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# A prospective multicenter trial on sentinel lymph node biopsy in patients with early-stage cervical cancer (SENTIX)

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## ABSTRACT

**Objective** Sentinel lymph node (SLN) biopsy has been increasingly used in the management of early-stage cervical cancer. It appears in guidelines as an alternative option to systematic pelvic lymphadenectomy. The evidence about safety is, however, based mostly on retrospective studies, in which SLN was combined with systematic lymphadenectomy.

**Materials and methods** SENTIX is a prospective multicenter trial aiming to prove that less-radical surgery with SLN is non-inferior to treatment with systematic pelvic lymphadenectomy. The primary end point is recurrence rate; the secondary end point is the prevalence of lower-leg lymphedema and symptomatic pelvic lymphocele. The reference recurrence rate was set up conservatively at 7% at 24 months after treatment. With a sample size of 300 patients treated per protocol, the trial is powered to detect a non-inferiority margin of 5% (90% power, p = 0.05) for recurrence rate, 30% reduction in the prevalence of symptomatic lymphocele or lower-leg lymphedema, with reference rates of 30% and 6% at 12 months (p = 0.025, Bonferroni correction). The patients eligible for SENTIX have stage IA1/LVSI+, IA2, IB1 (<2 cm for fertility sparing), with negative LN on pre-operative imaging. Intra-operatively, patients are excluded when there is a failure to detect SLN on both sides of the pelvis in cases of more advanced cancer (stage >IB1), or a positive intra-operative SLN assessment. The quality of SLN pathology evaluation will be assessed by central review. Three interim safety analyses are pre-planned when 30, 60, 150 patients complete 12 months' follow-up.

**Conclusions** The first patient was enrolled into the study in June 2016 and, by June 2018, 340 patients had been enrolled. The first analysis of secondary outcomes should be available in 2019 and the oncological outcome of 300 patients at the end of 2021. The trial is registered as a CEEGOG trial (CEEGOG CX-01), ENGOT trial (ENGOT-Cx 2), and at the ClinicalTrials.gov database (NCT02494063).

## INTRODUCTION

Sentinel lymph node (SLN) biopsy for the management of early-stage cervical cancer has been studied over a few decades.[1–4] It is considered an acceptable approach for the treatment of early stages in the National Comprehensive Cancer Network (NCCN) guidelines. In the new European Society of Gynaecological Oncology (ESGO)-European Society for Radiotherapy and Oncology (ESTRO)-European Society of Pathology (ESP) guidelines it is considered an adequate method for lymphatic staging in stage T1a and is strongly recommended as the first step of surgical treatment in all early stages in combination with systematic pelvic lymphadenectomy.[5] An increasing number of recent publications recommend SLN alone or the treatment of stage T1b1.[6–8] The enthusiasm for a new, less-invasive method, is understandable, since it decreases operation time and post-operative morbidity, especially the risk of lower leg lymphedema.[9 10] However, the abandonment of systematic pelvic lymphadenectomy, which has been a standard for many years, represents a considerable change in management. It is important to emphasize that the current evidence of the safety of SLN has a number of limitations. We do not know the risk of micrometastases in pelvic lymph nodes in cases with negative SLN because in all larger retrospective trials SLN was processed by an intensive pathology protocol while a standard protocol was typically used for an evaluation of all other pelvic lymph nodes. Moreover, in the majority of published series, SLN was followed by systematic lymphadenectomy. Prospective data on the oncological safety of patients after SLN alone are not yet available.

The protocol for the SENTIX trial (SENTinel lymph node biopsy in cervIX cancer) is designed to determine the oncological safety and post-operative morbidity of SLN biopsy only without subsequent pelvic lymph node dissection in women with early-stage cervical cancer. It was developed by the regional collaborative group (Central and Eastern European Gynecologic Oncology Group—CEEGOG), and reviewed by the SENTIX steering committee and the European Network for Gynaecological Oncological Trials (ENGOT). The null hypothesis is that the recurrence rate after SLN biopsy is non-inferior to the reference recurrence rate in patients after systematic pelvic lymphadenectomy, but that the less radical surgery is associated with significantly lower post-operative morbidity.

## METHODS AND ANALYSIS

### Trial design

The SENTIX trial is designed as an international multicenter prospective trial . The primary objective is to evaluate whether a less-radical surgical approach

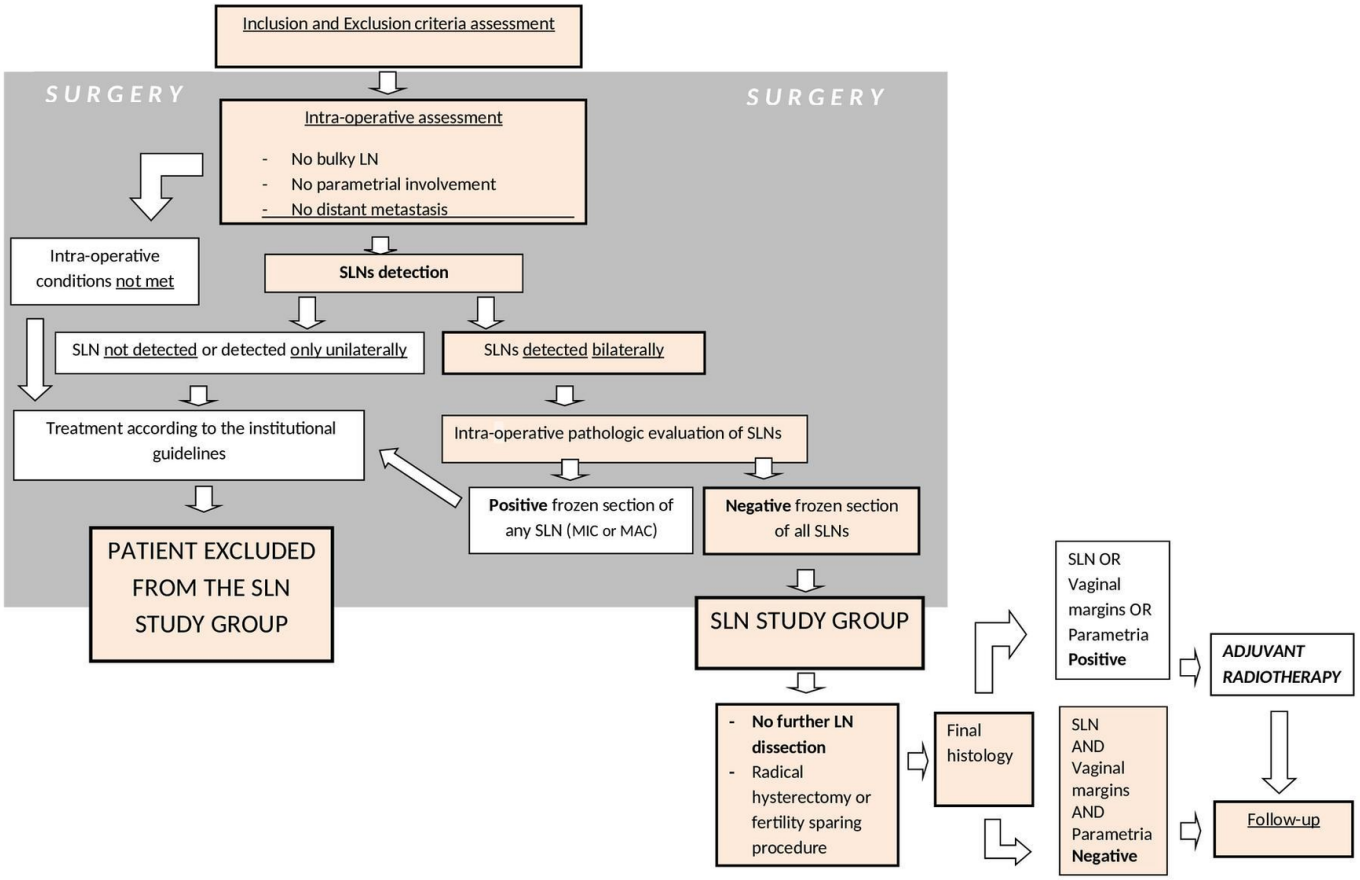


**Figure 1** Sentix trial algorithm. MAC, macrometastases; MIC, micrometastases; SLN, sentinel lymph node.

with sentinel lymph node biopsy is non-inferior to treatment with systematic pelvic lymphadenectomy in patients with early-stage cervical cancer and negative pelvic lymph nodes. The study chart is shown in Figure 1.

For SLN detection, all three available techniques (blue dye, radiocolloid, indocyanine green), or their combination, are acceptable in the trial. A combined technique using blue dye and radiocolloid or indocyanine green with fluorescence imaging are the recommended techniques. All approaches, including laparotomy, laparoscopy, or robotic surgery, can be used. Performance of radical hysterectomy (types B, C1, and C2) should be standardized according to the Querleu-Morrow classification system.[11] The type of radical hysterectomy should correspond to the tumor stage and size. Type B (modified radical hysterectomy) is acceptable only in tumors smaller than 2 cm in the largest diameter. Type C1 (nerve-sparing) should be preferred in stage IB1. Type C2 is an acceptable technique in tumors with deep stromal invasion.

Intra-operative SLN evaluation is a mandatory component of the trial. After intra-operative processing, all SLNs will be examined by the complete ultra-staging protocol. This protocol consists of two consecutive sections (4 µm thick) obtained at regular 150 µm intervals, which will be cut from each paraffin block until there is no lymph node tissue left. The first section will be stained with H&E and the second section will be examined immunohistochemically with an antibody against cytokeratins (AE1/AE3).

For pathology quality assurance (SLN ultra-staging), submission of all specimens from all removed lymph nodes will be required from at least two patients for each site (randomly selected by the trial coordinator) and reviewed centrally at the Department of Pathology, General Faculty Hospital in Prague. A site may be closed (decision taken by the SENTIX steering committee) if critical deviations are identified.

Patients without macrometastases or micrometastases in pelvic SLNs and with negative vaginal surgical margins and negative parametria will receive no adjuvant treatment. Patients with confirmed metastatic involvement on intra-operative SLN evaluation will be excluded from the SLN study group, and will be treated according to institutional guidelines. Adjuvant pelvic chemoradiotherapy will be recommended for patients with micrometastases or macrometastases detected on the final pathology SLN assessment, or in cases with parametrial infiltration. Patients with involved vaginal resection margins will receive vaginal brachytherapy.

Patients will be followed up until the trial is terminated, which is planned for 24 months after the surgery of the last accrued patient. The occurrence of lower-leg lymphedema, which is the secondary end point of the trial, will be assessed subjectively by the patient and objectively by the investigator. Leg circumferences (girths) on both sides will be measured at five standardized levels during the pre-operative visit and during follow-up visits for 2 years after surgery.

The minimum requirements for any center to participate include: (a) ≥10 cases of invasive cervical cancer of stages suitable for SENTIX (IA1 +LVSI–IB1) treated in the center each year; (b) experience with at least 15 patients with successful SLN detection in patients with cervical or endometrial or vulvar cancer; (c) pathologic ultra-staging available; (d) adequate administrative support

available; (e) agreement to the protocol, including requirements for pathology quality assurance; (f) local ethical committee approval.

The trial is registered at the ClinicalTrials.gov database (NCT02494063). The basis for successful enrollment is collaboration within the leading collaborative group CEEGOG (Central and Eastern European Gynecologic Oncology Group), which operates in a region that still has a high incidence of cervical cancer. By May 2018, 21 CEEGOG sites and altogether 46 sites from 18 countries were involved in the trial. The trial is funded by the Czech Health Research Council (No 16-31643A) and is performed according to the ENGOT model A.[12 13]

### Participants

Patients will be enrolled in the study when surgery is planned if the inclusion criteria are met; at this time a patient´s consent is requested. Additional criteria must be fulfilled during the surgery. Patients who are excluded during the surgery will receive standard treatment according to institutional guidelines.

Pre-operative inclusion criteria are the following: (a) FIGO stage IA1 + LVSI, IA2, IB1; (b) no evidence of bulky or suspicious pelvic lymph nodes or distant metastases in pre-operative conventional imaging studies; (c) performance status Eastern Cooperative Oncology Group (ECOG) 0–1; (d) age ≥18 years, ≤75 years; (e) squamous cell carcinoma or adenocarcinoma usual type (HPV-related); (f) suitable candidates for primary surgical treatment, such as radical hysterectomy in tumors ≤4 cm in the largest diameter or fertility-sparing treatment in tumors ≤2 cm in the largest diameter; (g) history of second primary cancer only if >5 years with no evidence of disease; (h) approved and signed informed consent.

Exclusion criteria comprised the following: (a) neoadjuvant chemotherapy; (b) pregnancy; (c) history of pelvic or abdominal radiotherapy; (d) HIV positivity/AIDS; (e) adenosquamous cancer or adenocarcinoma of an unusual type (non-HPV related such as mucinous, clear cell, mesonephric).

Intra-operatively, patients will be excluded from the SLN study group when there is: (a) a failure to detect SLN on both sides of the pelvis; (b) any type of metastasis detected by frozen section; (c) intra-operative evidence of more advanced disease (>IB1).

### Outcomes

The primary end point is the recurrence rate at the 24th month of follow-up. Cervical recurrences after fertility-sparing procedures do not apply. The prevalence of symptomatic pelvic lymphocele and lower extremity lymphedema, the two complications that are associated with lymph node staging, are secondary end points. Both primary and secondary end points will be compared with the reference rates based on available data from historical cohorts of the same populations of patients who underwent surgical treatment including systematic pelvic lymphadenectomy.

Other end points include disease-free survival, pelvic disease-free survival, false-negative rate of intra-operative pathologic SLN evaluation, disease-free survival in per-protocol population, pelvic disease-free survival in per-protocol population, recurrence rate safety margins, overall survival, quality of life, intra-operative morbidity, early post-operative and late post-operative morbidity.

### Sample size and statistical methods

The recurrence rate will be evaluated at the 24th month of follow-up to prove a non-inferiority of SLN biopsy to the reference value of 7% with a non-inferiority margin of 5%. A sample size of 300 cases achieves 90% power to detect a non-inferiority proportion (P0) of 12% using a one-sided Z test that uses S(P0) at a 0.05 level of significance.

The null hypothesis for secondary end points assumes a reduction in the prevalence of at least one of the two complications by at least 30% to the reference prevalence in patients after systematic pelvic lymphadenectomy, proven on the basis of bilateral $\alpha$ error 0.025 (Bonferroni correction) and power 90%. Reference prevalence was set at 30% for the lower extremity lymphedema and 6% for symptomatic lymphocele. The sample size of 300 patients should be sufficient to reach these parameters of secondary testing.

Two types of sample cohorts are defined in the protocol. The intention to treat cohort will comprise all patients who fulfill all pre-operative and post-operative inclusion criteria, with at least one follow-up visit available. The per-protocol cohort will comprise patients who, in addition to criteria for intention to treat, also had negative SLN status from the final pathology, who did not receive adjuvant radiotherapy, and who did not have other major protocol deviations.

An interim safety analysis was set up for the primary end point as the study stopping rule. Recurrence rate safety margin (>12%) will be examined when the first 30, 60, and 150 patients complete the 12-month follow-up. If the safety margin is exceeded, the trial will be terminated.

## DISCUSSION

The SENTIX trial is an international multicenter prospective trial. The primary objective is to determine whether a less-radical surgical approach with sentinel lymph node biopsy is non-inferior to the reference recurrence rate in the same historical cohorts of patients after systematic pelvic lymphadenectomy, and if the less radical surgery is associated with significantly lower prevalence of lower-leg lymphedema and/or symptomatic lymphocele. With a sample size of 300 patients, the trial is powered to detect a non-inferiority margin of 5% for the reference recurrence rate of 7% at 24 months of follow-up (90% power, p=0.05).

The protocol has been developed to be inclusive and reflect current clinical practice. All surgical approaches and all techniques of SLN detection are eligible for the study. Patients with or without intention to spare fertility can be enrolled in the study, even though the requirements for maximum tumor size are different. In fertility-sparing treatment, a 2 cm maximum tumor size is considered to be safe in accordance with current guidelines, whereas in the non-fertility-sparing group, the size can be up to 4 cm.[5] Although some older papers show worse results for SLN biopsy in tumors larger than 2 cm, recent studies on large cohorts of patients have proved a comparable detection rate and sensitivity of SLN assessment in pelvic node staging in groups of tumors up to 2 cm and between 2 and 4 cm.[7 13]

In addition to pre-operative inclusion parameters, patients must fulfill other intra-operative criteria. A mandatory component of the protocol is evaluation of an SLN frozen section and negative

intra-operative results. Patients in whom SLN is not detected on both sides of the pelvis or in whom there is any type of metastasis detected during surgery will be excluded from SLN study group. Further treatment should be performed according to the respective institutional guidelines. We estimate that in approximately 10% of patients, SLN metastatic involvement will be detected from the final pathology evaluation despite a negative intra-operative assessment. Those patients will be referred for adjuvant chemoradiotherapy, but they will be included in the intention to treat population. Patients with negative LN, parametria, and vaginal margins, will receive no adjuvant therapy, irrespective of the size of tumor.

SLN pathology evaluation is the key prerequisite for the safety of the trial. Each undetected metastasis in SLN can cause future recurrence and patient death due to to the risk of positivity of other pelvic lymph nodes left in situ and a lack of indication for adjuvant radiotherapy. Therefore, a central pathology review of SLN specimen is an integral part of the protocol. Another important safety measure is permanent data monitoring. Timely data completion is indispensable for interim safety analyses and for quality control of individual institutions.

An observational design was chosen as a pragmatic solution for the feasibility of the trial. Even though the benefits of subject randomization are obvious, randomization also has its weaknesses, especiallya need for large size of the cohort, and consequently, long duration of the trial. The time factor, in particular, is a key limitation and can lead to substantial bias, which can be more important for the quality of data than the advantage resulting from patients'´ randomization.

Surgical treatment is surgeon dependent and it is constantly evolving with new technology, approaches, radicality, and its combination with other treatment modalities. An oncological outcome after surgical treatment depends on other non-surgical fields, such as imaging or adjuvant therapy. Progress in all the above factors toghether with limitations in quality of surgical performance standardization makes the duration of surgical trials a key factor for outcome applicability. The results of long-lasting trials are often challenged if the methodology or quality of care does not correspond to clinical practice at the time when the results are published. An observational design can be a pragmatic solution especially for a disease with declining incidence. Recently, results of a well-conducted large observational study have changed the standard of care in patients with vulvar cancer and have enabled a significant reduction of radicality of surgery in the management of early-stage disease.[14 15]

The cohort which is studied in the SENTIX trial has a few challenges. The incidence of cervical cancer has been falling, mainly in regions with a good quality of complex care. The prognosis of patients with early-stage cancer and negative pelvic lymph nodes after surgery is excellent so the size of the cohort must be large to prove any significance. Moreover, technology of metastatic detection is progressing rapidly, which may shortly lead to new methods of detecting LN involvement. A single-arm trial was chosen as a pragmatic solution to obtain prospective data in a reasonable time. Fortunately, representative data after standard treatment, pelvic lymph node dissection are available, which makes it possible to set up a conservative and reliable reference value. The outcome of patients after SLN only will be compared with a reference rate calculated based on historical cohorts of the same patient populations treated by systematic pelvic lymphadenectomy.

The first patient was enrolled into the study in June 2016. By June 2018, 340 patients had been enrolled, from whom 285 were treated according to the protocol. We assume that the target accrual of 300 patients will be reached by the end of 2018. The first pre-planned analysis of secondary outcomes should be available in 2019, and the first analysis of the oncological outcome of 300 patients at 24 months should be conducted at the end of 2020.

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**Competing interests** None declared.

**Ethics approval** The protocol has been approved by the local ethical committee at the leading institution as well as at all participating sites.

**Provenance and peer review** Not commissioned, internally peer reviewed.

## REFERENCES

1. Rob L, Lukas R, Robova H, *et al*. Current status of sentinel lymph node mapping in the management of cervical cancer. *Expert Rev Anticancer Ther* 2013;13:861–70.
2. Cibula D, Abu-Rustum NR, Dusek L, *et al*. Bilateral ultrastaging of sentinel lymph node in cervical cancer: lowering the false-negative rate and improving the detection of micrometastasis. *Gynecol Oncol* 2012;127:462–6.
3. Lécuru F, Mathevet P, Querleu D, *et al*. Bilateral negative sentinel nodes accurately predict absence of lymph node metastasis in early cervical cancer: results of the SENTICOL study. *J Clin Oncol* 2011;29:1686–91.
4. Altgassen C, Hertel H, Brandstädt A, *et al*. Multicenter validation study of the sentinel lymph node concept in cervical cancer: AGO Study Group. *J Clin Oncol* 2008;26:2943–51.
5. Cibula D, Pötter R, Planchamp F, *et al*. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer. *Int J Gynecol Cancer* 2018;28:641–55.
6. Ferrandina G, Pedone Anchora L, Gallotta V, *et al*. Can we define the risk of lymph node metastasis in early-stage cervical cancer patients? A large-scale, retrospective study. *Ann Surg Oncol* 2017;24:2311–8.
7. 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.
8. Niikura H, Okamoto S, Otsuki T, *et al*. Prospective study of sentinel lymph node biopsy without further pelvic lymphadenectomy in patients with sentinel lymph node-negative cervical cancer. *Int J Gynecol Cancer* 2012;22:1244–50.
9. Yamazaki H, Todo Y, Takeshita S, *et al*. Relationship between removal of circumflex iliac nodes distal to the external iliac nodes and postoperative lower-extremity lymphedema in uterine cervical cancer. *Gynecol Oncol* 2015;139:295–9.
10. Hareyama H, Hada K, Goto K, *et al*. Prevalence, classification, and risk factors for postoperative lower extremity lymphedema in women with gynecologic malignancies: a retrospective study. *Int J Gynecol Cancer* 2015;25:751–7.
11. Querleu D, Cibula D, Abu-Rustum NR. 2017 update on the Querleu-Morrow classification of radical hysterectomy. *Ann Surg Oncol* 2017;24:3406–12.
12. du Bois A, Reuss A, Pujade-Lauraine E, *et al*. European network of gynaecological oncological trial groups' requirements for trials between academic groups and industry partners--first update 2015. *Int J Gynecol Cancer* 2015;25:1328–30.
13. Dostálek L, Zikan M, Fischerova D, *et al*. SLN biopsy in cervical cancer patients with tumors larger than 2cm and 4cm. *Gynecol Oncol* 2018;148:456–60.
14. Van der Zee AG, Oonk MH, De Hullu JA, *et al*. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. *J Clin Oncol* 2008;26:884–9.
15. de Hullu JA, Hollema H, Piers DA, *et al*. Sentinel lymph node procedure is highly accurate in squamous cell carcinoma of the vulva. *J Clin Oncol* 2000;18:2811–6.