Role of Lymphadenectomy for Uterine Sarcoma
A Meta-Analysis

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Objective: Uterine sarcomas are rare, highly aggressive tumors with an unfavorable prognosis. The role of lymphadenectomy (LAD) remains controversial for this particular tumor type. To examine whether LAD can assist in prognosis or clinical benefits for uterine sarcoma patients, we performed a meta-analysis based on published studies.

Methods: We initially identified published studies by searching the PubMed database up to 30 November 2015. Study quality was evaluated systematically using the Newcastle-Ottawa Scale for assessing the quality of studies for inclusion in meta-analyses. Pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated using Stata software version 12.0.

Results: Our search retrieved 14 eligible studies, involving a total of 4867 patients, including 1356 (27.9%) patients who had LAD. The pooled RR for uterine leiomyosarcoma (uLMS) in patients with LAD in 5 trials was 0.90 (95% CI, 0.62–1.31) and for endometrial stromal sarcoma (ESS) in 11 trials was 0.96 (95% CI, 0.69–1.34), suggesting that there was no significant benefit of LAD in improving overall survival ($P < 0.05$). A random-effects model was chosen to estimate the RRs in view of the significant heterogeneity in the included studies (uLMS: Cochran Q test: $P = 0.022$, $I^2 = 64.9\%$; ESS: Cochran Q test: $P = 0.005$, $I^2 = 60.1\%$). No publication bias was detected by the Egger and Begg tests (uLMS: Begg: $P = 0.221$, Egger: $P = 0.148$; ESS: Begg: $P = 1.000$, Egger: $P = 0.928$).

Conclusions: Based on currently available evidence, the findings of this meta-analysis suggest that LAD bears little prognostic or therapeutic benefit in patients with uterine sarcoma. Systematic LAD may not be recommended in patients with uLMS or ESS unless the patient has obvious extrauterine involvement, clinically suspicious enlarged nodes, or advanced sarcomas.

Key Words: Lymphadenectomy, Uterine sarcoma, Uterine leiomyosarcoma, Endometrial stromal sarcoma, Meta-analysis

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Uterine sarcomas are rare neoplasms of stromal and mesenchymal origin with poor prognosis and a tendency for early distant metastases. It has been estimated that about 3% of all uterine neoplasms are sarcomas.[1,2] According to the National Comprehensive Cancer Network (NCCN) 2015 classification, uterine sarcomas are categorized as uterine leiomyosarcoma (uLMS), endometrial stromal sarcoma (ESS), and undifferentiated uterine sarcoma (UUS).[2] During recent years, the nature of carcinosarcomas has been actively investigated. Although carcinosarcomas are highly aggressive tumors with poor prognosis that are recently staged as high-grade endometrial cancer.[3,4] Leiomyosarcomas represent the most frequent subtype of this heterogeneous group of tumors.[5] Undifferentiated uterine sarcomas are an extremely rare subtype characterized by aggressive clinical behavior and, 5-year survival rates ranging from 25% to 55%.[6] Recent data suggest that the incidence of lymph node metastases in UUS

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is higher than other uterine sarcoma subtypes, and tumor stage is a strong prognostic factor in UUS.[7–9] Due to the low incidence of, and limited data for, uterine sarcoma, there are no evidence-based guidelines for treatment of uterine sarcoma. The NCCN has established clinical practice guidelines that refer to a synopsis of currently available retrospective data.[2] According to the NCCN guidelines, the initial treatment for uterine sarcomas is hysterectomy with or without bilateral salpingo-oophorectomy.[2,10,11] However, the status of lymphadenectomy (LAD) in the management and staging of uterine sarcomas is still controversial, and there are no clear surgical guidelines.[11] Thus, the objective of this systematic review was to investigate the effects of LAD in patients with uterine sarcoma and their possible correlation with patient outcomes, and to recommend the most appropriate surgical procedure for this rare and aggressive uterine malignancy. Because carcinosarcomas are classified as an endometrial carcinoma subtype, and there are few studies on the propensity of UUS for lymph node involvement, they are not part of our study.

MATERIALS AND METHODS

Search Strategy

We searched the entire PubMed database up to 30 November 2015 for studies evaluating the effects of LAD on uterine sarcoma patients. We also searched the PubMed database based on the references in the studies that we included in our survey. The following search terms were used: "uterine sarcoma" or "uterine leiomyosarcoma" or "uLMS" or "endometrial stromal sarcoma" or "ESS" or "high-grade endometrial sarcoma" or "undifferentiated endometrial sarcoma" or "undifferentiated uterine sarcomas" or "UUS" or "lymphadenectomy" or "lymph node excision" or "lymph node resection" or "lymph node dissection" or "LAD" or "LND" or "LNE." These search themes were combined using the Boolean operator "AND" in several combinations without restrictions. The bibliography of each relevant article was also carefully examined to identify other eligible studies. If sources of study population recruitment overlapped by more than 1 study, only data from the most recent study or the largest published report were utilised. Only studies published in English were included in this meta-analysis.

Study Selection

Studies included in our meta-analysis had to meet all of the following criteria: (1) the study investigated the association between LAD and prognosis of uterine sarcomas; (2) the study included at least 15 cases; (3) the diagnoses of uterine sarcomas was confirmed by histology, pathology, or cytology; (4) the relative risks (RRs) and the corresponding 95% confidence intervals, or the number of events used to calculate them were reported; (5) the data were either retrospective or prospective; (6) the article was published in English. The major exclusion criteria were as follows: (1) cases involving carcinosarcoma; (2) the 5-year incidence of RR could not be collected; (3) overlapping or republished studies; (4) studies that were not published as full reports.

Data Extraction

Based on the inclusion criteria, 2 reviewers independently extracted the following data parameters for each eligible study: first author's name, year of publication, country of origin for the study, histological type of the tumor, source of controls, total number of patients analysed, the RRs and 95% confidence interval [CIs] of LAD, and the number of positive lymph nodes. Any discrepancies between the investigators were resolved by discussions until a consensus was reached. If they failed to reach a consensus, a third investigator (an experienced professional gynecologist) was consulted to resolve the dispute.

Assessment of Study Quality

Two investigators independently assessed the quality of each study included in this meta-analysis using the Newcastle-Ottawa Scale, which evaluates studies on three broad perspectives: (1) the selection of the study groups, (2) the comparability of the groups, and (3) the manner in which the outcome of interest was obtained for cohort studies. The Newcastle-Ottawa Scale assigns a maximum score of 4 for selection, 2 for comparability, and 3 for exposure. Hence, a score of 9 is the highest and reflects the highest quality. Disagreements were resolved by consensus.

Statistical Analysis

We computed a pooled RR and 95% CIs using Stata software version 12.0 to generate forest plots, determine statistical significance, and to assess the heterogeneity of the included studies. Statistical heterogeneity was evaluated using the χ^2 test based on Cochran Q statistic and the I^2 statistic, which ranged from 0% to 100% (I^2 = 0–25%, no heterogeneity; I^2 = 25–50%, moderate heterogeneity; I^2 = 50–75%, large heterogeneity; and I^2 = 75–100%, extreme heterogeneity).[12] The combined risk estimates were computed using a fixed-effects model or, in the presence of heterogeneity, a random-effects model.[13] Publication bias was evaluated by the Egger and Begg tests. For all tests, a *P* value less than 0.05 was considered statistically significant. All statistical tests were 2-sided.

RESULTS

Search Results

A total of 91 studies were initially identified based on the search criteria. Only 14 studies [5,8,14–25] met all inclusion/exclusion criteria for this meta-analysis. A flowchart for the study selection is shown in Figure 1.

Characteristics of Included Studies

Table 1 summarizes the detailed characteristics of the trials for uLMS included in this review, and Table 2 provides the same summary for ESS. For the purposes of this analysis, we divided patients into 2 treatment groups based on whether they received a lymph node dissection or not. Of the 14 included studies, the sample sizes ranged from 15 to 1396, and a total of 4867 patients were pooled; 1356 (27.9%) had the LAD procedure and 3337 (68.6%) did not receive the LAD procedure.

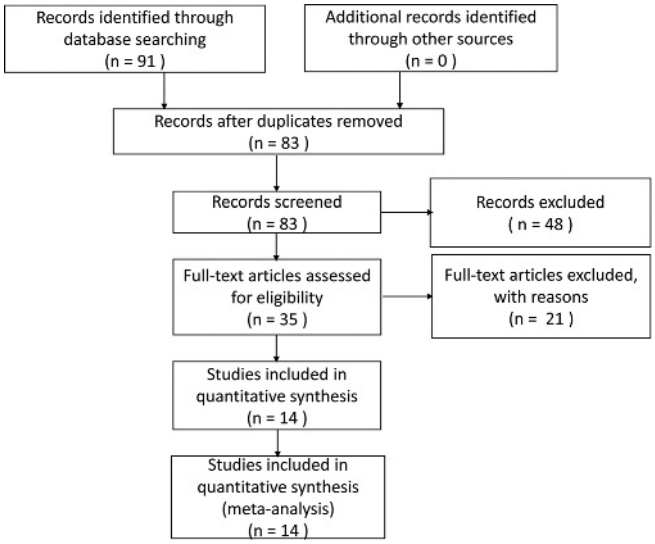

FIGURE 1. Flow chart of article selection.

Meta-Analysis of Undergoing LAD in the Overall Survival of Uterine Sarcoma Patients

To investigate the role of LAD of uterine sarcoma patients on overall survival, analysis was conducted using the available information in 14 studies. Tables 1 and 2 summarize the information from the 14 trials included in this analysis. Figure 2 shows the estimated pooled RRs associated with LAD for uLMS and ESS. Significant heterogeneities were detected (uLMS: $P = 0.022$, $I^2 = 64.9\%$; ESS: $P = 0.005$, $I^2 = 60.1\%$), so the random effects model was used. The overall pooled RR for uLMS (5 trials) was 0.90 (95% CI, 0.62–1.31), and for ESS (11 trials) was 0.96 (95% CI, 0.69–1.34), indicating that LAD has little effect in prolonging overall survival.

Sensitivity Analysis

In view of significant heterogeneities, sensitivity analysis was performed. Figure 3 shows the pooled RRs and 95% CIs of the sensitivity analysis; 1 study was removed in each turn. It seemed that omission of each study had no significant effect on the final result, which indicated that the main result was reliable and robust.

Publication Bias

Begg funnel plots are scatter plots of the log RR of individual studies on the horizontal axis versus the standard error of the estimate on the vertical axis. As shown in Figure 4, no publication bias exists. The Begg rank correction test and Egger linear regression detected evidence for publication bias among included studies for uLMS (Begg: $P = 0.221 > 0.05$; Egger: $P = 0.148 > 0.05$), for ESS (Begg: $P = 1.000 > 0.05$; Egger: $P = 0.928 > 0.05$).

DISCUSSION

Uterine sarcomas are rare malignant gynecological tumors with poor prognosis and aggressive potency and account for 3% of all uterine neoplasms.[1,2] Uterine sarcoma typically affects women older than 40 years with a median age at the time of diagnosis of 52 years.[16] In our study, the median age for uLMS was 51.84 years and 52.38 years for ESS. Patients frequently present with abnormal uterine bleeding (86%), abdominal pain (24%), and/or pelvic mass (15%).[26] The optimal treatment of uterine sarcomas is surgery, consisting of total abdominal hysterectomy with or without bilateral salpingo-oophorectomy. To date, the role of LAD in the management and staging of uterine sarcomas remains controversial. The NCCN also mentions individualized surgical resection including LAD based on clinical scenarios and intraoperative findings without providing clear guidance.

As shown in Figure 2, no matter uLMS or ESS, diamonds intersect with the invalid vertical lines (the summary estimates with corresponding 95% CIs include (1), which indicates that LAD has no influence on overall survival.

The role of LAD in the staging and prognosis of uLMS is defined poorly. Our results agree with the previous report by Kapp et al[5] showing the low risk of regional lymph node metastases and the sparse effectiveness of LAD in uLMS patients. As shown in Table 3,[5,14,16,17,27–38] the overall frequency of positive lymph nodes in uLMS was very low (7.4%), except for the report by Chen[28] of a high lymphatic metastasis rate of 75% (3 of 4 cases). Ayhan et al[17] reported lymph node metastasis in 8.8% (3 of 34 cases) of uLMS patients and demonstrated that lymphatic resection and the number of resected lymph nodes do not improve outcomes in overall and disease-free survival.

TABLE 1. Characteristics of clinical trials studying uLMS patients with and without LAD

Study	Years of Study	Country	No. Patients	Median Age, y	Cancer Type	LAD	No LAD	RRs	95% CIs	Lymph Node (+)
Leitao et al, 2003	1982–2001	USA	275	51	uLMS	37	71	0.7	0.46–1.06	3/37
Kokawa et al, 2006	1990–2003	Japan	36	52	uLMS	12	24	0.75	0.40–1.41	NA
Kapp et al, 2008	1988–2003	SEER	1396	52	uLMS	348	1047	1.15	0.98–1.35	23/348
Koivisto-Korander et al, 2008	1990–2001	Finland	39	52	uLMS	15	24	0.1	0.01–0.82	0/15
Ayhan et al, 2009	1982–2007	Turkey	63	NA	uLMS	34	29	1.32	0.74–2.35	3/34

NA, not available.

TABLE 2. Characteristics of clinical trials studying ESS patients with and without LAD

Study	Years of Study	Country	No. Patients	Median Age, y	Cancer Type	LAD	No LAD	RRs	95% CIs	Lymph Node (+)
Weitmann et al, 2001	1981–1998	Austria	31	NA	ESS	5	26	0.3	0.02–4.53	NA
Geller et al, 2004	1972–2003	USA	28	56.2	ESS	13	15	1.38	0.55–3.48	NA
Riopel et al, 2005	1974–2003.10	Canada	15	41	LGESS	8	7	13.33	0.90–197.87	5/15
Kokawa et al, 2006	1990–2003	Japan	15	56	ESS	3	12	0.5	0.10–2.55	NA
Amant et al, 2007	1986–2005	Belgium	31	44	ESS	6	25	1.04	0.14–7.72	1/6
Shah et al, 2008	1988.1.1– 2005.12.31	SEER	848	55.2	ESS	287	561	1.21	0.89–1.64	37/287
Koivisto-Korander et al, 2008	1990–2001	Finland	21	52	ESS	13	8	0.82	0.24–2.78	1/13
Chan et al, 2008	1988.1.1– 2003.12.31	SEER	831	52	ESS	282	543	1.17	0.91–1.50	28/282
Barney et al, 2009	1983–2002	SEER	1010	54	ESS	177	833	0.82	0.59–1.14	NA
Yoon et al, 2014	1990.1–2012.1	Korea	114	45	ESS	45	69	3.07	0.81–11.64	3/45
Zhou et al, 2015	1991.3–2013.2	NA	114	41	ESS	71	43	0.36	0.20–0.63	9/71

LGESS, low-grade endometrial stromal sarcomas.

However, some researchers hold different opinions. Morice et al[39] suggested that LAD should be performed in uLMS patients with enlarged nodes discovered during the surgical procedure. In general, lymph nodes greater than 1 cm in diameter are considered abnormal.[40] Kapp et al[5] found that patients with positive lymph nodes (n = 23) had an inferior survival rate of 26% compared with patients with negative lymph nodes (n = 324), who had a survival rate of 64.2%. Kapp et al also found that patients with 2 or more positive lymph nodes were found to have poorer survival compared with patients with only 1 positive lymph node. Although Tangjitgamol et al[41] concluded that lymph node size was not a good predictor of lymph node metastases in uterine cancer, removing the enlarged lymph nodes in uLMS was considerable.[42]

Pelvic and/or paraaortic lymph node dissection was not routinely recommended by most authors since retroperitoneal involvement was found to be rare in their sample.[11] The low incidence of lymph node metastasis is similar to those women with uLMS of other soft tissues.[43] Although LAD may improve surgical staging, it showed no evidence of benefit in terms of patient survival. Hence, routine lymph node dissection is not generally recommended. Further studies with large populations are needed to investigate whether LAD affects prognosis, 5-year overall survival, and other relevant clinical outcomes in uLMS. As shown in Table 4,[7,8,16,20–22,24,25,29,32,38,44–50] lymph node

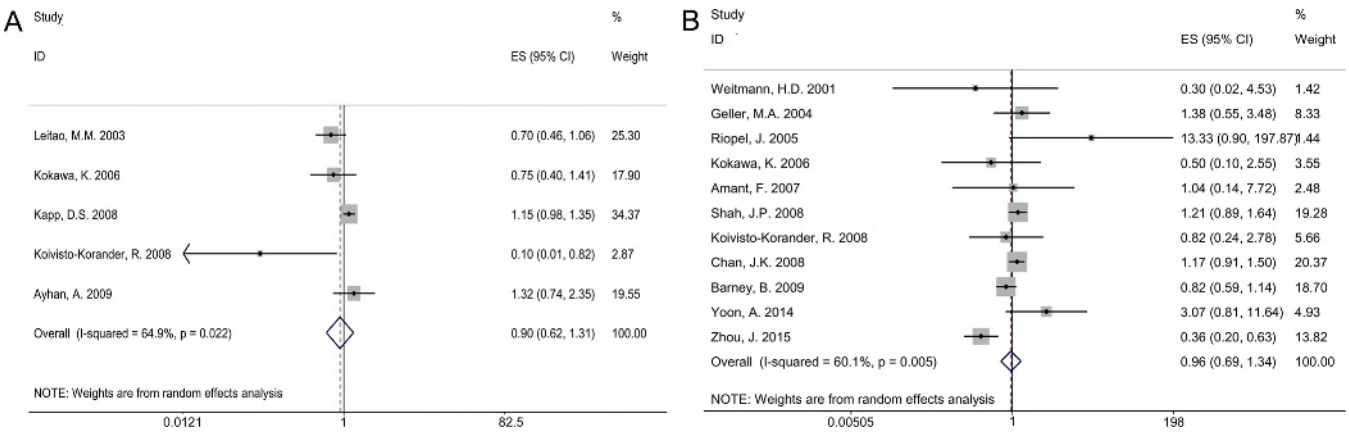

FIGURE 2. Pooled RRs of lymphadenectomy. Squares represent study-specific estimates (size of the square reflects the study-specific statistical weight); horizontal lines represent 95% CIs; diamonds represent summary estimates with corresponding 95% CIs. Summary RRs of lymphadenectomy for uterine leiomyosarcoma and endometrial stromal sarcoma. The overall pooled RR for uLMS (A: 5 trials) was 0.90 (95% CI, 0.62–1.31), and for ESS (B: 11 trials), 0.96 (95% CI, 0.69–1.34). Results for the test for heterogeneity: (A: uLMS) $P = 0.022$, $I^2 = 64.9\%$; (B: ESS) $P = 0.005$, $I^2 = 60.1\%$. A random-effects model was chosen to estimate the pooled RRs in view of the detected heterogeneity among these studies.

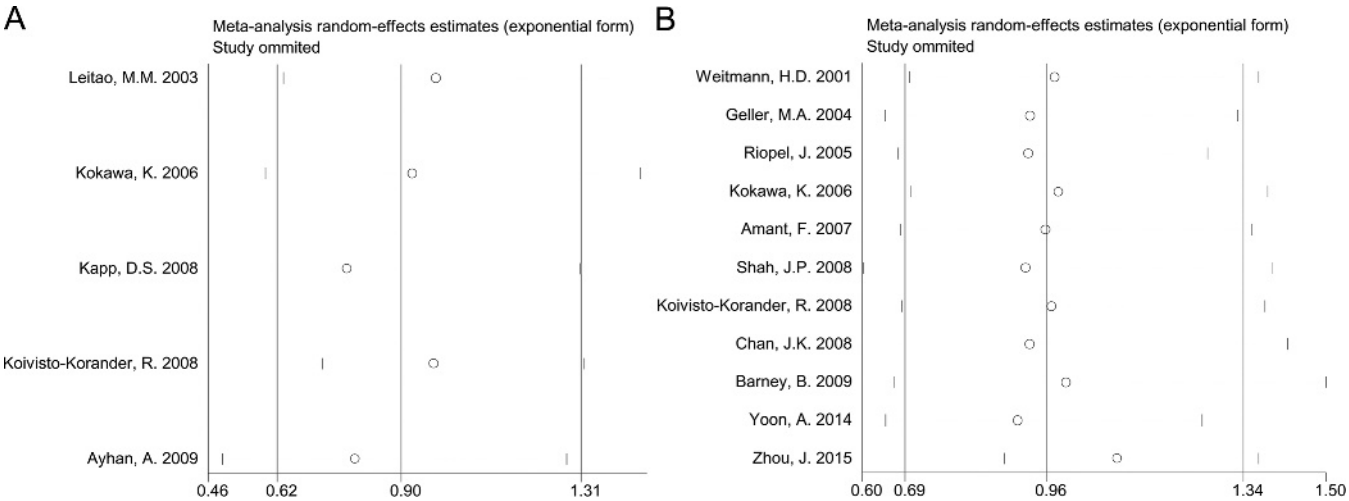

FIGURE 3. Sensitivity analysis. The figure shows the pooled RR and 95% CI of the sensitivity analysis. A, uLMS. B, ESS.

metastasis rates in ESS are reported between 0% and 40%, with an average of 10.7%. Most authors found that there was no significant difference in survival of patients with lymph node dissection or positive lymph nodes.[49] In a study by Amant et al,[21] LAD was performed in 6 (19.4%) of 31 patients with ESS; metastasis was found in only 1 patient (16.7%). The low recurrence in the Amant study suggested that systematic LAD is of little clinical benefit in early-stage ESS. Barney et al[23] analyzed 177 patients who underwent LAD at the time of surgery and concurred with the results of Shah et al,[8] who found that the dissection of involved lymph nodes in uterine sarcomas was of prognostic significance, but was not therapeutic. In a recent analysis of 94 ESS patients,[48] lymph node metastases were identified in 7 (19.4%) of 36 patients who underwent LAD (7/36). Among 45 ESS patients who underwent LAD, 3 were found to have lymphatic metastasis (6.7%).[24] Only Tanz et al[49]

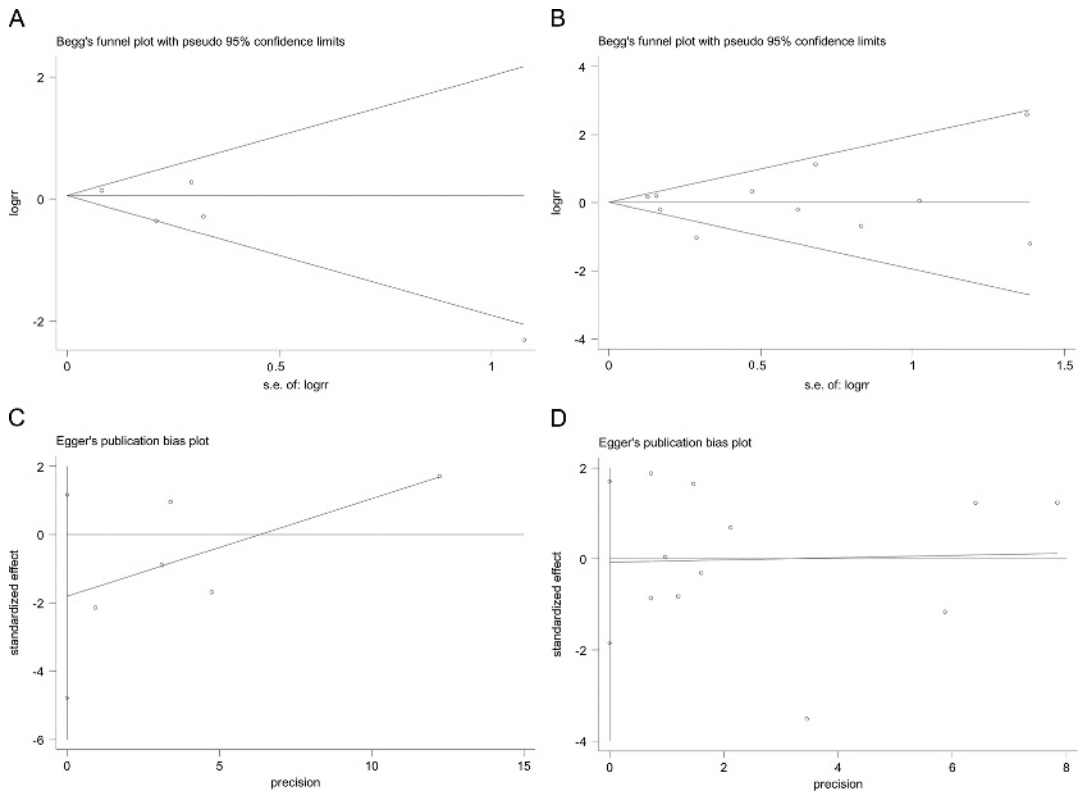

FIGURE 4. Tests for publication bias. Circles represent individual studies. The Begg rank correction test and Egger linear regression detected evidence for publication bias among included studies for uLMS (A, Begg: $P = 0.221 > 0.05$; C, Egger: $P = 0.148 > 0.05$), for ESS (B, Begg: $P = 1.000 > 0.05$; D, Egger: $P = 0.928 > 0.05$).

TABLE 3. Lymphatic metastasis rate in uLMS patients

		Lymph Node Metastasis	
Series	**Year**	**N**	**No. Positive (%)**
Barter et al	1985	7	0 (0)
Chen et al	1989	4	3 (75)
Goff et al	1993	15	4 (26.7)
Major et al	1993	57	2 (3.5)
Gadducci et al	1996	7	2 (28.6)
Ayhan et al	1997	17	1 (5.9)
Gard et al	1999	11	2 (18.2)
Leitao et al	2003	37	3 (8.1)
Giuntoli et al	2003	36	4 (11.1)
Hsieh et al	2003	9	0 (0)
Dinh et al	2004	8	0 (0)
Wu et al	2006	21	0 (0)
Kapp et al	2008	348	23 (6.6)
Koivisto-Korander et al	2008	15	0 (0)
Ayhan et al	2009	34	3 (8.8)
Hoellen et al	2014	6	0 (0)
Total		632	47 (7.4)

N, total number of patients.

reported a high lymph node metastasis rate of 40% (2 of 5) in ESS patients. Because of the relatively low incidence of ESS, it is difficult to analyze the incidence and prognostic significance of lymph node metastases in ESS patients. The results of our study (lymph node metastasis rate of 10.7%) seem to concur with those who found that adding LAD did not result in improved overall survival in ESS patients. These findings suggest there is urgent need for a larger patients sample to analyze the prognostic and clinical role of lymph node dissection in patients with ESS.

The 2009 International Federation of Gynaecology and Obstetrics surgical staging system for uterine sarcomas indicates that regional lymph node metastasis belongs to stage IIIC,[1] which implies that LAD may affect Federation of Gynaecology and Obstetrics staging and lead to stage migration in some patients. Hoellen et al[38] found that patients with lymph node metastases (n = 12) had a worse median survival of 13.5 months compared with patients without lymph node or distant metastases (n = 33), who had a median survival of 32 months. Among patients without lymph node or distant metastases (n = 29), those who underwent LAD (n = 21) had a better survival of 70 months compared with patients without LAD (n = 8), who survived for 21 months. These data are in line with several other publications: Chan et al[22] reported a large study (831 patients) showing a significantly poorer survival in patients with positive lymph node metastases compared to patients with negative lymph nodes (35.3% vs. 80.1%). Researchers in 2 studies observed that patients with 1 positive lymph node had superior survival compared with patients with 2 or more positive lymph nodes.[11,38] Therefore, lymph node dissection may provide prognostic information and treatment guidance. However, according to current data and relevant literature, LAD does not present any prognostic or potential therapeutic value at early stages in this subtype. It is important to keep in mind that uterine sarcomas tend to show distant hematogenous metastases (especially lung metastases), whereas lymph node metastases are less common.[38] Hence, in light of the sparse lymph node metastases of uterine sarcomas, LAD and reexploration solely for staging may not be recommended in uterine sarcomas patients.

Although this meta-analysis has no publication bias, significant heterogeneities were detected. Sensitivity analysis was performed to support the robustness and reliability of the main result (Fig 3). In our study, the pooled RRs were 0.90 (95% CI, 0.62–1.31) in patients with LAD for uLMS and 0.96 (95% CI, 0.69–1.34) in patients with LAD for ESS, suggesting no significant impact of LAD in reducing the RR ($P < 0.05$). Due to the heterogeneity in our study, additional randomized controlled studies are needed to further define whether LAD in the treatment of patients with uterine sarcoma has potential value in affecting 5-year disease-free survival and other relevant clinical outcomes.

Limitations of this Study

The potential limitations of the present study are as follows: First, the most noteworthy finding was the substantial heterogeneity. Possible reasons for the between-study

TABLE 4. Lymphatic metastasis rate in ESS patients

		Lymph Node Metastasis	
Series	**Year**	**N**	**No. Positive (%)**
Goff et al	1993	7	0 (0)
Gadducci et al	1996	3	0 (0)
Ayhan et al	1997	2	0 (0)
Riopel et al	2005	15	5 (33.3)
Reich et al	2005	9	3 (33.3)
Leath et al	2007	23	2 (8.7)
Amant et al	2007	6	1 (16.7)
Li et al	2008	1	0 (0)
Shah et al	2008	100	7 (7)
Koivisto-Korander et al	2008	13	1 (7.7)
Chan et al	2008	282	28 (9.9)
Signorelli et al	2010	19	3 (15.8)
Dos Santos et al	2011	36	7 (19.4)
Tanz et al	2012	5	2 (40)
Bai et al	2014	46	1 (2.2)
Hoellen et al	2014	7	2 (28.6)
Yoon et al	2014	45	3 (6.7)
Zhou et al	2015	71	9 (12.7)
Total		690	74 (10.7)

heterogeneity are the sources and countries of study. Second, we restricted our search strategy to articles published in English. High-quality articles that were published in other languages were not included because of difficulties in obtaining accurate medical translation and data. Despite these limitations, our findings provide insight into the management of uterine sarcoma. Finally, our meta-analysis is based on a limited number of studies; meta-analysis of higher-quality, multicenter studies that provide more robust data could validate our findings.

CONCLUSIONS

Establishing clear clinical guidelines for individualized surgical resection including LAD remains a challenge. As in previous reports, our retrospective data indicate that although surgical staging may be performed, systemic LAD did not have a statistically significant effect on overall survival. Lymph node metastases in patients with uterine sarcomas were too low to suggest systematic LAD, and little potential prognostic and clinical value is gained by LAD or resection of lymph nodes. However, selective LAD can be considered when patients have obvious extrauterine involvement, clinically suspicious enlarged nodes, and advanced sarcomas. Ideally, large-scale population-based studies are required to get more robust data to validate our findings.

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