The role of sentinel lymph node biopsy in cervical cancer: an overview of the literature

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Abstract

Cervical cancer is the second most common cancer in southern African women. Although the FIGO staging does not include lymph node status, lymph node metastasis is an important risk factor for recurrence and death in patients with early cervical cancer. Accurate information about lymph node metastasis is crucial to decide on optimal individualised treatment. Complete pelvic lymphadenectomy is the current standard used to obtain accurate information on lymph node status. Because of the low incidence of nodal metastasis in patients with early cervical cancer, identifying women in whom lymphadenectomy can be safely avoided would result in less morbidity associated with pelvic lymphadenectomy, without compromising overall and disease-free survival. Over the past 15 years, the role of sentinel lymph node (SLN) biopsy has been studied extensively in patients with early-stage cervical cancer. Assessment of the SLN in women with early-stage disease may potentially offer an alternative to complete lymphadenectomy. Data are limited with regard to the role of SLN assessment in patients with cervical cancer in low-resource settings where the prevalence of HIV and other gynaecological infections is high.

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Introduction

Cervical cancer is the second most common cancer in southern African women, with an incidence of 31.5 per 100 000 women in 2012.[1] Although the FIGO classification of cervical cancer does not include lymph node status, it is known that lymph node metastasis is an important risk factor for recurrence and death in patients with cervical cancer.[2,3] Information on the presence of metastatic disease in the lymph nodes is important in that it allows for the planning of optimal treatment strategies in patients with early-stage disease. Radical hysterectomy and complete pelvic with or without para-aortic lymphadenectomy is the current recommended surgical treatment for patients with early-stage cervical cancer (stage I-IIA). In the last two decades, laparoscopic surgery has been shown to have similar survival outcomes with less morbidity. Irrespective of the mode of surgery, pelvic lymphadenectomy is associated with prolonged duration of surgery, increased blood loss, nerve injury, lymphocyst formation, vascular injury and lower-extremity lymphoedema.[4,5]

Current treatment modalities for early-stage cervical cancer consist of surgery or chemoradiation therapy, with similar survival rates. If there is no metastatic spread to the lymphatic system, patients benefit more from surgical treatment, owing to the long-term complications associated with chemoradiation therapy. The prevalence of lymph node involvement is approximately 15% in stage IB1 cervical cancer.[3,6] This means that up to 85% of these women do not benefit therapeutically from lymphadenectomy, and the procedure could potentially be safely avoided if the lymph node status was known preoperatively. Currently, no imaging techniques are available with the ability to accurately determine lymph node status in patients with cervical cancer.[7,8]

Sentinel lymph node (SLN) biopsy is a diagnostic technique used to determine the local and regional lymph node involvement of cancer by identifying and examining a targeted lymph node sample, instead of having to perform a complete lymphadenectomy. This technique was initially described for penile cancer in 1977,[9] and later

validated for malignant melanoma and breast cancer, and was more recently accepted as a management option in carefully selected patients with vulva cancer.[10-13] The philosophy of the sentinel node is that the metastatic lymphatic spread of cancer occurs in a systematic fashion, first spreading to one node, before involving nodes in the rest of the lymphatic chain. This principle allows for the ability to assess the status of the first node in the lymphatic chain, known as the sentinel node, and to use this information to predict the status of the rest of the lymphatic chain in that region without having to remove all of the lymph nodes.[9,14] Additional advantages of SLN biopsy include the possibility of detecting aberrant lymph nodes not located in the expectant locations and therefore missed by complete lymphadenectomy, as well as allowing histological ultra-staging to be performed in the SLN.

SLN biopsy has been investigated in gynaecological oncology,[15] and it is now widely used in selected cases of women with early-stage vulvar cancer.[16] Techniques for the detection of SLNs in endometrial cancer have also been described. Several publications have suggested the feasibility of an algorithm for SLN biopsy in women with endometrial cancer.[17] In 1999, Echt et al suggested SLN biopsy as an option to identify the lymph node status in women with early-stage cervical cancer.[18]

Detection rates and sensitivity

The detection rate of SLN biopsy in cervical cancer has been reported to be between 60% and 100%.[19] This wide range is mainly based on small case series. Recent publications on the diagnostic accuracy of SLN biopsy in early cervical cancer are based on larger (> 100 cases) prospective and retrospective series (Table I).[20-23] Two systematic reviews of the literature before 2008-2009 have also been published. However, both do not include the four more recent publications stated previously.[8,19]

In 2008, the first SLN study on cervical cancer, conducted by Altgassen et al,[20] reported disappointing results. They reported an overall SLN detection rate of 89.7% and overall sensitivity of 77.4%. However, the sensitivity was found to be significantly higher when bilateral SLN detection was achieved (89.2%,) and in patients with a tumour size ≤ 2cm in diameter (90.9%).

In contrast to the publication by Altgassen et al, the three more recent publications from Lécuru et al,[21] Cormier et al[22] and Cibula et al[23] report higher unilateral detection rates, bilateral detection rates and sensitivity (Table I). It is likely that the lower unilateral and bilateral detection rates reported by Altgassen (89.7-42%), compared to Lécuru (97.8-76.5%) and Cormier (93.4-74.6%), were caused by a learning curve as Altgassen's was a pioneer study in which recruiting began in 1998. Another likely reason is the inclusion of all stages of cervical cancer. Extensive invasion of the lymph nodes often occurs in the advanced stages, thus possibly leading to a disruption of the lymphatic drainage system and the ability to identify the SLN. As with the detection rate, it is most likely that the lower sensitivity reported by Altgassen (77.4%), compared to Lécuru, Cormier and Cibula (92%, 87.5% and 91%, respectively), was caused by a combination of factors. In addition to the previously stated reasons, the lack of histological ultra-staging of the SLN would have further decreased the sensitivity of Altgassen's findings, compared to that in the three more recent papers.

The two systematic reviews from Selman et al[8] and Van de Lande et al[19] prior to the publication of the four more recent large publications stated previously, reported a similar detection rate of 95-96%, and a sensitivity of 89-91% to the more recent trials. Selman also compared SLN biopsy with imaging modalities (MR, CT and PET CT) to determine the lymph node status. They found that the SLN biopsy was superior compared to all of the imaging modalities.[8]

In summary, because of the limitations of the Altgassen publication, the sensitivity and negative predictive value (NPV) of the SLN biopsy is generally accepted to be between 87.5-92% and 96.8-98.2%, respectively, based on the three more recent large publications.[21-23] This

Table I: Summary of the diagnostic accuracy of sentinel lymph node biopsy in cervical cancer

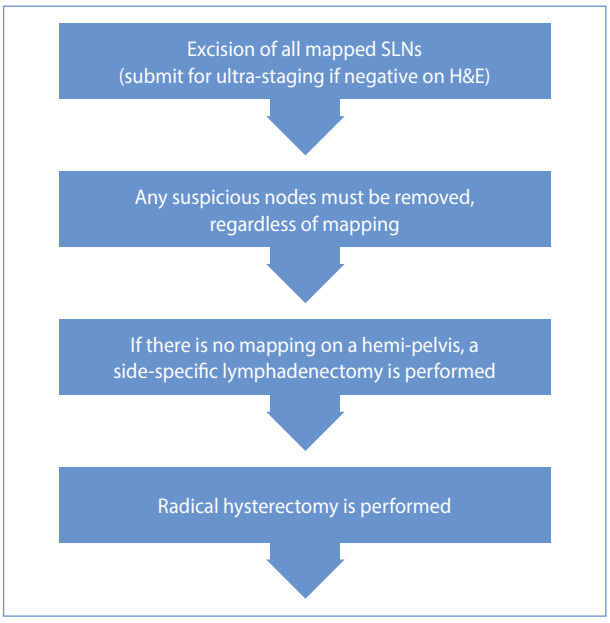
References	Design	Cases (n)	FIGO stage	UDR (%)	Sens UDR (%)	NPV UDR (%)	FNR UDR (%)	BDR (%)	Sens BDR (%)	NPV BDR (%)	FNR BDR (%)
Altgassen et al[20]	Prospective cohort	507	All	89.7	77.4	94.3	22.6	42	87.2	96.5	12.8
Lécuru et al[21]	Prospective cohort	139	≤ IB1	97.8	92	98.2	8	76.5	100		0
Cormier et al[21]	Prospective cohort	122	≤ IIA	93.4	87.5	96.8	12.5	74.6	92.6	98.9	7.4
Cibula et al[23]	Retrospective cohort	645	≤ IIB		91			72	97		1.3

BDR: bilateral detection rate, FIGO: *Fédération Internationale de Gynécologie et d'Obstetrique* (International Federation of Gynecology and Obstetrics), FNR: false negative rate, NPV: negative predictive value, Sens: sensitivity, UDR: unilateral detection rate

compares favourably to the validated SLN biopsy in breast cancer, with a sensitivity of 88.6-91.2% and NPV of 91.1-95.7%.[24,25]

The cervix as a midline organ

Many authors are of the opinion that, because the cervix is a midline organ, lymphatic drainage involves both sides of the pelvis. It has been shown that SLN status on one side of the pelvis does not predict the presence or absence of metastasis on the contralateral side.[19,22] For this reason, SLN should be evaluated side specifically and not patient specifically.[21-23,26,27] The algorithm for SLN mapping, published by Cormier et al, takes into account a side-specific evaluation and recommends unilateral lymphadenectomy on the side where a SLN is not detected, as well as the removal of clinically enlarged lymph nodes. This strategy results in a sensitivity of 100% and an NPV of 100% (Figure 1).[22] The need to remove clinically enlarged lymph nodes, irrespective of the dye or Technetium-99m (Tc-99m) uptake, is based on the fact that the lymph drainage may be disrupted because of tumour burden in the metastatic lymph nodes. It is also possible that lymph nodes may be "clogged" with debris, or that the lymph vessels may be disrupted following an inflammatory process caused by disease or surgery. This can possibly alter bilateral drainage towards unilateral drainage. In addition, enlarged lymph nodes can be a result of other conditions, such as infection, and histological confirmation of the metastases is required. For this reason, a complete lymphadenectomy is mandatory on the side where a SLN is not detected.[28]



H&E: haematoxylin and eosin, SLN: sentinel lymph nodes
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Figure 1: Sentinel lymph node surgical algorithm for early cervical cancer[22]

Detection techniques of the sentinel lymph node in cervical cancer

Cervical injection method

Multiple cervical injection techniques have been described in the published literature on this topic. An array of injection sites, depths and volume of radioisotopic labelling with Tc-99m, blue dye (Patent Blue®, methylene blue, isosulfan blue or Lymphazurin™), or a combination of the two, have been used. None of the techniques have been shown to have a significantly better detection rate.

The most commonly proposed technique consists of a two- or four-point peritumoural injection closest to the cervix-tumour interface with a 25-G spinal needle (Figure 2). Half of the volume should be injected deep into the stroma and half submucosally, with a total volume of 4 ml of blue dye and/or 0.1-0.5 mCi of radiolabelled filtered Tc-99m. Patients who have undergone a prior cone biopsy should be injected in the bed of the cone.

The injection of Tc-99m may be performed the day prior to surgery, or on the morning of surgery. The blue dye injection should be given in the operating theatre at the time of the examination under anaesthesia.[29]

Laparotomy versus laparoscopy

The SLN biopsy, initially described by Echt in 1999, was performed through laparotomy.[18] With the ongoing evolution of laparoscopic surgical techniques and the development of the laparoscopic gamma probe, Dargent, Martin and Mathevet proposed the laparoscopic SLN biopsy technique in 2000.[31] Because SLN biopsy has been developed to decrease surgical morbidity and postoperative complications by reducing the need for a complete pelvic lymphadenectomy, logic dictates that the future of SLN biopsy in cervical cancer lies in minimal invasive endoscopic surgical techniques. Although more challenging and with a longer learning curve, the laparoscopic SLN technique has been found to be safe and feasible. More recently, the use of robotic-assisted techniques has been successfully described in the literature.[32]

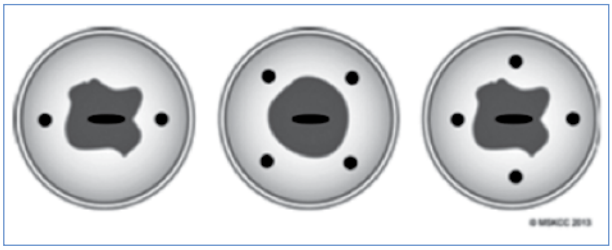

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Figure 2: Sentinel lymph node cervical injection sites options[30]

Mapping: technetium-99m versus blue dye

Different mapping techniques for locating the SLN have been reported. The most commonly used methods are radioisotopic labelling with Tc-99m and blue dye, or a combination of the two. Radioisotopic labelling has been reported to be more sensitive in penile, breast and vulvar cancer than blue dye in identifying the SLN. However, the complete lymphatic drainage route can be visualised by opening the broad ligament in cervical cancer. This is further enhanced by the magnification involved in the use of laparoscopy, making it possible to identify and follow lymphatic vessels which are blue labelled, until they reach the SLN.[22] Identification of the complete lymphatic tract towards the SLN is only possible in penile, breast and vulvar cancer following a large cutaneous incision.[31]

Although, according to the published literature, there is a trend that favours the combined technique in identifying the SLN, there is some uncertainty as to what would be the preferred method in cervical cancer, especially if the procedure is performed by laparoscopy. Table II summarises the literature on laparoscopic SLN detection rates using different mapping techniques in cervical cancer.

The multicentre pioneer study, conducted by Altgassen et al in 2008, reported a significantly higher detection rate with the combined technique (Tc-99m and patent blue) versus Tc-99m or patent blue solely.[20] The more recent studies (Lécuru et al and Cormier et al) both show a trend towards a superior detection rate using the combined technique (Tc-99m labelling and Patent Blue® dye), although the difference was not statistically significant.[21,22] When analysing side-specific diagnostic performance, no significant difference was found in the publication by Cormier et al between isosulfan blue dye and the combined technique.[22]

The systematic review performed by Van de Lande et al reported a significantly higher detection rate of 97% using the combined technique, compared to 92% and 88% using Tc-99m and blue dye, respectively.[19] The more recent systematic review by Selman et al reported a failure rate of 8.3% using blue dye alone, compared to 4.4% using the combined technique. This difference was not statistically significant.[8] Both of these systematic reviews were performed prior to the publication of the three trials by Altgassen, Lécuru and Cormier, and do not correct for a side-specific detection rate. In addition, both laparoscopy and laparotomy data were pooled in the systematic reviews.

Novel mapping technique

More recently, a novel mapping technique for cervical cancer SLN biopsy using indocyanine green (ICG) imaging

Table II: Sentinel lymph node detection rates using different mapping techniques

Publication	Blue dye mapping	Tc-99m mapping	Combined blue dye and Tc-99m	Type of surgery	Significance and comments
Devaja et al[33]	91% (78/86)	96% (83/86)	98% (84/86)	LSC/LTO	-
Lécuru et al[21]	89.9% (125/139) BD 68.8% (86/125)	93.9% (123/131) BD 66.7% (82/123)	97.8% (136/139) BD 76.5% (104/136)	LSC	Non-significant
Cormier et al[22]	BD 73.1% (38/52)	-	BD 85.5% (53/62)	LSC (30%) LTO (70%)	Non-significant (p-value 0.112)
Roy et al[34]	92.8% (141/152) BD 69.1% (105/152)	96.9% (161/166) BD 86.7% (144/166)	99.1% (106/107) BD 90.6% 97/107)	LSC	-
Altgassen et al[20]	82% (160/195)	81.8% (45/55)	93.5% (318/340)	LSC (56%) LTO (44%)	p-value < 0.001
Bats et al[35]	83.3% (20/24) BD 45% (11/24)	75% (18/24) BD 50% (12/24)	87% (20/23) BD 78% (18/23)	LSC	-
Rob et al[36]	80% (80/100) BD 62% (62/100) LSC group: 90.5% (19/21)		96.4% (80/83) BD 90% (75/83) LSC group: 100% (18/18)	LSC (21%) LTO (79%)	*Significant* *LSC group:* Non-significant
Plante et al[26]	79% (23/29) BD 55% (16/29)		93% (27/29) BD 72% (21/29)	LSC	Significant (p-value 0.04) *BD:* Significant (p-value 0.03)
Lambaudie et al[37]	90.9% (10/11) BD 63.6% (7/11)	90.9% (10/11) BD 63.6% (7/11)	100% (11/11) 100% (11/11)	LSC	-
Malur et al[38]	55.5% (5/9)	76.2% (16/21)	90% (18/21)	LSC (90%) LTO (10%)	-

BD: bilateral detection rate, LSC: laparoscopy, LTO: laparotomy
Only series with laparoscopic identification of the sentinel lymph node are included

and near-infrared (NIR) fluorescence imaging has been described.[39,40] ICG is an agent that emits fluorescence which is generated from the contact of ICG with plasma proteins. The fluorescence signal is captured by a NIR laser and NIR camera, which transcribes the signal into a black and white image. The real-time laparoscopic images are then merged with the NIR fluorescence images [which are pseudocoloured (lime green)] and displayed on the screen.[41] Therefore, the peritumoural cervical injection of IGC will lead to the identification of the SLN by the use of NIR fluorescence imaging.

A recent publication by Jewell et al showed that NIR fluorescence imaging with ICG had a bilateral detection rate of 79%.[39] This technique has the potential to improve the SLN detection rate in patients with cervical cancer. However, this novel technique requires the investment of a new camera.

Preoperative lymphoscintigraphy

The addition of preoperative lymphoscintigraphy gives the surgeon the additional value of localising SLN in abnormal anatomical locations. The systematic review by van de Lande demonstrated a high pooled SLN detection rate of 97% [95% CI: 95-98%] and high pooled sensitivity of 92% [95% CI: 84-98%] using a combination of lymphoscintigraphy and blue dye.[19]

Histological evaluation of the sentinel lymph node

The SLN biopsy technique in cervical cancer can be combined with an intraoperative histological examination (frozen section and/or imprint cytology) to identify patients amenable to radical hysterectomy without lymphadenectomy, or those with a positive SLN which might benefit from primary chemoradiation therapy. An intraoperative examination of the SLN in early cervical cancer has its limitations and heterogenic accuracy results are reported in the literature. Bats et al reported a sensitivity of 22.7% in 102 cases of intraoperative frozen section and imprinting cytology collected during the multicentre prospective *Ganglion Sentinelle dans le Cancer du Col* (SENTICOL) trial.[42] A higher sensitivity of 88.9% was reported in a more recent, retrospective single-centre study (94 cases).[43]

Recent reports have reviewed histological ultra-staging in SLN biopsy in cervical cancer to identify whether it may increase the likelihood of identifying metastatic disease that would be missed with a conventional histological examination.[44,45] Ultra-staging includes the addition of multiple serial sectioning of the node with immunohistochemistry assessment. This technique yields a higher detection rate of micrometastasis and isolated tumour cells. Although this technique is time consuming and costly, SLN biopsy is thought to be ideal for ultra-staging techniques, since only a limited number of lymph nodes need sectioning. Reports suggest that between 4% and 29% of additional metastasis (micrometastasis and/or isolated tumour cells) were found in SLN ultra-staging when conventional histology was reported to be negative.[22,46,47] A significant reduction of overall survival in the presence of micrometastasis in the SLN was reported by Cibula et al, following a recent multicentre retrospective cohort involving 645 cases, while an increase in risk was not associated with the detection of isolated tumour cells.[48]

Cervical sentinel lymph node biopsy in a low-resource setting

The incidence of cervical cancer is three times higher in southern Africa than that in countries with a high-resource setting.[1] The reasons for this high prevalence are multifactorial, and include the absence of population-based cervical cancer screening, further complicated by the high prevalence of HIV and HPV infection in the general population. In contrast to the situation in a high-resource setting, unfortunately only 20-34% of patients with cervical cancer in South Africa are amenable to surgery.[49] Therefore, the majority of patients in South Africa would not benefit from SLN biopsy, and chemoradiation therapy would be indicated. However, because of the high incidence of cervical cancer in low-resource settings, a considerable number of patients undergo radical surgery, including complete pelvic lymphadenectomy. The lymph nodes are not affected by disease in many of these patients, and lymphadenectomy could safely be avoided in these women if their lymph node status was accurately and reliably assessed. Therefore, laparoscopic SLN biopsy could potentially prevent complete pelvic lymphadenectomy-associated morbidities in a large number of patients. The feasibility of laparoscopic SLN biopsy in early cervical cancer has been well established in high-resource settings.[21-23] Yuan et al, in China, conducted the only study in a low-resource setting, in which the feasibility of methylene blue injections for SLN biopsy during laparotomy was explored.[50] This publication does not report on the incidence of HIV, tuberculosis and pelvic inflammatory disease. Also, surgery was performed by laparotomy. We could not find published data on the feasibility of laparoscopic SLN biopsy in early cervical cancer in low-resource settings with a high prevalence of HIV, tuberculosis and pelvic inflammatory disease. It is uncertain what the effect of these factors on the cervical lymph drainage would be, as well as how this would influence the detection rate and sensitivity of SLN.

The risk associated with not performing lymphadenectomy in early-stage cervical cancer with negative sentinel nodes is unknown. The most important clinical application of sentinel nodes is to identify patients with metastatic lymph node disease in units that do not perform surgery on these patients, but instead give chemoradiation therapy. Therefore, the exact place in the literature for SLN biopsy in settings where patients with early-stage disease, including bulky disease, are treated surgically regardless of lymph node status is yet to be determined.

Conclusion

Individualisation of treatment to reduce therapy-associated morbidity is an important consideration in the surgical treatment of women with early-stage cervical cancer. SLN mapping and biopsy, and in particular, the laparoscopic approach, is an important and potentially useful modality in cervical cancer treatment. Because of low nodal metastasis in patients with early cervical cancer, there is an obligation to investigate safe alternative surgical treatment options to prevent morbidity associated with current standard surgical treatment.

Over the past 15 years, SLN biopsy in early cervical cancer has gained more acceptance and may offer an alternative to complete pelvic lymphadenectomy in the future. The sensitivity and NPV of SLN biopsy are reported to be 87.5-92% and 96.8-98.2%, respectively, by three more recent large publications.[21-23] The use of a surgical algorithm (which takes into account a side-specific evaluation), unilateral lymphadenectomy, if SLN is undetected, and the removal of clinical enlarged lymph nodes, will further increase the sensitivity and NPV.[22]

It must be emphasised that the available data report on the detection rates and sensitivity of SLN in cervical cancer. They do not address the issue of risk associated with abandoning complete pelvic lymphadenectomy in cases with a negative SLN.

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