staging, and other factors may affect the heterogeneity. A random-effects model minimizes the effect of the heterogeneity, but does not completely eliminate it.

Table 3
Subgroup analysis comparing observation versus adjuvant radiotherapy for recurrence.

	Number of studies	Observation	AR patients (n)	OR (95% CI) for mortality	*P* value	Study heterogeneity	
						I^2	*P* value, Cochran Q
Study design							
RCT	2	69	61	1.11 (0.25–5.02)	0.89	68%	0.08
NRS	7	196	90	1.05 (0.58–1.92)	0.87	39%	0.13
Complete surgical staging							
Yes	8	261	145	1.28 (0.80–2.06)	0.30	30%	0.19
No	1	4	6	0.07 (0.003–1.51)	NA	NA	NA
Type of radiation							
EBRT only	3	149	89	2.05 (1.12–3.74)	0.02	0%	0.50
EBRT+ICBT	3	57	43	0.45 (0.18–1.14)	0.09	0%	0.45

AR, adjuvant radiotherapy/chemoradiotherapy; RCT, Randomized controlled trial; NRS, non-randomized study; EBRT, external beam radiotherapy; ICBT, intracavitary brachytherapy; OR, odds ratio; NA, not applicable.

In conclusion, chemotherapy or radiotherapy for postoperative management of early-stage uLMS does not significantly improve the oncological outcome compared with observation. Given the rarity of this disease and premature closure of the recent international collaborated RCT [9], it is unlikely that another RCT will be initiated to investigate the positive role of adjuvant therapy routinely used in current practice. Further studies are needed to identify the prognostic factors, develop better therapeutics, and identify biomarkers for treatment responses in early-stage uLMS. In the meantime, clinicians and patients should be informed with the best possible medical evidence.

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Declaration of Competing Interest

None of the authors has a conflict of interest to declare.

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Disclosures

The authors have no conflicts of interest or financial ties to disclose.

Author contribution

Conceptualization: S.S.; data curation: S.C., S.S.; formal analysis: S.C., S.S., M.C., S.K.; funding acquisition: S.S.; investigation: all authors; methodology: S.S., S.C.; project administration: S.S.; resources: all; software: M.C.; supervision: S.S., S.K.; validation: M.C., S.K.; visualization: S.K.; writing - original draft: S.S., S.C.; writing - review & editing: all authors.

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