



# A GCIG International Survey: Clinical Practice Patterns of Sentinel Lymph Node Biopsies in Cervical Cancer

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## Abstract

**Purpose:** To evaluate the practice patterns among centers and physicians worldwide regarding Sentinel Lymph Node Biopsies (SLNB) in Cervical Cancer (CC) patients.

**Method:** A validated 35-item questionnaire regarding SLNB in CC supported by the Gynecologic Cancer Intergroup (GCIG), and sponsored by the North-Eastern German Society of Gynaecologic-Oncology (NOGGO) was sent to all major gynecological cancer society's across the globe for further distribution from October 2015 and continued for a period of 7 months.

**Results:** One hundred and sixty-one institutions from around the world participated. One hundred and six (66%) of the participants were from university centers and one hundred and eleven (69%) were gynecologic oncologists. One hundred and fifty-two (97%) performed lymphadenectomy (LNE), and one hundred and forty-seven (94%) did so systematically; Ninety-seven (60%) used SLNB, due to lower morbidity (73%), reliability (55%) and time-saving (27%).

In cases of positive SLNB (pN+), 39% of respondents stopped the operation and sent the patient for Chemoradiation (CRT), 45% completed pelvic and paraaortic LNE, whereas 26% went on to perform a Radical Hysterectomy (RH) and systematic pelvic and paraaortic LNE.

In case of negative SLNB (pN0), 39% of institutions still performed a systematic pelvic and paraaortic LNE.

**Conclusion:** In this survey worldwide SLNB adoption is an encouraging 60%, yet ample differences exist regarding strategy, and to a lower extent the techniques used. Lack of experience is the most common reason SLNB is not performed.

Efforts to increase surgical education on SLNB technique and multicenter prospective trials providing evidence-based guidelines are warranted.

## Introduction

Cervical Cancer (CC) is the third most common female cancer worldwide and the fourth leading cause of cancer death in women [1]. In recent years the number of young women with CC, which is particularly prevalent in developing countries, has increased.

Metastatic lymph node involvement (pN+) of the pelvic lymph nodes (LNs) is the main prognostic factor in Early Stage Cervical Cancer (ESCC): 5-year overall survival in stage IB1 with and without pN+ is 75.9% vs. 94.8% respectively [2].

FIGO staging does not include evaluation of LNs status, which indeed cannot be reliably determined preoperatively: hence pelvic Lymphadenectomy (LNE) is a pivotal part of the treatment for most patients with CC [3]. However, notwithstanding the introduction of minimally invasive techniques such as laparoscopy and robotic surgery, LNE continues to be associated with substantial morbidity [4].

The reported incidence of pN+ in patients with ESCC is 0% to 4.8% in FIGO stage IA, less than 15% in patients with stage IB <2 cm, and 12% to 27% in stage IIA [5]. Thus >95% of stage IA do not need full LNE, and the majority of patients with ESCC will not benefit from a pelvic LNE. Conversely they are at risk of suffering from a variety of potential complications such as venous thromboembolism, or lymphocyst formation, and life-long sequelae comprising, neuropathy and Lower Extremity Lymphedema (LEL).

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Sentinel Lymph Node Biopsy (SLNB) has been effectively adopted for many years now and is currently the standard of care in patients with Breast Cancer (BC), vulvar cancer, and melanoma [6-8].

Numerous studies and publications have extensively documented both the feasibility of SLNB identification in patients with CC, as well as its validity mostly in selected patients, particularly in cases of tumors <2 cm [9,10]. Yet there is still much debate, and no international agreement has been reached as for the role of SLNB in the treatment of ESCC.

The main goal of this investigation was to evaluate physician practices on a global stage regarding the current use of SLNB in CC patients. Additionally, the potential interest of the gynecological world in taking part in future clinical studies about SLNB was determined.

## Materials and Methods

The present study was initiated by the North-Eastern-German Society of Gynaecologic-Oncology (NOGGO), was officially backed by the Gynecologic Cancer Intergroup (GCIg), and was also officially supported by the main gynecological oncologic societies and study groups worldwide.

After receiving approval from NOGGO, a full mailing list of all candidate members of major international gynecological cancer society's was obtained. Subsequently the survey was posted online ([https://de.surveymonkey.com/s/SLN\\_cervicalcancer](https://de.surveymonkey.com/s/SLN_cervicalcancer)) and mailed to the above-stated oncologic centers for further distribution from October 12, 2015 to May 06, 2016. Respondents could freely choose which format to use.

The 35-item questionnaire, focused on the LNE and SLNB in CC patients and validated in the German language, was defined based on interdisciplinary workshops and previous studies in other malignancies. It was tested by ten physicians for reproducibility and could be completed anonymously in an estimated 15 minutes' time. Many questions were to be answered in a multiple-choice fashion.

Answers were analyzed consecutively and comparisons were drawn among the various regions of the world, among centers with different patient volumes, as well as with regard to the kind of institution, i.e. university vs. general hospitals, and the subspecialty of the participant gynecologist, i.e. gynecologist oncologist vs. general gynecologist.

To encourage participation, all 27 study group members were sent two mailings of the survey and a reminder. All collected data were stored by an institutional research department at the institution of one of the authors. The entire questionnaire can be found in the supplement file of this article (Appendix 1).

### Statistical analysis

All results are presented as frequency and rate. Associations were evaluated using Chi<sup>2</sup>-test, Fisher's exact test or Kendall's tau b where appropriate. All data were analyzed using IBM® SPSS® Statistics 23 (SPSS Inc., Chicago, IL) and p<0.05 was considered statistically significant.

## Results

Answers from 161 centers from four continents were completed and returned to NOGGO. Groups were: Western and Southern Europe (WSE) (Belgium, Netherland, France, Italy, Spain, Israel) 35.4%; Central Europe (CE) (Austria, Germany, Switzerland) 24.2%;

Northern Europe (NE) (Denmark, Finland, Sweden, Norway) 6.8%; Anglo-Saxons (Ireland, UK, USA, Canada, Australia, New Zealand) 14.9%; Asia (Japan, Korea) 5%; and Other (Mexico, and unknown) 13.7%.

Roughly two thirds of respondents (66.6%) were from university clinics (106/161), one in four (24.4%) was a teaching hospital (39/161) and one in twelve (8%) was a tertiary care level center (13/161). Two out of three participants (69.2%) were gynecologic oncologists (111/161).

According to the average volume of patients treated annually over a period of three years, and also specifically in the last year, 8 subgroups were evaluated, from ≤ 20 to ≥ 300 patients. 57.8% of centers (93/161) had an average of up to 80 patients per year; 7.5% of centers (12/161) had treated >100 patients over the last year.

For the sake of brevity in this paper, these different groups will be referred to as the following when needed: A (geographically), B (volume), C (type of center), and D (subspecialty).

LNE (97.4%) (152/156), and precisely mainly a systematic LNE (94.8%) (147/155) was common to all participants (A-D). However SLNB use in CC was 60.6% (97/160) with nadir values as low as 30% in Northern Europe (NE), where imaging was instead relied upon (43%).

In addition, participants (A-D) carried out the procedure extremely seldom alone (0.8%), and generally replied that the most usual reason for not performing SLNB was lack of experience (>40%). Other regions of the world (88.9%) (p=0.031), low-volume centers (57.7%) (p=0.024), and general gynecologists (60.9%) (p=0.032) were definitively more prone to give this latter answer (Table 1).

Laparoscopy represented the most frequent surgical approach (60%), though in CE and Asia laparotomy was used more frequently. Robotic assistance was prevalent in NE (90%) and Anglo-Saxons (45.8 %) (p<0.001), in high-volume centers (55.6 %) (p<0.001), in university settings (37.7 %) (p=0.002), and among gynecologist oncologists (35.1 %) (p=0.040).

For all respondents (A-D), overwhelmingly, lower morbidity (>60% to 100%), with the exception of NE (33.3%) (p=0.128), and increased reliability (50% to 73 %), apart from CE (21.7%) (p=0.007), general gynecologists (30.8%) (p=0.005) and non-university settings (39.3%) (p=0.045), were deemed the main advantages of SLNB (Table 1). Additionally about one in four participants praised the reduced surgical time of the technique, compared to that of systematic LNE (15% to 35%). NE on the other hand considered SLNB neither faster (0%), nor associated with lower morbidity (33%).

SLNB was neither extremely popular for obese patients (16.5%), nor for elderly patients (16.5%): Anglo-Saxons (6.3%) and low-volume institutions (4.3%) were even less likely to use it in this latter group of patients (Table 1).

SLNB was generally more frequently performed for cancers ≤ 2 cm (46.9 %) and ≤ 4 cm (43.8%) regardless of histologic grade, lymph (L) and vascular (V) status. Only CE and Asia preferred it for lower grade (G1-G2) (>33%) (p=0.001), as well as non-university centers (26.8%) (p=0.009) and to a lower extent general gynecologists (29.6%) (p=0.038) (Table 2).

No group set age limits for SLNB, however remarkably few participants used it for patients desiring to preserve fertility (5.2%).

Low-volume centers (39.1%) and non-university hospitals (42.9%) ( $p=0.008$ ) predominantly performed SLNB in patients with no history of previous treatment; conversely Anglo-Saxons (43.8%) and Asia (50%) were using it more frequently independent of previous cancer therapy. Responders (A-D) were split with 45% waiting for final histology, as opposed to 55% relying on Frozen Section (FS): specifically Anglo-Saxons (33.3%) ( $p=0.115$ ), high-volume institutions (45.5%) ( $p=0.107$ ), and gynecologist oncologists (20.6%) ( $p=0.093$ ) associated Frozen Section (FS) to SLNB only when this would change their management, i.e. in fertility sparing cases.

Serial sectioning (SS) during FS was the norm (97% to 100%); Immunohistochemistry (IHC) use was also very common (86% to 100%), apart from Asia (50%) ( $p=0.179$ ).

Except for low-volume institutions (78.9 %) ( $p=0.022$ ), all participants (A-D) were consistent in answering that FS identified more frequently Macro Metastasis (MTS) (80% to 100%), micro MTS ( $\mu$ MTS) (45% to 65%) and finally Isolated Tumor Cells (ITC) (13% to 25%) respectively.

SLNB pN+ most often defined  $\mu$ MTS (78%), MTS (61%), and rarely ITC (19%).

Vice versa and interestingly, respondents (A-D) showed markedly different strategies following FS evaluation of SLNB.

In the case of FS pN+, 39% stopped the operation after SLNB and opted for chemoradiation (CRT), 45% completed pelvic and paraaortic LNE, and 26% went on to perform LNE and radical hysterectomy (RH). Asia (80%) ( $p=0.056$ ), high-volume centers (54.5%) ( $p=0.394$ ), and general gynecologists (45.5%) ( $p=0.011$ ) more commonly turned to this latter approach, as opposed to NE (0%) (Table 3).

Respondents (A-D) were almost equally split in case of FS pN0 SLNB, with 39% completing a systematic LNE and 41.6% avoiding any additional LNs removal: NE was the only exception with 100% additional systematic LNE.

Likewise, participants were divided when asked about their behavior in the presence of enlarged LNs at the time of SLNB pN0: 55.7% simply removed them, and always in the case of NE (100%), 38% added systematic LNE, and 6.3% left them, relying solely on SLNB, with a peak of 40% in Asia (40%).

Anglo-Saxons and Asia (56.3% and 63.7%, respectively) ( $p=0.090$ ), high-volume hospitals (58.3%) ( $p=0.132$ ) and gynecologic oncologists (40.8%) ( $p=0.243$ ) used Indo-Cyanine Green (ICG) more frequently (Table 4).

Site and modality of tracer injection were relatively standardized, apart from Anglo-Saxons who rarely (6.3%) and WSE who often (66.7%) ( $p=0.042$ ) used intra-cervical deep injection (Table 4).

The majority of respondents (72% to 100%) did not use colposcopic assistance to inject the tracer, and never high volume centers (100%); only exceptions were SWE and CE with 20.6% and 31.8% respectively of no users ( $p=0.090$ ). Finally, low-volume centers rarely injected in four quadrants (30.4%) ( $p=0.024$ ) (Table 4).

Almost 90% of respondents (A-D) used scintigraphy to detect SLN.

University centers tended to have a longer interval between tracer injection and LNs removal ( $p=0.005$ ) (Table 4).

Low-volume groups (61.9%) ( $p=0.009$ ) and general gynecologists

(66.7%) ( $p=0.014$ ) were less aware of their detection rate.

About 40% of respondents (A-D) had ongoing trials, >90% agreed to participate in a SLNB retrial, and 96.5% was ready to support international study concepts about the role of SLNB in the management of CC.

## Discussion

This study is the largest international survey on the current practice patterns of SLNB use in CC. Even though the overwhelming majority of centers across the globe perform LNE in CC, SLNB is not yet part of routine treatment of this malignancy.

FIGO staging in CC is and remains clinical, relying on clinical factors such as tumor dimension < or >4 cm. Indeed tumor size correlates closely with increased pN+, hence precise evaluation of LNs is important as therapeutic decisions are made [11].

The development and adoption of laparoscopy, and its intrinsic lower associated morbidity has additionally contributed to the standardization of LNE as part of a thorough staging of CC, now regarded as irreplaceable, leading some groups to advocate its use in extreme cases [12].

LNE is to be considered both the ultimate diagnostic tool, since it allows upstaging in up to 43% of patients, as well an important therapeutic step in the management of CC, according to the number and location of removed LNs in case of MTS and  $\mu$ MTS [13,14].

There is increasing evidence that SLNB in ESCC is accurate in detecting pN+, with results equivalent to Breast Cancer (BC), vulvar cancer and melanoma, tumors for which this method is an accepted standard of care [15]. SLNB has been incorporated in the National Comprehensive Cancer Network (NCCN) treatment algorithm of CC, and is now increasingly adopted.

Bats et al. [16] in a randomized trial in SLNB negative patients (SENTICOL 2, NCT01639820) tested both Quality Of Life (QoL) and safety matters: SLNB can indeed be used to identify which patients will highly benefit from a complete LNE from the ones in whom the procedure would potentially cause unnecessary iatrogenic damage with no therapeutic advantage.

A recent analysis of published studies reported a Detection Rate (DR) of 95% and sensitivity of 100% for SLNB in CC <2 cm [17].

Cibula et al. [18] described high sensitivity and low false negative rate (FNR) of SLNB when sentinel LNs were detected bilaterally, and proposed that this procedure and ultra staging should become standard practice in the surgical management of ESCC. The group at the MD Anderson Cancer Center recently stated: "We believe it is time to change the standard of care for women with early-stage cervical cancer to SLN biopsy only" [19].

Results with SLNB in ESCC are promising. Supporters of this technique praise its rapidity and reliability in selected patients, along with its decreased morbidity; its opponents, vice versa, question its feasibility, and highlight the paucity of sufficient scientific evidence, or even their deeper trust in imaging techniques [20-22].

Skeptics point out the high FNR, the importance of precise knowledge of LNs status in the parametrium, as well as the possible a typical site of pN+, which can be missed by SLNB. Further they question the use of SLNB in bulky tumors or Locally Advanced Cervical Cancer (LACC) with massive lymph node involvement, the

role of SLNB being different in ESCC as opposed to LACC [23-26].

Moreover, SLNB detractors also mention the additional costs of ultra-staging and subsequent therapy due to presence of  $\mu$ MTS, whereas unnecessary adjuvant treatment has also a price for the patients [25].

The debate about SLNB in CC is further complicated by the current uncertainty and lack of understanding of the clinical role of some additional pieces of information, i.e.  $\mu$ MTS or ITC, thus "questioning" the need for ultra-staging [22,27-31]. Indeed despite pN0 some groups still advocate in particular cases to perform a systematic LNE, or question the real meaning of pN0 with HPV detection in sentinel nodes [32].

Last but not least, fear of skip MTS, though rare, the current limits of FS evaluation of SLNB in CC, despite the long proven feasibility and role of SLNB in breast and vulvar cancer and melanoma, together with the absence of widespread acceptance of the few existing prospective studies have hindered international agreement on this procedure and its diffusion in clinical practice [27,33-35].

Nonetheless SLNB has potential advantages. It could reduce blood loss, operative time, increase identification of pN+ through ultra-staging, as well as allow for potential detection of an alternative lymphatic drainage site, and reduce morbidity [36].

SLNB in CC is still in its infancy and can well be defined as a work in progress. The lack of standardized strategies and the current ample differences in technique reflect more personal surgeon's experience and preferences, hence authors' opinions are still very heterogeneous and evolving [10,18,33].

For this reason and to optimize SLNB results, it is important to use algorithm and to carefully select patients preoperatively [31,37]. This includes evaluation of tumor size, the surgeon's learning curve and experience, histologic type, Lymphovascular Space Invasion (LVSI), preoperative treatment, Body Mass Index (BMI), bi-laterality, as well as the availability of reliable intraoperative pathological investigation, i.e. ultra-staging, and the standardization of the method including type, volume and timing of injection of the tracers, before SLNB could be used routinely [10,18,27,28-31,37,38].

Worldwide ESCC treatment strategies are far from being standardized and are currently under new scrutiny. In addition, stage-related mortality rates for CC in richer countries despite its marked decreased incidence have remained relatively stable, hence controlled radicality and patient's tailored treatment to cut down unnecessary iatrogenic morbidity are mandatory [11,22,39]. Likewise, despite the pivotal role of LNs status in the treatment of CC, the mere fact that  $>2/3$  of ESCC patients will be pN0 and will not profit from a complete LNE, but will potentially suffer life-long sequelae, is forcing the debate over the future role of SLNB in CC, and even more so with respect to subcategories like obese and elderly patients [10,39].

Unfortunately there is still limited awareness of therapy associated QoL in CC patients. A previous SGO survey on FS evaluation of LNs in CC showed that RH abortion in case of pN+ is still rare (21%) [40]. Similarly a quarter to four fifths of centers in our study still performs RH and systematic LNE in pN+ SLNB patients, who are bound to receive additional CRT.

Nonetheless the implementation of new techniques (ICG) could speed up the use and acceptance of SLNB in the diagnostic and therapeutic CC algorithm [37,38].

Our study has several flaws.

The primary limitation is sampling bias. Despite a much larger expected amount of responses worldwide, many countries were represented by a very limited number of groups, hence they are not adequately depicted, and the results are possibly not representative of the most commonly used SLNB strategies in ESCC worldwide.

Furthermore, there may have been a selection bias. Participants of centers performing SLNB were more likely to have higher surgical expertise and to complete the survey. Additionally, the predominance of academic institutions, gynecologic oncologists, and also members of the GCIG community, whose physicians are generally highly motivated in clinical trials and innovations, would once more mean that the outcomes may not correctly illustrate the view of the entire gynecological community.

The strengths of our study are the heterogeneity of participants both in regional terms, having received answers from four continents, as well as their different working environments, from low- to middle- and high-volume centers, university and general hospitals, and personal background, i.e. subspecialty.

The overall number of answers is sufficient to reliably highlight both common procedures used, as well as differences regarding SLNB in CC, whereas the matched comparison of different groups of respondents (B-D) is fully representative of the current state of this procedure in the gynecological universe.

Moreover responders predominantly expressed their availability and inclination to take part in multicenter prospective studies about SLNB in CC. Thus, this survey clearly shows the willingness, desire and need of participants to establish this technique, to define its indications by selecting a target population, and to standardize this procedure.

## Conclusion

The current questionnaire demonstrates encouraging levels of adoption of SLNB in CC across the globe; there is however a lack of international consensus, and considerable differences mostly regarding SLNB strategy in CC worldwide. This is not a complete surprise and may reflect the relatively limited efforts to surgically train gynecologic oncologists in SLNB technique, and to complete international trials, resulting in conflicting evidence in the literature.

There is a high need for educational and training programs, harmonization of guidelines and conduct for prospective trials to evaluate the role of SLNB in ESCC as well as in LACC.

The hope is to maximize the surgical information about LN status while limiting the unnecessary human cost associated with it, and eventually coming up with more definitive answers as to the optimal treatment of ESCC.

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