SENTICOL III: an international validation study of sentinel node biopsy in early cervical cancer. A GINECO, ENGOT, GCIG and multicenter study

Fabrice R Lecuru,1 Mary McCormack,2 Peter Hillemanns,3 Amelie Anota,4 Mario Leitao,5 Patrice Mathevet,6 Ronald Zweemer,7 Keiichi Fujiwara,8 Vanna Zanagnolo,9 Ane Gerda Zahl Eriksson,10 Emma Hudson,11 Gwenael Ferron,12 Marie Plante 13

ABSTRACT

Background  Radical hysterectomy and complete pelvic lymphadenectomies are the most commonly performed procedures for women with early-stage cervical cancer. Sentinel lymph node (SLN) mapping could be an alternative to routine pelvic lymphadenectomy, aiming to diagnose accurately nodal extension and decrease lymphatic morbidity. 

Primary Objective  To compare 3-year disease-free survival and health-related quality of life after SLN biopsy or SLN biopsy + pelvic lymphadenectomy in early cervical cancer.

Study Hypothesis  We hypothesize that disease-free survival is non-inferior and health-related quality of life superior after SLN biopsy compared with SLN biopsy + pelvic lymphadenectomy.

Trial Design  International, randomized, multicenter, single-blind trial. The study will be run by teams trained to carry out SLN biopsy, belonging to clinical research cooperative groups or recognized as experts in this field. Patients with an optimal mapping (Memorial Sloan Kettering Cancer Center [MSKCC] criteria) and a negative frozen section will be randomized 1:1 to SLN biopsy only or SLN biopsy + pelvic lymphadenectomy.

Inclusion, Exclusion Criteria  Patients with early stages (Ia1 with lymphovascular invasion to Ia1) of disease. Histological types are limited to squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma.

Primary Endpoint  Main endpoint will be co-primary endpoint, associating 3-year disease-free survival and quality of life (QoL-C30 and QLQ-CX24).

Sample Size  950 patients need to be randomized. Estimated dates for completing accrual and presenting results: study started on Q2 2018, last accrual is scheduled for Q2 2021, and last follow-up in Q2 2026.

Trial registration  ClinicalTrials.gov identifier: NCT03386734.

INTRODUCTION

Sentinel lymph node (SLN) mapping is gaining interest among gynecologic oncologists. This technique was introduced nearly 20 years ago, as a potential alternative to lymphadenectomy in the nodal staging of early cervical cancer.1 The concept is to perform a targeted biopsy on a small number of nodes deemed to be at the greatest risk of harboring metastases due to the specific drainage of the organ affected by malignancy. This approach has been validated in several solid tumors, such as breast cancer, melanoma, and vulvar cancer.

There is a strong rationale to justify this technique in early cervical cancer. The cervix is easily accessible with straightforward dye injection. Systematic pelvic lymphadenectomies are the most commonly performed procedures for women with early cervical cancer to decrease radicality with more conservative surgery, fertility preservation, and minimally invasive approaches.

Nearly 150 publications have reported SLN mapping in early cervical cancer; most are retrospective analyses but there are five prospective series and seven meta-analyses. The diagnostic accuracy of SLN mapping is critical. The main goal is to minimize the false-negative rate (ie, missing a metastatic node) as nodal status is an important determinant of treatment decisions and outcome. Bilateral pelvic detection of SLNs is of utmost importance in minimizing the false-negative rates and false-negative predictive values.23 The Memorial Sloan Kettering Cancer Center (MSKCC) team developed an SLN mapping algorithm known as ‘MSKCC criteria’ which suggests that this results in a significantly lower false-negative rate than merely removing colored nodes.4 In a meta-analysis by Tax and colleagues the false-negative predictive value was 0.08% when this algorithm was applied.5

We now realize that SLN mapping results in precision surgery and provides enhanced information. The technique identifies SLNs in ‘unexpected’ nodal basins in approximately 18% of patients, which are not dealt with by routine standard lymphadenectomies.6 Indeed, we observe the same anatomical
distribution of SLNs as that of solitary metastatic nodes described after historical extensive dissection. The anatomical distribution of SLNs is also consistent with the anatomical descriptions of main and accessory pathways of the lymphatic drainage of the uterus. Ultrastaging with serial sectioning and immunohistochemistry detects low-volume disease such as micrometastases or isolated tumors cells that would not have otherwise been detected by routine pathologic nodal processing. This increases the rate of patients with metastases and the sensitivity of the technique, making SLN mapping the most sensitive technique for the diagnosis of nodal involvement. One criticism is that SLNs are ultrastaged, whereas the non-sentinel nodes are not. Mathevet et al ultrastaged SLNs and non-SLNs and confirmed that the false-negative rate was the same. They also demonstrated a decreased post-operative morbidity and a better quality of life after SLN mapping than with lymphadenectomy through a randomized trial (SENTICOL II trial).

The Gynecological Cancer Intergroup (GCIG) organized a brainstorming session in Melbourne in 2014, to develop future trial concepts in cervical cancer. The committee stated that a validation study was necessary on SLNs, and launched the SENTICOL III trial. One of the requirements was to use innovative methodology. At that time we proposed using a co-primary endpoint, associating survival and quality of life. We also proposed a design with a comparison of prospective cohorts, coming from ‘SLN’ or ‘dissection’ centers. However, this methodology was criticized and a randomized design was finally chosen.

METHODS AND ANALYSIS

Trial Design
SENTICOL III is an international, randomized, multicenter, single-blind trial. It will compare SLN biopsy alone with SLN biopsy + pelvic lymphadenectomy for disease-free survival and health-related quality of life in patients with negative SLNs (figure 1).

Figure 1 Trial schema. DFS, disease-free survival; ICG, indocyanine green; OS, overall survival; QOL, quality of life; RFS, recurrence-free survival; SLN, sentinel lymph node.
Patients will undergo SLN biopsy using a strict methodology. For those in whom a radiotracer will be used, the injection will be performed the day before surgery. Long and short protocols are allowed. Pre-operative imaging is required for those who undergo radiotracer mapping, with single photon emission CT combined with CT being the recommended option but with lymphoscintigraphy also acceptable. Laparoscopic, robotic, or open access will be obtained and adhesiolysis will be performed if necessary. The cervical injection can be performed either before or after accessing the abdomen. At least two deep injections (3 and 9 o’clock) are needed (supplementary injections are allowed). Detection can be performed with isotope alone, isotope + blue dye, isotope + indocyanine green or indocyanine green alone. Blue dye alone is not allowed.

The MSKCC algorithm will be followed (figure 2).4 All peritoneal surfaces will be inspected and any suspicious lesions biopsied. If there is extra-cervical spread then SLN mapping is unnecessary and the procedure will be terminated as the patient will require other treatment. The retroperitoneal spaces must be systematically opened and examined. Any suspicious nodes are to be extracted regardless of mapping. The MSKCC criteria must be fulfilled, especially the bilateral detection of SLNs. The SLNs will be systematically analyzed by frozen section: SLNs should be cut in half along their long axis, one level in one of the two parts, staining with hematoxylin and eosin staining; LND, lymphadenectomy; SLN, sentinel lymph node.

Figure 2  Memorial Sloan Kettering Hospital algorithm.4 Surgical algorithm for early cervical cancer.4 Intracervical injection with isosulfan blue dye, 99m-technetium, or both; bincluding interiliac/sub-aortic nodes; cexceptions made for select cases, see text. H&E, hematoxylin and eosin staining; LND, lymphadenectomy; SLN, sentinel lymph node.

OUTCOMES

The primary objective is a co-primary objective associating disease-free survival and health-related quality of life. The hypothesis is that disease-free survival is non-inferior, and health-related quality of life better, after SLN biopsy compared with SLN biopsy + pelvic lymph node dissection. Secondary objectives include outcome of fertility-sparing surgery will be performed according to the tumor and patient’s characteristics. However, operative and post-operative treatment should comply with national or international guidelines. Open and minimally invasive access are allowed to accomplish the hysterectomy. Teams using minimally invasive surgery should be properly trained (according to data provided by the center). Results of the recently published locally advanced cervical cancer randomized trial should be discussed with patients.12 Patients will be stratified according to use of open minimally invasive surgery access.

SLNs will undergo permanent pathologic ultrastaging with serial sectioning each 200 μm, and staining with hematoxylin-eosin-safran. SLNs negative with hematoxylin-eosin-safran, will undergo immunohistochemistry with anti-cytokeratin AE1-AE3. Non-SLNs will be sectioned once and examined after staining with hematoxylin-eosin-safran. The standard definition of isolated tumor cells, micrometastases, and macrometastases will be used.13

Patients will be followed up post-operatively at 30 days and then every 3 months during the first year, every 4 months during the second year, and then every 6 months to complete 5 years of follow-up. These visits will focus on morbidity related to the treatment, especially lower-limb and lymphatic morbidity, survival and health-related quality of life (EORTC QLQ-C30). No systematic imaging is required for screening of recurrence.

This trial has been funded by a grant of Institut National du Cancer (INCA)(Le programme hospitalier de recherche clinique Cancer) for the French group and for the international coordination. Each participating group will find its own funding.

Setting

This study will take place in France with the collaboration of the INCA-labeled French Cooperative Group ARRCAY-GINECO. This large randomized study will also take place widely in Europe through the ENGOT network (European Network of Gynecological Oncology Trial groups) and in non-European countries thanks to GCIG and CCRN (Cervix Cancer Research Network) accredited centers. Three hundred centers will participate.

We will include patients with early cervical cancer of squamous, adenosquamous, or adenoscarcinoma histology. Stages Ia1 with lymphovascular space invasion to stage Ia1 will be included. The tumor size must be <40 mm on clinical examination and MRI. No suspicious node should be seen on MRI (RECIST 1.1). Patients must be ≥18 years of age, have an Eastern cooperative oncology group performance status of 0 to 2, have given written informed consent, and agree to comply with follow-up. For French patients, being affiliated to, or a beneficiary of, a social security category is mandatory. Exclusion criteria include pregnancy, previous pelvic or abdominal cancer, and previous chemotherapy or external beam radiation therapy for the cervical cancer (brachytherapy is allowed).

Patients with a proven allergy to blue dye, isotope, or indocyanine green will not be included.
Clinical Trial

pN1 patients through a specific cohort (taking into account the size of the metastasis), evaluation of mapping with indocyanine green, surgical mortality and morbidity, other dimensions of health-related quality of life, positive and negative predictive values of SLN, overall survival, recurrence-free survival, cost analysis in France, and lymphatic and lower limb complications.

The primary endpoint will be a co-primary outcome:
- Disease-free survival, defined as the time interval between randomization and physical or radiographic evidence of recurrence (local/distant) or second cancer or death (all causes), whichever occur first.
- Health-related quality of life assessed with European Organization for Research and Treatment QLQ-C30 and QLQ-CX24, with three targeted dimensions: pain, global health score, and physical functioning scores at 3 years.

Secondary endpoints will be:
- Disease-free survival of patients with isolated tumor cells, micrometastases, and macrometastases in SLNs.
- Detection rate and diagnostic accuracy of indocyanine green.
- Surgical morbidity assessed by the NCI-CTCAE v4.03 and the Clavien-Dindo classification and mortality (during 30 days and at 30-days post-operatively).
- Other dimensions of health-related quality of life of both QLQ-C30 and QLQ-CX24.
- True-positive results, true- and false-negative results in patients with SLN biopsy + pelvic lymph node dissection.
- Overall survival, defined as the time interval between randomization and death (all causes); patients who are alive will be censored at the last date of information.
- Recurrence-free interval, defined as the time interval between randomization and physical or radiographic evidence of recurrence (local/distant) or death (all causes), whichever occur first.
- Cost of the procedure, only for France.
- Lymphatic and lower limb complications, lower-extremity lymphedema screening questionnaire (only for France).

Quality assurance is an important concern in this trial. Several criteria for surgery and pathology will be surveyed: training of the surgeon, selection of patients, surgical training and quality, morbidity, false-negative rate and false-negative predictive values in the standard arm, training of the pathologist, etc. Centers will be selected according to their ability to comply with the protocol and quality criteria. Centers belong to GINECO, ENEGOT groups, GCIG, or are part of the CCRN.

Tumor specimens (cervical tumors, SLNs, and non-SLNs) and blood samples will be stored in the majority of centers. A translational programme is being developed and should improve the understanding and treatment of patients with early cervical cancer.

Sample Size

We aim to demonstrate the non-inferiority of SLN biopsy alone versus SLN biopsy + pelvic lymph node dissection for disease-free survival using a gatekeeping procedure to control the type I error rate. Using a 5% non-inferiority margin and a standard 3-year disease-free survival of 85%, 900 randomized patients are required to observe the required (unilateral \( \alpha \) error of 5%, a statistical power of 80%, and a 5-year follow-up). An interim analysis will be planned, when at least 132 events will be observed to reject H0 or H1 using the O’Brien-Fleming and \( \alpha \) spending function. Stopping guidelines for efficacy will be \(-2.532\) on the Z scale and \(-0.346\) for futility.

For health-related quality of life, three dimensions of the European Organization for Research and Treatment QLQ-C30 and QLQ-CX24 will be targeted: global health status, pain, and physical functioning. At 3 years, to demonstrate a superiority of at least one of the three targeted dimensions without significant deterioration in at least one with a minimal clinically important difference in mean score of at least five points (SD of 20), and a bilateral \( \alpha \) type 1 error of 0.016 (Bonferroni adjustment for three dimensions), 815 patients would be required with available health-related quality of life scores at 3 years to reach an 85% statistical power. Taking into account a 5% loss to follow-up, 950 patients are needed. Accrual will last for 3 years.14

Randomization and Blinding

Patients will be randomized in a 1:1 ratio using an interactive web response system in a 1:1 ratio of the two treatment arms: SLN biopsy alone versus SLN biopsy + pelvic lymph node dissection by minimization technique, and stratified by center and stage of the disease using the 2018 Federation Internationale de Gynécologie Obstétrique classification. A double-blind study is not feasible since the surgeon and treating physician will be aware of the details of the operation. Thus, the treatment will be blinded to the patients only.

Statistical Methods

Efficacy analyses will be conducted on an intention-to-treat population including all randomized patients whatever treatment received and whatever eligibility criteria. For non-inferiority analysis of disease-free survival, results will be also reported on a per protocol analysis. For the health-related quality of life analysis, a modified intention-to-treat population will be considered, including all randomized patients with at least the baseline health-related quality of life score available. Safety analyses will be conducted on all randomized patients, with at least one post-baseline safety assessment. This population will be considered for safety data and treatment exposure data.

All tests will be performed two-sided at a significance level of 5% (95% CI), with the exception of the tests for the primary endpoint of non-inferiority which will be one-sided at a statistical significance level of 5% (90% CI). Indeed, for health-related quality of life analyses, all tests will be performed two-sided at a significance level of 1.6%. For disease-free survival, the nominal significance levels for the interim and final analyses will be derived from the \( \alpha \) spending function with O’Brien-Fleming boundaries, which are dependent on the information fraction in the intention-to-treat population.

Confidence intervals will be calculated. These will be two-sided with a confidence level of 95% with the exception of the estimates for the primary endpoint using a confidence level of 100%— nominal \( \alpha \) and quality of life using a CI of 100–1.6, that is, 98.4%.

Clinical and demographic data at baseline will be described by treatment arm using rules form. The statistical parameters mean, median, SD, IQR, and range will be presented for continuous baseline variables. For categorical baseline variables, number and percentages will be calculated.

The Kaplan-Meier method will be used to estimate disease-free survival and other time-to-event endpoints. For the primary objective of non-inferiority in disease-free survival, the 2-year
disease-free survival rate will be computed with its 90% CI. Follow-up will be estimated using the reverse Kaplan-Meier method, and will be described using the median with its 95% CI. For the primary health-related quality of life analysis, a t-test will be used to compare the health-related quality of life level at 3 years according to treatment arm for each targeting dimension (global health status, pain, and physical functioning). The statistical level for significance will be 0.016. The normal distribution of the scores will be checked. For non-normal distributions, a non-parametric Mann–Whitney test will be used. Overall survival will be estimated using the Kaplan-Meier method, and will be described using the median with its 95% CI. A univariate Cox proportional hazards model will be used to estimate hazard ratios with 95% CI. Multivariate Cox analyses will be done in respect of the Peduzzi rule of one variable for 10 events. A univariate selection procedure will serve to identify eligible explanatory variables with a univariate Cox p value according to the Wald test of <0.10 as a potential prognostic value. For each Cox analysis, the proportionality assumption of the risk will be graphically checked.

For safety analyses, the report will take into account all adverse events observed during and after the acts performed or methods used. Categorical data will be summarized in contingency tables displaying frequencies and percentages. Continuous data will be presented using median, minimum, and maximum values. The safety data of the different strategies will be compared using the Kruskal-Wallis test or Fisher exact test or χ² tests. Particular interest will be given to rates of grade 3–4 toxicities according to the NCI-CTCAE v4.

**DISCUSSION**

Few oncologic surgical techniques have been validated by a complete pathway including proof of concept, a diagnostic accuracy study, safety study and then survival and quality of life by a randomized trial. SENTICOL III is an ambitious study, requiring a large number of patients and international collaboration. This type of study is clearly a challenge for the community, necessitating sharing ideas and energy to conduct a large trial despite budget and administrative constraints. Participation of the French cooperative group GINECO, ENGOT group, CCRN, GCIG, as well as referent centers around the world will offer a greater chance of successfully completing this ambitious trial.

SENTICOL III has several particularities. First, we decided to use the co-primary endpoints of survival and quality of life. This choice was guided by the aim to assess non-inferior survival in a randomized fashion as well as quality of life, which is equally important. It would have been difficult to make a choice between these two fundamental parameters. Women with early cervical cancer and negative SLNs have an excellent prognosis with long survival, thus making preservation of quality of life quite important. Second, assessment of quality criteria will be largely developed in this trial. This aspect is logically considered more in surgical studies. Respect of minimal rules and algorithms, verification of the surgical and pathological skills, etc, are mandatory to guarantee the validity of the results. It would not be acceptable for the results, and their interpretation and implementation, to be impaired by technical limitations. This aspect is not simple since surgery and pathology have several hand-craft aspects, and it emphasizes the need for a minimal standardization of techniques. Third, SENTICOL III is a large, international, randomized trial. This design is clearly the most difficult and the most challenging, with significant financial implications. Additionally, various research rules and requirements must be managed across multiple countries. However, this is necessary to achieve successful enrollment and provide robust results and, subsequently, implement the SLN technique safely.

Secondary objectives are important also. Treatment and survival of patients with minimal nodal disease is a major challenge for the coming years. These patients have been traditionally categorized as high risk and managed well. However, data coming from the SENTICOL I trial indicate that patients without, and with one, metastatic node share similar prognosis. 15 We clearly need modern data on this specific subset of patients, who could benefit from a more personalized treatment. Similarly, this study will evaluate the accuracy of indocyanine green for routine use. Indocyanine green is more and more commonly used despite not being approved in a majority of countries for SLN detection. A prospective trial recently showed that indocyanine green detects one or more and bilateral SLNs more often than blue dye alone (FILM study). 16 However, a large prospective validation will be welcome.

Finally, SENTICOL III is also a unique opportunity to record prospective data on this particular group of patients with early cervical cancer. We will obtain data on a large number of such patients who have not been investigated for many years. Several ancillary studies will be possible. It is at least a unique opportunity to develop translational research for this disease. Early cervical cancer has been less investigated than other gynecological tumors. Studies on human papilloma virus, patients’ immunity, and tumor biology are now necessary to enable progress in the treatment of pN1 patients, and also pN0 patients with recurrence or poor prognosis.

The SENTICOL III trial has received a large grant in France to cover the funding of each French patient and for international coordination. It was approved by the ethics committee and competent authority in France in late 2017 and accrual has just started. Other groups and CCRN centers should start soon, when administrative and ethical approval will be obtained.

**Author affiliations**

1. Gynecologic and Oncologic Surgery, GINECO, Georges Pompidou European Hospital, Paris, France
2. NRCI, UK, UCLH London, London, UK
3. Klinik fur Frauenheilkunde und Geburtshilfe, AGO, Medizinische Hochschule, Hannover, Germany
4. Statistics, GINECO, Centre Hospitalier Universitaire de Besancon, Besancon, France
5. Gynecologic Oncology, Memorial Sloan-Kettering Cancer Center, New York City, New York, USA
6. Centre Hospitalier Universitaire Vaudois Département de gynécologie-obstétrique et génétique medicale, Lausanne, Switzerland
7. Gynecologic Oncology, DGOG, UMC Utrecht Hersencentrum Rudolf Magnus, Utrecht, UK
8. Gynecologic Oncology, GOTHIC, Saitama Medical University, Hidaka, Japan
9. Gynecologic Oncology, MANGO, Istituto Eoomo di Oncologia, Milan, Italy
10. Gynecologic Oncology, NORD, Universitetet i Oslo, Oslo, Norway
11. Gynecologic Oncology, NRCI, Velindre Cancer Centre, Cardiff, UK
12. Gynecologic Oncology, GINECO, Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France
13. Gynecologic Oncology, CCTG, Fondation du CHU de Quebec, Quebec City, Quebec, Canada

Correction notice Since this article was first published online, the city and country in affiliation 8 has been updated to Hidaka, Japan.

Contributors All the authors will participate in the trial and lead it in their respective country. FL was responsible for writing the manuscript, which has been validated by all authors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

REFERENCES