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Brief Communication

Clinical outcome of lymphadenectomy in malignant ovarian germ cell tumors: a systematic review and meta-analysis

Ling Han[1,2], Yali Chen[1,2], Yana Liu[1,2], Ai Zheng[1,2], Hengxi Chen[1,2]

[1]Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, No. 20, 3rd Section, South Renmin Road, Chengdu 610041, Sichuan, China; [2]Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu 610041, Sichuan, China

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Abstract: Malignant ovarian germ cell tumors (MOGCTs) are predominately diagnosed in young patients and account for most preadolescent malignant ovarian tumors. Currently, due to the high sensitivity of MOGCTs to chemotherapy and the optimal survival rate after chemotherapy, some researchers have recommended opting for non-surgical treatment. However, the effect of lymphadenectomy (LND) on the survival of patients with MOGCT remains controversial. We conducted a systematic review and meta-analysis to compare the clinical outcomes of LND and non-LND in MOGCT surgeries in order to summarize the clinical experience. PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), International Clinical Trials Registry Platform (ICTRP), and Clinical Trials.gov were searched from inception to December 26, 2021. Data on the rates of survival, relapse, and adverse effects were evaluated using Review Manager software. Fourteen studies with 10,759 participants were included in this review. There were 5863 and 4896 patients in the LND- and LND+ groups, respectively. Pooled results showed that although disease-free survival (DFS) was significantly improved in the LND+ group compared to the LND- group (HR: 0.74; 95% CI: 0.56 to 0.97; 2091 participants), LND did not significantly affect overall survival (OS) (HR: 0.82; 95% CI: 0.51 to 1.31; 5298 participants). The operation time was significantly longer in the LND+ group than in the LND- group (P<0.001). Blood loss (P=0.004) and complication rate (P=0.003) were also significantly higher in the LND+ group than in the LND- group. There was no significant difference in mortality rate (P=0.500). LND was associated with an improvement in DFS. However, there was no significant difference in OS in MOGCTs. We recommend that LND should not be a routine surgery for children or young patients with MOGCTs; although it may be beneficial for older people, advanced stage tumors, specific pathological types, and non-chemotherapy patients.

Keywords: Malignant ovarian germ cell tumors, lymphadenectomy, survival, systematic review, meta-analysis

Introduction

Malignant ovarian germ cell tumors (MOGCTs) constitute approximately 5% of all ovarian tumors, with a yearly adjusted incidence rate of 3.7/100.000 [1]. MOGCTs are predominately diagnosed at 15-19 years of age and account for 80% of preadolescent malignant ovarian tumors [1, 2]. The pathological types of MOGCTs include dysgerminoma (DSG), yolk sac tumor (YST), endodermal sinus tumor (EST), immature teratoma (IMT), embryonal carcinoma (EC), non-gestational choriocarcinoma, and mixed GCTs [1]. They are highly malignant, rapidly growing, usually unilateral, and highly chemotherapy-sensitive [3]. A large study from Denmark reported that the 5-year relative survival of MOGCTs increased from 61% in 1978-1987 to 94% in 2008-2011 after the introduction of chemotherapy [4].

Although MOGCTs are sensitive to chemotherapy, surgery is the primary treatment option. Comprehensive staging surgery, including lymphadenectomy (LND), is recommended for early-stage tumors. For young patients who wish to preserve fertility, conservative surgery with preservation of the uterus and contralateral ovary is preferred. Chemotherapy is usually administered except for stage I, grade I IMT,

and stage I DSG after comprehensive staging surgery. Currently, due to the high sensitivity of MOGCT to chemotherapy and the optimal survival rate after chemotherapy, some researchers recommend a lesser degree of surgery [5, 6].

The effect of LND on survival in MOGCT patients remains controversial [5]. There are several arguments in favor of LND in MOGCTs: First, lymph node metastasis is high in MOGCTs [7-9]. Second, the performance of LND can help to determine its International Federation of Gynecology and Obstetrics (FIGO) stage and decide the postoperative adjuvant therapy when lymph node metastasis is present, and the tumor is in FIGO IIIc or above. The omission of LND may lead to a delayed diagnosis of stage III disease, resulting in delayed postoperative chemotherapy. Third, LND was reported to be an independent predictor of survival [10]. Conversely, the need for LND remains a topic of debate. First, several authors have reported that LND had no significant effect on survival [11-13]. Second, LND can increase the risk of bleeding or injury to the organ, chronic lower extremity lymphedema, and lymphocyst development [14]. Third, MOGCTs are highly chemosensitive and are associated with excellent survival rates even in advanced stage disease [15].

There is still no consensus among the different guidelines for performing LND. The European Society of Gynecological Oncology (ESGO), European Society for Medical Oncology (ESMO) and National Health Commission of the People's Republic of China recommend that LND should be performed only if there is evidence of lymph node abnormalities in MOGCTs [1, 16, 17]. The National Comprehensive Cancer Network (NCCN) recommends comprehensive staging surgery with or without fertility-sparing for patients with MOGCT [18]. The FIGO indicates that ovarian malignancies require comprehensive staging surgery with selective resection of at least the affected pelvic and paraaortic lymph nodes, but do not provide specific advice for MOGCTs [19].

To our knowledge, no meta-analysis has compared the impact of LND on the efficacy and safety of MOGCTs. In this study, we compared the clinical outcomes of LND and non-LND in MOGCT surgeries in order to summarize clinical experience and provide a practical clinical reference.

Methods

Protocol registration

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and was registered with the International Prospective Register of Systematic Reviews (CRD 42021284270) [20].

Eligibility criteria

Prospective randomized controlled trials and retrospective cohort studies that examined the impact of LND on the clinical outcomes of MOGCTs were considered for inclusion. Studies published in abstract form were considered for inclusion if data extraction was possible and treated as being at high risk of bias if insufficient information was available. Where data extraction was not possible, we excluded the study from this review. Women with MOGCTs who underwent surgery were included in this study. Those with unknown status of LND were excluded. The LND+ group was defined as LND performed in addition to other necessary surgical procedures, such as ipsilateral adnexectomy or bilateral adnexectomy, and or hysterectomy, omentectomy, abdominal washing for cytology, multiple peritoneal biopsies, and removal of any suspicious peritoneal lesions. The control group was the LND- group, which was defined as the necessary surgical procedure without LND.

Search strategy and study selection

PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.gov were searched from inception to December 26, 2021. The reference lists of the published reviews and retrieved articles were checked for additional trials. Predefined search strings were as follows: (germ cell tumor OR MOGCT OR DSG OR yolk sac OR EC OR IMT OR non-gestational choriocarcinoma) AND (ovary OR ovarian) AND (lymph node dissection OR lymph node excision OR lymph node involvement OR lymphadenectomy OR LND).

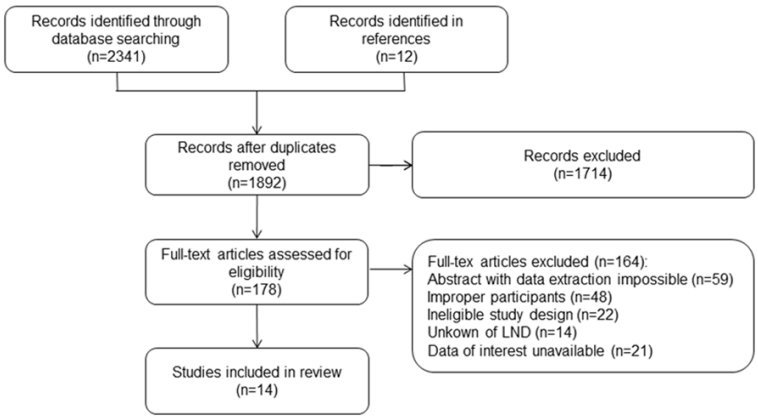

Figure 1. Flow diagram of literature searching and study selection.

Two researchers (LH and HC) independently screened the titles and abstracts to assess the eligibility of the studies. After initial selection, the full texts of all potential articles were independently read by two researchers (LH and HC) for further evaluation. Disagreements between authors were resolved by discussion with the AZ.

Data extraction

Data were extracted by two independent reviewers (YC and YL) in duplicates and recorded in a standardized database. We used a predefined extraction form including methods, study quality, participants, interventions, and outcomes. Any missing data was intended to be acquired by contacting the author via email. Review authors were blinded to the trial authors, institutions, sources of funding, and acknowledgments. A double data entry was conducted. Collected data included general information including authors, year of publication, country, study type, detailed information of included patients (age, FIGO stage, pathological type, volume of blood loss, operation time, complications, number of lymph node dissections, etc.), and outcome indicators.

Risk of bias assessment

Two reviewers (HC and LH) independently assessed the quality of the included studies. We resolved differences by discussion and, if no consensus was reached, by involving a third review author (AZ). All included studies were retrospective studies; therefore, the risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) based on three categories: selected cases, comparability of groups, and assessment of outcomes [21]. Studies that were awarded six or more stars were classified as having high quality.

Statistical analysis

Review Manager software (RevMan) version 5.4 was used for meta-analysis. Hazard ratios (HRs) with 95% confidence intervals (CIs) were used to combine data regarding survival curves. Odds ratios (ORs) were calculated for dichotomous variables with 95% CIs. The heterogeneity between studies was assessed using chi-square and I^2 test. A random-effects models were used for the meta-analysis. Finally, *P* values of <0.05 were considered statistically significant for the meta-analysis. These data could not be combined and are described in the Results section.

A funnel plot was used to assess the risk of publication bias for outcomes that included at least 10 studies. Subgroup analyses were used to explore the heterogeneity between the results. Subgroup analyses were based on the participant's age, FIGO staging, pathology, and subsequent chemotherapy.

Results

Study selection and characteristics

The study selection process is summarized in **Figure 1**. A total of 1892 articles were retrieved after the duplicates were removed. After screening the titles and abstracts, 178 full texts were retrieved for later assessment. Then, 164 articles were excluded from the abstract with data extraction impossible, improper participants, ineligible study design, unknown LND, and unavailable data of interest. Finally, 14 studies with 10,759 participants were included in this review.

All the included studies were retrospective research studies. Seven studies were from China, four from USA, one from Germany, one from Turkey, and one from France. There were

5863 patients in LND- group and 4896 patients in LND+ group. The general characteristics of the 14 studies were summarized in **Table 1**.

Survival

Based on data retrieved from survival curves, a meta-analysis of five included studies showed that LND did not significantly affect OS (HR: 0.82; 95% CI: 0.51 to 1.31; 5298 participants; P=0.40; I^2=70%; **Figure 2A**) [9, 11, 13, 14, 22]. However, a meta-analysis of four included studies showed that DFS was significantly improved in the LND+ group compared with the LND- group (HR: 0.74; 95% CI: 0.56 to 0.97; 2091 participants; P=0.03; I^2=0%; **Figure 2B**) [10, 12-14].

The meta-analysis of ten included studies showed no difference in the 5-year OS rate of MOGCTs between the LND+ group and LND- group (OR: 1.15; 95% CI: 0.75 to 1.78; 5854 participants; P=0.52; I^2=43%; **Figure 2C**) [9, 11-14, 23-27]. The publication bias of these studies was assessed using a funnel plot (**Figure 3**). As for 5-year DFS rate, there was also no significant difference between groups (OR: 1.29; 95% CI: 0.69 to 2.44; four studies; 2083 participants; I^2=38%; P=0.43; **Figure 2D**) [11, 12, 14, 24]. Two studies including 1959 participants investigated the relationship between LND and the 5-year disease-specific survival (DSS) rate [28, 29]. The meta-analysis showed that LND did not significantly affect DSS (OR: 1.13; 95% CI: 0.45 to 2.83; P=0.80; I^2=0%; **Figure 2E**).

Subgroup analysis based on tumor stage: For stage I MOGCTs, the meta-analysis of two included studies showed no difference in 5-year OS rate between the LND+ group and LND- group (OR: 0.70; 95% CI: 0.47 to 1.04; 3570 participants; P=0.08; I^2=0%; **Figure 2F**) [9, 11]. The other three included studies found similar results. Chen found that LND had no significant influence on survival in the early stages of MOGCTs (stage I, OS: P=0.411; cancer-specific survival (CSS): P=0.876; stage II, OS: P=0.120; CSS: P=0.061) [13]. Nasioudis found no significant difference in CSS between the LND+ and LND- groups for stage I (P=0.56); 5-year CSS rates were 99.2% and 99.35, respectively [28]. Qin found that LND did not significantly affect 5- and 10-year OS and DFS in stage I and II MOGCTs (all P>0.05) [12].

For stage III and stage IV, one study found that the LND+ group had better survival (stage III, OS: P=0.027; CSS: P=0.006; stage IV, OS: P=0.034; CSS: P=0.037) [13].

Subgroup analysis based on histological type: For pure IMTs, three included studies found no difference between the LND+ and LND- groups (P>0.05) [9, 12, 22]. The results for the YST and DSG were inconsistent. For MOGCTs containing yolk sac components, a meta-analysis of six included studies found statistical differences between the LND+ group and LND- group regarding 5-year OS rate (OR: 2.08; 95% CI: 1.05 to 4.13; 363 participants; P=0.04; I^2=0%; **Figure 2F**) [12, 22, 24-27]. Only one study recruited pure YST, and the result showed no significant difference (OR: 0.47; 95% CI: 0.09 to 2.58; 67 participants; P=0.39) [26]. Another study found that the more resected lymph nodes, the better the survival in pure YST (P<0.05) [22]. Two studies found no difference in survival between the LND+ and LND- groups for DSG (P>0.05) [9, 12]. Another study found that the survival of patients received 1-20 resected lymph nodes was better than that of patients in the LND- group (OS: P=0.012; CSS: P=0.013) [22].

Subgroup analysis based on age: One study found that LND did not improve the OS rate (P≥0.05) in children less than 14 years of age. For adult patients (20-39 years), LND improved the OS rate (P<0.05). Adolescent patients (15-19 years) with 1-20 resected lymph nodes tended to have a superior DSS (P=0.038), while patients aged 40 years and above might benefit from 21 or more resected lymph nodes for both OS and DSS rates (P<0.05) [22].

Subgroup analysis based on chemotherapy: One study found no difference in OS between the LND+ and LND- groups for patients who received chemotherapy (P=0.32); 5-year OS rates were 96.7% and 98%, respectively. For patients who did not receive chemotherapy, there was also no difference in OS between the LND+ and LND- groups (P=0.67); 5-year OS rates were 95.9% and 97.1%, respectively [9]. However, it is important to note that all the recruited patients were at an apparent early stage.

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

Study	Country	Study type	Age (median age)	Histological type	Stage	Chemoradiotherapy	Number of LND- group	Number of LND+ group	Quality assessment
Xu 2021	China	R	22	DSG	I-IV	85%	64	43	7
Wang 2020	China	R	22	DSG, EC, YST, IMT, Mixed, other	I-IV	NA	1303	1121	8
Nasioudis 2020	USA	R	23	DSG, YST, IMT, Mixed, other	I	48.9	1201	1287	8
Qin 2019	China	R	24	DSG, YST, IMT	I-III	87.5	130	126	8
Boyraz 2019	Germany	R	23.9	DSG, YST, IMT, EC, Mixed	I-IV	97	45	54	6
Nasioudis 2019	USA	R	21	DSG, YST, IMT, Mixed, other	I-IV	NA	802	662	6
Chen 2018	China	R	NA	DSG, IMT, Mixed	I-IV	NA	1178	818	8
Wang 2016	China	R	20.5	YST	I-IV	100	43	22	7
Liu 2013	China	R	21.0	DSG, YST, IMT, Mixed	I-IV	100	46	46	8
Mahdi 2011	USA	R	NA	DSG, IMT, Mixed	I	NA	590	493	8
Rouge 2011	France	R	22	YST, Mixed	I-IV	99	73	11	6
Chan 2007	USA	R	53	Germ cell tumor (not classified)	I	NA	313	182	6
Ayhan 2005	Turkey	R	18	YST, Mixed	I-IV	100	15	14	6
Nawa 2001	Japan	R	18	YST, Mixed	I-IV	100	20	3	6

DSG: dysgerminoma, YST: yolk sac tumor, IMT: immature teratoma, EC: embryonal carcinoma, NA: not available.

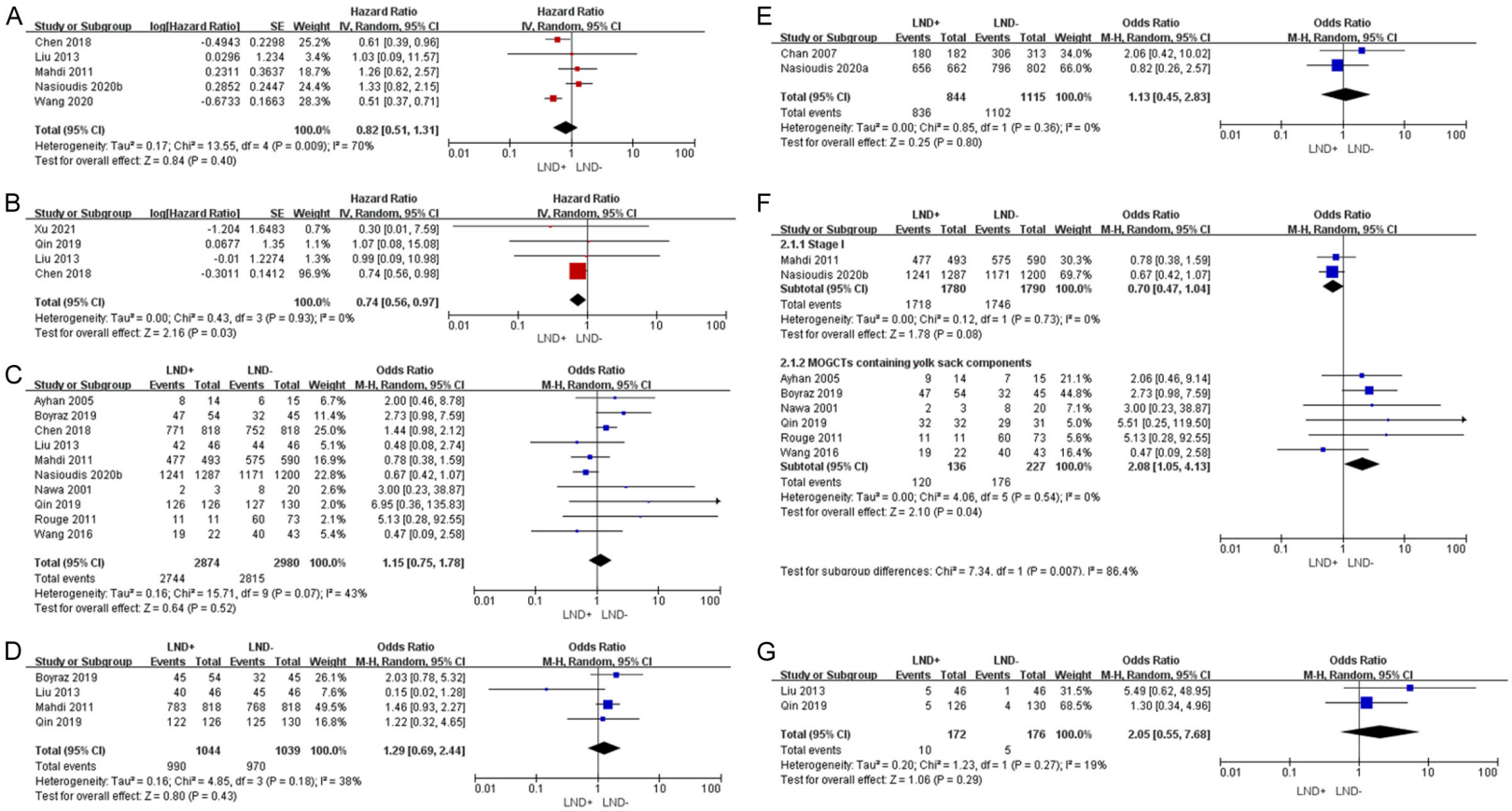

Figure 2. Forest plots for overall survival (OS) (A), disease-free survival (DFS) (B), 5-year OS (C), 5-year DFS (D), 5-yeardisease-specific survival (DSS) (E), subgroup analyses based on stage and pathology (F), and relapse (G).

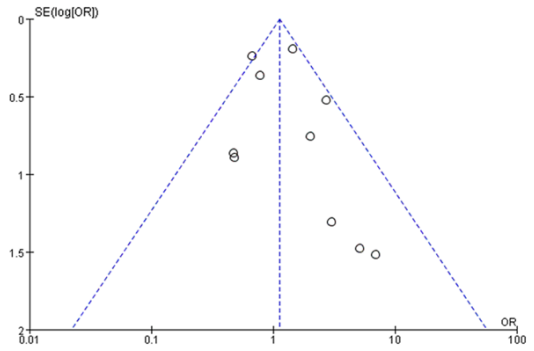

Figure 3. A funnel plot of publication bias of the included studies.

Relapse

Meta-analysis of the two included studies found no significant difference regarding relapse rate between LND+ groups and in LND- group (OR: 2.05; 95% CI: 0.55 to 7.68; 348 participants; P=0.29; I^2=19%; **Figure 2G**) [12, 14].

Adverse effects

One study reported adverse effects [14]. The operation time was significantly longer in the LND+ group than in the LND- group (P<0.001). Blood loss (P=0.004) and complication rate (P=0.003) were also significantly higher in the LND+ group than in the LND- group. There was no significant difference in mortality rate (P= 0.500).

Discussion

The surgical management of MOGCTs has been revolutionized over the past few decades, from comprehensive staging surgery to fertility-sparing surgery with preservation of the uterus and the contralateral ovary, which is currently the standard procedure for young eligible patients. Because MOGCTs are sensitive to chemotherapy, narrowing the scope of surgery to reduce surgery-related trauma without compromising the prognosis is often preferred.

The incidence of lymph node metastasis in MOGCTs differs between studies, ranging from 0% to 20.9% [10, 12, 22-24]. Xu et al. reported nine cases of lymph node metastasis in 43 patients with MOGCTs who underwent LND (20.9%) [10]. Boyraz et al. found 10 metastases in 54 patients with MOGCTs who underwent LND (18.5%) [24]. In a study by Wang et al., two out of 22 patients were found to have lymph node metastasis (9.1%) [22]. Qin et al. reported only one lymph node metastasis in 126 patients with MOGCTs with LND performed (0.8%) [12]. Ayhan et al. found no lymph node metastasis in 14 patients with MOGCTs who received LND [23]. The incidence of lymph node metastasis also differed according to stage and histology. Mahdi et al., Kumar et al., and Nasioudis et al. reported that the incidence of lymph node metastasis ranges from 9.6% to 10.5% in stage I of MOGCTs [11, 28, 30]. In a study by Kumar et al., the incidence of lymph node metastasis was 23.5%, 37.1%, and 42.9% in stage II-IV clinical cases, respectively [30]. Several studies have reported that DSG has higher rates of lymph node metastasis when compared with other histological types of MOGCTs [8, 9, 11, 28, 30]. The incidence of lymph node metastasis was 11.3% to 28.3% for DSG [9, 26, 28], 7.6% to 9.1% for YST [9, 11, 28, 30], and 1.4% to 7.8% for IMT [9, 11, 28, 30]. In addition, the lymph node is the second most common site of tumor recurrence after pelvic or abdominal cavity [12].

Considering the rate of lymph node metastasis and recurrence in MOGCTs, it is recommended by some researchers that LND should be performed to remove metastatic lymph nodes, identify occult LND metastasis, and guide postoperative treatment [11, 30]. The rate of LND appears to be stable, as reported in approximately one-third to one-half of the literature [11, 13, 15, 28]. However, other studies suggest that incomplete surgical staging in MOGCTs, including the absence of LND, increases recurrence rates but has no effect on OS [31, 32]. Regardless of the benefit, LND is associated with longer operation time, more blood loss, and more complications. Balancing the surgical benefit and risk, it is worth discussing when and for which population to perform LND.

Pooled results of this review showed that LND was associated with an improvement in DFS, but there was no significant difference in OS and DSS in MOGCTs. Although lymph nodes play an important role in tumor metastasis and the absence of LND may increase tumor recurrence [32], due to the high chemotherapy sensitivity of MOGCT to platinum drugs, the sal-

vage rates of tumor recurrence through chemotherapy are more than 95%, thus OS is not affected [7].

The LND values vary in different tumor stages. The pooled results of this study showed no difference in the 5-year OS rate between the LND+ group and LND- group in stage IMOGCTs. Several other included studies did not provide data in a form that we could meta-analyze, but the results were consistent with LND not providing a benefit in early stage (stage I and II) MOGCTs. One included study discussed LND in advanced-stage tumors and found that LND was correlated with better prognosis in stage III and IV MOGCTs, which is due to the difference in lymph node metastasis rates at different stages. Kumar et al. reported that MOGCTs in advanced stages III and IV had a higher rate of lymph node metastasis (38.1%) than in early stage I and II patients (11.8%) [30]. Thus, LND should be performed according to the tumor stage [13, 22]. Because patients with early stage tumors have a good prognosis without LND, LND could be ideal, and there is no evidence of lymph node metastasis on preoperative CT and intraoperative examination [9]. For the same reason, when a patient receives only appendectomy on the affected side and the staging surgeries are not completed due to various reasons, including emergency surgeries, the re-operation of comprehensive staging including LND could be avoided should no abnormal imaging and tumor makers exist [33].

YST, DSG, and IMT were found to be the most common subtypes in MOGCTs [6, 22, 34-36]. Our results found no significant difference in the 5-year OS rate in pure IMTs between the LND+ and LND- groups. There was a statistically significant difference in MOGCTs containing yolk sac components; however, most of these patients had mixed pathologies, making the results difficult to interpret. The prognostic results of LND for pure YST and DSG were inconsistent in this review. One study found that the survival rate of the DSG and YST was correlated with the number of resected lymph nodes, and LND was found to be essential in these two subtypes [22]. Several studies reported that the incidence of lymph node metastasis was the highest in DSG [9, 11, 30], and lymph node recurrence accounted for 26.4% of patients with recurrent DSG [8]. For these reasons, lymph node condition should be more carefully evaluated before and during the operation in DSG and YST when the decision not to perform LND is made.

Age appears to be an independent prognostic factor for MOGCTs. Young patients have a better prognosis than elderly patients, regardless of treatment [13, 37]. The European MITO-9 study also reported that age >45 years was a predictor of recurrence [6]. The Children's Oncology Group (COG) reported an excellent prognosis in pediatric MOGCTs when treated with conservative surgery and postoperative chemotherapy, which was also supported by the ESGO guideline of [1, 15]. As for the role of LND in MOGCTs stratified by age, one study included in this review found that LND did not improve the OS rate for children <14 years old but did for adolescents and adults [22]. The results of this study also suggested that the more lymph nodes were removed, the better the survival rate for patients aged 40 years and older [22]. However, this conclusion needs to be treated with caution due to the limited number of correlational studies.

The NCCN recommends chemotherapy after comprehensive staging surgery, except for stage I DSG or stage I, grade I IMT [18]. The ESMO guidelines recommend that patients with stage IA or properly staged patients with IB-IC DSG be exempt from chemotherapy and only receive active surveillance; the same strategies apply to properly staged IAG1-G3 IMT and IA-I B YST with negative postoperative tumor markers. Other patients should undergo chemotherapy after surgery [1]. Therefore, it is worth exploring whether patients with early MOGCT receiving incomplete staged surgeries can also be exempted from postoperative chemotherapy. One included study reported no difference in OS between the LND+ and LND- groups for patients with apparent early stage who received postoperative chemotherapy or no chemotherapy. This suggests that in apparently clinical stage patients, even without a comprehensive staging surgery (no LND), no chemotherapy can be comparable to chemotherapy [9]. NCCN suggested that for apparently clinical stage I patients with incomprehensive surgical staging without abnormal imaging or tumor makers, surveillance with monitoring is recommended [18].

This study had some limitations. All included studies were retrospective and had an increased risk of selection bias. The included studies differed in some important aspects of design, such as patient age, tumor stage, histological type, surgical method, and adjuvant chemotherapy, which could lead to biases. Despite these limitations, this study is the first meta-analysis to focus on LND with the prognosis of MOGCTs. This study will be helpful in understanding the prognostic benefits of performing LND in MOGCTs.

In conclusion, according to the included studies, our study revealed that LND was associated with an improvement in DFS; however, there was no significant difference in the OS of patients with MOGCTs. We recommend that LND should not be a routine surgery for children or young patients with MOGCTs. On the other hand, it may be beneficial for older people, advanced stage tumors, specific pathological types, and patients who are not eligible for chemotherapy.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hengxi Chen, Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, China. Tel: +86-13880494399; E-mail: wowochx@126.com

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