Role of Lymph Node Involvement and Lymphadenectomy in Patients with Different Subtypes of Uterine Sarcoma: A Systematic Review and Meta-Analysis

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Background: *To identify the influence of lymph node involvement (LNI) and lymphadenectomy on the prognosis of patients with uterine sarcoma.*

Methods: *PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Scopus, OpenGrey, and ClinicalTrials.gov were searched. Articles related to LNI or lymphadenectomy in patients diagnosed with any of the following subtypes of uterine sarcoma: uterine leiomyosarcoma (uLMS), low-grade endometrial stromal sarcoma (LGESS), high-grade endometrial stromal sarcoma (HGESS), undifferentiated uterine sarcoma (UUS), and adenosarcoma (ADS) were identified.*

Results*: A total of 25 studies with 19,926 patients were included. LNI was more common in patients with HGESS/UUS [rate 18%; 95% confidence interval (CI) 95%: 9%–28%], but less in uLMS (6%; 95% CI 4%–8%), LGESS (7%; 95% CI 4%–11%), or ADS (2%; 95% CI 1%–3%). Lymphadenectomy did not improve overall survival in patients with LGESS [hazard ratio (HR) 1.21, 95% CI 0.95–1.54], ADS (HR 0.90, 95% CI 0.73–1.10) or uLMS (HR 1.14, 95% CI 1.03–1.27), but it did improve overall survival in patients with HGESS/UUS (HR 0.63, 95% CI 0.48–0.85). Lymphadenectomy did not improve disease-free survival in patients with uLMS or ADS (HR 0.87, 95% CI 0.61–1.26).*

Conclusion*: LNI is relatively infrequent among patients with uLMS, LGESS, or ADS, and lymphadenectomy in such patients does not appear to improve survival. Incontrast, LNI is relatively common among patients with HGESS/UUS, and lymphadenectomy significantly improves overall survival. The available evidence supports routine lymphadenectomy for patients with HGESS/UUS, but not those with uLMS, LGESS, or ADS*

BACKGROUND

Neoplasms of the uterine corpus constitute the sixth most common cancer in women, with 417,000 new cases and 97,000 deaths reported globally in 2020.[1] Uterine sarcomas are a highly malignant cancer with poor prognosis, and they account for 3–7% of all uterine neoplasms.[2] According to the National Comprehensive Cancer Network (NCCN), uterine sarcomas are classified into five main histological subtypes: uterine leiomyosarcoma (uLMS), low-grade endometrial stromal sarcoma (LGESS), high-grade endometrial stromal sarcoma (HGESS) undifferentiated uterine sarcoma (UUS), and adenosarcoma (ADS).[3]

Primary treatment for uterine sarcoma is total hysterectomy (TH) and/or bilateral salpingo-oophorectomy (BSO), which can be followed by various postoperative therapies.[2,3] Lymph node involvement (LNI) can significantly worsen survival, so the International Federation of Gynecology and Obstetrics (FIGO) staging system takes it into account in the case of uLMS, ESS, or ADS.[2] LNI is typically managed by lymphadenectomy, which involves resecting nodal

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metastases. However, the use of lymphadenectomy for uterine sarcoma remains controversial.[2] On one hand, some studies concluded that lymphadenectomy could not improve overall survival (OS) in patients with uLMS, LGESS, or ADS.[4-6] In fact, lymphadenectomy has been associated with short- and long-term complications, including prolonged duration of surgery or hospitalization, greater intra-operative trauma or blood loss, and risk of lymphoceles and lower body lymphedema.[7,8] Consequently, the NCCN recommends against lymphadenectomy for any subtype of uterine sarcoma.[3] On the other hand, other studies have associated lymphadenectomy with better OS of patients with HGESS/UUS and better disease-free survival (DFS) of patients with uLMS.[9, 10]

To help resolve the controversy about whether to perform lymphadenectomy on patients with different subtypes of uterine sarcoma, we systematically reviewed and meta-analyzed the available literature. We included studies covering all five subtypes of the disease.

METHODS

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, and it was registered with PROSPERO (CRD42022353507).

Literature Search

We searched PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Scopus, OpenGrey, and ClinicalTrials.gov from their respective inceptions through May 31, 2022 for studies reporting the association between LNI or lymphadenectomy and prognosis in patients with uterine sarcoma. The following predefined search terms were used: ("uterine sarcoma" OR "sarcoma of uterus" OR "uterine leiomyosarcoma" OR "leiomyosarcoma of uterus" OR"uterine undifferentiated sarcoma" OR "undifferentiated sarcoma of uterus" OR "uterine endometrial stromal sarcoma" OR "endometrial stromal sarcoma of uterus") AND ("lymph node dissection" OR " lymph node excision" OR "lymph node involvement" OR "lymphadenectomy" OR "lymph node metastasis" OR "lymph node metastases"). There were no restrictions regarding publication date, article type, or publication status. The reference lists of eligible studies were also reviewed to identify additional studies.

Study Selection

Two authors (YF and YFZ) independently screened records for eligibility based on the titles and abstracts. Afterwards, the full texts of all potentially eligible articles were independently evaluated for final inclusion. Any disagreement was resolved by discussion with a third author (JL).

Our inclusion criteria were studies that (a) had an observational design (prospective cohort, retrospective cohort, or case-control); (b) enrolled participants who were diagnosed with LNI based on pathology and/or who underwent lymphadenectomy; (c) reported relevant data (see section 2.3); and (d) were available as full text. Studies were excluded if they (a) were published in languages other than English; (b) involved fewer than 15 patients;[11] (c) reported insufficient data to calculate hazard ratios (HRs) or incidence rate of LNI; or (d) were judged to be of poor quality (see section 2.4). LNI was defined as microscopically confirmed metastasis to pelvic
lymph nodes or para-aortic lymph nodes.[2]

Data Extraction

Two authors (YF and YFZ) independently extracted the following data from all included studies: name of the first author, publication year, country (or data source), year of patient enrollment, histological subtype of uterine sarcoma, primary treatment, incidence rate of LNI, and data on outcomes including OS and DFS. Due to similar tumor features, treatment and prognosis, we aggregated patients with HGESS or UUS into the same subgroup (HGESS/UUS) .[3, 12, 13] Discrepancies in extracted data were resolved through discussion with a third author (JL).

Assessment Of Study Quality

The methodological quality of the included studies was independently assessed by two authors (YF and TTS) using the Newcastle-Ottawa Quality Assessment Scale (NOS) .[14] For the criterion of 'Comparability of cohorts on the basis of the design or analysis', studies that controlled only for histology type (uterine sarcoma) received one star, whereas studies that also controlled for other primary surgical procedures (such as TH and/or BSO) were assigned two stars. For the criterion of 'Assessment of outcome', studies that used microscopic biopsy to diagnose LNI received one star. For the criterion of 'Adequacy of follow up of cohorts', studies with a follow-up rate higher than 85% were assigned one star. Only studies judged to be of high quality (at least six stars) were included in meta-analyses.

Statistical Analysis

Statistical analyses were performed using the metan, metabias and metaprop packages in STATA 15.0 (StataCorp, College Station, TX, USA). Incidence rates of LNI were subjected to random-effects meta-analysis using inverse variance modeling involving Freeman-Tukey double arcsine transformation.[15] In the case of zero events, we added 0.5 to each cell for correction when calculating the incidence rate of LNI.16 Whenever appropriate, we calculated HRs and the associated 95% confidence intervals (CIs) using the tool recommended by Tierney et al.[17] In studies where OS and DFS were reported only in the form of Kaplan-Meier curves, the necessary data were extracted using Engauge Digitizer 4.1 (http://sourceforge.net/projects/digitizer/).

Heterogeneity was quantified using the I2 statistic, and I2 ≥ 50% was taken to indicate high heterogeneity.[16] If heterogeneity was observed across studies within a given meta-analysis, we meta-analyzed the data using a random-effects model.[16] We generated a Galbraith radial plot to explore potential causes of heterogeneity.[18] We also conducted subgroup analyses based on publication year, country, histologic subtype, sample size and follow-up duration. Sensitivity analyses were performed by repeating the meta-analysis after systematically removing each study one-by-one. Publication bias was assessed by funnel plots, and potential asymmetry in the plots was assessed using Begg's test,[19] with $p < 0.1$ taken to indicate significant publication bias.

RESULTS

Characteristics of the Included Studies

The process of study selection is summarized in Figure 1. Database and additional searches retrieved a total of 1,014 records, from which 25 articles were ultimately included in our meta-analysis (Table I).[4-6,9,10,13,20-38] All 25 studies had a retrospective cohort design, they involved a total of 19,926 participants, and they came from 17 countries: United States (n = 5), Turkey (n = 6), China (n = 2), Spain (n = 1), Japan (n = 1), Italy (n = 1), and Tunisia (n = 1). The studies included data from two publicly available databases: the National Cancer Database (NCDB) (n = 4) and the Surveillance, Epidemiology, and End Results (SEER) database (n = 4), both from the US.

Figure 1: Flowchart showing the literature search strategy and study selection.

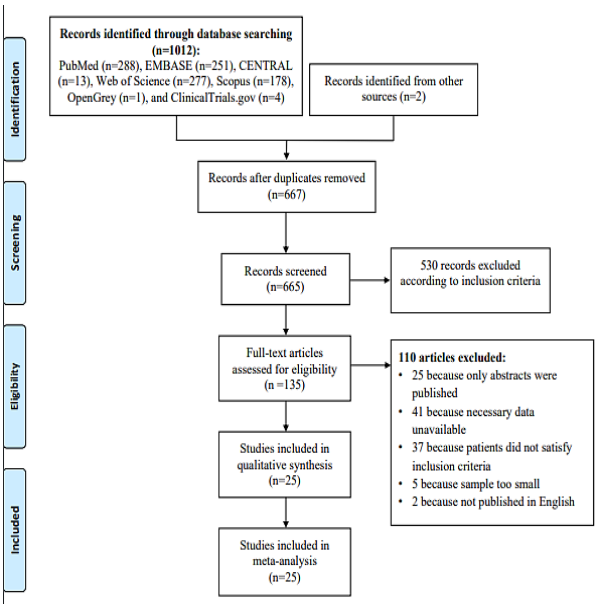


Table 1: Baseline and follow-up data on patients in the included retrospective studies

Tumor subtype	Author [ref]	Inclusion year	LNI	LND	Non-LND	n	Country	NOS	Surgery type	FIGO stage	Longest follow-up* (months)
HGESS or UUS	Nasioudis 9	2004-2015	22	280	126	406	NCDB	8	TH	I	168
	Cabrera 20	1995-2019	5	20	12	32	Spain	7	Various	I-IV	240
	Ayhan 22	2008-2017	14	54	NR	54	Turkey	7	TH ± BSO	I-IV	NR
	Seagle 13	1998-2013	141	712	NR	712	NCDB	8	TH	could not be determined	
uLMS	Ayhan 10	1996-2018	8	162	NR	162	Turkey	8	TH + BSO	I-IV	NR
	Nasioudis 9	2004-2015	42	1250	2267	3517	NCDB	8	TH	I	168
	Takehara 24	2000-2012	NR	33	227	260	Japan	8	TH + oophrectomy	I-IV	169.2
	Nesrine 26	2000-2014	NR	18	13	31	Tunisia	7	TH±BSO	I-IV	207
	Machida 5	1973-2013	188	3749	NR	3749	SEER	7	TH and others	I-IV	NR
	Raspagliesi 29	2004-2014	NR	NR	NR	91	Italy	6	TH ± BSO	I	49.6
	Seagle 4	1998-2013	189	2255	NR	2255	NCDB	8	TH ± BSO	I-IV	NR
	Tasci 30	1993-2009	8	36	59	95	Turkey	7	TH ± BSO	I-IV	183
	Ayhan 32	1982-2007	4	34	NR	34	Turkey	6	TH + BSO	I-IV	NR
	Kapp 34	1988-2003	23	347	NR	347	SEER	8	TH + BSO	I-IV	NR
	Akahira 35	1990-2004	NR	3	27	30	Japan	7	TH + BSO	I-IV	110
	Giuntoli 37	1976-1999	4	36	NR	36	USA	8	TH + BSO	I-IV	NR
	Leitao 36	1982-2001	3	37	NR	37	USA	7	TH ± oophrectomy	I-IV	NR
	Major 38	1979-1988	2	57	NR	57	USA	6	NR	I-II	NR
LGESS	Nasioudis 9	2004-2015	19	826	495	1321	NCDB	8	TH	I	168
	Ayhan 21	2008-2017	12	81	63	144	Turkey	8	TH ± BSO	I-IV	156
	Zhang 23	1969-2017	2	47	72	119	China	8	TH + BSO	I	576
	Comert 27	1985-2016	3	21	NR	21	Turkey	8	TH + BSO	I-III	NR
	Zhang 25	1998-2016	2	32	NR	32	China	7	TH + BSO	I-IV	NR
	Machida 5	1973-2013	192	2198	NR	2198	SEER	7	TH and others	I-IV	NR
	Seagle 13	1998-2013	87	846	NR	846	NCDB	8	TH	could not be determined	
	Shah 33	1988-2005	7	100	283	383	SEER	8	TH + BSO	I-IV	NR
ADS	Nasioudis 9	2004-2015	21	464	704	1168	NCDB	8	TH	I	168
	Zhang 25	1998-2016	0	6	NR	6	China	7	TH + BSO	I-IV	NR
	Nathenson 28	1982-2014	1	54	101	155	USA	8	TH + BSO	I-IV	182.4
	Machida 5	1973-2013	29	877	NR	877	SEER	7	TH and others	I-IV	NR
	Seagle 6	1998-2011	21	677	NR	677	NCDB	7	TH + BSO	could not be determined	
	Carroll 31	1982-2011	1	22	52	74	USA	8	TH + BSO	I-IV	241.1
	Overall		1,050	15,334	4,501	19,926					

* Data shown only for studies included in survival analysis.

Abbreviations: ADS, adenosarcoma; BSO, bilateral salpingo-oophorectomy; FIGO, The International Federation of Gynecology and Obstetrics; LGESS, low-grade endometrial stromal sarcoma; LND, lymphadenectomy; LNI, lymph node involvement; NCDB, the National Cancer Database; NOS, Newcastle-Ottawa Quality Assessment Scale; NR, not reported; SEER, Surveillance, Epidemiology, and End Results database; TH, total hysterectomy; HGESS/UUS, high-grade endometrial stromal sarcoma/undifferentiated uterine sarcoma; uLMS, uterine leiomyosarcoma.

LNI

Incidence Rate of LNI

Twenty studies [4,5,6,9,10,13,20-23,25,27,28,30-34,36,38] involving 15,316 patients investigated the incidence rate of LNI. A higher incidence rate of LNI was identified in patients with HGESS/UUS (rate 18%; 95% CI 9%–28%; I2 = 89.67%, p < 0.001), while a relatively low LNI was observed in patients with uLMS (rate 6%; 95% CI 4%–8%; I2 = 84.88%, p < 0.001), LGESS (rate 7%; 95% CI 4%-11%; I2 = 90.03%, p < 0.001), or ADS (rate 2%; 95% CI 1%-3%; I2 = 0%, p < 0.001; Figure 2). Because of the high heterogeneity in this meta-analysis, subgroup analysis based on data source, publication year, and sample size was performed. Sensitivity analysis was also performed. Neither analysis (data not shown) identified obvious sources of heterogeneity.

Relationship Between LNI and OS

Five studies[4,5,6,33,34] evaluated the relationship between LNI and OS in 10,203 patients with ADS, uLMS, or LGESS. The pooled data associated LNI with worse OS in these patients (HR 1.85, 95% CI 1.49–2.30; I2 = 75.5%, p < 0.001; Figure 3).

Given the high heterogeneity of the pooled data, subgroup analysis was conducted based on subtype, country, publication year and sample size. Sensitivity analysis was also performed. Neither analysis (data not shown) identified obvious sources of heterogeneity.

Figure 2: Forest plots of the incidence rate of lymph node involvement in patients with different subtypes of uterine sarcoma.

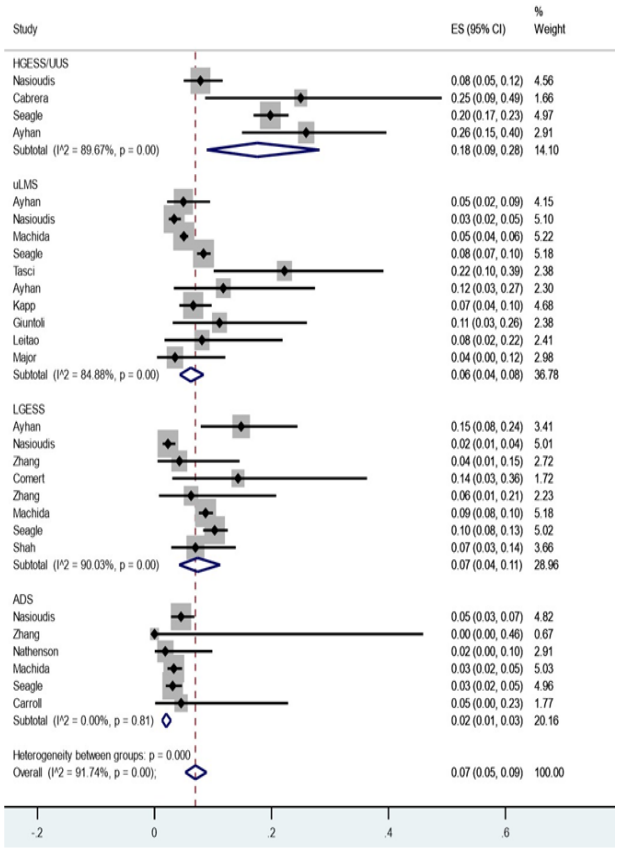
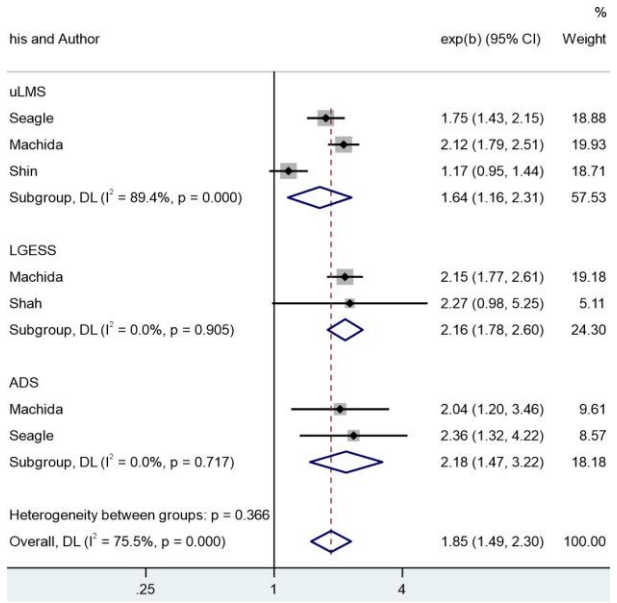


Figure 3: Forest plots of the potential relationship between lymph node involvement and overall survival in patients with different subtypes of uterine sarcoma.

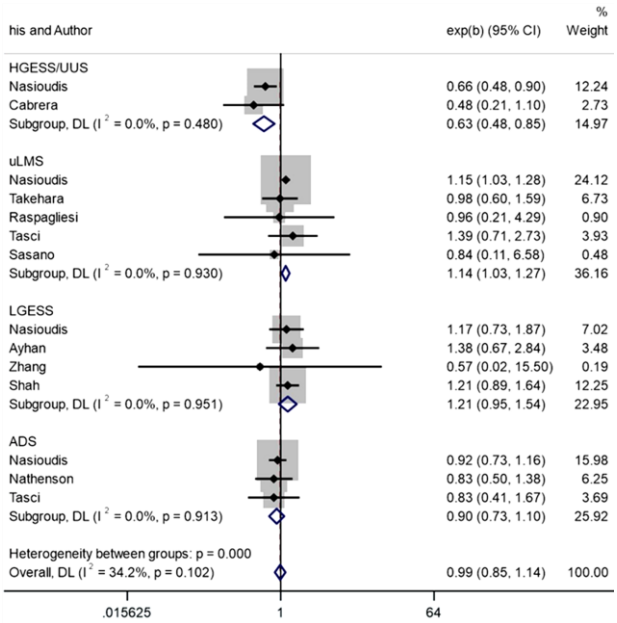


RELATIONSHIP BETWEEN LYMPHADENECTOMY AND SURVIVAL

Lymphadenectomy and OS

Eleven studies[9,20,21,23,24,28-30,31,33,35] including 7,795 patients investigated the relationship between lymphadenectomy and OS. Lymphadenectomy did not improve OS in patients with LGESS (1,967 cases, HR 1.21, 95% CI 0.95–1.54; I^2 = 0%, p = 0.121) or ADS (1,397 cases, HR 0.90, 95% CI 0.73–1.10; I2 = 0%, p = 0.297), but it was associated with worse OS in uLMS (3,993 cases, HR 1.14, 95% CI 1.03–1.27; I^2 = 0%, p = 0.011; Figure 4). Conversely, lymphadenectomy was associated with better OS in HGESS/UUS (438 cases, HR 0.63, 95% CI 0.48–0.85; I^2 = 0%, p = 0.002; Figure 4).

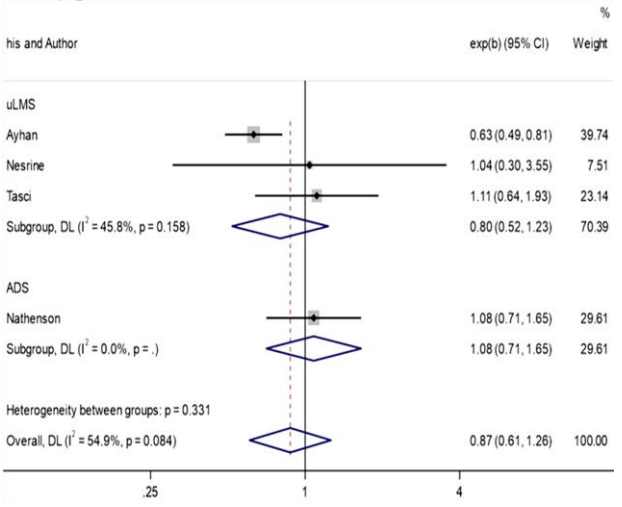
Figure 4: Forest plots of the potential relationship between lymphadenectomy and overall survival in patients with different subtypes of uterine sarcoma.



Lymphadenectomy and DFS

Four studies[10,26,28,30] including 593 patients with uLMS or ADS were pooled in a meta-analysis investigating the relationship between lymphadenectomy and DFS. Lymphadenectomy was not associated with better DFS in patients with uLMS or ADS (593 cases, HR 0.87, 95% CI 0.61–1.26; I^2 = 54.9%, p = 0.473; Figure 5).

Figure 5: Forest plots of the potential relationship between lymphadenectomy and disease-free survival in patients with different subtypes of uterine sarcoma.



PUBLICATION BIAS

Publication bias was assessed in the meta-analysis of the incidence rate of LNI based on 20 studies.[4-6,9,10,13,20-38] The funnel plot showed no obvious asymmetry and Begg's test was not significant (p = 0.128), suggesting no publication bias (Supplementary Figure S1).

DISCUSSION

LNI is associated with worse survival among patients with uterine sarcoma, but whether routine lymphadenectomy can improve survival remains controversial. Our meta-analysis of all available evidence suggests that the incidence rate of LNI can depend on the subtype of uterine sarcoma: patients with HGESS/UUS had the highest LNI rate (18%), whereas patients with uLMS, LGESS, or ADS had a lower LNI rate(≤ 7%). Our analysis suggests that routine lymphadenectomy may improve survival among patients with subtypes HGESS or UUS, but not among patients with subtypes LGESS, ADS or uLMS. Similarly, routine lymphadenectomy does not appear to improve DFS in patients with uLMS or ADS.

Our meta-analysis suggests that lymphadenectomy can improve OS of patients with HGESS or UUS, consistent with previous studies.[9, 13] Our findings are also in line with two previous meta-analyses showing that lymphadenectomy does not improve OS in patients with LGESS or uLMS.[11, 39] However, unlike the previous meta-analyses, we evaluated the association between lymphadenectomy and DFS in patients with ADS or uLMS, and we assessed all associations using HR, which may be more comprehensive than relative risk because it draws on all available data, including from patients who were lost to follow-up.[40] Our meta-analysis also included a larger number of studies and patients.

Although lymphadenectomy allows for accurate tumor staging and prediction of prognosis, it has been linked to the occurrence of several complications, including intraoperative blood loss, increased trauma, infection, deep vein thrombosis, pulmonary embolism, and lymphocele,[7, 41] which can reduce quality of life.[8] These considerations, combined with the present meta-analysis, argue against performing lymphadenectomy routinely in uterine sarcoma patients with uLMS, LGESS, or ADS.

An alternative treatment for such patients may be resection of suspicious lymph nodes based on enlargement detected by visual inspection or imaging.[30, 36] However, such detection may lack sensitivity or fail to predict LNI in patients with uterine neoplasm, as suggested in studies involving magnetic resonance imaging or positron-emission tomography integrated with computed tomography.[42-44] In contrast, sentinel lymph node (SLN) biopsy has been associated with sensitivity of 96%, negative prediction value of 99%,[45, 46] and similar survival as lymphadenectomy in patients with endometrial carcinoma.[47, 48] Thus, we propose performing SLN instead of routine lymphadenectomy on patients with uLMS, LGESS, or ADS.

Our study has several limitations. First, the included publications were all retrospective in design, which increases the risk of selection bias. Second, patients in the studies were at different FIGO stages, which may help explain the heterogeneity observed in several of our meta-analyses. Additionally, the types of operations undergone by the patients varied across the included studies, contributing heterogeneity in the pooled estimates. Third, the pooled results of HGESS/UUS subtype were based on relatively few studies and patients, which could lead to "small study bias".[49] Finally, although LNI was identified to be associated with worse prognosis, we were unable to evaluate the prognosis specifically of patients with LNI who underwent lymphadenectomy, which should be explored in future work.

Despite these limitations, our study appears to be the first meta-analysis to focus on the association between LNI or lymphadenectomy and the prognosis of patients with all five subtypes of uterine sarcoma. Our results may provide a basis for reconsidering lymphadenectomy as a routine treatment for patients with uterine sarcoma; it may need to be taken into account in future revisions of FIGO and NCCN guidelines.[2, 3]

DECLARATIONS

Financial Disclosure

The authors declare no conflict of interest.

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