Sentinel Lymph Node Biopsy in Endometrial Cancer

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This is the first edition of this paper.

1. Introduction

Sentinel lymph node biopsy (SLNB) involves removing a sentinel or watchman lymph node, the first node involved in the movement of a tumour from the primary cancer to the lymph nodes. If this is negative, it is surmised that the other nodes are not involved. It is likely that sentinel nodal status could influence the administration of adjuvant therapies such as radiation, chemotherapy or both. Among the gynaecological cancers, SLNB could perhaps make a significant impact in women with endometrial cancer. Moreover, sentinel node biopsy is performed in many women with breast cancer and is becoming the standard procedure for women with vulval cancer in the UK. A variety of methods have been described to detect a sentinel node in situ including coloured dyes and radioisotopes, the latter requires a specialised gamma detection probe.

2. Endometrial cancer

The cornerstone of treatment in most women with endometrial cancer is surgery involving a total hysterectomy and bilateral salpingo-oophorectomy with or without a lymph node dissection. In randomised controlled trials (RCTs) minimal access surgery, now the preferred approach, has been associated with reduced pain score, reduced hospitalisation, and earlier resumption of daily activities when compared with open surgery. Laparoscopic surgery lends itself to sentinel detection due to the increased magnification and illumination of the surgical field.

There is disagreement among UK cancer centres regarding the value of lymph node dissection because RCTs of full pelvic lymph node dissection have not shown an overall survival advantage,

However lymph node metastasis is one of the most important prognostic factors in endometrial cancer.

Some centres do not perform any form of node dissection, while others will perform a node dissection in aggressive endometrial cancers, such as grade 3 endometrioid or serous cancer of the uterus. It is important to differentiate lymph node sampling from a systematic dissection. Lymph node sampling involves removing a limited number of nodes, often if these are felt to be positive for metastatic spread, normally based on palpation and visual assessment of nodal size. A systematic lymph node dissection involves removing all the nodes within a nodal drainage basin irrespective of size. It is unlikely that a lymph node dissection removing micrometastases offers any therapeutic benefit but it may identify more aggressive cancers requiring further treatment such as chemotherapy.

3. What are the potential benefits of a sentinel lymph node biopsy?

Ideally, a SLNB should provide a more sensitive method of assessing the spread of apparent early stage endometrial cancer than a lymph node dissection, enabling targeted adjuvant therapy such as radiotherapy or chemotherapy. There is also evidence for higher detection of lymph node metastasis with SLNB compared with standard lymphadenectomy. A pelvic lymph node dissection involves removal of all the lymphatic tissue surrounding the iliac vessels whereas a para-aortic node dissection involves removal of nodes from the aorta and the inferior vena cava either to the level of the inferior mesenteric artery or the renal vessels. Dissection becomes difficult with increasing obesity and carries a risk of vascular or nerve injury. The risk of leg lymphoedema following a node dissection is under-reported, with rates varying between 5% and 38%. The debilitating effects of lower limb lymphoedema cannot, however, be overestimated since it has a marked effect on the quality of life of long-term survivors.

Replacement of a lymph node dissection by a SLNB reduces both acute and chronic morbidity in other cancers. It can be surmised that SLNB in endometrial cancer is associated with a reduction in morbidity compared with a full node dissection, although no data are available to support this.
4. **What are the benefits of adjuvant therapy?**

In a 2012 meta-analysis of eight trials\(^{18}\) that evaluated external beam radiation therapy (EBRT), it was concluded that ‘EBRT reduces the risk of locoregional recurrence but has no significant impact on cancer-related deaths or overall survival. It is associated with significant morbidity and a reduction in quality of life’. Consistent with this, two studies\(^{19,20}\) have reported that SLNB has led to changed radiotherapy management but have not provided data on long-term survival. The role of combined radiotherapy and chemotherapy is being investigated in two ongoing RCTs: GOG 249 and PORTEC 3.

The benefit of adjuvant chemotherapy for women with positive lymph nodes is supported by a 2013 meta-analysis.\(^{21}\) When compared with post-operative radiotherapy, giving combination chemotherapy resulted in significant improvement in overall and in progression-free survival.

5. **Which group of women with endometrial cancer could be offered sentinel lymph node biopsy?**

The majority of women with endometrial cancer will have grade 1 or 2 endometrioid type tumours. Risk of nodal involvement in this group of women is low. A historic case series,\(^{22}\) which included 180 women with grade 1 cancers, reported the incidence of pelvic node positivity as 0%, 3% and 11% in women with no, inner third and outer third myometrial invasion respectively. The risk of extraterine spread also increased with tumour grade. The preoperative grade based on endometrial biopsy may not always reflect the final grade of the hysterectomy specimen, with between 15% and 27% of women being upgraded.\(^{23}\)

In the UK, the majority of cancer centres and units will not offer such women a lymph node dissection as there is a low risk of finding a positive node. Instead the administration of adjuvant treatment for apparent stage I disease is based on the woman’s age, the presence of lymphovascular space involvement and the depth of myometrial invasion on the hysterectomy specimen. Unfortunately, a number of women with positive lymph nodes may miss out on the benefits of the adjuvant treatment chemotherapy, as outlined in the 2013 Cochrane review data.\(^{21}\)

Women with grade 3 endometrioid cancer and more aggressive tumour types, including serous cancers and clear cell cancers, are at much higher risk of extraterine spread. Up to 70% of women with serous carcinoma and 50% with clear cell cancers present with stage III or IV disease,\(^{24,25}\) using the International Federation of Gynecology and Obstetrics (FIGO) staging system. Type II tumours account for 10–20% of endometrial carcinomas but cause 40% of deaths.\(^{26,27}\) Many cancer centres will offer these women some form of lymph node dissection if the histopathological type is known preoperatively.

6. **Which group of nodes are important?**

The lymphatic drainage of the uterus normally occurs through the parametrium to the pelvic sidewall including spread to the iliac and obturator nodes. Metastatic disease may then spread from the pelvic sidewall to the common iliac and then para-aortic nodes. The alternative drainage, including the uterine fundus, may also occur along the ovarian vessels directly to the higher para-aortic nodes.\(^{28}\)

It therefore appears logical that fundal tumours may spread along the ovarian vessels directly to the aortic nodes above the inferior mesenteric artery at the level of the renal vein (especially on the left). This suggests that if the sentinel node was in the para-aortic region, it might be missed by techniques that involve injecting an agent into an area that drains to the pelvic nodes. However, data from several studies\(^{29,30–33}\) examining individual endometrial cancers that had been completely staged with both pelvic and para-aortic node dissection, suggested that isolated metastases to the high para-aortic region were between 1% and 6%. Abu-Rustum et al.\(^{29}\) reported a series of 42 patients surgically staged, which included all the tumour grades and histopathological types. Women who only had at least eight pelvic nodes removed were included as a form of quality control. Approximately 1% of women had isolated para-aortic
nodal metastasis with negative pelvic nodes. A further study\textsuperscript{30} suggested that only 1.5% of women will have positive para-aortic nodes when the pelvic nodes are negative. Even in women deemed to be high risk, a prospective study\textsuperscript{31} of 742 patients reported that only 3% had positive para-aortic nodes when the pelvic nodes were negative.

7. Where should the tracer be injected?

There are a variety of methods for injecting radioactive tracer or coloured dye. These include cervical injection, hysteroscopic injection and subserosal myometrial injection.

Cervical injection is the most convenient because of easy access to the cervix. It is similar to the technique used for cervical cancer SLNB. Some studies\textsuperscript{29,34} have reported cervical injection at a single site and others in conjunction with subserosal myometrial injection. The main concern with cervical injection only is the potential to miss metastatic spread through the ovarian drainage route to the para-aortic region, leading to false-negative results. However, Abu-Rustum et al.\textsuperscript{29} demonstrated that the addition of a fundal injection to the cervical injection did not appear to produce a higher detection rate. Rossi et al.\textsuperscript{35} injected indocyanine green (ICG) either into the cervix or the endometrium (through the hysteroscope) and concluded that cervical injection achieved a higher sentinel lymph node detection rate. There is no clear evidence as to which of the sites of injection and depth of injection is to be preferred. Injection into the cervical stroma just under the epithelium seems to be the most commonly used. Cervical injection seems to yield detection rates between 80% and 100%\textsuperscript{34}.

Multiple studies\textsuperscript{36–39} have used the hysteroscopic injection technique into the endometrium to identify the sentinel lymph node. It is suggested that by visualising the tumour, this technique reflects the true drainage of individual endometrial carcinoma patterns most accurately. The method is logistically the most complex and concerns have been raised that hysteroscopic injection has the potential risk of disseminating malignant cells through the fallopian tubes. The detection rate does not appear to be superior to the other two methods and has been reported to be between 50% and 82%.\textsuperscript{36–39} Niikura et al.\textsuperscript{39} compared hysteroscopic with cervical injection and found cervical injection to be superior for sentinel node detection.

Subserosal myometrial injection is favoured by some investigators. This technique is thought to have better detection for both drainage pelvic and para-aortic pathways but requires intraoperative injection of the tracer into the uterine body, which makes the use of technetium-99m ($^{99m}$Tc) technically difficult. Preoperative injection of $^{99m}$Tc under ultrasound guidance would make this approach uncomfortable for the patient and rather difficult to inject the posterior aspect of the uterine corpus. It seems that detection rate increases with the number of injections at different sites of the uterine corpus. Detection rates vary widely; in the range of 0–92%\textsuperscript{40–42}.

8. What detection techniques are used?

Sentinel node mapping involves injecting a tracer substance into the vicinity of the primary tumour, followed by detection of the tracer and the removal of the lymph node for histopathological analysis. A variety of substances have been used.

8.1 Technetium-99m colloid

$^{99m}$Tc can be administered on the day before or on the same day as surgery, which allows for the preoperative detection of the sentinel node/s on each side with a single-photon emission computed tomography (SPECT) scan. This allows for accurate preoperative location of the node/s.\textsuperscript{43} Intraoperatively the $^{99m}$Tc is detected using a gamma probe. Many centres combine $^{99m}$Tc with the use of a blue dye to provide a visual identification of the lymphatic channels leading to the sentinel nodes.
Occasionally a sentinel node will not be identified on one side of the pelvis; in this situation, a formal/complete lymph node dissection is commonly carried out on that side of the pelvis. Reasons for the failure to identify a node include problems with injection of the primary tumour site and blockage of lymphatic channels due to the tumour. The latter occurs especially with large primary tumours.  

8.2 Blue dye

A variety of blue dye substances are available including isosulfan blue 1%, methylene blue 1% and patent blue 2.5%. The blue dye is injected 10–20 minutes prior to the start of surgery, allowing time for the dye to enter the lymphatic channels and flow to the lymph nodes. Advantages of this method include the ease of use and the lack of need for specialist equipment. Disadvantages include the need to open the whole retroperitoneal space to visualise the nodes and the requirement for a degree of subjectivity with visual assessment. A small number (fewer than 1%) of women injected will have an allergic reaction including anaphylaxis.

8.3 Newer detection methods

Use of near infrared (NIR) imaging to detect a fluorescent dye such as ICG is a new technique with some evidence to suggest it may be superior to blue dye alone. 45 This method combines the benefits of the blue dye technique (visibility) with nuclear medicine techniques (penetration of signal through intact tissue) in a single modality, and is based on the ability of a specific dye or fluorophores, such as ICG, to fluoresce in the NIR light range. The fluorescence occurs when a laser is emitted from an NIR imager which excites the dye; this produces a wavelength that is converted into a fluorescent image. The imager can be integrated into the laparoscope or robotic system. 35,46

9. How should sentinel nodes be analysed?

Standard histopathological assessment of lymph nodes will fail to detect micrometastases. Hafner et al. 47 reported that using routine haematoxylin and eosin (H&E) histology, the chance of identifying a cluster of less than three cell diameters is only 1%. Sentinel lymph nodes are normally subjected to ultrastaging. This involves taking multiple sections from the single node combined with immunohistochemistry (IHC). Ultrastaging is time consuming and expensive, making it unsuitable for larger numbers of nodes. The contribution of IHC is particularly relevant since between 18% and 20% of patients were upstaged after detection of micrometastases.48,49 In women with low risk endometrial cancer (grade 1 or 2 with less than 50% myometrial invasion), ultrastaging resulted in an almost 50% increase in the number of positive lymph nodes identified compared with standard techniques.50 In a large study of apparently early stage endometrial cancer, Holloway et al. 46 demonstrated that the addition of SLNB mapping and ultrastaging to staging lymphadenectomy significantly increased the detection of lymph node metastasis. The sentinel lymph node mapped patients had twice as many lymph node metastases as the non-mapped group (30.3% versus 14.7%; \( P < 0.001 \)). The relationships between micrometastases and risk of recurrence and prognosis have been demonstrated in an increasing number of malignancies including cancers of the breast, vulva, stomach, colon and prostate, and melanoma. This suggests that micrometastases are an indication for adjuvant therapy. 51 Data for endometrial carcinoma are still emerging and currently there is no consensus on how to treat micrometastases for this type of cancer.

Newer commercial automated nodal assessment technologies, including one step nucleic acid amplification, are emerging with a small study 52 reporting a positive predictive value of 93.3% and sensitivity of 82.4% in endometrial cancer.
9.1 How reliable is a sentinel lymph node biopsy?

The reliability of SLNB is based on the detection rate of the sentinel node, the sensitivity of the procedure and the false-negative rate. Within the context of SLNB, it is almost impossible to find false positives and the specificity is therefore considered 100%. Because there are three potential nodal basins for lymphatic drainage in endometrial cancer; two pelvic and the para-aortic area, it is important to define how detection, sensitivity and false-negative rates are measured. The majority of studies report pelvic SLNB data based on the procedure performed: i.e. two sides of the pelvis counts as two procedures. If a sentinel node is not detected on one side it is often recommended that a full pelvic node dissection is carried out on that side.53

9.2 Detection rate

The Sentinel Node and Endometrial Cancer (SENTEI-ENDO) study54 included 125 women with endometrial cancer treated in nine French cancer centres by cervical injection of $^{99m}$Tc and patent blue dye. All the participating centres had previously performed at least 30 SLNBs in endometrial cancer and used ultrastaging of the SLNB. These results were compared in a meta-analysis of 26 studies published in 2011.55

In the SENTI-ENDO study54 the detection rate in the left and right hemipelvis was 77% and 76% respectively, with a detection rate per woman of 89%. Of note, 5% of woman had para-aortic sentinel lymph nodes, all of whom also had pelvic sentinel lymph nodes. This study was powered to consider each hemipelvis separately. Kang et al.55 assessed studies using a variety of techniques and reported a detection rate of 78% per procedure on the hemipelvis, with the hysteroscopic route being associated with a lower detection rate than cervical injection.

9.3 Sensitivity

The sensitivity in the SENTI-ENDO study54 was 100% per procedure but 84% per woman. The meta-analysis by Kang et al.55 reported a similar result, with 93% sensitivity per woman with the majority, but not all, of the studies using ultrastaging. This did not change when studies including more than 30 women only were used to calculate sensitivity.

9.4 False-negative rate and negative predictive value

The false-negative rate represents the rate of technique failure and is especially important if SLNB is used to determine whether adjuvant chemotherapy is given. In the SENTI-ENDO study,54 the false-negative rate was 0% and there was a negative predictive value (NPV) of 100% per procedure. Of note, three women had positive nodes (two pelvic and one para-aortic) and a negative pelvic SLNB on the contralateral side of the pelvis. In this context, the NPV was 97% per woman. In the Kang meta-analysis,55 the calculated false-negative rate was 1% based on a risk of positive nodes of 10%.

SLNB is the standard of care in many women with breast cancer. The detection and false-negative rates in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 breast cancer study56 were 97% and 9.8% respectively. In vulval cancer, the GOG 173 study57 reported a sensitivity of 91%, a false-negative rate of 1.6% and a NPV of 98% in tumours less than 4 cm in size. In both the SENTI-ENDO study54 and the Kang meta-analysis,55 SLNB for these two cancers compared favourably.

10. Opinion

Sentinel node detection in endometrial cancer is feasible and has reasonable test performance. It has been suggested that it may resolve the debate within the gynaecological cancer community in the UK on whether or not to carry out pelvic node dissection in endometrial cancer.58 Current protocols for SLNB
recommend that if a sentinel node in one side of pelvis is not identified then a full pelvic node dissection should be carried out on that side. This would be a significant change of practice for some in the UK, especially in low risk women. Alternatively, it could be argued that if a centre’s current practice is not to perform a lymph node dissection then if no sentinel lymph node is identified then a full dissection should be avoided pending further published data.

It is unclear whether the sentinel lymph node status could replace or complement indications for adjuvant treatment based on uterine factors or a woman’s age. It is likely it would become an additional factor in a similar manner to breast cancer management. It is also unclear which group of women with endometrial cancer would benefit most. Determining the risk of lymph nodal involvement preoperatively is difficult and lymph nodal involvement is one of the best prognostic factors and criteria for adjuvant treatment. With the low morbidity of the SLNB procedure, it might be desirable if all women could undergo SLNB to help in the selection of those who require chemotherapy or radiotherapy.

There are questions to be addressed before the routine adoption of SLNB in endometrial cancer, including the best detection technique and which group of women, if any, would benefit. When these questions are answered, it will remain to be seen if SLNB makes a difference to overall survival or quality of life of women with endometrial cancer. Due to the variation in national practice, the UK is well placed to perform a prospective RCT of SLNB versus no node dissection in women with endometrial cancer, or perhaps a three arm trial of SLNB versus node dissection and SLNB versus no lymph node dissection based on a centre’s current practice.

References


