

The role of sentinel lymph node biopsy in cervical cancer

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Introduction

Lymph node dissection traditionally has been an essential component in surgical cancer staging for many different malignancies to evaluate for metastases. Lymphatic assessment plays a vital role in prognosticating and establishing the need for adjuvant therapy.¹ Sentinel lymph node (SLN) mapping and biopsy has been proposed to identify tumour metastases while reducing the morbidity associated with systematic lymph node dissection. A SNL is the first group of lymph nodes to drain an organ before it enters the lymphatic basin. The principle that if one or more SLNs are negative for malignancy then the remaining regional nodes in the lymphatic basin will also be negative is the basis behind omission of the traditional systematic lymph node dissection which will add little value and increase morbidity.^{2,3} Table 1 demonstrates the theory behind SNL mapping.

Table 1. Theory behind Sentinel Lymph mapping

1. The lymphatic drainage systems of the body's organs are predictable and systematic. The SLN is the first lymph node or group of lymph nodes in the lymphatic chain to receive drainage from an organ.
2. If an organ becomes infiltrated with a primary tumour then the SLN is the most likely to harbour metastases, in cancers with lymphatic spread
3. A marker, when injected into or near the organ should mimic the organ/tumours lymphatic drainage and allow mapping of the lymphatic system and the SLN with good sensitivity and specificity
4. Identification, excision and examination of the SLN only versus a systematic lymph node dissection will result in less morbidity
5. Inability to identify a SNL should be considered a mapping failure and result in a complete systematic lymphadenectomy

Sentinel lymph node (SLN) biopsy has been validated and is the standard of care for cancers such as breast and select early stage vulvar cancer to minimise the morbidity associated with systematic lymph node dissection.^{1,2} Controversies around its use in endometrial cancers still exist particularly around appropriate patient selection and high-risk disease however its use has been supported but is not yet standard of care by groups such as National Comprehensive Cancer Network (NCCN), Society of Gynecologic Oncology (SGO) and in the recent Sentinel Consensus

document by the British Gynaecological Cancer Society.^{4,5} In a recently published online survey of gynaecologic oncologists in the USA 98% performed SLN biopsy in early stage endometrial cancer despite the lack of randomized control trials comparing full systematic lymphadenectomy versus SLN biopsy alone.⁶ Of the gynaecologists who performed SLN biopsy in endometrial cancer, 64% also performed SLN mapping in cervical cancers as seen in a survey by Chambers.⁵ As with endometrial cancer there is a growing body of evidence to support the substitution of systematic pelvic lymph node dissection (PLND) with SLN biopsy in apparent early stage cervical cancer.^{3,7} While we await the results of two large prospective trials SENTIX and SENTICIL III which are evaluating the oncological safety of SLN biopsy alone versus PLND in cervical cancer it has been recommended that we should perform SLN biopsy along with complete PLND.

Systematic pelvic lymphadenectomy versus sentinel lymph node biopsy

Lymph node involvement is the single most important prognosticator in cervical cancer and is essential in post-operative treatment planning to prevent recurrence and improve disease free survival (DFS).⁸ Traditional surgery in the form of a radical hysterectomy followed by systematic PLND ± para-aortic LND is considered for Stage Ia2-IIa cervical cancer. In stage Ia1 disease with lymphovascular invasion (LVSI) PLND is recommended along with simple hysterectomy. In Stage Ia with no LVSI a simple hysterectomy or conisation alone is done as the likelihood of lymph node metastases is less than 1%.⁸ Interestingly the literature states that 80% of operated early stage cervical cancer patients have negative lymph nodes and perhaps in the setting of SLN biopsy would have undergone unnecessary PLND.⁹

The advantage of SLN biopsy versus systematic PLND is obvious, shorter operative time, fewer neurovascular complications and infection and a significant reduction in lymphocyst and limb lymphoedema, a very debilitating condition for which there is no cure.^{4,10} Other important considerations for SLN biopsy is intra operative assessment and the possibility of avoiding dual therapy in cervical carcinoma namely radical hysterectomy and PLND followed by chemo-radiation which has a well-documented increase in morbidity versus the respective treatment modalities alone.¹¹

The NCCN recommends performing SLN biopsy prior to performing systematic PLND in early cervical carcinoma as a treatment option, while 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 stage Ia1 and submitting the SLNs for intraoperative assessment to triage patients towards radical surgery or definitive chemoradiotherapy. Furthermore, this guideline recommends SNL biopsy alone in stage Ia disease.^{12,13}

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Techniques for sentinel lymph node mapping in cervical cancer

As per the British Cancer Society Consensus the use of sentinel lymph node algorithms can be considered in Stage Ia2-Ib1 disease with a tumour size of <2cm along with no evidence of metastases on imaging.⁴ The reliability of SLN biopsy in tumors larger than 2cm is questioned in the literature as the detection rate is significantly lower in a number of studies yet this has been disputed in others showing similar accuracy rates particularly if indocyanine green (ICG) is used to map.^{9,14,15,16}

The SLN biopsy techniques are done similarly to endometrial cancer with intracervical injection of either ICG or technetium-99 (Tc99) radiocolloid along with methylene blue dye (BD). Ideally the injection should be a superficial and deep injection in the normal stroma as intra tumoral injection can affect SLN detection.¹ The most common injection sites are at 3 and 9 o'clock.

Indocyanine green (ICG) fluorescent injection with near-infrared fluorescence imaging has the advantage of offering real time assessment of the SNL during surgery with a quick transcutaneous reveal time of 5 – 60 minutes.¹⁷ The near infrared detection technology systems are available in both video telescopes used for laparoscopic and robotic surgery and handheld video devices for open surgery, they are easy to use and are reproducible.² Image 1 and 2 demonstrate SNL mapping of a 31 year old with Stage 1a cervical adenocarcinoma, using ICG and near-infrared fluorescence imaging to detect the SNL.

Image 1 Left external iliac SNL and lymphatic tracts.

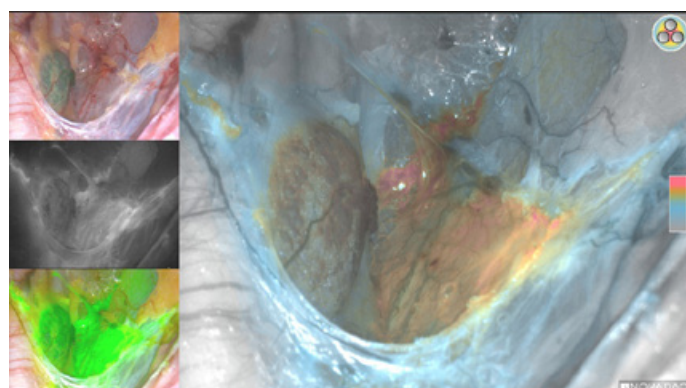


Image 2 Resection of left external iliac SNL



Tc99 and BD requires preoperative injection of radiocolloid followed by lymphoscintigraphy and mapping as well as injection of blue dye in the operating theatre. This is a costly and time consuming and requires the services of nuclear medicine department.

ICG SLN mapping has better detection rates and bilateral detection rates than Tc99 and BD.^{2,4} Detection rates of SLNs range

between 96% - 100% for ICG and 95% - 97.8% for Tc99 ±BD in various studies and bilateral detection rates are around 88%-95.2% vs 66%-69.6% for ICG and Tc99±BD respectively.^{18,19} It is important to state that detection rates and a reduction in false negative mapping improves significantly when done by surgeons with experience in SLN mapping.¹ There is no consensus in the guidelines on the minimum number of cases needed in the learning curve for SLN mapping or the case load the surgeon should have to maintain skill.⁴

Surgical algorithms have been designed in SNL biopsy to enhance detection rates and should be adhered to when performing SNL mapping.²⁰ Table 2 summarises SLN mapping algorithm.

1.	Excision of all mapped SNLs – submit for ultrastaging if H&E negative
2.	Any suspicious LN must be removed regardless of the SLN mapping results
3.	If there is no SLN found on a hemi pelvis then a side specific systematic PLND must be performed, (including interiliac nodes)
4.	Parametrectomy en bloc with resection of primary tumour in all cases

Sentinel lymph node pathological evaluation and ultrastaging

Definitions of lymph node involvement and prognostic significance

An understanding of the definitions of lymph node involvement is pivotal to understanding SNL mapping and some of the ambiguities around this concept. Table 3 summarises the definitions of lymph node involvement. Standard histopathological evaluation is unlikely to detect MIC deposits or isolated tumour cells.

Macro metastases (MAC)	Tumour deposit of >2mm
Micro metastases (MIC)	Tumour deposit of 0.2mm – 2mm
Isolated tumour cells (ITCS)	Tumour deposit of no greater than 0.2mm

The clinical significance of low volume metastases (MIC and ITC), has not yet been determined in cervical cancers, with no clear recommendations defining treatment options should the LN involved have MIC or ITCs due to the lack of data. If uniform ultrastaging guidelines are followed on SNL biopsies it is estimated that an additional 15% of nodal metastases will be detected compared to PLND alone. This is because of the inclusion of MIC and ITCs in the diagnosis of positive LN.¹⁰

Two studies aimed at trying to identify the prognostic significance of low volume metastatic disease have been published.^{21,22} MIC was defined as being the most significant negative prognosticator in women with negative PLND who had retrospective analysis and ultrastaging of lymph nodes p=0.017 and along with MAC was associated with a decrease in overall survival HR=6.86 (95% CI 2.09-22.61). It is important at this stage to state that most MIC will be missed by routine pathological evaluation of complete PLND. Given this information it appears the need for adjuvant therapy would be favoured should MIC be isolated on SNL. It would be ethically unacceptable to do a study randomizing low volume metastatic disease to adjuvant treatment or clinical follow up given the above information and thus the clinical significance of low volume disease may never be truly understood.

Ultrastaging of sentinel lymph nodes for cervical cancer

There is an increased detection of nodal metastases on SNL biopsies with the use of pathological ultrastaging versus PLND alone.^{1,18} This improved accuracy is due to the stringent pathological assessment done with ultrastaging where each SLN is sectioned

into 2mm segments for histopathological evaluation. This process is costly and time consuming and is only feasible when performed on a small number of sentinel nodes versus the entire pelvic lymph node conglomerate.¹⁰

In the largest published retrospective study looking at SLN in cervical cancer, where SLN biopsy was done followed by full PLND there was a sensitivity of 91% for the whole cohort and a sensitivity as high as 97% in the group of women where bilateral sentinel lymph nodes were detected. The sensitivity here is described as the number of positive sentinel lymph nodes amongst those with any positive nodes on PLND. The false negative rate (FNR) was 2.8%, where positive nodes were found in the PLND and not in the sentinel node. The high sensitivity and low FNR here are attributable to ultrastaging and the inclusion of any type of metastases namely MIC and ITC being defined as a positive LN. It was estimated that if conventional histopathological evaluation were done on the sentinel nodes and all MICs and ITCs were missed then the sensitivity would have decreased to 80% with FNR of 6.4%. This illustrates the importance of ultrastaging in the setting of SLNB especially where PLND is going to be omitted.²³

Ultrastaging is a labour intensive process which requires serial sectioning of the sentinel node and each tissue block is examined with hematoxylin and eosin (H&E). If no tumour cells are identified, then immunohistochemical staining with pancytokeratin antibodies must be done in order to enhance detection of MIC and ITC. Unpublished data has shown huge variation in the ability of pathologists to detect metastases with ultrastaging. Current issues include no international consensus on protocols for ultrastaging and lack of experience of pathologists. Table 4 shows the recommended standardised protocol for ultrastaging put forward by ESGO/ESTRO/EPSC which is designed to detect most MIC.¹⁰

Table 4. ESGO/ESTRO/EPSC ultrastaging protocol for early stage cervical carcinoma¹⁰

1. Dissect off surrounding adipose tissue. Sectioning to be done perpendicular to the long axis at 2mm intervals
2. Examine each tissue block at different levels with H&E if no tumour is found
3. If no tumour cells seen with H&E – do immunohistochemistry with pancytokeratin antibodies
4. Cut 4 sections at 200-micron intervals through the block staining 1 section each with Hand E and pancytokeratin

Intra operative sentinel lymph node evaluation

It is well established that combined treatment involving radical hysterectomy and PLND followed by chemo-radiation is associated with much higher morbidity than surgery or chemoradiation alone. If indicated chemo radiation alone has similar DFS rates in early stage cervical cancer to surgery.^{11,24} For this reason one of the key objectives of ESGO/ESTRO/EPSC guideline is avoidance of combined therapy in patients with early stage cervical cancer.¹⁰

Preoperative evaluation with either MRI or expert ultrasound is advocated to exclude metastatic disease followed by SLN evaluation as the first step of surgery with frozen section and assessment in theatre. Radical hysterectomy and PLND should be abandoned if there is intraoperative confirmation of a positive sentinel node and the patient should be sent for chemoradiation.²⁵

Intraoperative assessment and frozen section has a poor sensitivity for various reasons including difficulty handling fresh specimens, the issue of time constraints and histological accuracy while the surgeon waits to proceed or abandon surgery and of course the lack of clinical experience or exposure of the pathologist to cervical cancer. Intraoperative assessment of SNL detection rates varies widely among studies from 23% detection to 89%. Given that, the one- step evaluation protocol is quite limited but is still advocated to avoid morbidity associated with dual therapy.¹⁰

Minimally invasive surgery versus open surgery for the management of early stage cervical cancer

Majority of the published data on SLN mapping sensitivity and detection rates has been reported in patients who underwent minimally invasive surgery either laparoscopic or robotic. Subsequently a large prospective trial the LACC trail, comparing open radical hysterectomy and PLND to minimally invasive surgery (MIS) radical hysterectomy and PLND showed a 3-fold increased risk of recurrence in the MIS arm (7/312 vs 27/319, HR=3.74, 95% CI 1.63-8.58 p = 0.002). There was also a decrease in overall survival in the MIS arm p =0.004.²⁶ Besides the LACC trail Melamed et al reported a 48% higher hazard of death from any cause for patients who has MIS radical hysterectomy to those who had open surgery (HR= 1.48, 95%CI 1.10-1.98).¹ In view of the above publications there seems to be a shift back to open surgery for early stage cervical cancer. Important questions to consider will be if the SNL mapping detection rates and sensitivity are equivalent in open surgery to MIS or should one start with laparoscopic SNL mapping and then proceed to open surgery? The use of ICG with handheld near-infrared device in theory should not be any different.

Conclusion

Sentinel lymph node mapping is emerging as an alternative standard of care in the management of women with early stage operable cervical cancer. Besides the obvious benefit of decreased morbidity should PLND be replaced by SLN biopsy only, SNL has other advantages. Intraoperative evaluation of the SNL allows for tailored management of each patient. Most macrometastatic disease will be detected on SNL biopsy allowing the surgeon to abandon radical surgery and refer the patient for chemo-radiation eliminating the possible morbidities associated with combined treatment. The sensitivity of frozen section in theatre is limited and there will still be a number of patients where lymph node involvement will only be found later on ultrastaging requiring the need for adjuvant therapy anyway. The other benefit of SNL biopsy with ultrastaging is the significant increased detection of metastatic disease thereby improving lymph node staging in comparison to the traditional approach.

The prognosis of women with early stage cervical cancer is excellent with disease free survival rates quoted as being as high as 96.5% after 2.5years in the LACC trial for those undergoing open radical hysterectomy and PLND.²⁶ SNL alone would merely be improving the morbidity of patients with emphasis on those with negative SNL biopsy or those with a positive SNL diagnosed at surgery. It may also detect more lymphatic disease predominantly MIC and ITC with strict ultrastaging and improve the rate of recurrence by sending patients for adjuvant therapy although we do not truly understand the clinical significance of low volume metastatic disease. Nevertheless, the importance of uniform ultrastaging protocols, appropriate patient selection, strict adherence to the SLN mapping algorithm is essential as mortality in recurrent cervical cancer is catastrophically high. Failure to detect a positive LN could result in death. While we await the results of prospective studies that are assessing the oncological safety of SLN biopsy alone, omission of PLND is reserved for Stage 1a disease where the likelihood of lymph node metastases is less than 1% and traditional surgery didn't routinely require PLND. For all other cases SNL must be followed by complete PLND.

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