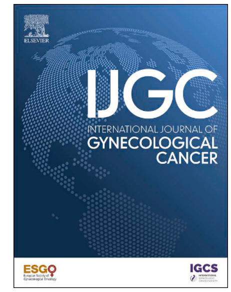
ORIGINAL RESEARCH

Incidence and impact of low-volume lymph node metastasis in apparent early-stage ovarian cancer: MICR-OVARY study



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Received 22 December 2025, Accepted 2 March 2026; Available online xxx

ABSTRACT

Objective: Sentinel lymph node (SLN) biopsy is an emerging technique in apparent early-stage ovarian cancer, with the potential to detect low-volume lymph node metastases. However, the prognostic value of low-volume metastases is still unknown. This study aimed to assess the incidence and the prognosis of low-volume metastases detected in patients with apparent early-stage ovarian cancer undergoing SLN biopsy as part of a clinical trial.

Methods: Retrospective, multi-center, international study. Inclusion criteria were apparent International Federation of Gynecology and Obstetrics 2014 stage I to II epithelial ovarian cancer, undergoing SLN biopsy with systematic bilateral pelvic and para-aortic lymphadenectomy, and complete peritoneal surgical staging, from October 2012 to December 2023. In the absence of lymph-node macro-metastasis, at least 4-level ultra-staging at the SLN was performed. Fertility-sparing surgery or no SLN detection were exclusion criteria. Low-volume metastases were defined as any tumor deposit $\leq$2 mm (isolated tumor cells as $<$0.2mm, micro-metastasis as 0.2-2 mm). Descriptive statistics and survival analyses, including multi-variable Cox regression, were performed.

Results: SLN mapping was attempted in 260 patients. At least 1 SLN was detected in 199 (76.5%) patients, and low-volume metastases were found in 14/199 (7.0%), including 7 (3.5%) isolated tumor cells and 7 (3.5%) micro-metastases. Macro-metastases were identified in 18/199 (9.0%) patients. Among patients with lymph node metastases, 29/32 (90.6%) received adjuvant chemotherapy, including 11/14 (78.6%) with low-volume metastases. Median follow-up was 37 months (95% confidence interval [CI] 34.5 to 39.5). Three-year disease-free survival was 89.9% in node-negative patients, 100.0% in patients with low-volume metastasis, and 64.2% in patients with macro-metastasis ($p < .001$). Three-year overall survival was 98.2%, 100.0%, and 87.8%, respectively ($p < .001$). Lymph node macro-metastasis was the only factor independently associated with worse disease-free survival (hazard ratio 1.532, 95% CI 1.111 to 2.112, $p = .009$) and overall survival (hazard ratio 1.894, 95% CI 1.091 to 3.286, $p = .001$).

Conclusions: Lymph node low-volume metastases in apparent early-stage ovarian cancer were present in 7% of patients, and none of these patients experienced recurrence or death. Lymph node macro-metastasis independently impaired disease-free and overall survival.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Sentinel lymph node biopsy with ultra-staging has been recently investigated as an experimental technique in apparent early-stage ovarian cancer, with the potential to detect low-volume metastasis. While in other malignancies low-volume metastases have been shown to carry prognostic significance and influence adjuvant treatment decisions, the frequency and the prognostic value of these in ovarian cancer are still unknown.

WHAT THIS STUDY ADDS

In a population of patients with apparent early-stage ovarian cancer undergoing sentinel lymph node biopsy and ultra-staging, the incidence of lymph node low-volume metastases was 7%, and none of these patients experienced recurrence or death. Patients with low-volume metastases showed better disease-free survival compared with those with macro-metastasis. This data contribute to novel evidence regarding the clinical behavior of low-volume metastases detected through sentinel node ultra-staging.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

The observation that patients with low-volume nodal metastases had favorable outcomes highlights an opportunity for future prospective research. These results may support future studies aimed at refining risk stratification and tailoring adjuvant therapy in selected patients.

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https://doi.org/10.1016/j.ijgc.2026.104638

Keywords:
Ovarian Cancer; Sentinel Lymph Node Micro-Metastasis; Isolated Tumor Cells; Survival; Incidence

INTRODUCTION

Ovarian cancer remains one of the most lethal gynecologic malignancies, causing over 206,000 deaths globally in 2022. Despite regional declines in incidence, mortality is expected to rise by nearly 70% by 2050, largely due to population aging and disparities in access to care in low- and middle-income countries.[1-3] Apparent early-stage ovarian cancer accounts for approximately 15% of new diagnoses, and surgical staging results in upstaging in about 19% of patients.[4,5]

Pelvic and para-aortic lymphadenectomy is recommended as part of surgical staging in apparent early-stage ovarian cancer, particularly in high-grade histologies.[4,5] However, sentinel lymph node (SLN) biopsy has been recently investigated as an experimental technique in this setting.[6,7] SLN biopsy is routinely performed in several solid cancers and is already a well-established procedure in other gynecologic malignancies.[8] This biopsy is usually processed by the ultra-staging technique, which consists of performing serial multi-level sections with the use of immunohistochemistry to detect the presence of low-volume metastases once macro-metastases have been excluded by standard hematoxylin and eosin (H&E) staining on bisection. The use of ultra-staging for SLN analysis has led to the identification of low-volume metastases that are defined as tumor deposits $\leq$2 mm.

Though in other malignancies some types of low-volume metastases have been shown to carry prognostic significance and influence adjuvant treatment decisions,[9,10] the frequency and the prognostic value of low-volume metastases in ovarian cancer are still unknown. The aim of this study was to assess the incidence and the prognostic impact (defined as disease-free and overall survival) of low-volume metastases detected through SLN biopsy in patients with apparent early-stage ovarian cancer.

METHODS

This is a retrospective, multi-center, international cohort study based on data collected from previous clinical trials evaluating SLN biopsy,[6,7,11] approved by the local ethical committee (ID: 6794, on September 26, 2024). The study included consecutive patients with apparent International Federation of Gynecology and Obstetrics (FIGO) 2014 stage I to II epithelial ovarian cancer undergoing SLN biopsy and systematic bilateral pelvic and para-aortic lymphadenectomy, with complete peritoneal surgical staging (hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal biopsies, and washing/peritoneal fluid cytology; appendicectomy in mucinous tumors), from October 2012 to December 2023. Ultra-staging ($\geq$4 levels) was performed only when no macro-metastasis was identified on initial H&E evaluation. Fertility-sparing surgery and no SLN detection were exclusion criteria. All patients underwent pre-operative abdominal imaging (computed tomography and/or magnetic resonance imaging scan) to exclude nodal metastases or peritoneal carcinomatosis. SLN biopsy was performed at each institution according to local protocols: the tracer could be indocyanine green (ICG), technetium, blue dye, or a combination of these; the site of injection could be the infundibulo-pelvic ligament and/or utero-ovarian ligament or cervix; and timing could be before or after mass removal (always the case if SLN was performed during re-staging surgery). Tracer dose and injection volume were determined based on each center's protocol.

All SLNs were fixed in 10% buffered formalin and underwent bisection with H&E staining to assess the presence of macro-metastases. If macro-metastasis was detected, the SLN was not further investigated by ultra-staging. If that was not detected, serial cross-sectioning along their major axis at 1 to 2 mm intervals was performed until no lymph node (LN) tissue remained. Each of these slices underwent serial sectioning with a minimum of 4 levels. Two sections were performed at each level: 1 that was stained with H&E and 1 for immunohistochemistry with cytokeratin AE1/3. Macro-metastases were defined as cancer deposits larger than 2.0 mm; micro-metastases were defined as deposits between 0.2 and 2.0 mm; and isolated tumor cells were defined as deposits no greater than 0.2 mm, including the presence of single non-cohesive cytokeratin-positive cancer cells.[12] For the purposes of this study, low-volume metastases included both isolated tumor cells and micro-metastases. Non-SLNs were fixed in 10% buffered formalin and processed with H&E staining.

Re-staging surgery was performed on patients diagnosed with ovarian cancer who had not undergone surgical staging at primary surgery. Patients with FIGO stage IIIC based on retroperitoneal LN metastases only were re-classified as stage IIIA1, according to the latest FIGO classification.[13]

Adjuvant treatment and follow-up were conducted according to international guidelines (and based on histology risk factors).[4] All patients with LN macro-metastases received platinum-based chemotherapy. Management of patients with low-volume metastases was not standardized across centers. Decisions regarding adjuvant therapy in these cases were made at the discretion of each institutional multi-disciplinary team.

Statistical Analysis

Descriptive analyses were reported as absolute frequency (percentage) for categorical variables and as median and range or interquartile range (IQR) for continuous variables. Disease-free survival was defined as the time interval between the date of primary surgery and the evidence of the first disease recurrence or death from disease. Overall survival was defined as the time interval between the date of primary surgery and the date of death from any cause. Both intervals were censored at the date of last follow-up if no event was observed. We used the Kaplan–Meier method to estimate the distribution of time-to-event end points of disease-free survival and overall survival, and differences among curves were assessed by the log-rank test.[14,15] Univariable and multi-variable analyses were performed using the Cox proportional hazard model, and hazard ratios (HRs) were reported with their 95% confidence intervals (CIs).[16] Only variables significantly affecting disease-free survival or overall survival ($p < .05$) in univariable analyses were tested in multi-variable analyses. Survival analyses and multi-variable models were considered exploratory. Differences in patient characteristics between those with low-volume metastases versus macro-metastases were evaluated with Student's *t*-test for continuous variables and the chi-square test for categorical variables. Statistical tests were 2-

sided, and differences were considered significant at a level of $p <$ .05. IBM SPSS software version 29.0 and R version 4.1.2 were used for statistical analysis.

In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

RESULTS

SLN mapping was attempted in 260 patients across 13 centers. Of these, at least 1 SLN was detected in 199 (76.5%), who were included in the study (Figure S1). Patients characteristics are listed in Table 1. The majority of patients were diagnosed with serous histology (n = 95, 47.7%), grade 3 (n = 85, 42.7%), and FIGO stage IA (n = 66, 33.2%). In total, 136 patients (68.3%) had ≥20 LNs removed during lymphadenectomy.

Details of SLN detection technique are reported in Table S1: ICG alone was the most used tracer (n = 103, 51.7%), and injections were most frequently performed in both the infundibulo-pelvic ligament and utero-ovarian ligaments (n = 129, 64.8%), predominantly after adnexectomy (n = 130, 65.3%). The site of SLN detection was para-aortic/caval alone in 102 (51.2%), pelvic alone in 26 (13.1%), and both pelvic and para-aortic in 71 (35.7%) patients. The median number of retrieved SLNs was 1 per patient for both for the pelvic (IQR 0-1) and para-aortic area (IQR 1-2). Comparison of patients characteristics according to SLN mapping is showed in Table S2.

Low-volume metastases were detected in 14/199 (7.0%) patients, including 7 (3.5%) patients with isolated tumor cells and 7 (3.5%) with micro-metastases. Comparison of baseline characteristics of patients with node-negative disease, macro-metastases, and low-volume metastases is summarized in Table 1. Patients with low-volume metastasis were more frequently operated on by laparotomy at first surgery, had a higher incidence of stage T1A, and experienced no recurrences or deaths. Patients with macro-metastasis had a higher incidence of serous histology, adjuvant chemotherapy, and maintenance therapy.

In 12 of 14 (85.7%) patients with low-volume metastasis, the low-volume metastases were found in 1 SLN, while in the remaining 2 of 14 (14.3%) patients, they were detected in a non-SLN on routine histologic evaluation. Overall, 18 LNs harbored low-volume metastases (3 patients had 2 positive SLNs each: 1 in the pelvic and the other in the para-aortic/caval area; and 1 patient had 2 positive SLNs in 2 different sites of the para-aortic/caval area). Of the 18 LNs with low-volume metastases, 11 (61.1%) were located in the para-aortic/caval area and 7 (38.9%) in the pelvic area (Fig. 1). Macro-metastases were present in 18/199 (9.0%) patients.

Adjuvant platinum-based chemotherapy was administered to 6 of 7 (85.7%) patients with isolated tumor cells, to 5/7 (71.4%) patients with micro-metastasis, and to 18/18 (100%) patients with macro-metastasis. Maintenance therapy was not given to any patients with isolated tumor cells, while it was prescribed to 1/7 (14.3%) patients with micro-metastasis (poly(adenosine diphosphate-ribose) polymerase inhibitor [PARP-i]) and to 7/18 (38.9%) patients with macro-metastases (6 received PARP-i and 1 bevacizumab) (Table S3). Characteristics of each patient with low-volume metastases are reported in Table 2.

The median follow-up time was 37 months (95% CI 34.5 to 39.5) for the entire cohort and 41 months (95% CI 38.8 to 43.2) for patients with macro-metastasis, 17 months (95% CI 7.2 to 26.7) for patients with low-volume metastasis, and 37 months (95% CI 34.5 to 39.5) for patients without metastasis. The 3-year disease-free survival of the entire cohort was 87.7% (95% CI 82.6 to 92.8), and the 3-year overall survival was 97.2% (95% CI 94.4 to 99.9). When stratified by LN status, 3-year disease-free survival was 89.9% (95% CI 84.8 to 95.0) in patients without LN metastasis, 100.0% (95% CI not estimable [n.e.]) in patients with low-volume metastasis, and 64.2% (95% CI 40.5 to 87.9) in patients with macro-metastasis (overall $p <$ .001; no LN metastasis versus low-volume metastasis: p = .352; no LN metastasis versus macro-metastasis: $p <$ .001; low-volume metastasis versus macro-metastasis: p = .040) (Fig. 2A).

The 3-year overall survival was 98.2% (95% CI 95.6 to 100) versus 100.0% (95% CI n.e.) versus 87.8% (95% CI 71.9 to 100) in patients with no LN metastasis versus low-volume metastasis versus macro-metastasis (overall $p <$ .001; no LN metastasis versus low-volume metastasis: p =. 678; no LN metastasis versus macro-metastasis: $p <$ .001; low-volume metastasis versus macro-metastasis: p = .234) (Fig. 2B).

Multi-variable analysis showed that LN macro-metastasis was independently associated with worse disease-free survival (HR 1.532, 95% CI 1.111 to 2.112, p = .009) and overall survival (HR 1.894, 95% CI 1.091 to 3.286, p = .001) (Table 3).

DISCUSSION

Summary of Main Results

In this cohort of patients with early-stage ovarian cancer undergoing SLN biopsy with ultra-staging and systematic lymphadenectomy as part of prior clinical trials, we identified a low-volume metastasis rate of 7%. Compared to those with LN macro-metastasis, patients with low-volume metastases had a lower incidence of serous histology, received adjuvant and maintenance therapy less frequently, and had a lower recurrence or death rate. Overall, low-volume metastases were associated with favorable outcomes, whereas LN macro-metastasis was associated with impaired disease-free survival and overall survival.

Results in the Context of Published Literature

To date, data specifically addressing the incidence and prognostic impact of nodal low-volume metastases in apparent early-stage ovarian cancer are lacking, and most of the available evidence on low-volume metastases derives from endometrial and cervical cancer. Therefore, to the best of our knowledge, this is the first report to analyze the incidence and prognostic impact of nodal low-volume metastasis in apparent early-stage ovarian cancer. Unlike in other gynecologic malignancies, the incidence and prognostic significance of low-volume metastases in ovarian cancer remain uncertain. Moreover, there is no consensus on whether adjuvant therapy is warranted when low-volume metastases are the only identified risk factor. In fact, common clinical practice often mirrors treatment paradigms from other gynecologic cancers, such as endometrial and cervical cancer, where micro-

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Table 1 Patient Characteristics

Characteristic	Total (*N* = 199)	No lymph node metastasis (*N* = 167)	Macro-metastasis (*N* = 18)	Low-volume metastasis (*N* = 14)	*p*-Value	Effect size
Age, y, median (IQR)	53 (46-61)	54 (46-63)	49 (38-61)	53 (49-57)	.35	0.001
Surgical approach of the first surgery					.02	0.20
- Laparotomy	118 (59.3)	92 (55.1)	14 (77.8)	12 (85.7)		
- Minimally invasive	81 (40.7)	75 (44.9)	4 (22.2)	2 (14.3)		
Restaging operation	60 (30.1)	56 (33.5)	2 (11.1)	2 (14.3)	.06	0.17
Final histology					.047[a]	0.16
- Serous	95 (47.7)	77 (46.1)	14 (77.8)	4 (28.6)		
- Endometrioid	40 (20.1)	33 (19.8)	2 (11.1)	5 (35.7)		
- Clear cell	47 (23.6)	42 (25.1)	1 (5.6)	4 (28.6)		
- Mucinous infiltrative	12 (6.0)	10 (6.0)	1 (5.6)	1 (7.1)		
- Undifferentiated	1 (0.5)	1 (0.6)	0	0		
- Transitional	1 (0.5)	1 (0.6)	0	0		
- Mixed	2 (1.0)	2 (1.2)	0	0		
- Missing	1 (0.5)	1 (0.6)	0	0		
Grade[b]					.51	0.13
- 1	38 (19.1)	33 (19.8)	2 (11.1)	3 (21.4)		
- 2	22 (11.1)	20 (12.0)	2 (11.1)	0		
- 3	85 (42.7)	65 (38.9)	13 (72.2)	7 (50.0)		
- Not applicable	47 (23.6)	42 (25.1)	1 (5.6)	4 (28.6)		
- Missing	7 (3.5)	7 (4.2)				
TNM (T)					<.001[c]	0.30
- T1a	82 (41.2)	68 (40.7)	5 (27.8)	9 (64.3)		
- T1b	9 (4.5)	7 (4.2)	1 (5.6)	1 (7.1)		
- T1c	64 (32.2)	61 (36.5)	1 (5.6)	2 (14.3)		
- T2a	20 (10.1)	15 (9.0)	5 (27.8)	0		
- T2b	17 (8.5)	15 (9.0)	1 (5.6)	1 (7.1)		
- T3a	7 (3.5)	1 (0.6)	5 (27.8)	1 (7.1)		
SLN metastasis[d]	27 (13.6)					
- SLN metastasis pelvic	9 (4.5)	NA	3 (16.7)	6 (42.8)	.10	0.29
- SLN metastasis para-aortic	25 (12.6)	NA	15 (83.3)	10 (71.4)	.42	0.14
Chemotherapy					.043[e]	0.18
- No	44 (22.1)	41 (24.6)	0	3 (21.4)		
- Carboplatin alone	39 (19.6)	32 (19.2)	7 (38.9)	0		
- Carboplatin paclitaxel	102 (51.3)	80 (47.9)	11 (61.1)	11 (78.6)		
- Other	2 (1.0)	2 (1.2)	0	0		
- Missing	12 (6.0)	12 (7.2)	0	0		
Maintenance therapy					[c]<.001	0.35
- No	180 (90.4)	156 (93.4)	11 (61.1)	13 (92.9)		
- PARP-i	17 (8.5)	10 (6.0)	6 (33.3)	1 (7.1)		
- Bevacizumab	1 (0.5)	0	1 (5.6)	0		
- Letrozole	1 (0.5)	1 (0.6)	0	0		

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Table 1 (*continued*)

Characteristic	Total (*N* = 199)	No lymph node metastasis (*N* = 167)	Macro-metastasis (*N* = 18)	Low-volume metastasis (*N* = 14)	*p*-Value	Effect size
Recurrence	23 (11.6)	15 (9.0)	8 (44.4)	0	<.001	0.33
Death	8 (4.0)	4 (2.4)	4 (22.2)	0	<.001	0.29

Abbreviations: G, grade; IQR, interquartile range; NA, not applicable; PARP-i, poly(ADP-ribose) polymerase inhibitor; SLN, sentinel lymph node; TNM, Tumor—Node—Metastasis.
[a] Serous versus endometrioid versus other.
[b] High-grade serous reported as G3, low-grade serous reported as G1, χ^2 G1 vs G2 vs G3.
[c] T1 vs T2-T3.
[d] One patient could have had positive SLNs in both pelvic and para-aortic areas.
[e] No vs yes.

metastases are typically managed as macro-metastases, and isolated tumor cells have classically not been considered clinically significant and are managed as negative nodes.[17,18] Nevertheless, recent studies on endometrial and cervical cancers have attributed a negative prognostic significance to isolated tumor cells as well,[9,19] particularly in endometrial cancer.[10]

In contrast, our series showed that the absence of recurrences or deaths among patients with low-volume metastases confirms the favorable outcome in this sub-group. Nevertheless, we acknowledge that in our study, 85.7% patients with isolated tumor cells and 71.4% of those with micro-metastases received adjuvant chemotherapy, which may have contributed to the favorable survival. Without SLN biopsy, these patients would not have been correctly staged, and some of them might have been inappropriately excluded from adjuvant treatment. Therefore, distinguishing the intrinsic prognostic impact of low-volume metastases from the effect of systemic therapy remains challenging. On the other hand, despite 100% of patients with macro-metastases undergoing adjuvant chemotherapy, survival outcomes were significantly worse compared to those with low-volume metastases, showing them as an independent risk factor for recurrence and death, potentially also linked to the relatively low use of maintenance therapy in these patients (38.9%). The higher incidence of serous histotype in the macro-metastasis group is consistent with the more aggressive biological behavior and propensity for early lymphatic dissemination typically observed in high-grade serous ovarian cancer, whereas other histologic sub-types usually demonstrate a more indolent metastatic pattern.[20]

Overall, our results need to be interpreted with caution, given the low number of patients with low-volume metastases and the relatively short follow-up time. In fact, only a few patients had tumors that would typically not require adjuvant therapy (eg, IA, G1—2, non-serous) but were found to have low-volume metastases, limiting the ability to assess the intrinsic prognostic impact of low-volume metastases (Table 2). In a study on breast cancer by De Boer and colleagues,[21] regional LNs low-volume metastases were associated with a reduced 5-year disease-free survival among women with favorable early-stage breast cancer who did not receive adjuvant

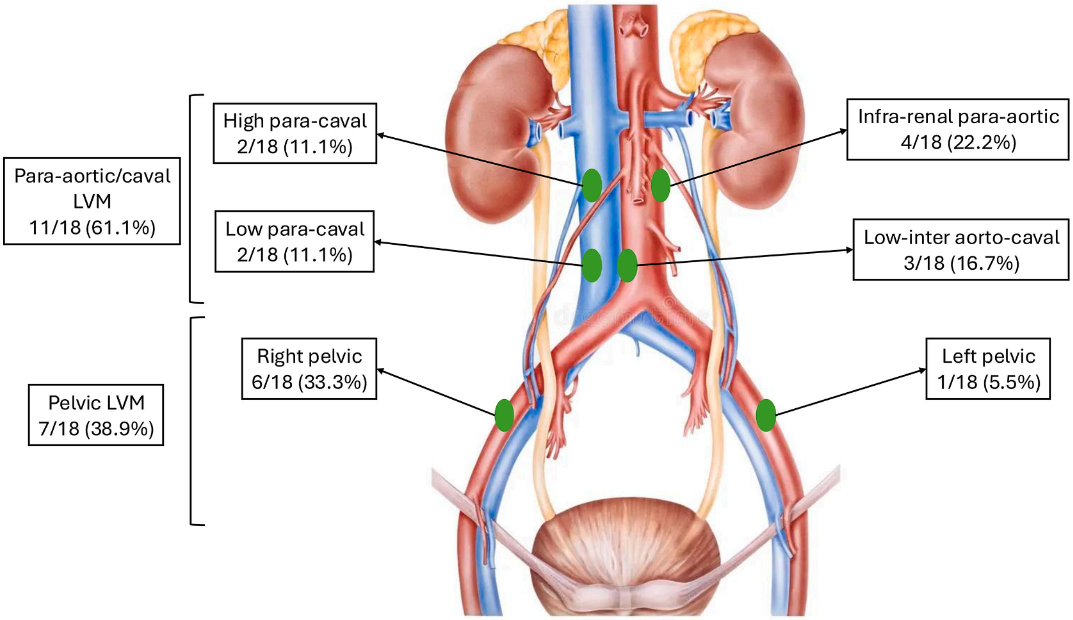

Figure 1 Site of lymph nodes with low-volume metastasis. *Three patients had 2 positive SLNs each (1 in the pelvic area and the other in the para-aortic/caval area), and 1 patient had 2 positive SLNs in 2 different sites of the para-aortic/caval area. SLN, sentinel lymph node

Table 2 Characteristics of Patients with Low-Volume Metastases

Patient	Age	Re-staging	Histology	Grade	TNM (T)	Size of the largest LN metastasis	Size of the largest LN metastasis (mm)	Site of SLN metastasis	Adjuvant chemo	Follow-up time	Recurrence	Death
#1	71	No	Clear cell	NA	pT1A	Micro	1	PA	CP	8	No	No
#2	51	No	Endometrioid	3	pT1A	ITC	0.1	Pe, PA	CP	9	No	No
#3	57	No	Clear cell	NA	pT2B	ITC	0.1	PA	CP	24	No	No
#4	62	No	Endometrioid	1	pT3A	ITC	Isolated cells	PA	CP	36	No	No
#5	35	No	Endometrioid	1	pT1A	Micro	0.5	PA	CP	34	No	No
#6	54	No	Mucinous	3	pT1A	Micro	2.0	Pe	No	24	No	No
#7	52	No	Serous	High	pT1B	Micro	Isolated cells	Pe	No	17	No	No
#8	49	No	Clear cell	NA	pT1A	ITC	0.1	Pe, PA	CP	43	No	No
#9	49	No	Serous	High	pT1C	ITC	0.1	PA	CP	8	No	No
#10	45	No	Serous	High	pT1A	Micro	2	PA (non SLN)	CP	78	No	No
#11	53	No	Endometrioid	3	pT1A	Micro	0.8	Pe (non SLN)	CP	16	No	No
#12	47	Yes	Serous	High	pT1C	ITC	Isolated cells	Pe	CP	6	No	No
#13	53	Yes	Clear cell	NA	pT1A	ITC	Isolated cells	PA	No	10	No	No
#14	58	No	Endometrioid	1	pT1A	Micro	1	Pe, PA	CP	93	No	No

Abbreviations: CP, carboplatin-paclitaxel; ITC, isolated tumor cell; NA, not applicable; PA, para-aortic; Pe, pelvic; SLN, sentinel lymph node; TNM, Tumor—Node—Metastasis.

therapy, whereas in patients with low-volume metastases who received adjuvant therapy, disease-free survival was improved.

Implications for Practice and Future Research

SLN biopsy in ovarian cancer represents a tool to detect low-volume LN involvement (which would remain undetected without ultra-staging), conferring the potential for reduced morbidity and the opportunity to personalize adjuvant and maintenance treatments.

Future studies should focus on the standardization of ultra-staging protocols for SLNs and on defining optimal adjuvant and maintenance therapy for patients with LN low-volume metastases. Furthermore, radiomics and liquid biopsy might play a role in diagnosing low-volume metastases and in correlating the presence of low-volume metastases in LNs with patient prognosis.[22,23]

Strengths and Weaknesses

The main strength of this study is the ability to collect SLN biopsy outcomes in a multi-center setting, which is particularly relevant given the low incidence of apparent early-stage ovarian cancer and the rarity of nodal low-volume metastases. However, we must report some limitations. First, its retrospective nature with intrinsic selection biases, even if consecutive patients undergoing SLN biopsy within clinical trials were included. Second, the relatively low number of patients with low-volume metastases: survival analyses were performed by grouping both isolated tumor cells and micro-metastasis categories under the low-volume metastasis definition, which limits the ability to clarify the independent prognostic role of each metastatic size category. Thirdly, 2 patients had low-volume metastases in a non-SLN: as non-SLNs did not undergo ultra-staging, these might have been macro-metastases

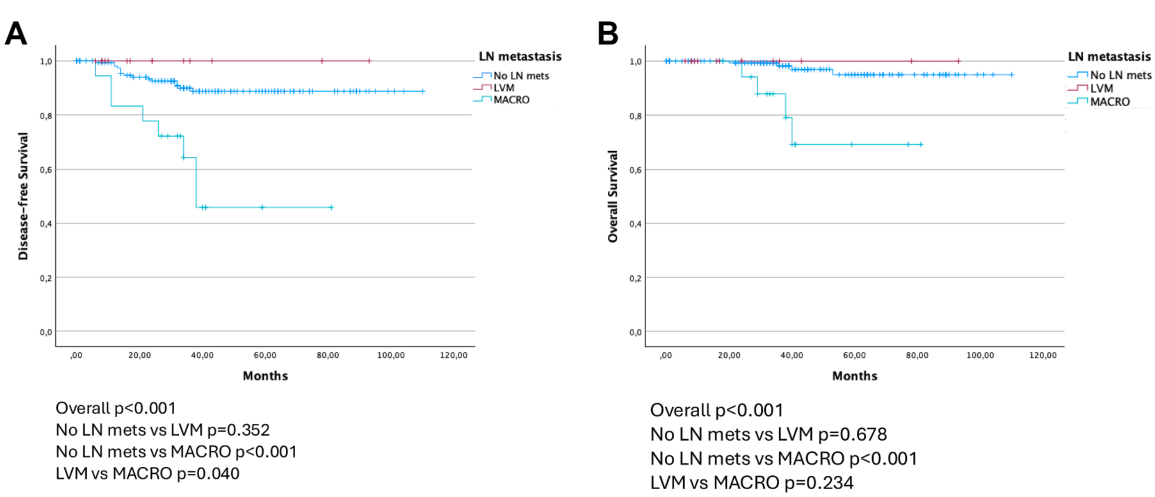

Figure 2 (**A**) Disease-free survival according to presence and size of lymph node metastasis. (**B**) Overall survival according to presence and size of lymph node metastasis.

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Table 3 Univariable and Multi-variable Analyses for Disease-Free Survival (DFS) and Overall Survival

Characteristic	Disease-free survival				Overall survival			
	Univariable HR (95% CI)	*p*-Value	Multi-variable HR (95% CI)	*p*-Value	Univariable HR (95% CI)	*p*-Value	Multi-variable HR (95% CI)	*p*-Value
Age - <60 - ≥60	1.022 (0.419 to 2.490)	.962			2.618 (0.321 to 21.329)	.369		
Final histology - Serous - Others	0.818 (0.361 to 1.854)	.630			0.522 (0.125 to 2.187)	.374		
Grade - 1 - 2/3/NA	1.080 (0.693 to 1.684)	.734			3.137 (0.748 to 13.154)	.118		
TNM (T) - pT1 - pT2/3	1.537 (1.170 to 2.020)	**.002**	1.332 (0.981 to 1.810)	0.067	1.681 (1.052 to 2.687)	**.030**	1.264 (0.725 to 2.205)	.409
Number of removed lymph nodes - <20 - ≥20	0.494 (0.168 to 1.453)	.200			0.341 (0.042 to 2.780)	0.315		
Lymph node metastasis - No/ low-volume metastasis - Macro	1.755 (1.318 to 2.337)	**<.001**	1.532 (1.111 to 2.112)	**.009**	2.137 (1.342 to 3.401)	**.001**	1.894 (1.091 to 3.286)	**.023**
Chemotherapy - No - Yes	1.455 (0.642 to 3.298)	.369			1.933 (0.440 to 8.494)	0.383		

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; TNM, Tumor–Node–Metastasis.
Variables with $p < .05$ in univariable analysis or deemed clinically relevant were included in the multi-variable model; all others were excluded.

of which only a small part was detected because the node was only partially sampled. SLN biopsy and ultra-staging protocols were not standardized throughout the included centers, although only SLNs processed with at least 4-level ultra-staging were included. Heterogeneity of the technique used to map SLN might have affected the detection rate and potentially the accuracy of SLN. There was also a relatively short median follow-up of patients in the low-volume metastasis group. Lastly, the learning curve must be mentioned, as it might have affected the detection rate and accuracy of SLN.

ORIGINAL RESEARCH

CONCLUSIONS

In this study, we found that the incidence of LN low-volume metastases in apparent early-stage ovarian cancer was 7%. Patients with LN low-volume metastasis did not experience any recurrence or death and showed better 3-year disease-free survival than patients with macro-metastasis. LN macro-metastasis was independently associated with worse survival outcomes. These results need to be interpreted with caution, given the low number of patients with low-volume metastases and the relatively short follow-up time.

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Funding/Support This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interests None declared.

Acknowledgments The authors would like to thank the surgical teams and scrub nurses at participating institutions. Moreover, they would like to express their profound gratitude to Prof Giovanni Scambia for his teachings and inspirations.

Appendix A. Supplementary data Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijgc.2026.104638.

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