GYNECOLOGY

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

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BACKGROUND: Systematic paraaortic and bilateral pelvic lymphadenectomy is the standard of a comprehensive surgical staging in presumed early epithelial ovarian cancer, but no prospective randomized evidence suggests a possible therapeutic value. Moreover, this procedure is associated with potential severe morbidity. The Sentinel Lymph Nodes in Early-Stage Ovarian Cancer trial is a prospective study designed to test whether sentinel node detection can accurately predict nodal status in a cohort of women with early epithelial ovarian cancer.

OBJECTIVES: We here present the results of the first part of the Sentinel Lymph Nodes in Early-Stage Ovarian Cancer trial, regarding the feasibility of the sentinel lymph node technique and the preliminary findings regarding its safety and accuracy.

STUDY DESIGN: The Sentinel Lymph Nodes in Early-Stage Ovarian Cancer trial is a prospective, phase II, single-arm study included patients with presumed stages I—II epithelial ovarian cancer planned for immediate or delayed minimally invasive comprehensive staging. The ovarian pedicle is injected with 2 mL of a 1.25 mg/mL indocyanine green solution. The pelvic and lumboaortic retroperitoneum is then accessed and inspected to identify and remove sentinel nodes. After sentinel node procedure, staging is completed including systematic pelvic and paraaortic lymphadenectomy. Assuming a sensitivity of 98.5% in predicting positive sentinel lymph nodes at histology, a pathological lymph node prevalence of 14.2%, a precision of estimate (ie, the maximum marginal error) d = 5%, a type I error $\alpha = 0.05$, a sample size of 160 patients is needed to test the general hypothesis. Here we present the preliminary results on the first 31 patients enrolled.

RESULTS: Thirty-one patients were included. Sentinel node was identified in 21 patients (detection rate, 67.7%). The detection rate was significantly higher in women undergoing immediate vs delayed staging (88.9% vs 41.7%, $P = .003$). Four patients had positive nodes. In all the patients with lymphatic dissemination, a positive sentinel node was identified (sensitivity, 100%; false-negative rate, 0%; negative predictive value, 100%). One (3.2%) intra- and 2 (6.5%) postoperative grade I complications occurred.

CONCLUSION: Our data show that the detection of sentinel node in early epithelial ovarian cancer is low when patients are submitted to delayed-staging surgery. However, sentinel node procedure is feasible and has the potential to provide reliable and useful information on nodal status and may allow the avoidance of systematic lymphadenectomy in the majority of patients.

Key words: early ovarian cancer, indocyanine green, laparoscopy, lymphadenectomy, minimally invasive surgery, sentinel node

Epithelial ovarian cancer (EOC) still represents the most lethal gynecological tumor with the stage at the time of disease presentation remaining the determining factor in life expectancy.[1]

Only 20—25% of patients are initially diagnosed at the early stage of disease, but almost 30% of them are actually upstaged because of peritoneal or lymph node involvement.[2] The incidence of lymph node metastasis in apparent early-stage EOC is estimated to be around 14—15%[3,4]; approximately 35% of patients have only pelvic-positive nodes, 37% have only paraaortic-positive nodes, and the remaining 28% have both pelvic and paraaortic involvement.[4]

Preoperative imaging has shown low sensitivity in detecting lymph node metastasis; as a consequence, the performance of a complete pelvic and paraaortic lymphadenectomy is recommended as part of surgical staging for this disease,[5,6] and, in fact, data on nodal status appear relevant to guide decisions on adjuvant therapy.[4] However, the prognostic importance of the information provided by full nodal dissection must be balanced against the morbidity related to such a radical surgical procedure: major vessel injuries, excessive blood loss, nerve lesions, increased operative time, lymphocysts formation, lymphorrhea, and lower extremities edema have all been described as possible complications of lymphadenectomy.[7—11]

Although current guidelines recommend lymph node dissection up to the level of the renal vessels, the extent of lymph node dissection differs from center to center, likely because of the technical difficulty of the procedure and the possible presence of patients' comorbidities.[12—14]

Lymphatic mapping for the assessment of sentinel lymph nodes (SLNs) is a widely accepted part of the surgical treatment of breast and cutaneous melanoma.[15,16] This practice is being successfully implemented also in several gynaecological malignancies including vulvar, cervical, and endometrial cancers, allowing a better individualization of treatment.[17—20]

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AJOG at a Glance

Why was the study conducted?

This prospective trial was conducted to assess whether sentinel lymph node biopsy is a feasible and reliable procedure in early-stage ovarian cancer.

Key findings

The detection rate was 67.7%. In all the patients with lymphatic dissemination, a positive sentinel lymph node was identified (sensitivity,100%; false-negative rate, 0%; negative predictive value, 100%).

What does this add to what is known?

Sentinel lymph node biopsy may be a promising procedure that could reduce the morbidity of surgical staging by lymphadenectomy while accurately identifying patients with lymph node metastasis who benefit from adjuvant therapy.

So far, only 5 case series and 3 case reports have investigated the role of SLN biopsy in early-stage EOC.[21,22] These studies reported inconclusive findings because of several limitations, including small sample sizes (overall only 34 EOC patients were enrolled), variable injection sites (ovarian cortex, proper and infundibulopelvic ligament, mesoovarium, and cervix), and tracers (charcoal solution, Technetium-99, and methylene blue, indocyanine green) and wide detection rates.[21]

The Sentinel Lymph Nodes in Early-Stage Ovarian Cancer (SELLY) trial is a prospective study designed to test whether SLN detection can accurately predict nodal status in a cohort of women with early EOC. We here present the preliminary results of the trial in terms of feasibility, safety, and accuracy (defined by detection rate, false-negative rate, negative predictive value, and specificity).

Materials and Methods

Study design and participants

The SELLY trial is a prospective, multicenter study designed to assess the feasibility, safety, detection rate, and the sensitivity/negative predictive value of SLN in assessing the presence or absence of lymph node metastasis in early-stage EOC patients. The enrollment started in March 2018.

The study accrues patients at 4 Italian hospitals (Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome; Ospedale degli Infermi, Biella; University of Insubria, Varese; and National Cancer Institute Regina Elena, Rome), and it is expected to enroll a total of 176 patients. Details of the protocol are provided at clinicaltrials.gov (https://www.clinicaltrials.gov/ct2/show/NCT03452982).

Participating surgeons are required to have an extensive background in gynecological oncology in particular in advanced surgical procedures for early EOC, defined as the performance of at least 10 laparoscopic systematic pelvic and paraaortic lymphadenectomies per year before the initiation of enrollment.

Patients are eligible if they have an apparent International Federation of Gynecology and Obstetrics stages I–II histologically proven EOC and if they are submitted to immediate or delayed (in case of an incidental diagnosis of EOC) minimally invasive comprehensive staging surgery. Other eligibility criteria include an age between 18 and 80 years; an Eastern Cooperative Oncology Group performance status $\leq$2; an adequate respiratory, hepatic, cardiac, bone marrow, liver, and renal function (creatinine clearance >60 mL/min according to Cockroft formula); and negative preoperative computer tomography scan imaging for positive nodes (defined as lymph modes <1 cm in their larger axis).

Patients are excluded in case of evidence of carcinomatosis; mucinous-only—definitive histology (ie, 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 paraaortic region; hepatic dysfunction defined as a model for end-stage liver disease score of 10 or greater; renal dysfunction defined as serum creatinine of 2.0 mg/dL or greater; a history of allergy to indocyanine green, iodine, iodine dyes, isosulfan blue, or triphenylmethane; a history of a malignant lymphoma; a history of a malignant tumor in the abdominal cavity; previous abdominal radiation therapy; pregnancy or lactation; and refusal to provide written informed consent.

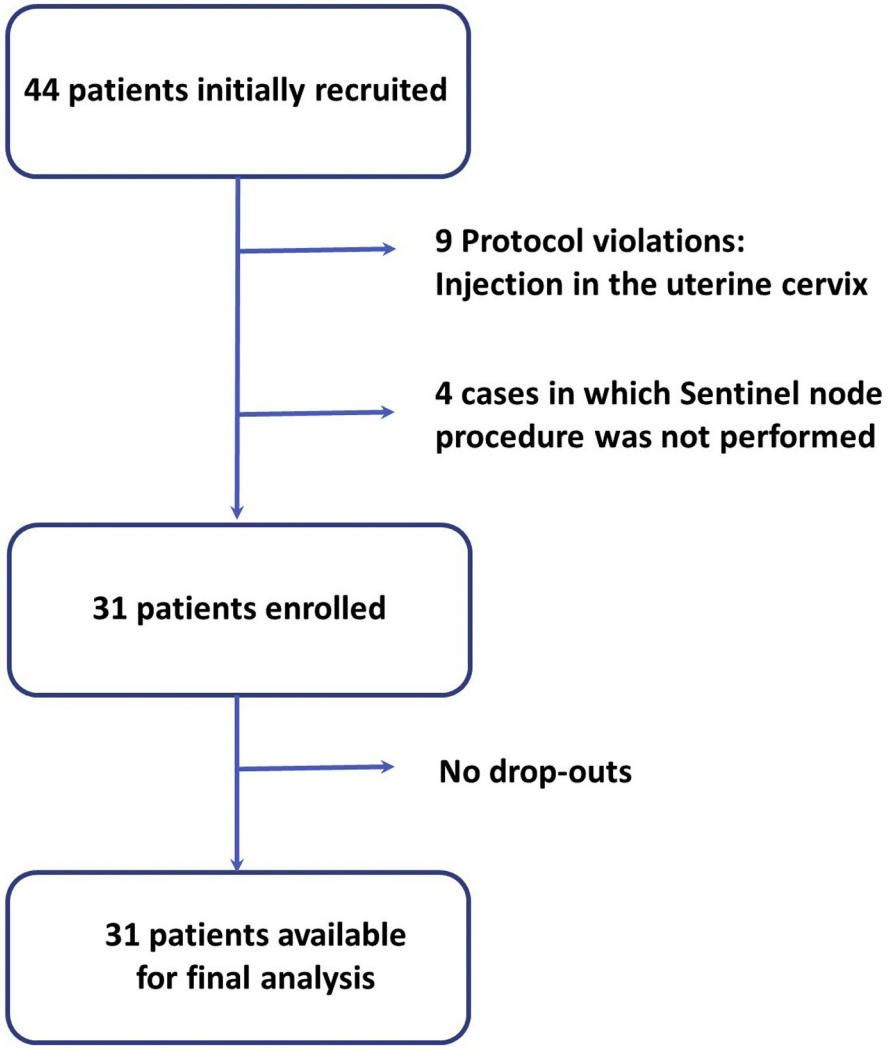
The protocol was approved by the Institutional Review Board of the Department of Sciences of Women's and Child's Health of the Policlinico Universitario A. Gemelli IRCCS and at each participating center, and all patients enrolled gave their written informed consent for participation. Patients' data were prospectively collected in a web-based software (REDCap).[23] The specific case of 1 patient with isolated tumor cells in a paraaortic SLN has already been described in a previous publication by our group.[19]

Procedures

Two milliliters of a 1.25 mg/mL indocyanine green (ICG) solution (Novadaq Technologies, Mississauga, ON, Canada) are injected with a 200 mm long, 20 gauge spinal needle inserted into the perivascular connectival tissue of the infundibulo-pelvic ligament and, when hysterectomy has not been previously accomplished, into the uterine stump of the ligamentum ovarii proprium (ie, the uteroovarian ligament) of the affected, previously removed, ovary/ies. In case of a laparoscopic staging, the needle will be inserted transcutaneously under laparoscopic guidance.[21,22]

The ICG dose of tracer was chosen following the results of other international trials in gynecological malignancies.[19-22,24,25] Approximately 5–20 minutes after the injection, the bilateral pelvic and aortic retroperitoneum is

FIGURE 1
Study algorithm



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inspected, switching the camera to near infrared mode to identify any lymphatic fluorescence imaging.

Laparoscopic PinPoint (Novadaq Technologies), an Olympus system (Olympus Winter and Ibe GmbH, Hamburg, Germany), or a robotic system (DaVinci Surgical System, Da Vinci Surgery, Sunnyvale, California) is used to detect ICG-positive SLN.

Once mapping of the pelvic and aortic region is completed and documented through a graphical data map, identified SLNs are excised, labeled for location, and sent separately for ultrastaging analysis. Fluorescent channels are followed in both directions to identify lymph nodes to be excised.

After the SLN procedure, systematic pelvic and paraaortic lymph node dissection up to the level of the renal vessels, as well as other surgical staging procedures, are performed according to the National Comprehensive Cancer Network guidelines.[12] A conservative surgical option with the preservation of contralateral ovary and uterus is offered to young patients with unilateral tumors and a strong desire of fertility preservation after accurate counseling.[26] Also in cases of fertility-sparing surgery, bilateral systematic pelvic lymphadenectomy is accomplished.

All sentinel lymph nodes resected are examined by hematoxylin and eosin staining. The negative ones are ultrastaged following a protocol based on multiple hematoxylin and eosin sections combined with immunohistochemistry (anticytokeratin AE1:AE3; Ventana Medical Systems, Inc, Tucson, AZ).[27]

Macrometastases are defined as foci of metastasis greater than 2 mm, micrometastases between 0.2 and 2 mm, and isolated tumor cells less than 0.2 mm in greatest dimension or individual pathological cells staining positive for pancytokeratin AE1 or AE3.[28] Pathological specimens are analyzed by dedicated pathologists at each institution.

Patients are monitored for any adverse event or toxicity up to at least day 30 after surgery. Adverse events are classified according to the Clavien-Dindo classification[29] and assigned relationship (suspected or ascertained) to ICG usage.

Outcomes

The present report shows a preliminary analysis of the first 31 patients enrolled in the SELLY protocol. The primary endpoint of this preliminary analysis was to assess the feasibility of the SLN procedure in EOC with ICG injected into the ovarian pedicle. The secondary endpoints were a pilot analysis regarding the safety (in terms of complication rate), detection rate (defined as the rate of intraoperative detection of at least 1 SLN per patient), and the negative predictive value of the technique.

Statistical analysis

Statistical analysis has been performed using STATA (STATA/IC 13.0 for Windows; StataCorp LP, College Station, TX).

Results are presented as absolute frequency (percentage) for nominal variables and as median (minimum-maximum) for continuous variables not normally distributed. Mann-Whitney tests and a $\chi 2$ or Fisher exact test have been used as appropriate to assess whether there were differences in clinical, pathological, and surgical

TABLE 1
Baseline and pathological characteristics according to sentinel lymph nodes mapping

Characteristics	All cases (n = 31)	Successful mapping (n = 21)	Unsuccessful mapping (n = 10)	*P* value
Age, y	56.3 (48.5–64)	55.4 (45–67)	58.1 (53–62.8)	.519
BMI, kg/m^2	25.2 (21.7–27.8)	25.2 (21.3–27.2)	25.1 (23.4–28)	.894
ASA				.756
0	1 (3.2)	1 (4.8)	0 (0.0)	
1	14 (45.2)	9 (42.9)	5 (50.0)	
2	16 (51.6)	11 (52.4)	5 (50.0)	
Charlson Comorbidity Index	2 (0–5)	2 (0–5)	2.5 (0–4)	.466
Type of surgery				
Immediate staging	18 (58.1)	16 (76.2)	2 (20.0)	.003
Delayed staging	13 (41.9)	5 (23.8)	8 (80.0)	
Histology				.705
Serous high-grade carcinoma	15 (48.4)	9 (42.9)	6 (60.0)	
Mixed serous-mucinous	2 (6.5)	2 (9.5)	0 (0.0)	
Clear cell carcinoma	5 (16.1)	3 (14.3)	2 (20.0)	
Endometrioid carcinoma	8 (25.8)	6 (28.6)	2 (20.0)	
Undifferentiated	1 (3.2)	1 (4.8)	0 (0.0)	
Grading				.669
2	7 (22.6)	4 (19)	3 (30.0)	
3	19 (61.3)	14 (66.7)	5 (50.0)	
Not applicable	5 (16.1)	3 (14.3)	2 (20.0)	

Results are presented as n (percentage) or median (minimum-maximum) as appropriate.

ASA, American Society of Anesthesiologists physical status classification system; *BMI*, body mass index.

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characteristics of patients with successful vs unsuccessful mapping. Significance was set at $P < .05$.

Sample size

Sample size for the overall protocol has been calculated according to Hajian-Tilaki[30] for diagnostic studies: assuming a sensitivity of 98.5% in predicting positive sentinel lymph nodes at histology, a pathological lymph node prevalence of 14.2%, a precision of estimate (ie, the maximum marginal error) of d = 5%, a type I error of $\alpha = 0.05$, a sample size of 160 patients is needed to test the general hypothesis (ie, to answer whether SLN [s] identified with ICG can accurately predict nodal status at histology of patients with apparently early EOC). Assuming a dropout rate of 10%, a total of 176 patients will be enrolled in the study.

For this preliminary analysis, we arbitrarily decided that an initial sample of 30 patients would have been sufficient to detect possible criticisms of the protocol and to draw preliminary conclusions regarding the feasibility of the technique.

Data collection and management

A customized electronic case report form has been created for the study and is completed for all patients who have given informed consent. Study data are collected prospectively and managed using REDCap electronic data capture tools hosted at Fondazione Policlinico Universitario A. Gemelli, IRCCS (https://redcap.policlinicogemelli.it).

Only people officially registered as study investigators or data managers will receive a user login to access the REDCap web platform and enter/manage data.

Ethical issues

This trial is carried out in compliance with the protocol, designed to ensure adherence to good clinical practice, as described in:

1. ICH Harmonised Tripartite Guidelines for Good Clinical Practice, 1996. Note for guidance on good clinical practice CPMP/ICH/135/95.
2. EU Directive 2001/20/EC, 2005/28/EC.
3. Declaration of Helsinki (1964, and its amendments and subsequent clarifications).

TABLE 2
Surgical characteristics according to sentinel lymph nodes mapping

Characteristics	All cases (n = 31)	Successful mapping (n = 21)	Unsuccessful mapping (n = 10)	*P* value
Route of surgical staging				.583
LPS	26 (83.9)	18 (85.7)	8 (80.0)	
Robot	4 (12.9)	2 (9.5)	2 (20.0)	
LPS with conversion to LPT	1 (3.2)	1 (4.8)	0 (0.0)	
Operative time, min	230 (110–540)	263 (145–540)	210 (110–350)	.268
Blood loss >0 mL	26 (83.9)	19 (90.5)	7 (70.0)	
Median EBL in case of blood loss, mL	150 (50–500)	150 (50–500)	100 (50–200)	.231
Extension of lymphadenectomy				.483
Pelvic	0 (0.0)	0 (0)	0 (0.0)	
Paraaortic	1 (3.2)	1 (4.8)	0 (0.0)	
Pelvic and paraaortic	30 (96.8)	20 (95.2)	10 (100)	
Lymph nodes removed (median, per patient)	26 (11-58)	27 (12-58)	25 (11-38)	.693
<20	10 (32.3)	7 (33.3)	3 (30.0)	.853
≥20	21 (67.7)	14 (66.7)	7 (70.0)	
Intraoperative complications	1 (3.2)	1 (100)	0 (0)	1.000
Postoperative complications	2 (6.5)			
Grade I	2 (100)	0 (0.0)	2 (100)	.034

Results are presented as n (percentage) or median (minimum-maximum) as appropriate.

EBL, estimated blood loss; *LPS*, laparoscopy; *LPT*, laparotomy.

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Results

A total of 44 patients were considered eligible and provided their consent to the procedure. In 9 of these, a protocol violation occurred (ie, the injection of ICG was not performed into the ovarian pedicle), and in 4 of them, the procedure was not accomplished because the surgeon did not participate to the protocol. As a consequence, 31 patients have been included in the present study (Figure 1).

Baseline and pathological characteristics of the entire population and stratified according to mapping results are provided in Table 1. In 21 of the total 31 cases, at least 1 SLN was identified, for an overall detection rate of 67.7%. A significantly lower proportion of the patients in the delayed-staging group (ie, staging in a subsequent operation, within 30 days after an initial surgical procedure for the removal of a suspicious ovarian mass) had a successful SLN mapping compared with the patients receiving immediate staging (5 of 13, 38.5%, in the delayed-staging vs 16 of 18, 88.9%, in the immediate-staging group; $P = .003$).

Most of the patients (27 of 31, 87.1%) had an apparent stage I disease. Overall, 5 of 31 patients (16.1%) were upstaged after surgical staging: 3 (9.7%) because of lymph node metastasis and 2 (6.4%) because of peritoneal metastasis. No metastatic nodes were found on the side opposite the affected ovary. Serous high-grade histology was the prevalent histotype in our population.

Surgical characteristics are shown in Table 2. All patients but 1 underwent both pelvic and paraaortic nodal dissection. In all cases paraaortic dissection was extended up to the level of the left renal vein. The median number of lymph nodes removed per patient was 26.5 (range, 11–58): the median number of pelvic and paraaortic lymph nodes was 12 (range 4–43) and 10 (range 2–29), respectively.

All patients received an adequate dissection of at least 10 lymph nodes[31]; in 21 patients (67.7%), the number of lymph nodes removed was ≥20 lymph nodes. One intraoperative complication (superficial bladder injury repaired by laparoscopy) (3.2%) and 2 postoperative grade I complications (1 chyloascites treated with a low-fat diet and 1 fever treated with antipyretics) (6.5%) were registered.

Data regarding SLN detection are provided in Table 3. In 11 cases more than 1 SLN was identified. In 4 cases (19.0%), the SLN identified was only in the pelvic area, in 13 (62.0%) it was only in the paraaortic area and in 4 cases (19.0%) in both. The specific anatomical locations of the SLN identified are graphically shown in Figure 2. All SLNs were found on the same side of the affected ovary. No case of intra-

or postoperative complication related to the injection of ICG was registered.

Final pathological characteristics are summarized in Table 4. There were 4 cases of SLN positivity (12.9%): 1 case of isolated tumor cells (3.2%) and 3 cases of macrometastases (9.7%). No cases of false-negative and false-positive SLN were registered both when considering only patients with successful mapping (n = 21) and when considering the entire population (n = 31), for a false-negative rate of 0%, a sensitivity, specificity, and positive and negative predictive value of 100%.

The main findings of the present preliminary study (ie, the overall detection rate, the main anatomical locations of SLNs, the complication rate, and the accuracy of SLNs in predicting nodal status in early ovarian cancer) are summarized in Table 5.

TABLE 3
Data regarding sentinel lymph node detection

Characteristics	All cases (n = 31)
Injection site	
Infundibolopelvic ligament	16 (51.6)
Legamentum ovarii proprium	0 (0)
Both	15 (48.4)
SLN identification	
Yes	21 (67.7)
No	10 (32.3)
Number of SLN identified	2 (1-7)
Median (range)	
1	10/21 (47.6)
2	4/21 (19.0)
>2	7/21 (33.3)
Location of SLN, %	
Pelvic only	4 (19.0)
Lumboaortic only	13 (61.9)
Both pelvic and lumboaortic	4 (19.0)
Specific location of the SLN (patients = 21[a])	
External iliac vessels	6/21 (28.6)
Common iliac artery	2/21 (9.5)
Paracaval	3/21 (14.3)
Inframesenteric intercavoaortic	5/21 (23.8)
Supramsenteric intercavoaortic	2/21 (9.5)
Inframesenteric paraaortic	6/21 (28.6)
Supramesenteric paraaortic	1/21 (4.8)
Intraoperative complications correlated to the SLN detection technique	0 (0)
Yes	0 (0)
No	31 (100)
Adverse events within 30 days correlated to the SLN detection technique	
Yes	0 (0)
No	31 (100)

Results are presented as n (percentage).

SLN, sentinel lymph node.

[a] In 4 cases, SLNs were identified in more than 1 area.

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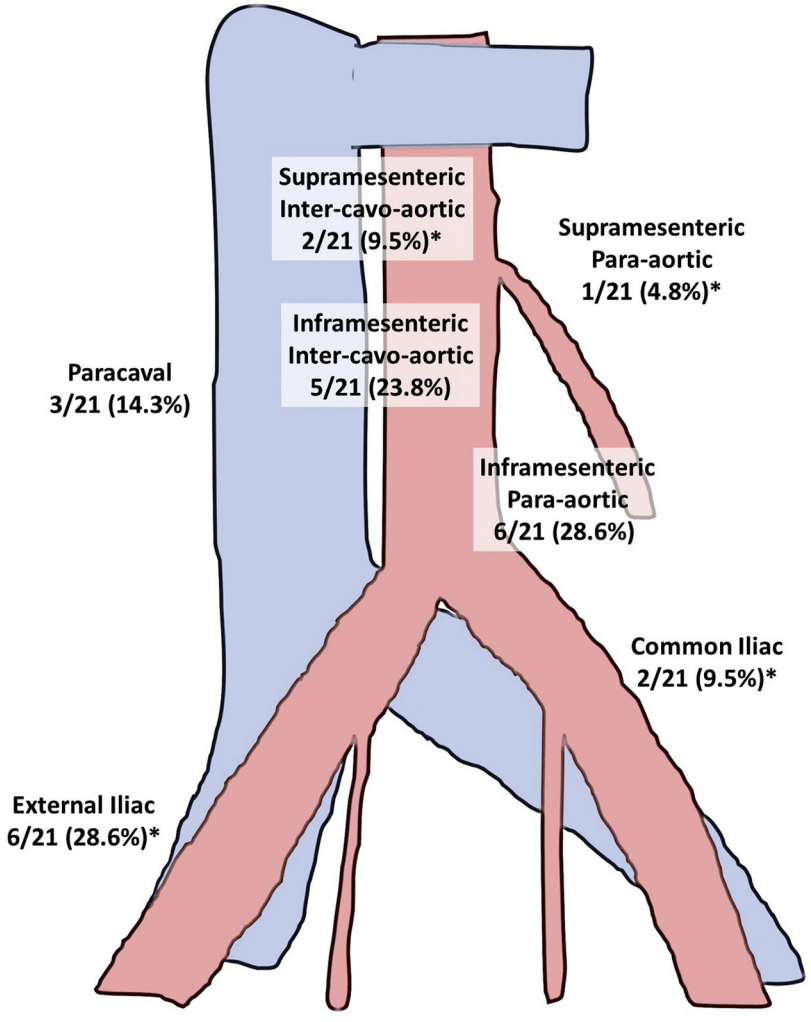
Comment

Principal findings

The present study represents a preliminary safety and efficacy report of the SELLY protocol, a study designed to answer whether SLN(s) identified with ICG can accurately predict nodal status at histology of patients with apparently early-stage EOC. From our preliminary analysis, we can highlight some initial interesting points:

1) The identification of SLN in early EOC using minimally invasive surgery is challenging, even in the hands of expert surgeons treating a high volume of cases in this field because of the technical difficulty of the procedure. Of the 44 women who initially provided informed consent, the procedure was correctly accomplished (because of abandoning by the surgeon or protocol violations) in only 31, and SLN was correctly identified in 21, for an overall detection rate of 67.7%.
2) The fact that we did not register any complication related to the technique suggests that the incidence of common adverse events should be low. Obviously a definitive answer regarding the overall morbidity of the procedure will be drawn at the end of the enrollment of the entire protocol.
3) All cases of nodal positivity were identified by SLN in our series. In other words, our results may suggest that, when there is a correct detection of the SLN, the technique is accurate and reliable in identifying whether retroperitoneal spread of disease has occurred in early EOC. Obviously these preliminary results are not able to answer the overall question

FIGURE 2
Location of the sentinel nodes



In 4 cases, SLNs were identified in more than one area.
The symbol * indicates areas that have been mapped simultaneously in these 4 cases

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regarding the real sensitivity and negative predictive value of the methodology. However, these findings strongly encourage us in completing the SELLY study.

Results of the study in the context of other observations

Compared with previously published data, our detection rate was lower (67.7% vs median 88%).[21] These data may be explained by the inclusion of patients planned for delayed surgical staging, which significantly reduced this value in our series (41.7%, compared with 88.9% in the immediate-staging group).

Because the proportion of patients undergoing delayed staging represents a not negligible number of all the subjects with apparently early EOC, we decided to also candidate these women to the SELLY protocol. As far as the site of injection concerns, the ovarian pedicle represents a safe and reproducible choice.

The ovarian cortex, on the one hand, has been claimed to be a challenging site in case of bulky ovarian mass and a risky one because of possible tumor dissemination.[32] On the other hand, although it has been previously described, there is no clear anatomical background to currently support cervical injection.[21]

Finally, considering the tracer, ICG already has been used in many gynecological malignancies, has had a long record of safety for more than 50 years, and does not require preoperative organization such as the usage of a radioactive isotope does.[19-22,24,25,33]

Clinical Implications

Although radical lymphadenectomy in early EOC currently has an irreplaceable role in accurately defining the stage, its therapeutic value could only be supposed from indirect evidence. The only prospective randomized trial designed to assess the potential therapeutic value of this procedure in presumed early EOC did not reach the statistical power to detect a difference in survival.[34]

The retrospective analysis of the surgical data of a European Organisation for Research and Treatment of Cancer trial,[35] the Surveillance, Epidemiology, and End Results database,[36] and The Netherlands Cancer Registry[31] suggest that the removal of lymph nodes as part of a staging procedure for early stage EOC is associated with an improved survival. On the other hand, the meta-analysis performed on 4 randomized controlled trials highlighted an evident survival benefit for supposed early EOC patients receiving adjuvant chemotherapy, especially if suboptimally staged.[37]

Altogether these data outline that the role of adjuvant chemotherapy and the completeness of surgical staging in early stage EOC are interlinked issues, and it is controversial whether one treatment could avoid the other.[31,37,38] It is more logical to hypothesize that the combination of adequate surgery and proper chemotherapy will result in optimal outcomes.

In this context, SLN biopsy could represent a good compromise. In several solid malignancies, this technique has already been proven as

TABLE 4
Final pathological characteristics

Characteristics	All cases (n = 31)
Final FIGO stage	
IA	12 (38.7)
IB	3 (9.7)
IC3	1 (3.2)
IIA	4 (12.9)
IIB	6 (19.4)
IIIAi	2 (6.5)
IIIAii[†]	2 (6.4)
IIIB	1 (3.2)
Overall N status	
Negative	27 (87.1)
Positive	4 (12.9)
SLN histology	
Negative	17/21 (81.0)
ITCs	1/21 (4.8)
Micro M	0/21 (0)
Macro M	3/21 (14.3)
Non-SLN histology	
Negative	21/21 (100)
ITCs	0/21 (0)
Micro M	0/21 (0)
Macro M	0/21 (0)
Pelvic lymph nodes histology	
Negative	29/30 (96.7)
Positive	1/30 (3.3)
Lumbaraortic lymph nodes histology	
Negative	29 (90.3)
Positive	3 (9.7)

Results are presented as n (percentage).

FIGO, International Federation of Gynecology and Obstetrics; *ITC*, isolated tumor cell; M, metastases; *N*, lymph nodes; *SLN*, sentinel lymph node.

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accurate, cost effective, and related to a marked improvement in postoperative morbidity. If this procedure is demonstrated to be effective and reliable also in early EOC, it would represent a further step toward a less invasive, oncologically safe treatment.

Research implications

From an anatomical point of view, final results of this trial will provide new insights about the possible routes of the ovarian lymphatic drainage. Potential future applications of this technique may include its possible combination with serum biomarkers and radiomics (ie, the quantitative analysis of preoperative ultrasound and/or computed tomography scan images of ovarian masses).

The correlation of this information with SLN status could allow clinicians not only to assess nodal positivity but also to predict lymphatic spread beyond SLN, thus guiding postoperative therapy toward a better personalization of the treatment plan.

Strengths and limitations

To the best of our knowledge, this is the largest study published on SLN in EOC. The possible limitations of the present preliminary report include the relatively small number of patients included and the absence of an exact timing for the detection of SLN. Our data show that detecting SLN may be a difficult and somewhat frustrating procedure (with a low detection rate and a high rate of abandonment of the procedure or protocol violations). Better surgeon education about the protocol should overcome these latter deficiencies and may allow a more efficient running of the study, especially after this encouraging preliminary analysis.

It is, however, likely that even if SLN biopsy in early EOC is proven to be a feasible and reliable procedure, it will not be easily embraced at any center and by any surgeon.

On the other hand, this complexity may be one of the reasons for such a low number of patients who received SLN for early EOC reported in the literature. Of note, the detection rate is significantly lower when delayed staging procedures are accomplished (compared with immediate staging).

From a merely technical point of view, we noticed that the main problem with endoscopic detection of SLN is the spillage and spread of the tracer in the retroperitoneal space, with the consequent impossibility to identify the real drainage of the fluorescent dye. In light of our clinical experience, we suggest some possible solutions to increase the detection of SLN in early EOC: (1) to avoid the use of laparoscopic needles inserted through the trocars but rather to insert the needle transcutaneously and to guide it to the ovarian pedicle with laparoscopic forceps because this may prevent inadvertent spillage of ICG in the trocar and consequent spread of the tracer in all the operative field with a huge reduction in the ability to correctly identify the SLN; (2) to aspirate while

TABLE 5
Main findings of the study

Characteristics	All cases (n = 31)
Detection rate	67.7%
Overall complication rate	9.6%
Complications related to the SLN technique	0%
False-negative rate	0%
Negative predictive value	100%
Sensitivity	100%

SLN, sentinel lymph node.
Uccella et al. Sentinel-node biopsy in early stage ovarian cancer. Am J Obstet Gynecol 2019.

retracting the needle from the ovarian pedicle because this precaution will avoid the spillage of the tracer; and (3) to get the scope very close to the lymphatic tissue to allow a better definition of the lymphatic drainage of the tracer and an easier identification of the correct SLN, particularly in the lumboaortic area.

Conclusion

In conclusion, the present study represents an initial report of a much larger and more ambitious project. It aims at reducing the exposure to the potential toxicity related to a complex surgical operation only to those patients who are really going to benefit from that procedure.

This early preliminary analysis provides extremely encouraging results in defining the possible role of SLN in early EOC and fosters us to continue in the enrollment of patients. Our findings suggest that, although technically challenging, minimally invasive surgical detection of SLN is feasible and potentially reliable in early EOC. Final results of our trial and of the others currently ongoing studies (NCT03452982, NCT02540551, NCT02997553) may definitely establish whether this procedure can provide reliable and useful information on the presence or absence of nodal spread of disease. ■

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References

1. Torre LA, Trabert B, DeSantis CE, et al. Ovarian cancer statistics, 2018. CA Cancer J Clin 2018;68:284–96.
2. Park HJ, Kim DW, Yim GW, Nam EJ, Kim S, Kim YT. Staging laparoscopy for the management of early-stage ovarian cancer: a meta-analysis. Am J Obstet Gynecol 2013;209:58.e1–8.
3. Piver MS, Barlow JJ, Shashikant BL. Incidence of subclinical metastases in stage I and II ovarian carcinoma. Obstet Gynecol 1978;52:100–4.
4. Kleppe M, Wang T, Van Gorp T, Slangen BFM, Kruse AJ, Kruitwagen RFPM. Lymph node metastasis in stages I and II ovarian cancer: a review. Gynecol Oncol 2011;123:610–6.
5. Yuan Y, Gu ZX, Tao XF, Liu SY. Computer tomography, magnetic resonance imaging, and positron emission tomography or positron emission tomography/computer tomography for detection of metastatic lymph nodes in patients with ovarian cancer: a meta-analysis. Eur J Radiol 2012;81:1002–6.
6. Prat J. FIGO Committee on Gynecologic Oncology: staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynecol Obstet 2014;124:e1–5.
7. El-Ghobashy AE, Saidi SA. Sentinel node sampling in gynaecological cancers: techniques and clinical applications. Eur J Surg Oncol 2009;35:675–85.
8. Ghezzi F, Malzoni M, Vizza E, et al. Laparoscopic staging of early ovarian cancer: results of a multi-institutional cohort study. Ann Surg Oncol 2012;19:1589–94.
9. Ghezzi F, Cromi A, Uccella S, et al. Laparoscopy versus laparotomy for the surgical management of apparent early stage ovarian cancer. Gynecol Oncol 2007;105:409–13.
10. Gallotta V, Ghezzi F, Vizza E, et al. Laparoscopic staging of apparent early stage ovarian cancer: results of a large, retrospective, multi-institutional series. Gynecol Oncol 2014;135:428–34.
11. Lee M, Kim SW, Paek J, et al. Comparisons of surgical outcomes, complications, and costs between laparotomy and laparoscopy in early stage ovarian cancer. Int J Gynecol Cancer 2011;21:251–6.
12. National Comprehensive Cancer Network. NCCN practice guidelines. Ovarian cancer, including fallopian tube cancer and peritoneal cancer. Version 2.2018 through March 9, 2018. Available at: www.nccn.org. Accessed June 25, 2019.
13. Carnino F, Fuda G, Ciccone G, et al. Significance of lymph node sampling in epithelial carcinoma of the ovary. Gynecol Oncol 1997;65:467.e72.
14. Wang J, Li J, Chen R, Lu X. Survival effect of different lymph node staging methods on ovarian cancer: an analysis of 10 878 patients. Cancer Med 2018;7:4315–29.
15. Veronesi U, Viale G, Paganelli G, et al. Sentinel lymph node biopsy in breast cancer: ten-year results of a randomized controlled study. Ann Surg 2010;251:595–600.
16. Wong SL, Faries MB, Kennedy EB, et al. Sentinel lymph node biopsy and management of regional lymph nodes in melanoma: American Society of Clinical Oncology and Society of Surgical Oncology clinical practice guideline update. Ann Surg Oncol 2018;25:356–77.
17. Robison K, Fiascone S, Moore R. Vulvar cancer and sentinel lymph nodes: a new standard of care? Expert Rev Anticancer Ther 2014;14:975–7.
18. Holloway RW, Abu-Rustum NR, Backes FJ, et al. Sentinel lymph node mapping and staging in endometrial cancer: a Society of Gynecologic Oncology literature review with consensus recommendations. Gynecol Oncol 2017;146:405–15.
19. Salvo G, Ramirez PT, Levenback CF, et al. Sensitivity and negative predictive value for sentinel lymph node biopsy in women with early-stage cervical cancer. Gynecol Oncol 2017;145:96–101.
20. Uccella S, Buda A, Morosi C, et al. Mini-laparoscopy vs standard laparoscopy for sentinel node dissection: a pilot study. J Minim Invasive Gynecol 2018;25:461–6.
21. Uccella S, Gisone B, Stevenazzi G, Ghezzi F. Laparoscopic sentinel node detection with ICG for early ovarian cancer: description of a technique and literature review. Eur J Obstet Gynecol Reprod Bio 2018;221:193–4.
22. Uccella S, Fagotti A, Zannoni GF, Coleman RL. Presumed early ovarian cancer

with isolated tumor cells in para-aortic sentinel nodes. Int J Gynecol Cancer 2019;29:216–20.
23. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.
24. Rossi EC, Kowalski LD, Scalici J, et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol 2017;18:384–92.
25. Frumovitz M, Plante M, Lee PS, et al. Near-infrared fluorescence for detection of sentinel lymph nodes in women with cervical and uterine cancers (FILM): a randomised, phase 3, multi-centre, non-inferiority trial. Lancet Oncol 2018;19:1394–403.
26. Ghezzi F, Cromi A, Fanfani F, et al. Laparoscopic fertility-sparing surgery for early ovarian epithelial cancer: a multi-institutional experience. Gynecol Oncol 2016;141:461–5.
27. Kim CH, Soslow RA, Park KJ, et al. Pathologic ultrastaging improves micrometastasis detection in sentinel lymph nodes during endometrial cancer staging. Int J Gynecol Cancer 2013;23:964–70.
28. Edge SB, Compton CC. AJCC cancer staging manual, 7th ed. New York: Springer; 2010.
29. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187–96.
30. Hajian-Tilaki K. Sample size estimation in diagnostic test studies of biomedical informatics. J Biomed Inform 2014;48:193–204.
31. Kleppe M, van der Aa MA, Van Gorp T, Slangen BF, Kruitwagen RF. The impact of lymph node dissection and adjuvant chemotherapy on survival: a nationwide cohort study of patients with clinical early-stage ovarian cancer. Eur J Cancer 2016;66:83–90.
32. Negishi H, Takeda M, Fujimoto T, et al. Lymphatic mapping and sentinel node identification as related to the primary sites of lymph node metastasis in early stage ovarian cancer. Gynecol Oncol 2004;94:161–6.
33. Hope-Ross M, Yannuzzi LA, Gragoudas ES, et al. Adverse reactions due to indocyanine green. Ophthalmology 1994;101:529–33.
34. Maggioni A, Benedetti PP, Dell'Anna T, et al. Randomised study of systematic lymphadenectomy in patient with epithelial ovarian cancer macroscopically confined to the pelvis. Br J Cancer 2006;95:699–704.
35. Trimbos JB, Vergote I, Bolis G, et al. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of Cancer-adjuvant Chemotherapy in Ovarian Neoplasm Trial. J Natl Cancer Inst 2003;95:113–25.
36. Chan JK, Munro E, Cheung MK, et al. Association of lymphadenectomy and survival in stage I ovarian cancer patients. Obstet Gynecol 2007;109:12–9.
37. Lawrie TA, Winter-Roach BA, Heus P, Kitchener HC. Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. Cochrane Database Syst Rev 2015:CD004706.
38. Colombo N, Sessa C, du Bois A, et al. ESMO—ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Available at: https://guidelines.esgo.org/media/2017/03/Final-article-Colombo-et-al-2019.pdf. Accessed June 25, 2019.

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