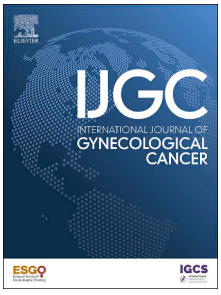
CLINICAL TRIALS

Validation of the Sentinel Lymph Node Technique in Early-stage Ovarian Cancer (SENTOV II)



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ABSTRACT

Background: Pelvic and para-aortic lymphadenectomy remains the standard procedure for nodal staging in apparent early-stage ovarian cancer, but it is associated with considerable morbidity and lacks clear evidence of improving survival. Sentinel lymph node mapping may offer a less invasive alternative while still enabling accurate upstaging in a sub-set of patients with occult lymph node metastasis.

Primary Objective: This study aims to evaluate the negative predictive value of the sentinel lymph node technique for detecting lymphatic metastases in early-stage ovarian cancer compared with systematic pelvic and para-aortic lymphadenectomy (gold standard).

Study Hypothesis: The sentinel lymph node technique is non-inferior to systematic lymphadenectomy for detecting lymphatic metastasis.

Trial Design: This is a multi-center phase III clinical trial. Eligible patients with confirmed early-stage ovarian cancer will undergoing sentinel lymph node mapping and a subsequently complete staging surgery, including systematic lymphadenectomy. The concordance between both methods will be analyzed.

Major Inclusion/Exclusion Criteria: Inclusion: Women aged $\geq$18 years, with histologically confirmed epithelial ovarian malignancy in apparent International Federation of Gynecology and Obstetrics I to II stage, planned for staging surgery either at the time of initial surgery (after intra-operative frozen section confirmation) or after a deferred histologic diagnosis.

Exclusion: Age $<$18 years, previous vascular or lymphatic pelvic/aortic surgery, previous lymphoma or abdominopelvic tumors, allergy to Technetium-99m or indocyanine green, pregnancy/lactation.

Primary Endpoint: Negative predictive value of the sentinel lymph node technique compared to systematic lymphadenectomy for lymph node metastasis.

Sample Size: The planned sample size is 100 patients with negative sentinel lymph node results to ensure adequate statistical power (80%) to detect a negative predictive value for the sentinel lymph node technique above 95%. An interim analysis will be performed once 50% of the recruitment has been reached to adjust the exact total sample size. Recruitment period is estimated at 24 to 36 months in 11 high-volume Spanish centers.

Estimated Dates for Completing Accrual and Presenting Results: Patient accrual: November 2025 to November 2028.

Final results expected: January 2029.

Trial Registration: NCT06963268

Keywords:
Sentinel Lymph Node; Ovarian cancer; Early-stage; Lymphatic mapping

INTRODUCTION

Among patients with apparently early-stage ovarian cancer confined to the ovary or the pelvis, comprehensive surgical staging reveals occult disease, leading to upstaging in about 20% of cases, increasing the rate to 35% or 40% in those with serous histology or high-grade tumors.[1] Specifically, lymph node involvement is estimated to be present in approximately 13% of these patients.[1] Routine systematic lymphadenectomy remains

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controversial because of its associated morbidity and the lack of demonstrated survival benefit.[2] Nevertheless, omission of lymphadenectomy can lead to under-diagnosis, potentially excluding some patients from adjuvant chemotherapy or maintenance therapy.

In this context, selective sentinel lymph node biopsy aims to identify the first lymph node draining the tumor, such that the absence of metastasis predicts negative status in the remaining nodes within that anatomical region. Over the past decades, sentinel lymph node mapping has been successfully introduced into the surgical management of other gynecologic malignancies, but experience with sentinel lymph node mapping in ovarian cancer is limited, with only a few phase II clinical trials and several heterogeneous retrospective studies reported.[3-10]

The SENTOV I trial[6] laid the groundwork for this research by demonstrating the feasibility and safety of the technique, with high detection rates (93% in the pelvic region and 100% in the para-aortic region). Similarly, the recent MELISA trial,[7] which used a comparable protocol, reported a 90% detection rate and a 0% false-negative rate. In contrast, the SELLY trial[8] reported a lower detection rate of 73.3%, although it raised some methodological concerns. The combination of tracers (Technetium-99m and indocyanine green) and the use of low doses (0.25 mL) of indocyanine green in the first 2 studies (SENTOV I and MELISA) likely contributed to their superior outcomes compared with the SELLY trial, according to a recent meta-analysis.[11] Indocyanine green diffusion can lead to over-migration and the identification of "empty packages" (supposed lymph nodes without histological lymphatic content), with a higher risk of spillage in the abdominal cavity if we use high doses (2 mL).[8,12] Moreover, achieving consistent sentinel lymph node detection in the pelvic region remains particularly challenging, prompting the investigation of alternative injection sites, such as the cervix.[13,14]

Based on the available scientific evidence, we have designed this multi-center clinical trial using a dual tracer, a homogeneous technique, a larger sample size, and the implementation of cervical injection as a potential strategy to improve pelvic sentinel lymph node detection rates.

We hypothesize that the sentinel lymph node technique is non-inferior to systematic pelvic and para-aortic lymphadenectomy in detecting lymphatic metastasis in early-stage ovarian cancer, with the potential to minimize unnecessary surgical morbidity without compromising oncologic outcomes.

METHODS

Trial Design

This is a multi-center phase III clinical trial designed to validate the negative predictive value of the sentinel lymph node technique in detecting lymph node metastases in apparent early-stage epithelial ovarian cancer. It is a prospective single-arm diagnostic accuracy study in which all eligible patients will undergo sentinel lymph node mapping (index test), followed by systematic bilateral pelvic and para-aortic lymphadenectomy (gold standard), allowing intra-patient comparison between the 2 techniques.

Sentinel lymph node mapping will be performed using a dual-tracer approach, combining Technetium99m-nanocolloid albumin and indocyanine green. The tracers will be injected at 2 anatomical sites: the infundibulopelvic ligament stump and the cervix. For bilateral disease, both sites will be injected at each side. In women who have previously undergone hysterectomy, only the infundibulopelvic injection will be performed (Fig. 1).

Tracer injection will be performed only after histologic confirmation of malignancy, either intra-operatively by frozen section or at the time of restaging after previous confirmed diagnosis. After injection, intra-operative identification of sentinel lymph nodes will be conducted with a gamma probe to detect radioactivity from Technetium-99m and a near-infrared fluorescence imaging system to visualize indocyanine green in the lymphatic channels and nodes. The migration of tracers will be assessed at least at 0, 15, and 30 minutes after injection. If migration is not observed within 30 minutes, re-injection of indocyanine green will be allowed as per the protocol (only with indocyanine green). Identified sentinel lymph nodes will be excised from the pelvic and para-aortic regions, recording anatomical location. After sentinel lymph node mapping and excision, all patients will undergo full standard surgical staging, including peritoneal washings, total hysterectomy and bilateral salpingo-oophorectomy, omentectomy, and systematic bilateral pelvic and para-aortic lymphadenectomy up to the level of the renal veins.

All sentinel lymph nodes will be serially sectioned at 2-mm intervals along its short axis, following an ultra-staging protocol. A total of 2 sections were examined at each level: 1 was stained with hematoxylin and eosin and 1 was used for immunohistochemistry with CK AE1/3. Nodal metastasis was defined as follows: macro-metastasis ($>$2 mm), micro-metastasis (2 mm to $>$0.2 mm), and isolated tumor cells (0.2 mm). For the purposes of the primary end point analysis, all categories of nodal metastasis (including low-volume metastases) will be considered positive results.

The schema of the study protocol is shown in Figure 2.

Patient recruitment is planned over a 24-month to 36-month period across 11 high-volume gynecologic oncology centers in Spain, with established expertise in gynecologic oncology surgery and technical requirements for sentinel lymph node mapping. Participating centers are required to manage a minimum of 10 cases of early-stage ovarian cancer per year. Initial cases will be performed under supervision of the principal investigator and excluded from analysis until each surgical team demonstrates proficiency in the sentinel lymph node technique, ensuring standardization and minimizing the impact of the learning curve. Formal recruitment will begin only after this training phase is completed.

This trial has been registered at ClinicalTrials.gov (NCT06963268). The study protocol was approved by the institutional review board EU Clinical Trials Regulation and ethics committee under approval code EU CT 2024-520189-67-00.

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Participants

Inclusion criteria: Women aged $\geq$18 years at enrollment; signed informed consent before any study-related procedures;

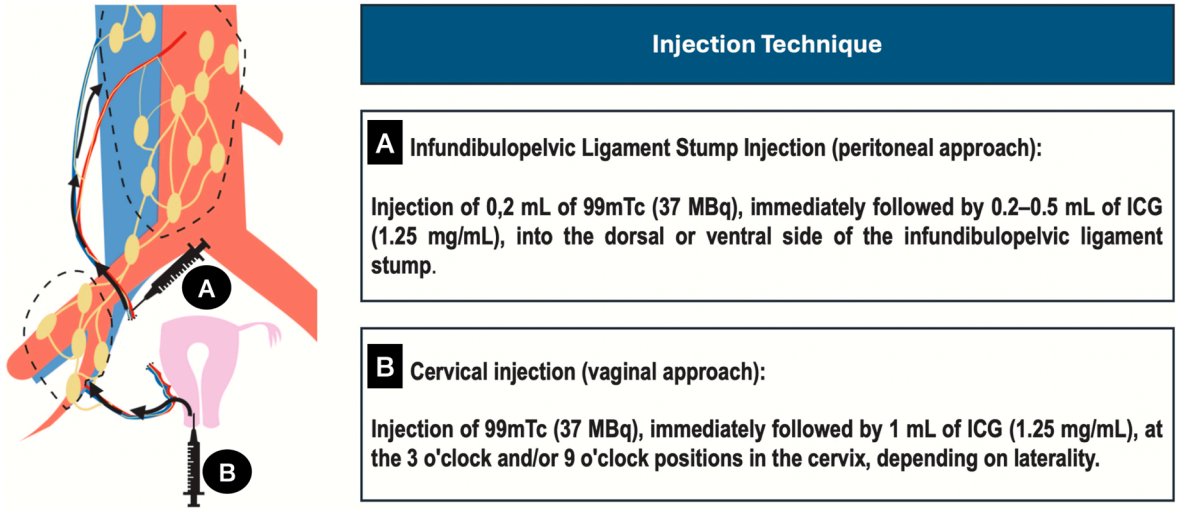

Figure 1 Injection technique: (A) infundibulopelvic ligament stump injection (peritoneal approach); (B) cervical injection (vaginal approach). 99mTc, 99m-Technetium; ICG, indocyanine green.

histologically confirmed epithelial ovarian malignancy apparently confined to the ovary or pelvis (International Federation of Gynecology and Obstetrics stage I to II); scheduled for surgical staging either at the time of initial surgery (after intra-operative frozen section confirmation) or after a deferred histologic diagnosis.

Exclusion criteria: Failure or withdrawal of informed consent; age $<$18 years; previous vascular surgery involving the aorta, vena cava, or pelvic vessels; previous pelvic or para-aortic lymphatic surgery; history of lymphoma; previous abdominopelvic malignancy; known allergy to Technetium-99m or indocyanine green; pregnancy or lactation.

Primary Endpoints

Primary objective: To determine the negative predictive value of the sentinel lymph node technique for the detection of lymph node metastasis calculated per anatomical territory (pelvic and para-aortic) and overall (per patient), using systematic lymphadenectomy as the reference standard.

Secondary objectives: To evaluate the sensitivity, specificity, positive predictive value, and diagnostic accuracy of the sentinel lymph node technique compared with systematic lymphadenectomy; assess the level of concordance between sentinel lymph node mapping and systematic lymphadenectomy in detecting lymph node metastasis using the Cohen κ coefficient; determine the detection rate of pelvic and para-aortic sentinel lymph node detection by anatomical injection site; evaluate the rates of "empty nodal packets;" evaluate the rate of upstaging after ultra-staging; document intra-operative and post-operative complications (according to the Clavien–Dindo classification) related to sentinel lymph node mapping and lymphadenectomy.

Sample Size

The planned sample size is 100 patients with negative sentinel lymph node results to ensure adequate statistical power (80%) to detect a negative predictive value for the sentinel lymph node technique above 95%, with a precision of $\pm$5% and a confidence level of 95%. With a negative predictive value of the sentinel lymph node greater than 96%, a sample size of 100 patients with a negative sentinel lymph node will yield a 95% confidence interval (calculated using the Clopper-Pearson method) that excludes the 90% negative predictive value threshold of standard testing methods. Because 100 patients with negative sentinel lymph node tests are needed, the total number of patients in the clinical trial will depend on the ratio of positive to negative sentinel lymph node tests. Therefore, once 50 tests have been performed, the ratio of sentinel lymph node—negative to sentinel lymph node—positive results will be evaluated to determine the final sample size accordingly.

Based on an estimated recruitment capacity of 10 potential cases per center per year and considering participation of 11 centers over 24 months, approximately 200 to 220 patients with suspected ovarian malignancy are expected to be recruited. From our previous experience,[6] only two-thirds of these will be confirmed malignant tumors, leading to an estimated exclusion of 67 to 73 patients. An additional 25% exclusion rate (due to mapping failures, protocol deviations, or other issues) is anticipated among eligible malignant cases, yielding an expected final evaluable cohort of 100 to 113 patients with negative sentinel lymph nodes.

Statistical Methods

Primary and secondary end points will be analyzed using descriptive and inferential statistics. Descriptive statistics will be used to summarize baseline demographic and clinical characteristics of the study population. The negative predictive value, sensitivity, specificity, positive predictive value, and overall accuracy of the sentinel lymph node technique will be calculated with 95% confidence intervals. Rates will be described and compared using χ^2 or Fisher's exact test, as appropriate. Concordance between sentinel lymph node mapping and

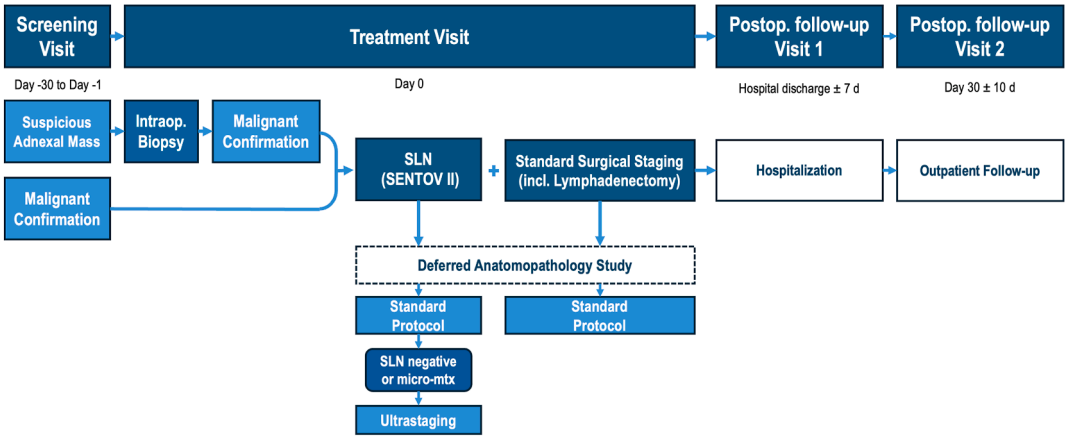

Figure 2 Study procedure diagram. Intraop., intra-operative; SLN, sentinel lymph node; incl., including; micro-mtx, micro-metastases; Postop., post-operative.

lymphadenectomy will be evaluated using the κ statistic. A significance level of 0.05 (2-sided α error of 5%) will be used for all statistical tests, except for the study's primary efficacy hypothesis of non-inferiority, which will be assessed using a 1-sided test with an α level of 0.05. The analysis will be performed according to intention-to-treat and per-protocol populations. Interim analyses and handling of missing data will follow the detailed statistical analysis plan.

DISCUSSION

The SENTOV II trial is designed to address an unresolved clinical challenge in the surgical management of apparent early-stage epithelial ovarian cancer: whether sentinel lymph node mapping can provide an accurate, reproducible, and less morbid nodal assessment compared with systematic lymphadenectomy. Building on previous phase II studies and recognizing the high morbidity and the absence of a clear survival benefit associated with systematic lymphadenectomy, this trial aims to validate a dual-tracer, anatomically optimized sentinel lymph node mapping protocol. If successful, the findings could pave the way for a paradigm shift in the staging of apparent early-stage ovarian cancer, minimizing surgical morbidity while maintaining oncologic safety. Determining the true negative value of the technique is a prerequisite to establish whether there is sufficient scientific basis to justify a randomized study comparing the use of sentinel lymph node mapping alone versus lymphadenectomy to compare the oncologic outcomes between both groups.

The largest trial published to date, the SELLY study,[8] offered valuable preliminary insight into the feasibility of sentinel lymph node mapping in ovarian cancer. However, certain methodological deviations limit the interpretation and generalizability of the findings, thereby justifying further prospective investigation. Only 30% of patients underwent utero-ovarian ligament injection, meaning that successfully pelvic mapping was achieved in less than one-third of the cohort, with no clear explanation provided. Furthermore, detection rates were notably low (51% pelvic, 51% para-aortic, and 58.6% overall), substantially inferior to previous series, such as SENTOV I and MELISA.[6,7] Several factors may account for these discrepancies: the use of a single tracer (indocyanine green alone) instead of a dual tracer (indocyanine green + Technetium-99m), the high indocyanine green dose (2 mL) compared with low-dose protocols (0.2 mL) in previous studies, and significant inter-center heterogeneity. Moreover, mapping failures were classified as false negatives, even when metastases were located in unmapped regions where tracer migration had not occurred, potentially distorting the accuracy estimates.

In contrast, the SENTOV II trial directly addresses these limitations through a prospective, multi-center design with a strict protocol standardization. We considered 3 key factors in designing the trial: the type of tracer, the dose/volume of the tracer, and the injection site.

Based on previous phase II studies (including the SENTOV I and MELISA trials[6,7]) that demonstrated high detection rates and a favorable safety profile for sentinel lymph node mapping in ovarian cancer, we chose to use a dual-tracer approach (Technetium-99m and indocyanine green). A recent meta-analysis reinforced these findings, showing that the combined use of Technetium-99m and indocyanine green significantly improves detection rates, particularly, in the para-aortic field (87.1% with Technetium-99m vs 55% with indocyanine green alone). Lower indocyanine green volumes (range; 0.2-0.5 mL) appear to be associated with higher detection rates than 2 mL, especially in the para-aortic field (88.3% vs 55%).[11] The SELLY trial[8] showed that using a high volume of indocyanine green (2 mL) as a single tracer results in a lower overall detection rate (73.3%) and a high false-negative rate (26.6%). We also explored the use of indocyanine green alone at a low volume (range; 0.2-0.5 mL), which yielded limited migration rates (52% pelvic, 81% para-aortic) and a high rate of empty packets, suggesting that indocyanine green alone may not be the optimal tracer.[12] For the reasons mentioned previously, we decided to use a combination of Technetium-99m and low-dose indocyanine green.

Another crucial aspect that can influence sentinel lymph node detection is the injection site of the tracers. The infundibulopelvic and utero-ovarian ligaments have been the most used sites for tracer injection in previous studies. However, one area requiring improvement is pelvic sentinel lymph node detection, which has shown a modest average detection rate of 59.5%.[11] This trial will

consider cervical injection as an alternative to utero-ovarian injection, based on 2 exploratory observational studies that reported 100% concordance in identifying the same pelvic sentinel lymph nodes from the cervix and the utero-ovarian ligament.[13,14] This approach could represent a significant step forward in standardizing and simplifying the sentinel lymph node mapping procedure for this indication because cervical injection offers a simpler and more reproducible method for pelvic mapping. Based on this anatomical rationale and although we acknowledge, we aim to respond to a well-documented challenge in the literature. For this reason, cervical injection is included in the SENTOV II trial protocol instead of using the utero-ovarian stump for pelvic sentinel lymph node detection.

Furthermore, a histological ultra-staging protocol for the sentinel lymph node is essential for detecting low-volume metastases (micro-metastases and isolated tumor cells), which may be missed with standard hematoxylin-eosin staining.[15] Ultra-staging has been shown to improve the detection rate of metastases, with 70.6% of patients with lymph node metastases identified through this technique.[11] Although ultra-staging enhances the diagnostic sensitivity of sentinel lymph node mapping by allowing the detection of low-volume metastases, the clinical and therapeutic implications of these findings remain uncertain. Current guidelines do not offer definitive recommendations on the management and their prognostic value is still debated. To the best of our knowledge, a retrospective, multi-center, international study[16] was the first to evaluate prognostic implications of ultra-staging in this setting (showing that 78.6% of patients with low-volume metastases received adjuvant chemotherapy, reflecting a clinical tendency to align management with paradigms from other gynecologic malignancies), and survival outcomes suggested a favorable prognosis in patients with low-volume metastases, significantly higher than the observed in those with macro-metastases.[16] Further studies evaluating long-term outcomes are needed to clarify the significance of these findings and guide treatment decisions.

The SENTOV II trial aims to address several critical issues that have limited the generalizability and clinical adoption of sentinel lymph node mapping in ovarian cancer to date. If sentinel lymph node mapping is shown to be non-inferior to systematic lymphadenectomy for nodal staging, it would represent a significant step forward in sparing patients from extensive nodal dissection without compromising staging accuracy or the optimal selection of adjuvant and maintenance therapy.

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