Incidence of lymph node metastasis in early-stage low-grade serous ovarian cancer: a systematic review

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HIGHLIGHTS

⇒ The rate of positive lymph nodes in patients with clinically presumed early-stage low-grade serous ovarian cancer was 12.6%.
⇒ The upstaging rate due to lymph node metastasis alone was 10.5%.
⇒ None of the studies included report specific complications of the lymph node dissection.

ABSTRACT

Objective The objective of this systematic review was to assess the incidence of lymph node metastasis in patients with clinically presumed early-stage low-grade serous ovarian cancer that underwent primary surgical treatment.

Methods This study was registered in PROSPERO (CRD42022308923). A systematic literature review was conducted following the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) checklist. PubMed/MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Ovid, and Scopus databases were searched since inception and up to March 2022. The inclusion criteria were: pathological confirmation of low-grade serous ovarian cancer (clinically presumed FIGO 2014 stages I-IIA at time of surgery) that underwent primary surgical treatment, including pelvic and/or para-aortic lymph node dissection.

Results The search identified 3763 articles; 59 were considered potentially eligible after removing duplicates, and eight studies finally met the selection criteria. In total, 35 of 277 (12.6%) patients had lymph node metastasis, and only four studies reported upstaging due to lymph node metastasis in 16 of 153 (10.5%) patients. None of the eight studies included reported the rate of complications or complications specifically for the subgroup of patients with early-stage low-grade tumors.

Conclusion In patients with early-stage low-grade serous ovarian cancer, lymph node assessment should be discussed when counseling for primary surgical staging.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Low-grade epithelial ovarian tumors have a smaller risk of lymph node metastasis compared with high-grade epithelial tumors. However, the risk differs among histological subtypes (endometrioid, mucinous, or serous) and could be higher for low-grade serous tumors compared with the other low-grade epithelial tumors.

WHAT THIS STUDY ADDS

⇒ The risk of lymph node metastasis of low-grade serous tumors is higher than that previously reported for other low-grade epithelial tumors and the upstaging rate due to lymph node metastasis alone is higher than 10%.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The reported rate of lymph node involvement and the impact of its identification in adjuvant management decisions may justify the performance of lymph node assessment; however, the effect of this finding on oncological outcomes has not been demonstrated and given the rarity of this tumor is highly unlikely to be evaluated in prospective trials.

INTRODUCTION

Ovarian cancer is the eighth most common cancer among women worldwide, with 6.6 cases per 1 00 000 women and 313 959 new cases reported in GLOBOCAN 2020. It has a disproportionately high mortality rate of 4.2 cases per 100.000 women,[1] and only about a third of the patients present with early-stage disease.[2] Primary surgical treatment is the preferred therapy for this population.

Low-grade serous ovarian cancer represents about 10% of epithelial ovarian cancer cases.[3] Although there are differences with high-grade serous ovarian cancer in molecular biology, clinic characteristics, and prognosis, these patients are treated similarly. Low-grade serous ovarian cancer is considered relatively insensitive to systemic chemotherapy; however, it remains a standard treatment in advanced disease after maximum surgical effort.[4 5]

The indication for lymph node dissection in ovarian cancer patients has been debated during the last several years for high-grade epithelial ovarian cancer. Recently a prospective trial[6] demonstrated no benefit

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of systematic lymphadenectomy in advanced disease with macroscopically complete resection and clinically apparent normal lymph nodes. On the other hand, for clinical early stages (International Federation of Gynecology and Obstetrics (FIGO) 2014 stage I-IIA) comprehensive surgical staging, including systematic bilateral pelvic and para-aortic lymphadenectomy up to the renal veins, still could have a crucial role due to the occult lymph node metastasis in apparent early-stage disease of nearly 15%[7] and the subsequent change in the adjuvant treatment.[5 8 9]

The incidence of lymph node metastasis may change according to histologic subtype and grading. A previous report showed that the incidence is only 2.9% in low-grade early-stage epithelial ovarian cancer.[10] As the incidence for low-grade serous ovarian cancer could be higher than for low-grade endometrioid or mucinous histological types, the objective of this systematic review was to assess the incidence of lymph node metastasis in patients with clinically apparent early-stage low-grade serous ovarian cancer who underwent primary surgical treatment.

METHODS

The Meta-analyses Of Observational Studies in Epidemiology (MOOSE) checklist was used to conduct this systematic review and the protocol was registered in PROSPERO (CRD42022308923). MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Ovid, and Scopus databases were searched since inception and up to March 2022. The search strategy is reported in the Online supplemental file 1. We also searched the reference lists of eligible studies and used forward citation tracking with Google Scholar to identify further eligible manuscripts. Similar methodology has been reported by the authors previously.[11]

All types of studies published in the English language literature were included, except for case reports, abstracts, commentaries, and unpublished studies. The inclusion criteria were pathologically confirmed low-grade serous ovarian cancer (clinically presumed FIGO 2014 stages I-IIA at time of surgery) that underwent primary surgical treatment, including pelvic and/or para-aortic lymph node dissection. Any surgical route (laparotomy or minimally invasive surgery) was allowed. Only grade 1 tumors were considered if the tumor grade was specified, given significant variations in their classification into low- and high-grade for grade 2 tumors. For studies that did not specified tumor grade, all low-grade tumors were included.[12]Criteria for exclusion were patients under 18 years of age, neoadjuvant chemotherapy administration, and evidence of lymph node metastasis, either on pre-operative images, or at the time of surgery.

When two or more articles were published by the same authors or using the same data source, only the most recent article was included. The measured outcomes were the incidence of pelvic and/or para-aortic lymph node metastasis as defined by the authors, the rate of upstaging exclusively due to lymph node involvement, and the rate of complications associated with lymph node dissection as defined by the authors. Studies not reporting the number of resected nodes could be included in the review, and for studies reporting the number of lymph nodes resected at least 10 nodes per patient had to be resected to be included in the review.

Study Selection

Two authors (JR, DV-C) independently assessed all titles and abstracts of records retrieved from the search strategy for inclusion. The final selection of studies for inclusion was undertaken independently by three authors (RP, JR, DV-C) and any disagreement was resolved through discussion. We designed a form to extract data, which was pilot tested. Two authors (JR, DV-C) extracted the data independently using the form for eligible studies. Any disagreement about extracted data was resolved through discussion until a consensus was reached.

The information was presented as medians or means (according to its normal distribution) and percentages with absolute counts, if it was a quantitative or qualitative variable, respectively. The descriptive statistics were performed in SPSS 2.0. According to local regulations, no institutional review board agreement was required for this type of study. Ethical approval was not required as only data from previously published studies were retrieved and analyzed. No new data are presented.

RESULTS

The search identified 3763 articles; after duplicates were removed, 1874 articles were evaluated, and the title and abstract screening of these references identified 59 studies as potentially eligible for this review. The full-text screening excluded 51 studies, and eight studies finally met the selection criteria. Four studies were excluded because they did not provide information according to histological types, one was a literature review and did not have new patients reported, four did not include low-grade tumors, and 42 did not provide separate information for early-stage low-grade serous tumors (Figure 1 and Online supplemental file 2).

The total number of patients included in the eight studies was 2964, but only 277 patients had early-stage low-grade serous tumors and were considered for the analysis. Seven studies were retrospective series[13–19] and one study was a population-based study.[20] The accrual time was from 1975 up to 2018. Three studies included only FIGO stage I tumors[14 19 20] and five included FIGO stage I and II tumors.[13 15 16] We selected only patients with tumors up to FIGO stage IIA tumors for the review. Tumor grade was reported and classified as low grade in five studies[13–15 17 18] and reported as grade 1 serous tumors in three studies.[16 19 20]

The details about the performed surgeries were not described in three studies,[15 17 20] it was described as staging surgery or primary surgery in three studies,[16 18 19] as a surgery that included hysterectomy, bilateral salpingo-oophorectomy, peritoneal random peritoneal biopsies, and omentectomy in one study,[13] and as bilateral salpingo-oophorectomy (97.5%), hysterectomy (82.8%), omentectomy (98.8%), and appendectomy (68.1%) in one study.[14] Two studies[13 14] included patients with primary surgery and reclassification surgery; four included only primary surgery treatment,[15 16 18 19] and it was not reported in two of the studies.[17 20] Details about included studies are provided in Table 1. Given the nature of the studies and the intervention, with only single-arm studies, we did not evaluate the risk of bias for included studies as this would not provide reliable information.

Six studies reported pelvic and para-aortic lymph node dissection,[13–16 18 19] one[20] did not report specifically if pelvic and para-aortic dissection was performed, and one[17] reported some patients with

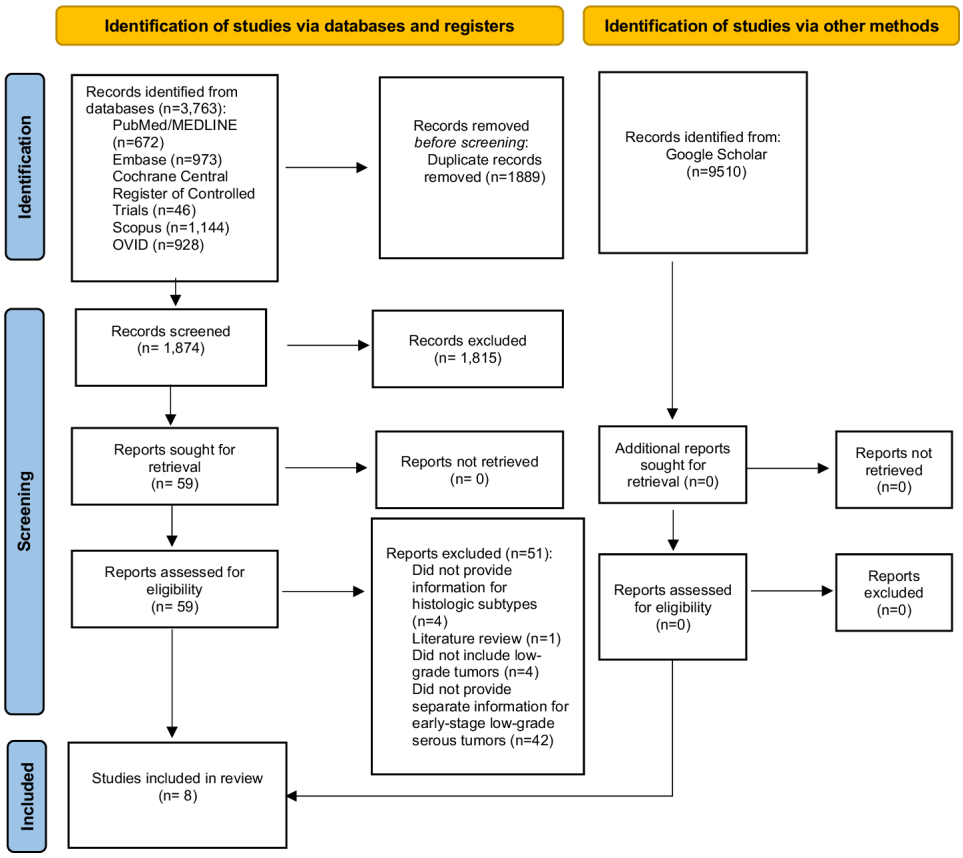

Figure 1 PRISMA flow diagram for study selection.

pelvic and others with pelvic and para-aortic dissection. Two studies included the number of resected lymph nodes; one reported for inclusion a minimum of 10 pelvic and 10 para-aortic nodes,[14] and one at least 20 nodes in total.[20] Five studies reported the median number of resected nodes, although three studies[14 16 19] reported data only for the complete cohort of included patients and not independent information on early stages. The median number of resected nodes were 45,[14 19] 69,[16] 27,[20] and 41.[18]

In total, 35 (12.6%) of 277 patients had lymph node metastasis. All studies reported at least one case of lymph node involvement, and the location was reported only in three studies,[13 17 19] one patient with pelvic and para-aortic involvement in one study, 14 of 14 patients with pelvic and 4 of 14 patients with para-aortic metastasis in the second study; and in the third study four only pelvic and eight both pelvic and para-aortic region. The rate of lymph node metastasis for each study ranged from 2.7%[13] to 25%.[18] Three studies[14 17 19] reported the number of patients upstaged exclusively because of lymph node metastasis. Of 153 patients, 25 (16.3%) had lymph node metastasis and 16 (10.5%) were upstaged only due to lymph node involvement. Unfortunately, none of the eight included studies reported the rate of complications or complications specifically for the subgroup of interest of patients with early-stage low-grade serous tumors. Details about lymph node procedures are provided in Table 2.

According to our protocol, we did two subgroup analyses. For the first analysis, excluding the population-based study, in seven studies[13–19] 210 patients were reported and 29 patients had confirmed lymph node metastasis (13.8%). When only patients with stage I were analyzed, 183 patients from three studies[14 19 20] were included and 24 (13.1%) had lymph node metastasis. The results of the subgroup analyses showed no relevant effect on the general results.

DISCUSSION

Summary of Main Results

In our review, the overall rate of lymph node metastasis in patients with early-stage low-grade serous ovarian cancer was 12.6%. Patients were upstaged exclusively because of lymph node metastasis in 10.5% of cases. The rate of involvement in this group of patients may justify lymphadenectomy in primary surgical management.

Results in the Context of Published Literature

For all low-grade early-stage epithelial tumors, the incidence of lymph node metastasis has been reported previously in less than 3% of cases,[10 20] unlike high-grade tumors where a lymph node metastasis rate of 10% or higher[7 13 20] has been reported. In high-grade tumors, a plausible impact on oncologic prognosis[21] is assumed by the lymph node dissection and the recommendation of systematic lymphadenectomy in clinical early stages as part of the primary surgical treatment in international guidelines is recommended.[5 9]

The ovarian epithelial tumors are heterogeneous, in mucinous and endometrioid tumors molecular and clinical behavior can differ from that of serous tumors.[22 23] These differences are reflected among others on the risk of lymph node metastasis; for expansile (low-grade) mucinous tumors the rate of involvement could be nearly zero[24 25] and it is less than 2% for low-grade endometrioid tumors.[14 20] However, this risk is up to 10% for low-grade serous tumors.

Table 1 Major characteristics of studies included in the systematic review

Author/year	Accrual time	Study type	N total	N early (I-IIA) low-grade serous	Age (years)	FIGO stage clinically presumed	Histologic subtype grade	Procedure/fertility-preserving	Procedure/primary vs re-staging
Bogani 2017[13]	1975–2016	Retrospective	290	37	49.8 (18.1–76) median	I-II (85.9%, 14.1%)	Low-grade	Hysterectomy, bilateral salpingo-oophorectomy, peritoneal random peritoneal biopsies; omentectomy	Both
Minig 2017[14]	2000–2016	Retrospective	163	56	50 median (18–81) whole cohort	I	Low-grade	Bilateral salpingo-oophorectomy (97.5%), hysterectomy (82.8%), omentectomy (98.8%), and appendectomy (68.1%)	Both
Heitz 2018[16]	2000–2016	Retrospective	762	5	57 median (18–82) whole cohort	pT1a-pT2aM0 (I-II)	Grade 1	Staging surgery	Primary
Nasioudis 2018[20]	1988–2014	Population-based SEER	1242	67	51 median	IA, IB, IC	Grade 1	NR	NR
Wafa 2019[18]	2000–2017	Retrospective	37	4	48 (26–76) whole cohort	pT1a-pT2aM0 (I-II)	Low-grade	Primary surgery	Primary
Simon 2020[15]	2000–2017	Retrospective	126	11	53 median (19–82)	I-II	Low-grade	NR	Primary
Chen 2021[17]	2005–2015	Retrospective	196	37	NR as median or average	I-IIA	Low-grade	NR	NR
Durmuş 2022[19]	1999–2018	Retrospective	148	60	49.1 mean (21–84)	I	Grade 1/low-grade	Both (complete surgery consisted of total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and peritoneal biopsies)	Primary
Total			2964	277					

FIGO, International Federation of Gynecology and Obstetrics; NR, not reported; SEER, Surveillance, Epidemiology, and End Results Program.

Table 2 Lymph node procedures and pathology report.

Author/year	Lymph node procedure	Lymph node count: total	N N(+)	Location N(+)	N N(+) / total as percentage (%)	N upstaged due to N(+)
Bogani 2017[13]	Pelvic and para-aortic dissection	NR	1	Pelvic and para-aortic	2.72	NR
Minig 2017[14]	Pelvic and para-aortic dissection (minimum number of 10 pelvic nodes and 10 para-aortic nodes)	45 median (whole cohort)	6	NR	10.71	3
Heitz 2018[16]	Pelvic and para-aortic dissection	69 median (whole cohort)	1	NR	20	NR
Nasioudis 2018[20]	NR (at least 20 nodes)	27 median	6	NR	8.95	NR
Wafa 2019[18]	Pelvic and para-aortic dissection	41 median	1	NS	25	NR
Simon 2020[15]	Pelvic and para-aortic dissection	NR	1	NR	9.09	NR
Chen 2021[17]	Pelvic (more than 10 nodes) in 25 patients and systematic lymph node dissection (more than 10 pelvic and 5 para-aortic nodes) in 12 patients	20 (pelvic) in 25 patients and 25 plus 8 (pelvic and para-aortic in 12 patients)	7	14/14 pelvic, 4/14 para-aortic in the whole cohort.	18.91	4
Durmuş 2022[19]	Bilateral pelvic lymphadenectomy and para-aortic lymphadenectomy	45 median (whole cohort)	12	4 only pelvic, 8 both pelvic and para-aortic	20	9
Total			35		12.64	

NR, not reported; NS, not specified.

The relevance of lymph node metastasis identification is associated with the requirement for adjuvant treatment and the oncological prognosis of patients. Guidelines[5 9] recommend abstaining from adjuvant chemotherapy in patients with early stages (FIGO 2014 IA-IB) of low-grade serous ovarian cancer but recommend using combined systemic chemotherapy in cases of lymph node metastasis or if other advanced-stage features are present (FIGO 2014 IC-IV stage). Lymph node metastasis in advanced low-grade epithelial ovarian tumors is frequent with involvement in more than 70% of patients.[15 18] However, it has been suggested that the lymph node dissection of microscopic disease has no impact on overall survival or progression-free survival in this population.[15] The reporting of only early stages is limited in the literature; most studies report all low-grade early-stage tumors together or with all stages, and the risk of lymph node metastasis could have been underestimated previously.

Among the most relevant outcomes remains the rate of upstaging exclusively due to lymph node metastasis as a justification for the procedure; in our review it was 10.5%, whereas a previous systematic review that assessed the upstaging rate of the procedures that are performed in the primary surgical treatment of patients with epithelial ovarian cancer found that the upstaging rate for hysterectomy, omentectomy, peritoneal biopsies, appendectomy, and cytology did not exceed 10%.[26]

Unfortunately, in our review the studies included did not specifically report adverse events associated with lymphadenectomy; however, it is well known even from prospective randomized trials that lymph node dissection raises the risk of complications related to the surgery as evidenced by higher median blood loss, requirement for transfusions, intensive care support, higher infections, and reintervention rates.[6 27]

Strengths and Weaknesses

The main strength of our review is the rigorous process for data collection, and we have a pre-registered protocol with specified selection criteria and a rigorous process for data analysis. Our review is limited for several reasons. The clinical heterogeneity of the studies must be highlighted as we included case series studies and a population database study. The retrospective nature of all studies included in the review, with potential selection and publication bias, and the relatively small number of patients included in the results given the limited report of this specifical population, are limiting factors, particularly since we did not have information from most studies for adverse events, for upstaging exclusively for lymph node metastasis, and lymph node metastasis location. There was no central pathology review, surgical quality report beyond lymph node count for all studies, or complete information about preoperative imaging studies. As we limited the search to published data in the English language, we could have missed some relevant references published in other languages, and as the studies were conducted over a long period, there could be performance bias.

Implications for Practice and Future Research

This systematic review confirms that the risk of lymph node metastasis for early-stage low-grade serous ovarian cancer is different than for other low-grade epithelial tumors. As the identification of lymph node

involvement will change the recommendation of adjuvant chemotherapy, lymphadenectomy should be recommended. We encourage collection of prospective information in this population with subsequent data analysis according to the tumor type for future publications.

CONCLUSION

Given the rate of lymph node metastasis in clinically presumed early-stage low-grade serous ovarian cancer and the impact of its identification on adjuvant treatment decisions, lymph node assessment should be considered as part of primary surgical staging.

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