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Clinical trial

Sentinel-node biopsy in apparent early stage ovarian cancer: final results of a prospective multicentre study (SELLY)☆

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ABSTRACT

Aim: To evaluate the sensitivity and specificity of sentinel-lymph-node mapping compared with the gold standard of systematic lymphadenectomy in detecting lymph node metastasis in apparent early stage ovarian cancer.
Methods: Multicenter, prospective, phase II trial, conducted in seven centers from March 2018 to July 2022. Patients with presumed stage I-II epithelial ovarian cancer planned for surgical staging were eligible. Patients received injection of indocyanine green in the infundibulo-pelvic and, when feasible, utero-ovarian ligaments and sentinel lymph node biopsy followed by pelvic and para-aortic lymphadenectomy was performed. Histopathological examination of all nodes was performed including ultra-staging protocol for the sentinel lymph node.
Results: 174 patients were enrolled and 169 (97.1 %) received study interventions. 99 (58.6 %) patients had successful mapping of at least one sentinel lymph node and 15 (15.1 %) of them had positive nodes. Of these, 11 of 15 (73.3 %) had a correct identification of the disease in the sentinel lymph node; 7 of 11 (63.6 %) required ultra-staging protocol to detect nodal metastasis. Four (26.7 %) patients with node-positive disease had a negative sentinel-lymph-node (sensitivity 73.3 % and specificity 100.0 %).
Conclusions: In a multicenter setting, identifying sentinel-lymph nodes in apparent early stage epithelial ovarian cancer did not reach the expected sensitivity: 1 of 4 patients might have metastatic lymphatic disease unrecognized by sentinel-lymph-node biopsy. Nevertheless, 35.0 % of node positive patients was identified only thanks to ultra-staging protocol on sentinel-lymph-nodes.

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1. Introduction

Epithelial ovarian cancer (EOC) is the 7th most common cancer in women globally, affecting approximately 310,000 women per year and accounting for more deaths than any other cancer of the female reproductive system [1].

Only 30 % of newly diagnosed EOC patients are supposed to have an early stage disease [2]. In these patients, surgical staging including pelvic/para-aortic lymphadenectomy defines recurrence risk and helps clinicians allocating patients to adjuvant treatment [2,3]. Almost 15 % of the presumed early stage EOC are actually upstaged due to lymph node involvement [4,5].

Although node-positive patients can significantly benefit from chemotherapy and maintenance treatment, the therapeutic role of lymphadenectomy, especially in node-negative patients, is still matter of debate [6].

Pelvic and para-aortic lymphadenectomy is associated with major comorbidities including vascular and nerve injuries, increased blood loss and operative time, lymphocysts formation, lymphorrhoea and lower limb lymphedema [7]. Moreover, there is no agreement on the extension of lymph node dissection, although it is recommended to remove at least 20 nodes up to the level of the left renal vein [8–11].

Sentinel lymph node (SLN) mapping represents an effective and accurate procedure to identify.

lymph node metastasis in various solid cancers [12–16]. The feasibility of this technique in EOC has only been described in small prospective studies with differences in the type of tracer and the injection site [7].

The SEntineL Lymph Node in early-stage ovarian cancer (SELLY) trial was designed with the primary objective to estimate the sensitivity and specificity of SLN mapping using fluorescence imaging of the tracer indocyanine green (ICG) in detecting lymphatic metastases in patients with apparent early stage EOC.

2. Materials and methods

2.1. Study design and participants

The SELLY trial (NCT03563781) is a prospective, multicenter, phase II trial. Consecutive patients were enrolled from seven institutions (both tertiary academic and community hospitals). Participating surgeons were required to have performed at least 20 systematic pelvic and para-aortic lymphadenectomies/year, before the initiation of enrollment [17].

Patients were eligible if they had an apparent International Federation of Gynecology and Obstetrics (FIGO) stage I-II histologically proven EOC, addressed to immediate or delayed surgical staging after preoperative computed tomography (CT) scan imaging showing no suspicious lymph nodes (defined as lymph nodes < 1 cm in their short axis). Other eligibility criteria included an age between 18 and 80 years, a Performance Status (ECOG) ≤ 2, an adequate respiratory, hepatic, cardiac, bone marrow, liver and renal function (Creatinine Clearance > 60 mL/min according to Cockroft formula).

Patients were excluded in case of intraoperative evidence of carcinomatosis, mucinous-only final histology (i.e. mucinous histology without mixed features), previous vascular surgery of the aorta, inferior vena cava and/or iliac vessels, previous lymphadenectomy or lymph node sampling in the iliac or para-aortic region, history of allergy to indocyanine green, iodine, iodine dyes, isosulfan blue, or triphenylmethane, history of a malignant lymphoma, history of a malignant tumor in the abdominal cavity, previous abdominal radiation therapy, pregnancy or lactation, refusal to provide written informed consent.

If patients were recognized to have extra pelvic disease at the time of surgery after tracer injection, they were not considered eligible for the SLN mapping.

The protocol was approved by each center Institutional Review Board and all patients enrolled gave their written informed consent for participation. Patients' data were prospectively collected in a web-based software (REDCap) [18].

This trial was carried out in compliance with the protocol, designed to ensure adherence to Good Clinical Practice [19].

2.2. Procedures

Fifteen surgeons participated to the trial and were instructed by the principal investigator (GS) to confirm standardization of the technique displaying educational videos during site initiation visits and distributing periodic vademecum materials. Surgery was performed with open or minimally invasive approach according to surgeon's preference and the patient/tumor characteristics.

The SELLY trial methodology has previously been published in detail and has been reported in Supplementary material [20,21]. Briefly, after frozen section reporting EOC, two mLs of a 1.25 mg/mL indocyanine green (ICG) solution were injected into the perivascular connective tissue of the infundibulo-pelvic ligament and, when feasible, into the uterine stump of the ligamentum ovarii proprium (i.e., the utero-ovarian ligament) of the affected, previously removed, ovary/ies.

Once mapping of the pelvic and aortic region was completed and documented through a graphical data map, identified SLN(s) was excised, labeled and sent separately for final histology with ultrastaging analysis. After that, bilateral systematic pelvic and para-aortic lymph node dissection up to the level of the left renal vein, as well as other peritoneal staging procedures, were performed according to the National Comprehensive Cancer Network® guidelines [8]. Patients were monitored for any adverse event or toxicity up to at least day 30 after surgery. Adverse events were classified according to the Clavien-Dindo classification and assigned relationship (suspected or ascertained) to ICG usage [22].

2.3. Outcomes

The primary endpoint was the estimation of the sensitivity of SLN in predicting nodal status. Sensitivity was defined as the proportion of patients with node-positive disease who had successful SLN mapping (either paraaortic or pelvic) and had metastatic disease correctly identified in the SLN.

The secondary endpoints included specificity, defined as the proportion of patients with negative nodes who had successful SLN mapping (either para-aortic or pelvic) and had negative SLN specimens, safety (complications rate of the procedure) and detection rate. The detection rate was calculated as the number of patients with at least one detected SLN divided by the total number of patients who underwent the procedure.

2.4. Statistical analysis

Patients who had mapping of at least one SLN were included in the sensitivity and specificity analysis (per protocol). All patients who received study intervention (injection of dye), regardless of mapping result, including those deemed ineligible for SLN mapping, were included as part of the assessment of mapping and the safety analysis in an intention-to-treat approach. Sample size for the overall protocol has been calculated according to Karimollah Hajian-Tilaki 2014 for diagnostic studies [23]: assuming a sensitivity of 98.5 % in predicting positive SLNs at histology, a pathological lymph node prevalence of 14.2 %, a precision of estimate (i.e., the maximum marginal error) d= 5 %, a type I error $\alpha = 0.05$, a sample size of 141 patients is needed to test the general hypothesis (i.e. to answer whether SLN(s) identified with ICG can accurately predict nodal status at histology of patients with apparently early EOC). Assuming a drop-out rate of 20 %, a total of 176 patients should have been enrolled in the study.

Statistical analysis has been performed using IBM-SPSS Statistical

Software. Results are presented as absolute frequency (percentage) for nominal variables and as median (interquartile range, IQR) for continuous variables not normally distributed. Mann-Whitney tests and $\chi 2$ or Fisher's exact test have been used as appropriate, in order to assess if there were differences in clinical, pathological and surgical characteristics of patients with successful versus unsuccessful mapping. Significance was set at $P < 0.05$.

3. Results

Between March 2018 and July 2022, 174 patients were enrolled and 169 (97.1 %) received complete study interventions (injection of dye, attempted SLN mapping, and para-aortic +/- pelvic lymphadenectomy) as shown in Fig. 1.

Baseline and pathological characteristics of the entire population and stratified according to mapping results are provided in Table 1. Enrollment per center is reported in Supplementary Table 1.

The median age of patients was 55 years (IQR 49–63). 80 of 174 (46 %) patients had serous histology and 99 (56.9 %) had high-grade. 20 of 174 (11.5 %) had lymph-node metastasis in the SLN or lymphadenectomy specimens. Advanced FIGO stage cases (IIIB) were only diagnosed upon final pathology as they initially displayed apparent radiological early stage and PIV according to Fagotti's score of 0.

Among the 20 (11.5 %) patients with at least one intraoperative complication, 1 (0.6 %) grade 5 adverse event occurred; moreover, 31 postoperative complications occurred in 25 patients (14.4 %; 12 G1; 9 G2; 2 G3, 2 G4) [22,24]. None of the adverse events reported above was found to be study procedure related (see Supplementary Table 2).

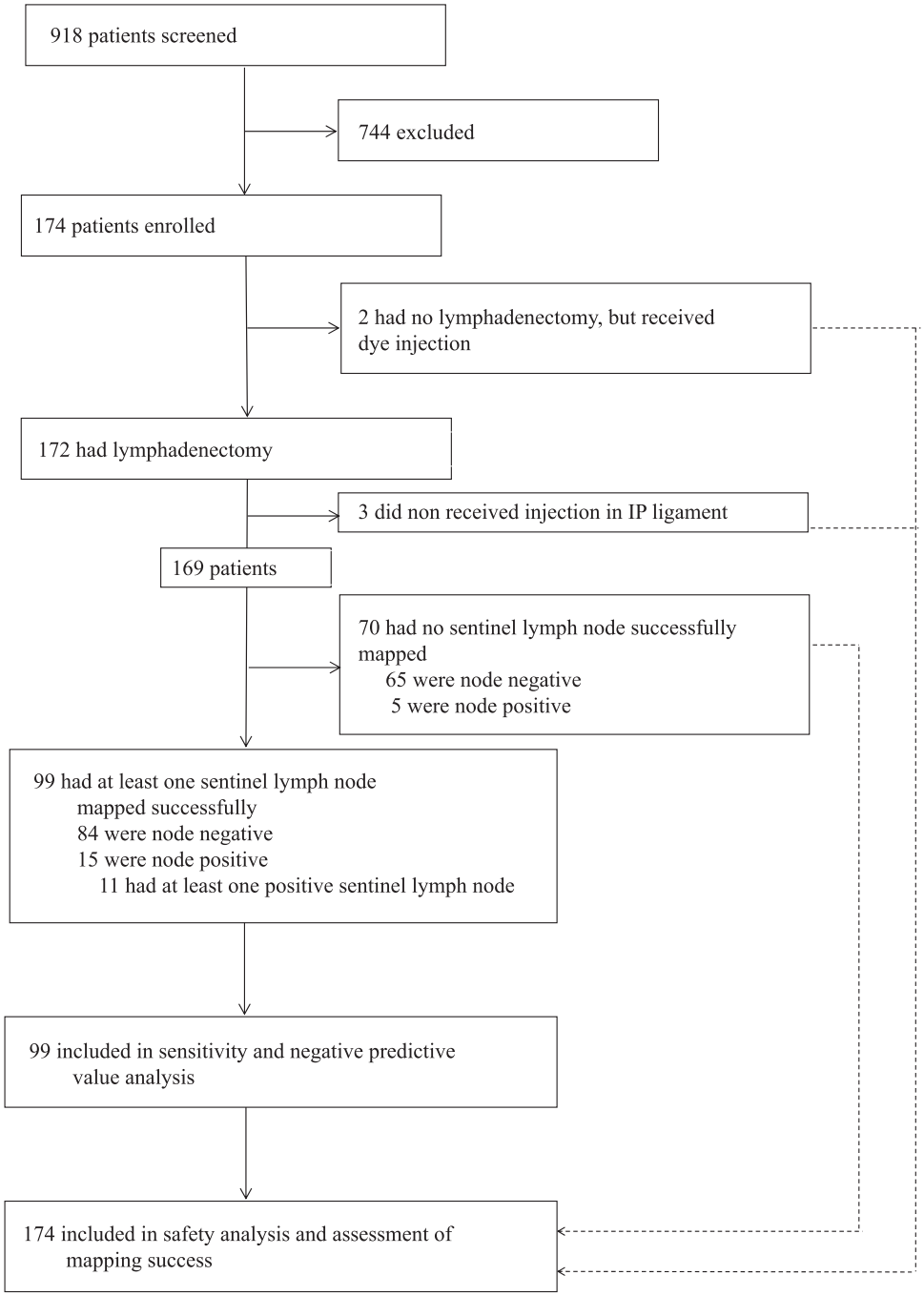

Fig. 1. Study interventions.

Table 1
Baseline and pathological characteristics.

Characteristics	All cases (n = 174)	Successfull mapping (n = 102)	Unsuccessfull mapping (n = 72)
Age (years) *	55 (49–63)	55 (48–63)	56 (52–63)
BMI (kg/m^2) *	23·6 (21·6–26·9)	23·7 (20·9–26·7)	23·5 (22·0–27·3)
ASA			
0	1 (0·6)	1 (1·0)	0
1	17 (9·8)	11 (10·8)	6 (8·3)
2	106 (60·9)	55 (53·9)	51 (70·8)
3	4 (2·3)	3 (2·9)	1 (1·4)
4	1 (0·6)	1 (1·0)	0
Missing	45 (25·9)	31 (30·4)	14 (19·4)
Charlson Comorbidity Index *	4 (3–6)	4 (3–6)	4 (4–6)
Type of surgery			
Immediate staging	122 (70·1)	77 (75·5)	45 (62·5)
Delayed staging	52 (29·9)	25 (24·5)	27 (37·5)
Previous Hysterectomy			
Yes	8 (4·6)	5 (4·9)	3 (4·2)
No	166 (95·4)	97 (95·0)	69 (95·8)
Histology			
Serous High Grade Carcinoma	80 (46·0)	43 (42·2)	37 (51·4)
Mucinous or serous-mucinous	6 (3·4)	5 (4·9)	1 (1·4)
Serous Low Grade Carcinoma	2 (1·1)	1 (1·0)	1 (1·4)
Transitional Cell Carcinoma	1 (0·6)	1 (1·0)	0
Mixed	2 (1·1)	2 (2·0)	0
Clear Cell Carcinoma	35 (20·1)	18 (17·6)	17 (23·6)
Endometrioid Carcinoma	32 (18·4)	23 (22·5)	9 (12·5)
Undifferentiated	1 (0·6)	1 (1·0)	0
Borderline	1 (0·6)	1 (1·0)	0
Metastasis	1 (0·6)	1 (1·0)	0
Other	13 (7·5)	6 (5·9)	7 (90·7)
Grading			
1	10 (5·7)	7 (6·9)	3 (4·2)
2	23 (13·2)	15 (14·7)	8 (11·1)
3	100(57·5)	56 (54·9)	44 (61·1)
Not applicable	40 (23)	23 (22·5)	17 (23·6)
Missing	1 (0·6)	1 (1·0)	0
Final FIGO Stage			
IA	60 (34·5)	34 (33·3)	26 (36·1)
IB	11 (6·3)	6 (5·9)	5 (6·9)
IC1	16 (9·2)	13 (12·7)	3 (4·2)
IC2	10 (5·7)	4 (3·9)	6 (8·3)
IC3	3 (1·7)	1 (1·0)	2 (2·8)
IIA	24 (13·8)	15 (14·7)	9 (12·5)
IIB	22 (12·6)	12 (11·8)	10 (13·9)
IIIAii	12 (6·9)	11 (10·8)	1 (1·4)
IIIA2	4 (2·3)	1 (1·0)	3 (4·2)
IIIB	10 (5·7)	3 (2·9)	7 (9·7)
N.A.	2 (1·1)	2 (2·0)	0

BMI: Body Mass Index.
ASA: American Society of Anesthesiologists.
FIGO: International Federation of Gynecology and Obstetrics (Fédération Internationale de Gynécologie et d'Obstétrique).
N.A.: not applicable
* Data are reported as median and inter-quartile range

Surgical findings in patients receiving complete study interventions are reported in Table 2.

Bilateral pelvic and para-aortic lymph node dissection was performed in 163 of 169 patients (96.4 %). Overall, the median number of nodes removed per patients was 20 (range 15–29). The infundibolopelvic ligament was injected alone in 118 of 169 patients (69.8 %) while in 51 (30.2 %) together with the legamentum ovarii proprium.

Mapping was successful, identifying at least one SLN, in 99 of 169 patients (58.6 %). Overall, 208 SLNs were identified. The distribution and frequency of their locations are represented in Fig. 2.

Table 2
Surgical findings in assessable patients (n = 169).

Characteristics	All cases (n = 169)	Successfull mapping (n = 99)	Unsuccessfull mapping (n = 70)	p value
Extension of lymphadenectomy:				0.210
Paraaortic	6 (3.6)	5 (5.1)	1 (1.4)	
Pelvic and Paraaortic	163 (96.4)	94 (94.9)	69 (98.6)	
Lymph nodes removed				
Number by patient	20 (15–29)	21 (15–29)	20 (14–29)	0.691
< 20	79 (46.7)	45 (45.5)	34 (48.6)	0.689
≥ 20	90 (53.3)	54 (54.5)	36 (51.4)	
Pelvic lymph nodes				0.627
< 10	72 (44.2)	40 (42.6)	32 (46.4)	
≥ 10	91 (55.8)	54 (57.4)	37 (53.6)	
Para-aortic lympho nodes				0.671
< 10	95 (56.2)	57 (57.6)	38 (54.3)	
≥ 10	91 (55.8)	54 (57.4)	32 (45.7)	
Injection Site				
Infundibolopelvic ligament	118 (69.8)	64 (64.6)	54 (77.1)	0.081
Infundibolopelvic ligament and Legamentum ovarii propriium	51 (30.2)	35 (35.4)	16 (22.9)	
SLN identification				
Yes	99 (58.6)			
No	70 (41.4)			
Number of SLN identified				
1	48 (48.5)			
2	23 (23.2)			
More than 2	28 (28.3)			

The most frequent sites were low para-caval (34 [17 %]), para-aortic infra-renal (33 [16 %]), low inter aorto-caval (26 [12.7 %]), para-aortic infra-mesenteric (26 [12.7 %]) and left external iliac (25 [12 %]). A lower proportion of the patients in the delayed-staging group had a successful SLN mapping compared with the patients receiving immediate staging, however this was not statistically significant (49.0 % vs 62.5 % p = 0.105). Among patients undergoing both IP and utero-ovarian ligament injections (51, 30.2 %) as well as systematic pelvic and aortic lymphadenectomy, SLN detection rate was 35/51 (68.6 %) with a sensitivity of 75.0 % and accuracy of 97.1 %.

Twenty of 169 (11.8 %) patients had positive nodes (including isolated tumor cells [ITC]) and 15 of 99 (15.1 %) patients who had a successful SLN mapping had positive nodes. Of these, 11 of 15 (73.3 %) patients had a correct identification of the disease in the SLN (isolated tumor cells 3; micrometastasis 1; macrometastasis 7). Seven out of 11 (63.6 %) patients required ultrastaging protocol to detect nodal metastasis (7/20 – 35.0 % of total node-positive patients). Four (26.7 %) node-positive patients had negative SLN(s) (details in Supplementary Fig. 1). Among them, two patients with pelvic positive pelvic-nodes underwent injection of dye in the legamentum ovarii proprium without mapping on the side of metastasis. All these patients had grade 3 disease and elevated pre-operative CA125 levels.

Sensitivity and specificity are shown in Table 3 and were 73.3 % and 100.0 %, respectively.

Nine of 15 (60%) patients with positive nodes and SLN identified had only SLN containing metastatic disease while two of 11 (18%) patients having positive SLN had additional positive non SLNs. In the overall node-positive population (N = 20), 45.0 % exclusively exhibited metastatic disease in SLNs. SLNs had metastatic disease in 13 of 208 [6.2 %] v compared to non-SLNs (13 of 3829 [0.34 %]).

Considering clinical risk factors for lymphatic metastatic disease in

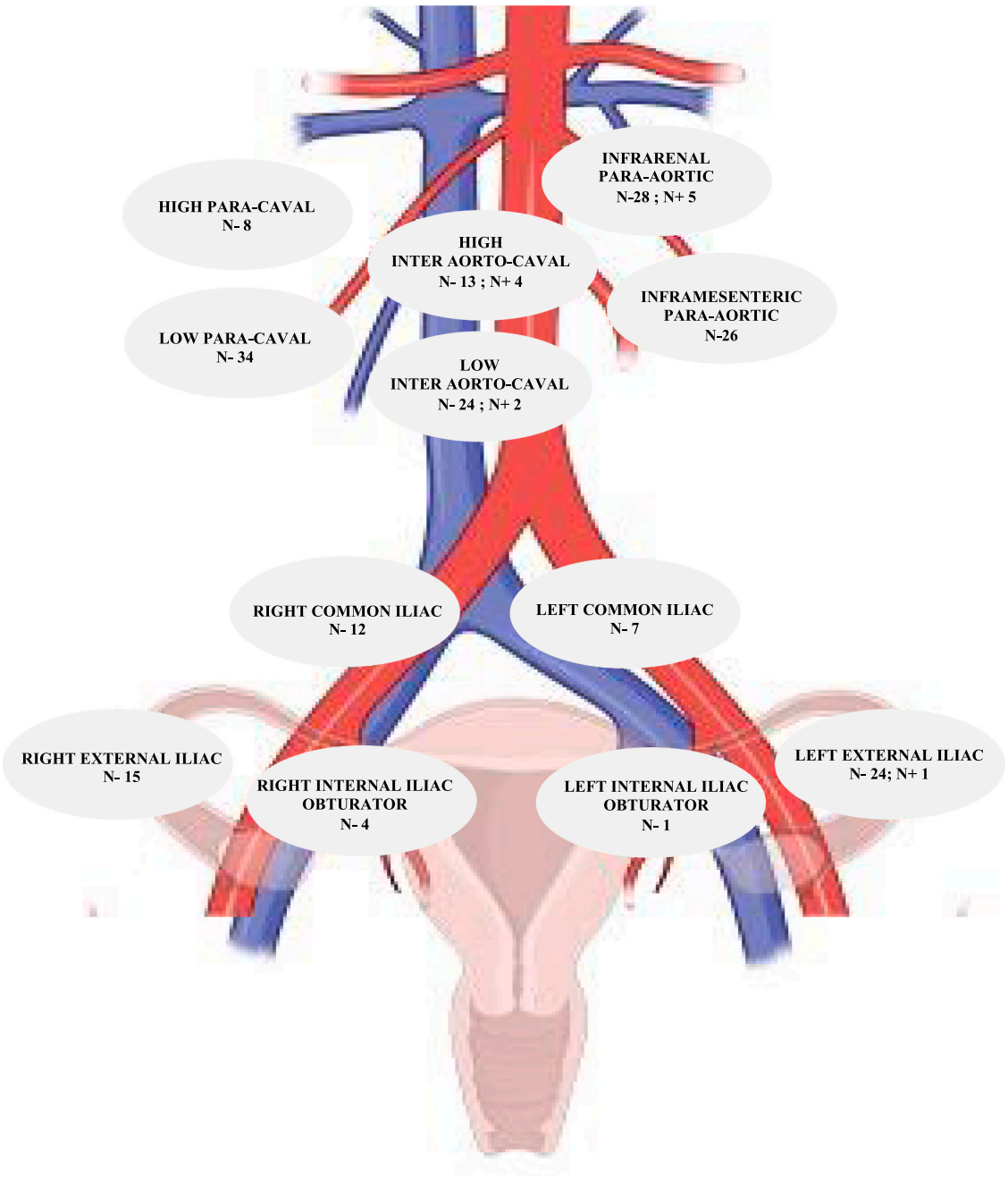

Fig. 2. Distribution and frequency of SLN locations (N-=negative SLNs; N + =positive SLNs).

Table 3
Diagnostic performance.

Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Accuracy (%) (95% CI)	PPV (%) (95 % CI)	NPV (%) (95 % CI)	TP (n)	FP (n)	TN (n)	FN (n)	Total (n)
73.3 (50.9–95.7)	100.0	96.0 (92.1–99.8)	100.0	95.5 (91.1–99.8)	11	0	84	4	99

Isolated Tumor Cells considered as positive.
PPV Positive Predictive Value.
NPV Negative Predictive Value.
TP True Positive
FP False Positive
TN True Negative
FN False Negative
CI Confidence Interval

early stage ovarian cancer, all patients with positive nodes had at least one known risk factor; in particular Ca125 levels were significantly more elevated in node positive EOC patients compared to the node negative ones ($p = 0.053$) [25] (see Supplementary Table 3).

4. Discussion

The results of this prospective multicenter study show that SLN biopsy did not reach the expected sensitivity (73.3 %), although 100 % of specificity and 96 % of accuracy. The false negative rate was 26.6 % meaning that 1 out of 4 early stage EOC patients might have her metastatic lymphatic disease unrecognized by SLN biopsy. Moreover, the observed negative predictive value of 95.5 % indicates that lymph nodes status cannot be fully predicted by SLN evaluation alone. Considering that the negativity of a SLN could serve as a reliable surrogate marker of negative lymph node status along the entire pathway of lymphatic drainage, the obtained results suggest that SLN cannot safely replace lymphadenectomy in the staging of early stage EOC.

Moreover, the technique itself was challenging limiting the feasibility and reproducibility of the approach: in 41.4 % (70 of 169) of the patients the injection of dye failed in identifying a SLN even though it should be noted that only 30.2 % received injection in both the infundibolopelvic ligament and the legamentum ovarii proprium. In this context, one may argue that the injection of the dye after the salpingo-oophorectomy has been performed, could represent a limitation of the technique impacting the flow of the dye and potentially creating retro- and intra-peritoneal spillage of ICG thus making difficult the SLN detection. However, direct injection into the mass can potentially lead to intraoperative spillage of the ovarian mass, with consequent impact on patients prognosis. Moreover, the volume required in the protocol (2 mL) could have been excessive considering the thickness of peritoneal layer potentially leading to leakage and consequently impacting the study's outcomes; additionally, the protocol did not initially include the provision for a second injection following the failure of the first one, although it could have potentially aided in the recovery of some cases. The detection rate reported in this study should be put in the context of other published series. In particular, Lago et al. [26] reported the preliminary results of the SENTOV trial showing a detection rate of 100 % in the para-aortic area and 93 % in pelvic area in 20 patients with ovarian cancer. The updated series reported a detection rate of 91.3 % and 90 % in the pelvic and para-aortic region, respectively [27]. The higher detection rate reported by these studies [26,27] could be attributed to the use of two tracers (ICG and technetium-99 m nanocoloid), to the lower volume of ICG injected (0.5 mL), as well as the evolvement of a single center. Moreover, the lack of standardization in the timing from tracer injection to SLN identification may have negatively affected the detection rate.

We have to acknowledge that in 9 patients out of 72 (12.5 %) the SLN was identified but at the pathology report it contained only fat tissue thus considered as unsuccessful mapping.

On the other hand, the study revealed that 7 of 20 (35.0 %) patients with positive nodes were diagnosed thanks to a pathologically performed ultrastaging protocol on SLN. Occult lymph node metastases in apparent clinically early stage disease range from 6 % to 30 % (mean incidence 15 %), depending on the histological subtypes and grading (para-aortic representing the primary site of lymph node metastasis, often occurring also as isolated metastases in 50–70 %; pelvic and para-aortic LNs in 30 % or pelvic LNs alone in 20 % of cases) [28].

Our data suggests that ultrastaging protocol allowed the identification of otherwise occult lymph node metastasis. Nevertheless, indication to chemotherapy would have been given despite of the upstaging according to international recommendations [29].

Up-to-date, lymphadenectomy has been considered the standard of care, with the exception of well-differentiated and mucinous carcinomas, in which the risk of lymph node metastasis is very low, for surgical staging, guiding the adjuvant chemotherapy regimen, and providing prognostic information.

Although crucial diagnostic information are provided by systematic lymphadenectomy, the only available randomized controlled trial to evaluate its therapeutic role did not show a statistically significant disease free and overall survival difference between systematic lymphadenectomy and lymph nodal sampling [6]. Retrospective evidence suggests that an adequate systematic lymphadenectomy is associated with an improved survival of early stage EOC [11,30]. Nevertheless, no overall survival benefit has been shown while the procedure has been related to increasing post-operative complications and time to chemotherapy [31].

For its procedural complexity requiring surgical expertize, and the occurrence of potentially associated intra- and post-operative complications, SLN mapping has been proposed as a potential alternative to lymphadenectomy in early-stage ovarian carcinoma. Currently, the experience with this alternative staging procedure is limited to feasibility studies, different with respect to ovarian pathology, methodology, injection side, dye and cohort size. The pooled SLN detection rates across 9 studies including 113 patients have been reported to be around 93.3% per patient [7]. Very few data are available on the link between the side of injection and the side of SLN identification as it is for endometrial cancer patients [32]. Major strengths of this study are its prospective design with predetermined statistical endpoints and the inclusion of multiple sites including non-academic institutions. A median number of 20 nodes (considered "adequate" lymphadenectomy) were removed per patients with overall 208 identified SLNs, making enrolled patients optimally staged.

Moreover, in this study a uniform ultrastaging protocol has been adopted by all the participant pathological labs ensuring reproducible information as already shown [26]. Main limitations are the lack of oncological outcomes related to the presence of low volume lymph node metastases and the generalizability of the technique given the participation of only highly experienced surgeons. Moreover, it should be considered that neither lymph node regions (pelvic and para-aortic) nor laterality (right and left) was taken into account in the analysis of mapping data. Specifically, the mapping of pelvic sentinel lymph nodes was not assessed in almost 70 % of the enrolled patients, leading to a significant absence of pelvic region mapping and limiting the conclusions of the present study. In those patients undergoing both IP and utero-ovarian ligament, in fact, the detection rate was slightly higher (68.6 %). Recent data showed the possibility of injecting the cervix rather than the utero-ovarian ligament to potentially achieve adequate information regarding the pelvic area decreasing surgical complexity [33]. This should serve as valuable insight for future studies. Moreover, combining ICG with 99mTC-nanocolloid might have enhanced the identification of SLN but the latter tracer can be challenging for community hospitals and not feasible in patients with only a suspicious diagnosis of ovarian cancer, namely all immediate staging patients.

The inclusion of ITC in the positive nodes group can be also argued; nevertheless, although the biological/prognostic significance of ITCs in ovarian cancer is unknown, their presence, is designated as pN0(i +) according by the AJCC staging system. Another issue is the fact that SLN was performed on the results of frozen section analysis. EOC is a heterogeneous disease with many features able to greatly impact the rate of positive lymph nodes. In detail, low and high grade serous carcinoma may rise above 10 % [34]; on the other hand, in low grade endometrioid and expansile mucinous ovarian carcinoma, the metastasis detection rate accounts for less than 2 % [35].

A better understanding of tumor biology could further refine this risk enabling a more effective selection of EOC patients for SLNs. Finally, the results of pre-planned translational sub-studies within the SELLY trial on liquid biopsy will clarify whether circulating tumor DNA could be informative not only for cancer genomic profiling but also as an additional risk factor for distant metastasis.

5. Conclusion

In a multicenter setting, sentinel-lymph node biopsy in apparent early stage epithelial ovarian cancer had a low detection rate and sensitivity. Nevertheless, 35.0 % of node positive patients was identified only thanks to ultra-staging protocol of sentinel lymph node(s), making this technique an important tool to avoid potential undetected lymph node disease.

CRediT authorship contribution statement

Camilla Nero: Conceptualization, Writing - Original Draft; **Nicolò Bizzarri:** Writing - Review & Editing; **Francesco Cosentino:** Writing - Review & Editing; **Pierandrea De Iaco:** Writing - Review & Editing; **Enrico Vizza:** Writing - Review & Editing; **Stefano Uccella:** Writing - Review & Editing; **Diana Giannarelli**: Formal analysis; **Tina Pasciuto:** Formal analysis; **Anna Fagotti:** Conceptualization, Writing - Original Draft; **Giovanni Scambia:** Conceptualization, Writing - Original Draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113435.

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