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Mapping sentinel lymph nodes in early-stage ovarian cancer (MELISA) trial - a further step towards lymphadenectomy replacement

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HIGHLIGHTS

- SLN mapping with ICG and ^{99m}Tc tracers has a 90% detection rate and 100% negative predictive value in early ovarian cancer.
- Para-aortic drainage represents the primary lymphatic spread of ovarian cancer.
- Ultrastaging accurately shows low-volume metastasis, helping to manage early-stage epithelial ovarian cancer.

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ABSTRACT

Objective. Sistematic pelvic and para-aortic lymphadenectomy is part of the staging surgery for early-stage epithelial ovarian cancer, with no therapeutic value. The Mapping Sentinel Lymph Nodes In Early-Stage Ovarian Cancer (MELISA) trial prospectively assessed the SLN detection rate and the diagnostic accuracy of the SLN mapping technique in patients with early-stage epithelial ovarian cancer.

Methods. This prospective, single-arm study included patients diagnosed with early-stage epithelial ovarian cancer (FIGO stages I and II), via either primary surgery or re-staging surgery. SLN mapping was performed by injecting 0.2 mL of 37-mBq ^{99m}Tc-nanocoloid albumin and 2 mL of 2.5 mg/mL indocyanine green into the infundibulopelvic and utero-ovarian ligaments. After removal of SLNs, a complete systematic pelvic and para-aortic lymphadenectomy was performed. SLN Ultrastaging analysis was applied. The primary outcome was the overall SLN detection rate, either with one or both tracers. Secondary outcomes were the diagnostic accuracy of detecting lymph node metastases and factors that may influence SLN detection.

Results. Thirty patients were included. SLNs were identified in 27 patients (90%). Detection rates in primary and re-staging surgery were 89% and 92%, respectively. Para-aortic drainage was the predominant lymphatic spread, observed in 26 of 27 patients. Ultrastaging pathologic reports listed 1 SLN with macrometastasis, 1 with micrometastasis, and 5 with isolated tumor cells; the sensitivity of SLN mapping was 100%, with a false-negative rate of 0%. Univariate analysis showed a nonsignificant higher proportion of patients with uterine fibroids, adenomyosis, and endometriosis (100%, 67%, 67%, respectively) in patients in whom SLNs were not detected.

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Conclusion. SLN mapping has a high detection rate (90%) and is an accurate technique for detecting lymph node involvement in early-stage epithelial ovarian cancer. SLN mapping is a potential alternative to systematic lymphadenectomy to reduce associated morbidity, but further research is needed to evaluate the impact of SLN mapping on oncologic outcomes and its cost-effectiveness.

1. Introduction

Epithelial ovarian cancer (EOC) is detected at an early stage in up to 20% of patients, requiring complete staging surgery to assess peritoneal or lymph node involvement, to determine prognosis and appropriate adjuvant therapy [1]. Although systematic pelvic and para-aortic lymphadenectomy is part of the staging surgery for early-stage EOC [2,3], the incidence of lymph node metastasis is approximately 15–20%. Lymphadenectomy is an invasive and laborious procedure that can lead to intra-operative and post-operative complications, adversely affecting the patient's quality of life. Therefore, the prognostic value of full lymph node dissection must be carefully balanced against the associated morbidity, particularly the risk of lower-leg lymphedema. [4,5] Moreover, no evidence suggests that full lymph node dissection has any added therapeutic value [6].

In recent decades, sentinel lymph node (SLN) mapping has emerged as an alternative to lymph node dissection and has been incorporated into surgical treatment for other gynecologic malignancies to reduce associated morbidity [7,8]. Furthermore, comprehensive evaluation of the SLNs through ultrastaging and immunohistochemical analysis improves the detection of low-volume disease [9]. However, the role of SLN mapping in managing early-stage EOC is still under investigation. Previous studies [10–12] have demonstrated the feasibility and safety of SLN mapping in early-stage EOC. Nevertheless, several key questions regarding the technique, including aspects such as the choice of tracers and injection site selection, as well as detection outcomes, still lack conclusive answers. Findings from a recent meta-analysis [13] aknowledge the limited quality of existing evidence and underscore the necessity for further studies and evaluation before implementing SLN mapping as routine clinical practice.

We conducted the Mapping Sentinel Lymph Nodes In Early-Stage Ovarian Cancer (MELISA) trial, a prospective study designed to evaluate the SLN detection rate and the diagnostic accuracyof SLN mapping in patients with early-stage EOC, compared with the reference standard of complete pelvic and para-aortic lymphadenectomy.

2. Methods

2.1. Patients

This prospective trial was approved by our Institutional Review Committee (HCB/2021/0130) and registered on ClinicalTrials.gov (NCT05184140). From September 2021 to March 2023, all patients with an ovarian tumor suggestive of early-stage ovarian cancer in the Hospital Clinic of Barcelona, an academic tertiary hospital, were considered for enrollment. Inclusion criteria were (1) histologically confirmed EOC (International Federation of Gynecology and Obstetrics 2014 stages I and II), determined by frozen section from the primary surgery for EOC or by deferred diagnosis after adnexectomy (followed by re-staging surgery); (2) aged 18 years or older; and (3) Eastern Cooperative Oncology Group performance status ≤2. Patients were excluded if they (1) had benign or borderline tumors or pathologically confirmed metastasis or other non-EOC malignant histologic diagnosis; (2) had undergone previous radiotherapy or vascular or lymph node dissection surgery (pelvic or para-aortic field); (3) had previous adverse events after exposure to the radiotracer, iodine component, or indocyanine green (ICG); or (4) were pregnant or lactating. All patients underwent preoperative imaging assessment, including transvaginal ultrasonography and preoperative magnetic resonance imaging (unless contraindicated, in which case they underwent computed tomography), and provided written informed consent. All surgeries were performed by three experienced surgeons form the gynecologic oncology department.

2.2. Procedures

A detailed description of the SLN mapping procedure was previously published by our team [14]. The protocol permitted surgical approach by laparotomy or minimally invasive surgery (MIS). The current study encompassed two types of SLN mapping surgeries: primary surgery, in which the EOC diagnosis was determined by a frozen section of the ovarian tumor; and re-staging surgery, performed in patients who had already undergone ovarian tumor resection but received a deferred EOC diagnosis. For primary surgery, before removal of the adnexal tumor, 0.2 mL of saline solution containing 37 mBq ^{99m}Tc-nanocoloid albumin (^{99m}Tc; ROTOP NanoHSA, ROTOP PHARMAKA AG, Germany) was injected close to the ovarian cortex, into the infundibulopelvic and utero-ovarian ligament. A 22-gauge needle was used for open surgery and a 23-gauge needle for MIS. After 15 min, the adnexal tumor was removed and sent for frozen section assessment. Once malignancy was confirmed, 0.2 mL of ICG (2.5 mg/mL) was injected into the ipsilateral infundibulopelvic and utero-ovarian ligament stumps. If bilateral adnexal masses were detected, the same protocol was applied to both tumors. In patients undergoing re-staging surgeries, both tracers were injected into the ipsilateral infundibulopelvic and utero-ovarian ligament stumps (^{99m}Tc and then ICG).

Right after the ICG injection, a surgical exposure of the pelvic and para-aortic retroperitoneum was performed to identify the SLNs. SLN detection was guided by the gammadetector probe (Navigator, USSC, Norwalk, USA) and simultaneously using a near-infrared camera (Karl Storz Endoscopy, Germany, or PinPoint Novadaq, Canada). For each lymphatic region, any lymph node detected to be ICG-positive and/or containing >10% of the highest lymph node activity was considered a SLN. Ultrastaging analysis was performed for all identified SLNs, and the number and exact location of each SLN was recorded. Afterwards, according to current guidelines, a complete standard staging surgery was performed, including a pelvic and para-aortic lymphadenectomy up to the left renal vein [2,3].

Non-SLN were sectioned once and examined by hematoxylin and eosin analysis only. SLNs were cut into serial cross sections to the major axis of the lymph node every 1 to 2 mm. Subsequently, the ultrastaging protocol was performed, consisting of two consecutive histologic sections (4 μm thick) obtained at regular intervals of 150 μm, with 4 to 6 levels in each paraffin block. The first section was stained with hematoxylin and eosin, and if results were negative, the second section was stained immunohistochemically with an AE1-AE3 antikeratin antibody (Dako). SLNs were considered positive for malignancy if they had isolated tumoral cells (ITC; ≤0.2 mm), micrometastases (0.2 mm to ≤2 mm), or macrometastases (>2 mm).

The patients were monitored for 30 days. Surgical complications, including intraoperative and postoperative complications [15], reoperations, and adverse effects related to the tracer within 30 days after surgery, were recorded.

2.3. Outcomes

The primary outcome of the study was to determine the overall detection rate of SLNs. This outcome was defined as the proportion of individuals in whom at least one SLN was detected with ^{99m}Tc and/or ICG tracer, either in the pelvic or para-aortic field, after SLN mapping was performed.

The secondary objectives of the study were as follows: a) to identify any factors or variables that may influence SLN detection, providing insights into the effectiveness and reliability of the mapping technique, and b) to evaluate the diagnostic accuracy (sensitivity, false negative (FN) rate and negative predictive value (NPV)) of SLN mapping for detecting lymph node metastases by comparing it with the reference standard of complete pelvic and para-aortic lymphadenectomy.

Sensitivity was defined as the proportion of patients with node-positive disease correctly identified by a SLN. Patients were considered to have node-positive disease in the presence of macrometastases, micrometastases, or ITCs. The false-negative rate was defined as the proportion of patients with node-positive disease not identified by a SLN. The NPV was defined as the proportion of patients negative for metastatic disease according to an SLN who truly had node-negative disease.

2.4. Statistics

The determination of the required sample size was estimated based on previous studies, which showed that lymphatic drainage could be achieved in over 90% of cases [13,16].To ensure a conservative approach, we anticipated a detection rate of 85%. Assuming a precision of 15%, a power of 90% and a one-sided confidence level of 95%, we estimated that a total of 30 participants would be needed for the current study. Qualitative variables were presented as absolute and relative frequencies (percentages), and quantitative variables were presented as means or medians and ranges. A univariate analysis was conducted, defined by the detection of at least one SLN. Patient characteristics were compared between these two cohorts (i.e., those in whom at least one SLN was detected and those in whom no SLNs were detected) using the Fisher exact test for categorical variables and the Wilcoxon test for continuous variables. The diagnostic performance of SLN mapping was evaluated using sensitivity and negative predictive values, along with their corresponding 95% confidence intervals (CI). The gold standard for this evaluation was pathologic analysis of all nodes identified during lymphadenectomy. A significance level of 5% was chosen for determining statistical significance, and all calculations were performed using STATA 16.1 software.

3. Results

A total of 82 patients were initially assessed for eligibility. After exclusions shown in the CONSORT diagram (Fig. 1), 30 patients (18 in the primary surgery group and 12 in the re-staging surgery group) were assessed for SLN mapping and included in the final analysis. Reasons for exclusion included Eastern Cooperative Oncology Group performance status >2, suspected lymph node involvement based on preoperative imaging, lack of frozen section analysis of the ovarian tumor, subperitoneal injection technically not possible, abdominal carcinomatosis found intraoperatively, and other non-EOC malignant histologic diagnosis reported. The median age was 56 years (range 35–84) and the median body mass index was 24.77 kg/m^2 (range 17.7–33.6). Seven patients (23%) underwent MIS and 23 (77%) underwent laparotomy. Clinical and surgical baseline characteristics of included patients are presented in Table 1.

In one of 30 patient, the radiotracer was not injected into the utero-ovarian ligament owing to a prior hysterectomy performed before the surgery. In two additional patients, adnexectomy was conducted along with hysterectomy for oncologic safety reasons, and as a result, the ICG injection was not performed. All patients underwent a SLN detection and a subsequent complete standard staging ovarian surgery, including a complete pelvic and/or para-aortic lymphadenectomy.

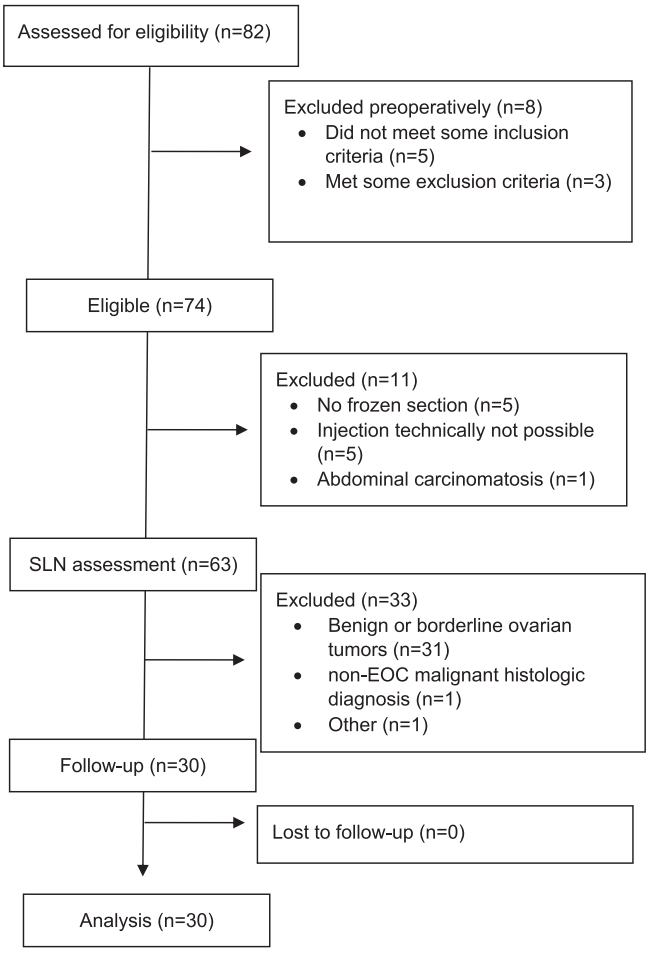

Fig. 1. CONSORT flow diagram.

3.1. Characteristics of SLN detection

At least one SLN was detected with 99mTc and/or ICG tracer in 27 of the 30 patients, resulting in an overall detection rate of 90%. The SLN detection rate was 89% (16/18 patients) in the primary surgery group and 92% (11/12 patients) in the re-staging surgery group ($p > 0.99$). Surgeons resected a mean of 2.07 SLNs per patient (range 1–7), for a total of 62 resected SLNs. In 14 of 27 patients (52%), SLNs were exclusively detected in the para-aortic field; in 1 patient (4%), only in the pelvic field; and in 12 patients (44%), in both fields. Among patients with drainage primarily to the pelvic field (13 patients), the mean number of SLNs detected in that field was 1.8 (range 1–4). Among patients with drainage primarily to the para-aortic field (26 patients), the mean number of SLNs detected in that field was 1.5 (range 1–3). The distribution of SLN drainage in the para-aortic field was as follows: supramesenteric region in 12 of 26 patients (46%) and inframesenteric region in 20 of 26 patients (77%), with drainage occurring in both supramesenteric and inframesenteric regions in 6 patients (23%). A detailed map of SLN drainage distribution is shown in Fig. 2. All SLNs exhibited ipsilateral drainage with respect to the tumor side.

After SLN detection, all patients underwent complete pelvic and para-aortic lymphadenectomy. The overall median number of lymph nodes removed was 22 (range 10–52), with a median of 11.5 lymph nodes (range 4–31) in the para-aortic field and 12 (range 6–28) in the

Table 1
Baseline characteristics and univariate analysis of factors affecting sentinel lymph node (SLN) detection in 30 patients.

		SLNs detected, no. (%)		p
	No. (%)	Yes, $n = 27$	No, $n = 3$	
Median age (range; years)	56 (35–84)	55.1	57.3	0.863[a]
Median body mass index (range; kg/m^2)	24.8 (17.7–33.6)	24.8 (6.0)	23.3 (5.2)	0.809[a]
Eastern Cooperative Oncology Group performance status	26 (87)	23 (85.2)	3 (100)	1.000[b]
0	4 (13)	4 (14.8)	0 (0)	
1	0 (0)	0 (0)	0 (0)	
>1				
Median tumor size (range; cm)	10.8 (3.6–66.0)	11.0 (13.0)	10.0 (13.0)	0.703[a]
Tumor location				0.716[b]
Right	15 (50)	14 (52)	1 (33)	
Left	11 (37)	9 (33)	2 (67)	
Bilateral	4 (13)	4 (15)	0 (0)	
Median CA125 (range; U/mL)	33.9 (1–1479)	38.9	23.3	0.534[a]
Previous surgery	16 (53)	14 (52)	2 (67)	1.000[b]
Type of surgery				
Frozen section + immediate staging	18 (60)	16 (59)	2 (67)	1.000[b]
Deferred re-staging surgery	12 (40)	11 (41)	1 (33)	
Surgical approach				
Minimally invasive	7 (23)	6 (22)	1 (33)	1.000[b]
Laparotomy	23 (77)	21 (78)	2 (67)	
Intraoperative and/or histologic findings				
Intraoperative adherences	8 (27)	7 (26)	1 (33)	1.000[b]
Fibroids	18 (60)	15 (56)	3 (100)	0.255[b]
Adenomyosis	6 (20)	4 (15)	2 (67)	0.094[b]
Endometriosis	7 (23)	5 (19)	2 (67)	0.128[b]

[a] Wilcoxon rank-sum test.
[b] Fisher exact test.

pelvic field. The detection rate did not significantly differ between the MIS (6/7, 86%) and laparotomy (21/23, 91%) groups ($p > 0.999$). Univariate exploratory analysis showed a no statistically significant difference in the detection rate among patients with uterine fibroids, adenomyosis, and endometriosis. Results of the univariate exploratory analysis of factors affecting SLN detection are shown in Table 1.

3.2. Diagnostic performance

Lymph nodes metastases were identified in 5 of 27 patients (19%). All of these metastases were correctly identified by SLN technique. The sensitivity of the SLN technique was 100% (95% CI 56.6–100.0), with a false-negative rate of 0% (95% CI 0–43.4), and the negative predictive value was 100% (95% CI 85.1–100). Ultrastaging enabled the detection of 7 SLN metastases in 5 patients (19%): 1 macrometastasis, 1 micrometastasis, and 5 ITC. The specific location of SLN involvement is shown in Fig. 2. In one patient with a right ovarian tumor and ITC in two para-aortic SLNs, micrometastases were found in a pelvic lymph node where no pelvic SLN was identified. No other lymph node involvement was found in the remaining patients. Table 2 provides a description of the surgical and pathologic characteristics of the patients in our study.

3.3. Morbidity and side effects

No severe intraoperative or postoperative complications related to the technique were encountered. There were no reoperations performed within 30 days from surgery, and no adverse effects related to the tracers were reported.

4. Discussion

The MELISA trial aimed to evaluate SLN mapping in patients undergoing either primary or re-staging surgery for early-stage EOC. SLN mapping had an overall detection rate of 90% and accurately predicted nodal status in the final histology report, with a false-negative rate of 0% and a negative predictive value of 100%. Notably, three of five patients with SLN metastases were identified by ultrastaging. The SLN detection rates exhibited variations between the pelvic and para-aortic fields, with a higher rate observed in the para-aortic field.

The MELISA trial stands as one of the few prospective trials investigating SLNs in clinical early-stage EOC. The detection rate observed in this trial is consistent with findings from other gynecologic cancer sites such as cervical or endometrial cancer [17,18]. However, there is heterogeneity in previously published SLN detection rate data in apparent early-stage EOC. For instance, Lago et al. reported promising results, with a detection rate of 100% [10,19] (7, 14), whereas Uccella et al. reported a lower detection rate of 67.7% in preliminary results from the SELLY trial [12]. The detection rate might be influenced by various factors, including the type of surgery performed (primary or re-staging surgery), the tracers used, and the timing of tracer injection.

In the SELLY trial [12], the SLN detection rate in re-staging surgeries was notably lower than in primary surgeries. Similarly, a meta-analysis [13] evaluating the SLN detection rate in ovarian cancer patients reported an overall detection rate of 93%, but the rate in re-staging surgeries was only 78.9%. In the current study, we observed a similar detection rate between primary and re-staging surgeries. Although factors such as uterine fibroids, adenomyosis, or endometriosis might impact SLN detection, our univariate analysis did not identify these factors as statistically significant, potentially due to the small sample size limiting data interpretation. It is noteworthy that SLNs were not detected in three patients with uterine fibroids; nevertheless, further research and more extensive data are needed to conclusively affirm this relationship.

Although ICG has been used as a single agent for lymphatic mapping in cervical and uterine cancer [3,7], its use as a standalone agent for lymphatic mapping in early-stage EOC is more challenging. Unlike in other gynecologic cancer procedures, the injection in EOC is performed within the surgical field, and lymphatic ovarian drainage from the aortocaval and pelvic region is broad. These factors make the implementation and use of ICG as a single agent difficult due to rapid ICG lymphatic migration and tissue dissemination. In the current study, we combined ^{99m}TC and ICG to enhance the advantages of both tracers, as previously reported [10,13]. Additionally, the optimal timing of tracer injection remains unclear. Injecting the tracer into ovarian ligaments before tumor resection may be considered ideal, preserving unaltered lymphatic pathways [11,20–23]. However, this can be more challenging with large tumors that cannot be spilled out. Conversely, other studies [10,12,24] have reported performing the injection right after adnexa removal and malignancy confirmation, potentially simplifying the technique. Pooled data indicated similar detection rates before and after adnexa removal (98.9% and 89.7%), respectively, with no statistically significant difference [13].

Regarding ovarian SLN mapping, the current study showed that para-aortic drainage was the primary location of lymphatic spread, consistent with previous reports [13]. However, in contrast with previous reports, the SLN detection rate in the pelvic field was lower in the current study. Although a small percentage of patients in the current study did not have a uterus, it is unlikely that the absence of the uterus alone significantly impacted the pelvic SLN detection rate. Instead, the lower SLN detection rate in the pelvic field may be primarily attributed to tracer leakage throughout the retroperitoneal pelvic spaces during the injection, which makes it more challenging to detect pelvic SLNs due to background contamination. To address this

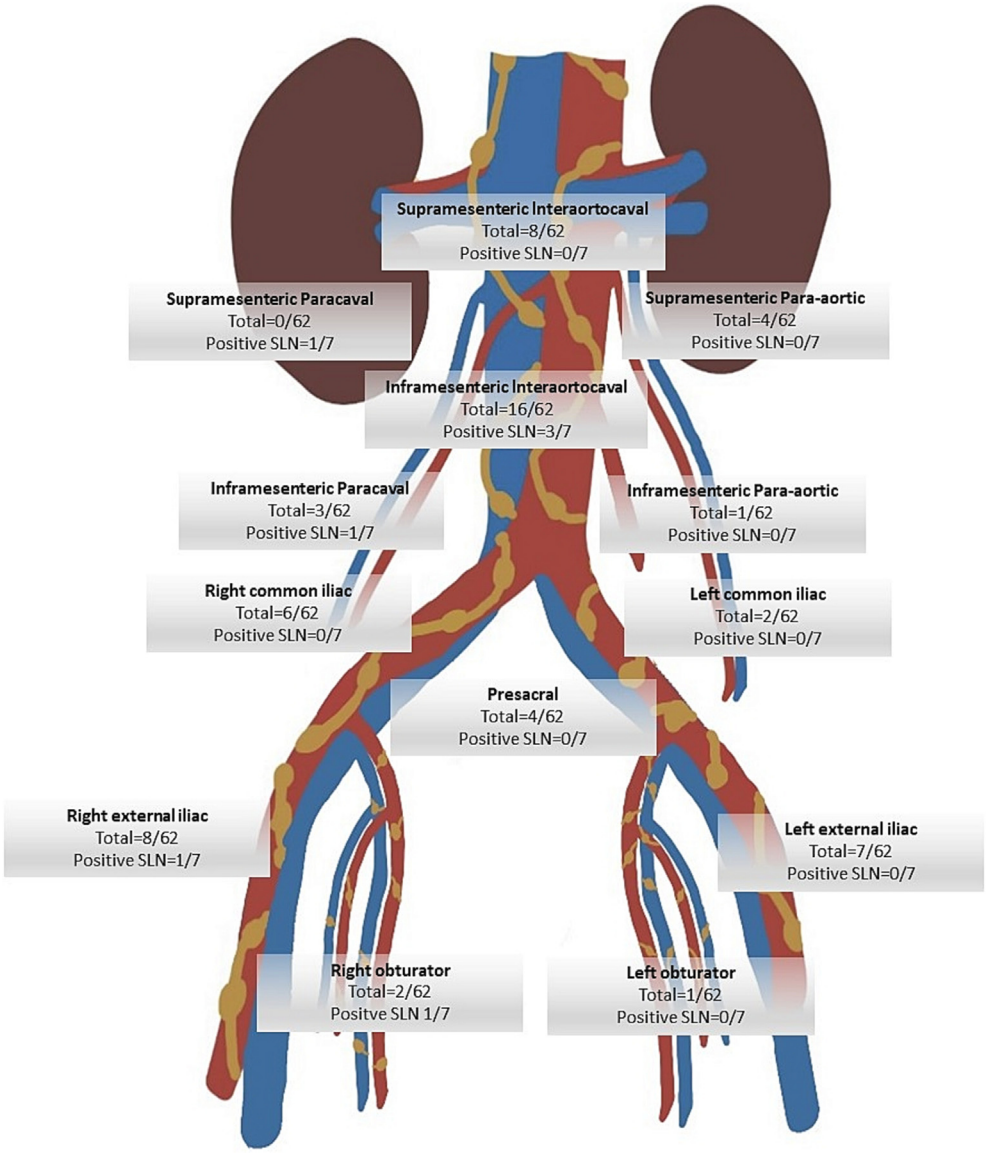

Fig. 2. Anatomic location and positivity of sentinel lymph nodes (SLNs) in 27 patients.

drawback, Uccella et al [25] assessed lymphatic pelvic drainage by performing a cervical injection with ICG and compared outcomes with those of injecting blue dye into the utero-ovarian ligament in endometrial cancer staging surgeries. They found equivalent pelvic SLN detection in all patients using both tracers, suggesting that the two injection sites could be interchangeable, potentially increasing the pelvic SLN detection rate.

In the current study, all SLNs were correctly identified by SLN mapping, consistent with the literature [13] Surprisingly, a high proportion of patients with ITC was observed in the current study. The role of ultrastaging in ovarian SLN detection has been rarely reported [26], and there are no data on the survival impact of low-volume metastasis in these patients. However, our results shed light on the significance of low-volume metastasis in early-stage EOC. One patient had ITC in two aortic SLNs with no pelvic drainage, but a micrometastasis was found in the pelvis. Consequently, further consideration is needed for un-drained specific region. For other gynecologic cancer sites, complete site-specific lymphadenectomy is considered when no drainage is identified in a specific region [27]. An SLN mapping algorithm could recommend more than the removal of only the detected SLNs to enhance the sensitivity and negative predictive value of the procedure.

The strength of the MELISA trial is its prospective design and consecutive recruitment of patients in a tertiary high-volume center. However, the sample size may be a limitation, because the trial was designed to assess the detection rate rather than the diagnostic accuracy or survival impact of the SLN mapping procedure. Our study indicate that SLN mapping in EOC is more difficult and might be more time-consuming than in other gynecologic cancers. The large area of lymphatic drainage implies having a thorough knowledge of the pelvic and aortic retroperitoneal anatomy in order to perform a safe dissection and correctly identify the two main lymphatic drainage pathways from the ovary.

Despite the promising results and diagnostic accuracy of SLN mapping in early-stage EOC, the available data on oncologic outcomes remain limited. Further results from ongoing [28–30] and future prospective trials are eagerly anticipated to shed light on potential differences in oncologic outcomes and feasibility, taking

Table 2
Postoperative characteristics of enrolled patients ($n = 30$).

Characteristic	No. (%)
Surgical characteristics	
SLN detection	
Yes	27 (90)
No	3 (10)
SLN location (n = 27)	
Para-aortic	14 (52)
Pelvic	1 (4)
Both	12 (44)
SLN detection by tracer	
Tc99	9
ICG[a]	3
Both	15
Intraoperative complications related to SLN detection	0 (0)
Pathologic characteristics	
FIGO stage	
IA	7 (23)
IB	1 (3)
IC1	7 (23)
IC2	3 (10)
IC3	2 (7)
IIB	4 (13)
IIIA1(I)	2 (7)
IIIA1(II)	2 (7)
IIIA2	2 (7)
Histologic diagnosis	
Serous high-grade carcinoma	12 (40)
Serous low-grade carcinoma	2 (7)
Endometroid carcinoma	6 (20)
Clear cell carcinoma	7 (23)
Expansile mucinous carcinoma	1 (3)
Infiltrative mucinous carcinoma	2 (7)
SLN metastases (n = 27)	
Yes	5 (19)
No	22 (81)
Size of SLN involvement ($n = 27$)	
ITC	5 (19)
Micrometastasis	1 (4)
Macrometastasis	1 (4)
Non-SLN metastases	
Pelvic lymph node dissection	1 (3)
Para-aortic lymph node dissection	0 (0)

Abbreviations: SLN, sentinel lymph node; FIGO, International Federation of Gynecology and Obstetrics; ITC, isolated tumor cells.
[a] ICG tracer was administered in 29 patients.

into account cost and personnel constraints. These studies will provide valuable insights and help establish the role of ovarian SLN mapping in the management of EOC.

5. Conclusion

The MELISA trial showed that SLN mapping in patients with early-stage EOC had a high overall detection rate and a 100% negative predictive value when done using ICG and ^{99m}Tc tracers. However, further collaborative research is needed to evaluate the diagnostic accuracy and survival impact of ovarian SLN mapping in early-stage EOC to enhance our understanding and optimize the clinical application of SLN mapping.

Credit authorship contribution statement

- N.A is the principal investigator,conceptualized and designed the study, collected and.
analyzed data, writedthe original manuscript.
- P·P and S·V-S contributed to conceptualizing the project, methodology, and edited the manuscript.
- C·C-C collected data, methodology, and edited the manuscript.
- F.M contributed to data curation, formal analysis, methodology, and edited the manuscript.
- A.G, T.M, P·F, N·C-D collected data, methodology, and edited the manuscript.
- A.S collected data and methodology.
- B·D-F and A-T contributed to conceptualizing the project, consulted for clinical expertise,reviewed the data and analyses, and edited the manuscript.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest related to the above presented work.

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