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Review Article

Sentinel lymph node (SLN) concept in cervical cancer: Current limitations and unanswered questions

David Cibula [a,*], W. Glenn McCluggage [b]

[a] Gynecologic Oncology Center, Department of Obstetrics and Gynecology, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Czech Republic
[b] Department of Pathology, Belfast Health and Social Care Trust, Belfast, United Kingdom

HIGHLIGHTS

- Detection of micrometastases increases sensitivity of SLN, so SLN ultrastaging should be performed if PLND is avoided.
- Intraoperative SLN evaluation fails to detect 30–50% of metastases.
- Micrometastases in SLN is associated with decreased survival equivalent to macrometastases.
- The risk of micrometastases in pelvic LN in cases with negative SLN is not known.
- There is no prospective evidence on safety of SLN only concept in cervical cancer.

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ABSTRACT

Sentinel lymph node (SLN) biopsy has been increasingly used in the management of early-stages cervical cancer instead of systematic pelvic lymph node dissection (PLND). The aim of this article is to give a critical overview of key aspects related to this concept, such as a necessity for reliable detection of micrometastases (MIC) in SLN and the requirements for SLN pathologic ultrastaging, low accuracy of intraoperative detection of SLN involvement, and still a limited evidence of oncological safety of the replacement of PLND by SLN biopsy only in ≥IB1 tumours due to unknown risk of MIC in non-SLN pelvic lymph nodes in patients with negative SLN, and absence of any prospective evidence.

Contents

* Corresponding author at: Gynecologic Oncology Center, Department of Obstetrics and Gynecology, Apolinarska 18, Prague 2 120 00, Czech Republic.
E-mail address: dc@davidcibula.cz (D. Cibula).

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1. Introduction

Sentinel lymph node (SLN) biopsy, instead of systematic pelvic lymph node dissection (PLND), is increasingly being used in the standard management of early-stage cervical cancer. The benefit for the patient is obvious. Less-radical lymph node (LN) dissection diminishes the risk of lower-leg lymphoedema, which is a severe morbidity that persists for life. New ESGO/ESTRO/ESP (European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology) guidelines recommend performing SLN biopsy as the first step of the primary surgical management in all early stages of cervical cancer (except T1a1) and submitting the SLNs for intraoperative assessment to triage patients towards radical surgery or definitive chemoradiotherapy [1]. These guidelines even accept SLN biopsy without additional PLND as a preferred method of LN staging in stage T1a cervical cancer. The National Comprehensive Cancer Network (NCCN) guidelines also recommended performing SLN biopsy in addition to PLND as an alternative option for LN staging in the early stages of cervical cancer [2]. There have been a growing number of publications which recommend replacing PLND with SLN biopsy in all early stages of cervical cancer, and there are currently two ongoing prospective trials evaluating oncological safety following SLN biopsy as a primary endpoint (SENTIX = NCT02494063; SENTICOL III = NCT03386734).

SLN is already implemented as a standard of care in cutaneous malignant melanoma, breast and vulvar cancer, and it has recently appeared in international guidelines regarding endometrial cancer management [3]. Since cancers arising in different organs differ in many regards, it is impossible to extrapolate from one organ site to another. Vulvar cancer is probably the closest to cervical cancer in terms of preferable lymphatic spread, the presence of anatomically well-defined regional LN, and the crucial importance of LN involvement for patient prognosis. Both prospective and retrospective studies have confirmed the safety of abandoning inguinofemoral lymph node dissection in patients with vulvar tumours smaller than 4 cm and negative SLN [4,5].

The aim of this critical commentary is to point out certain limitations and unanswered questions associated with the SLN biopsy concept in cervical cancer. Some of these will likely be answered by the ongoing prospective studies; in others, it is likely that evidence will not be obtained in the near future and uncertainty will remain.

2. Definitions of LN involvement

LN involvement is categorised as macrometastases (MAC) (tumour deposit greater than 2 mm), micrometastases (MIC) (tumour deposit greater than 0.2 and up to 2 mm) and isolated tumour cells (ITCs) (tumour deposit no greater than 0.2 mm). According to TNM 8, MAC is reported as pN1, MIC as pN1(mi) and ITCs as pN0 [6]. This categorisation applies to all tumour sites, although, as discussed below, the clinical impact of these different types of metastases for cervical cancers has not yet been determined. We also make the point that in many of the studies discussed later, no distinction is made between ITC, MIC, and MAC.

3. Importance of SLN pathological ultrastaging

SLN biopsy is considered to be more accurate in the assessment of pelvic LN involvement than a complete PLND [7,8]. Higher accuracy, manifested as more frequent detection of positive LNs, is a result of an intensive pathological assessment of a small number of SLNs. This pathological ultrastaging increases the probability of finding smaller metastases. For the pathologist (and pathology department), this is a demanding and time-consuming technique, which cannot be applied to all pelvic LNs in systematic PLNDs.

The high sensitivity of the SLN assessment for the detection of pelvic nodal involvement has been shown in many retrospective and prospective studies; in this context, sensitivity is defined as the proportion of patients with positive SLN amongst those with any positive LN (SLN or non-SLN) [9–12]. In the French prospective study, sensitivity was 100% and the false negative rate of SLN status was 0 in a subgroup with bilateral SLN detection [9]. It should, however, be emphasised that the high sensitivity and low false-negative rate of SLN assessment is partially due to the fact that the presence of any type of metastasis in SLN, including MIC or ITC, which are mostly detected by ultrastaging and not by standard pathological evaluation, is considered to be a positive finding. In the largest published retrospective study on SLNs in cervical cancer, the sensitivity reached 91% in the whole cohort and 97% in a subgroup with bilateral SLN biopsy [11]; in all these cases, PLND was performed following SLN biopsy. There were 18 (2.8%) false negative cases with negative SLN but another positive pelvic LN. Significantly, in addition to these false negative cases, metastatic involvement was detected in other pelvic LNs in an additional 23 cases (3.6%) in whom only MIC or ITC were found in the SLN. These cases were not considered false negative in spite of the detection of MAC in non-SLN, but only MIC or ITC in SLN. Had SLNs undergone conventional pathological assessment only, and assuming that such conventional assessment would detect all MAC, but no MIC or ITC, the sensitivity would have dropped to 80%. A conventional SLN evaluation (without ultrastaging) would fail to detect pelvic LN involvement in 6.4% of patients which would make SLN biopsy without additional PLND an unreliable and unsafe method of LN staging. Obviously, the reliability of SLN assessment is of even greater importance when systematic PLND is not performed. In such cases, if ultrastaging is not undertaken, positive LNs could potentially be left in the pelvis and N1 status would be under-diagnosed, meaning these patients would not receive appropriate adjuvant treatment. In other words, SLN pathological ultrastaging is an essential component underpinning the SLN concept in cervical cancer if PLND is to be abandoned.

4. Intraoperative SLN assessment

In early-stage cervical cancer management, new ESGO/ESTRO/ESP guidelines state that one key objective is the avoidance of a combined treatment by radical surgery followed by pelvic radiotherapy. Therefore, MRI or expert ultrasound is recommended as a mandatory preoperative work-up, and intraoperative SLN evaluation should be the first step of the surgery [13]. In the case of intraoperative detection of a positive SLN, a radical procedure including further PLND and radical hysterectomy should be abandoned, and the patient should be referred for chemoradiation. The goal is to decrease serious morbidity due to the combination of radical surgery and pelvic radiotherapy. This one-step approach is even more important in fertility-sparing management (trachelectomy or conisation).

In the intraoperative assessment of SLNs, there is always a compromise between accuracy on the one hand and time constraints and the potential loss of tissue for detailed ultrastaging outside of the intraoperative setting on the other. The SLNs (there may be more than one on each side) should be dissected carefully from the surrounding adipose tissue and each LN sliced at 2 mm intervals (with smaller nodes, this may mean that they are simply bisected) and 1 or 2 sections cut from each slice. However, the blocks should not be deeply levelled since this will result in loss of tissue for ultrastaging. For a lymph node with obvious gross tumour, a single section is adequate for frozen section and in such cases it is useful to keep the surrounding adipose tissue attached to the node to assess extranodal extension. A fact that is often not appreciated by surgeons is that it is difficult to handle and slice fresh LNs and to obtain good quality sections which include the full-face of the nodes; these are possible reasons why MIC and ITC (and even small MAC) may be missed on frozen section examination. It is also worth making the point that in developed countries, early-

stage cervical cancer (greater than stage pT1A1, which will usually be treated by loop excision) is uncommon and most pathologists will not be required to deal with a large number of such cases.

Studies have shown that intraoperative SLN assessment is not very sensitive in identifying nodal involvement [14–16]. The SENTICOL French prospective study failed to detect LN involvement intraoperatively in 15 out of 20 patients, including not only MIC or ITC (12 cases), but also 3 cases of MAC [15]. In a Canadian study of 211 patients, 10 of 13 cases with positive SLNs were false negative by frozen section, including 7 MIC, 2 ITC, and 1 MAC with a size of 2.9 mm [17]. In a study of 225 patients co-authored by one of us (DC), intraoperative SLN evaluation correctly detected only 39 of 73 cases (53%) with positive SLNs and missed 8 cases of MAC, 18 of MIC, and 8 of ITC [16]. A better sensitivity of 89% for the detection of MAC and MIC by frozen section was reported in a French study which included 94 patients [18]. In this study, however, there were only 11 patients with LN involvement, including 2 with MIC.

Given the above, it is clear that a one-step protocol of triaging patients towards radical hysterectomy or primary chemoradiation is limited by the high false-negative rate of intraoperative SLN evaluation. However, intraoperative evaluation results in the detection of LN involvement in approximately 50% of patients with positive LNs and detects a majority of MAC.

5. Protocol for pathological evaluation of SLNs

Adequate pathological examination of SLNs outside of the intraoperative setting (discussed above) involves ultrastaging, which mandates serial sectioning of each node at multiple levels, and immunohistochemical staining with pancytokeratin antibodies (usually AE1/AE3) if the tumour is not identified on examination of routinely stained sections. There are multiple ultrastaging protocols in different institutions, and it is difficult to definitively recommend a particular protocol; it is hoped that national and international pathology societies will recommend standardised ultrastaging protocols which can be implemented in all institutions undertaking SLN assessment in cervical cancer patients. Given the absence of a standardised protocol, we suggest a protocol below which is designed to pick up almost all MIC. While this protocol is labour intensive for the pathologist and laboratory staff, it is important to pick up MIC for the reasons detailed below. Given their size, reliable detection of all ITC would require hundreds of slides per SLN, which is not feasible in routine practice. As such, it has to be accepted that even if an intensive protocol for ultrastaging is used, this means that in the current groups of N0 patients, a certain proportion of cases with ITC and a small number of cases with MIC is represented.

After dissecting off the surrounding adipose tissue, each node (it is not uncommon for more than one SLN to be identified on each side) should be sliced at 2 mm intervals perpendicular to the long axis; these steps will have already been undertaken if frozen section has been performed. It is acceptable to put more than one slice of node into a single cassette. Each tissue block should be examined at different levels with haematoxylin and eosin (H and E) stain if a tumour is not identified in the initial sections. If tumour cells are not seen on examination of the routinely stained sections at the different levels, the detection of MIC and ITC is facilitated by immunohistochemistry with pancytokeratin antibodies.

We suggest cutting 4 sections at 200-micron intervals through the block and staining one section each with H and E and a pancytokeratin antibody (the latter if no tumour is seen on the H and E stained slides). It is useful to have an additional unstained section available at each level in case there is a problem with the H and E or cytokeratin stain. Additionally, if MIC or ITC are identified on an H and E or cytokeratin stain, the extra unstained sections can then be stained by H and E to evaluate whether the tumour focus becomes larger. The 200-micron (0.2 mm) interval should ensure that a large percentage of MIC are identified. Assuming a 1 cm sentinel node which is sliced into 5 pieces and examined in 2 tissue blocks, this protocol generally results in approximately 20 pairs of H and E and cytokeratin stained slides (10 per cassette/tissue block) if the initial H and E is negative for tumour; if 2 sentinel nodes are submitted, this would equate to approximately 40 pairs of H and E and cytokeratin stained slides. Using such a protocol, the number of slides is usually considerably greater than that generated by a conventional PLND procedure and this technique is expensive given the number of immunohistochemical stained slides. An additional point to make is that, as well as being labour-intensive for the pathologist, ultrastaging is also time-consuming for laboratory staff undertaking the cutting of the sections. Adequate time for cutting sections and guidance in working out the number of sections needed will be required since such ultrastaging techniques are not routinely undertaken and, given the rarity of early-stage cervical cancer, will not be commonplace. Clinicians will also need to be aware that ultrastaging takes time and the report will be somewhat delayed.

Cytokeratin-positive cells within LNs should always be correlated with the morphology. Müllerian inclusions (endosalpingiosis, endometriosis) and mesothelial cells may rarely be present in pelvic LNs and are cytokeratin-positive; if mesothelial cells are suspected, immunohistochemical staining with calretinin (a mesothelial marker) may be of value. If the cervical neoplasm is an adenocarcinoma or adenosqamous carcinoma, endosalpingiosis and endometriosis may result in particular diagnostic difficulties. Occasionally, histiocytes may be mistaken for tumour cells and, conversely, ITC may mimic histiocytes (known as histiocyte-like tumour cells) [19]; in such cases, a combination of cytokeratin staining and staining with the histiocytic marker CD68 will assist. Dendritic cells within LNs are often cytokeratin-positive but these have a different morphology from tumour cells, and if the pathologist is aware of this pitfall, diagnostic difficulty should not ensue. Fig. 1 illustrates some of the lesions which may be seen within LNs.

6. Prognostic significance of micrometastases

One of the benefits of SLN biopsy and its ultrastaging is the detection of an additional approximately 15% of patients with positive LNs, providing that MIC and ITC are considered positive for metastasis. Only limited data are, however, available as to whether low-volume LN involvement (MIC or ITC) is important for the prognosis and management of cervical cancer patients.

A large retrospective cohort study of 645 cases, published in 2012, was conducted with the aim of addressing the prognostic significance of different types of LN metastases in cervical cancer [20]. In all patients, SLN biopsy was followed by PLND and all SLNs were examined using a pathology ultrastaging protocol. MAC and MIC were detected in pelvic LNs, including SLNs, in 47 and 46 cases, respectively. In 645 cases with a median follow-up of 40 months, the presence of both MAC and MIC was associated with significantly decreased overall survival (HR = 6.85 (95% CI, 2.59–18.05) and HR = 6.86 (95% CI, 2.09–22.61), respectively). The importance of MIC on the prognosis of cervical cancer patients has been supported by another study with a different approach. The authors identified 83 patients with negative pelvic LNs and retrospectively subjected all the pelvic LNs to pathology ultrastaging [21]. The presence of MIC, detected by ultrastaging, was found to be the most significant prognostic factor for disease recurrence (OR = 11.73; $P = 0.017$); this was in comparison to other commonly used prognostic factors such as depth of stromal invasion (OR = 1.16), tumour size (OR = 4.42) and lymphovascular space invasion (OR = 1.19).

Two ongoing European prospective trials planning to accrue 600 and 475 patients who will have only SLN biopsy (SENTIX and SENTICOL III) will shed some light on the significance of LN MIC. Estimating a 10% rate of MIC in SLNs, these studies should result in cumulative data on 100 cases with MIC. However, data on the oncological outcome from both trials will not be available until 2020 and 2025 at the earliest. To have an idea about the size of a prospective study which would be required to come up with evidence regarding the prognostic significance of MIC, we can make a simple calculation. Considering a 10% incidence of

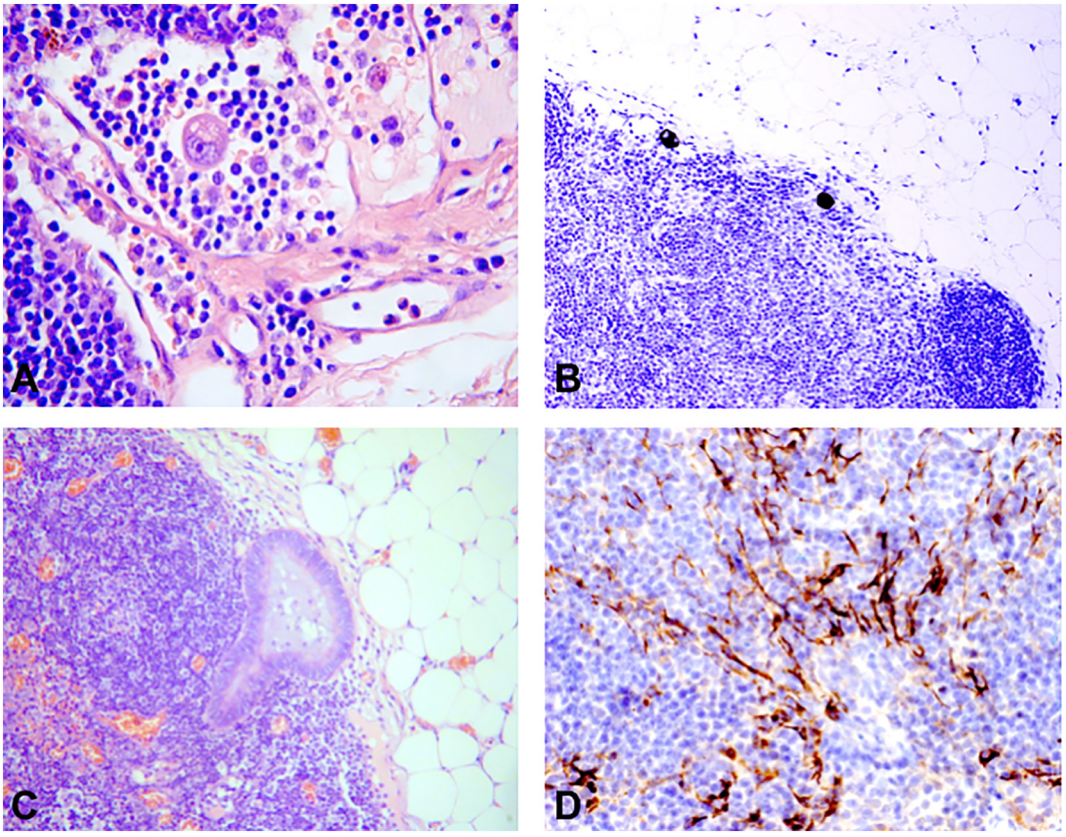

Fig. 1. Isolated tumour cell within subcapsular sinus of lymph node (A). Two isolated tumour cells exhibit positive staining with AE1/3 cytokeratin antibody (B). Endosalpingiosis within capsule of lymph node (C); this may result in a misdiagnosis of metastatic tumour if the primary cervical neoplasm is an adenocarcinoma or adenosquamous. Positive staining of lymph node dendritic cells with AE1/3 (D).

MIC in early-stage disease, and an 8% risk of recurrence in LN-negative patients, a sample size of 100 cases with MIC and 600 with negative LNs would be required to identify a 10% increase in recurrence rate between groups with negative LNs and MIC on the level of $\alpha = 0.05$. Such a study would also require a standardised comprehensive SLN ultrastaging protocol.

Assuming that MIC is a negative prognostic factor, can these patients benefit from adjuvant radiotherapy? Achieving evidence on this ultimate question from prospective trials is almost impossible. Besides an unrealistic number of patients with early-stage disease being needed to collect enough cases with MIC, a randomisation to the arm of no adjuvant treatment would most likely not be accepted by many patients and physicians. A recently published ESGO survey showed that 93% of respondents consider MIC an indication for adjuvant treatment after surgery [1]. Taking into account all aspects, including a declining incidence of cervical cancer in regions with available resources for routine SLN ultrastaging, excellent prognosis of early stages, discrepancies in recommendations for adjuvant treatment, and constant evolution of the management of cervical cancer, it is unlikely that prospective evidence on the role of adjuvant radiotherapy in patients with MIC in SLN will be obtained soon, if ever. A similar trial on ITC would be even more complicated due to unreliable pathological detection of ITC, even with lower prevalence and a presumed better prognosis in comparison to MIC.

7. Risk of micrometastases in non-sentinel pelvic LNs

One of the key arguments for abandoning systematic PLND is the results from both retrospective and prospective studies, which provide evidence on the high reliability of SLN assessment for staging of other pelvic LNs. As discussed, a sensitivity of greater than 90% has been reported for pelvic LN staging in those patients with bilateral SLN detection. In the majority of these cohorts, the SLN biopsy was followed by a systematic PLND. While SLNs were assessed using a pathology ultrastaging protocol, other pelvic LNs were processed conventionally. Therefore, there has always been a methodological bias when comparing SLN and non-SLN status. The majority of the current evidence regarding the reliability of negative SLNs in predicting other negative pelvic LNs ignores the fact that we do not know the risk of MIC, which can remain undetected in non-SLN by conventional LN evaluation. So far only 5 studies have assessed both SLNs and all other pelvic LNs by ultrastaging, with 3 false negative cases in one study with 26 patients and no false negatives in the other 4 (combined total of 64 cases) [22–26]. Although the risk of MIC in non-SLNs with negative SLNs seems to be very low, all available evidence comes from a cumulative group of 90 patients in which the methodology of pathological evaluation was not identical, and the risk of LN involvement was low (12 cases).

8. Conclusion

Clinical practice has been shifting towards the acceptance of the replacement of full PLND by SLN biopsy in the management of cervical cancer patients. Besides decreasing morbidity due to the abandonment of PLND, SLN biopsy offers other benefits. It enables intraoperative assessment of key pelvic LNs and tailoring of patient management in one step. It also improves LN staging by detecting up to 15% of additional patients with LN involvement secondary to intensive pathological utrastaging.

When introducing the SLN concept into clinical practice, we should bear in mind that cervical cancer in the early stages has an excellent prognosis after standard surgical treatment. A recent randomised trial showed 96.5% disease-free survival after open surgery in a group of

312 patients with early-stage cervical cancer with a median follow-up of 2.5 years [27]. Unlike in breast cancer, other tumour-related factors (tumour type, grade, hormone receptor status, etc.) are less important for prognosis in cervical cancer, and LN involvement remains the most important prognostic factor. Our requirements for management should be very rigorous, since mortality in recurrent disease is very high and failure to detect LN involvement can be fatal for a patient.

It has been shown that metastatic involvement of non-sentinel pelvic LN can be found in some patients with only MIC in SLN. If only SLN biopsy was performed without systematic PLND, these LN positive cases would not be detected without ultrastaging. Therefore, one of the prerequisites for the replacement of PLND by SLN biopsy only is the unification of a protocol for ultrastaging. The minimal criteria should include processing of all SLNs in their entirety and, if metastases are not identified on initial sections, examination of multiple levels and cytokeratin immunohistochemical staining in order to detect as many small MAC and MIC as possible. We have suggested a protocol and hope that national and international pathology societies will recommend standardised ultrastaging protocols.

Intraoperative assessment allows for detection of the majority of MAC. In these patients, a combined treatment can be avoided if radical surgery is abandoned and the patient is referred for primary chemoradiation. However, patients should be informed before their surgery that, in spite of a negative intraoperative SLN evaluation, LN metastases are identified later in 30–50% of cases following pathological ultrastaging. These patients will receive a combined treatment in spite of the intraoperative LN examination.

The presence of MIC in LN is currently broadly accepted as an indication for adjuvant radiotherapy. Available evidence showing that MIC is a significant negative prognostic parameter comes only from retrospective studies. Some prospective data should be obtained from ongoing prospective trials, but this data will not be available earlier than in 2020 (SENTIX trial) and 2025 (SENTICOL III trial). The risk associated with ITC will remain unknown even after these studies have been published, due to other limitations, such as low prevalence of ITC and unreliable ITC detection even by SLN ultrastaging.

Finally, it should be emphasised that the oncological safety of PLND replacement by SLN biopsy has not yet been validated by a sufficient prospective trial. The majority of available data comes from retrospective studies which combined SLN biopsy with systematic PLND and used different protocols for SLN ultrastaging. Since other pelvic LN in these studies were evaluated by a standard pathological protocol, the risk of MIC/ITC in cases with negative SLN is not known.

It is likely that the 2 ongoing prospective trials discussed above will confirm the safety of SLN biopsy only. We should, however, await this evidence and take into account the excellent outcome of current surgical treatment, including systematic PLND, in this particular group of patients with negative LN.

Disclosure statement

The authors declare that there are no conflicts of interest.

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