Sentinel Lymph Node Biopsy

Subjects: Oncology

Contributor: Ane Gerda Zahl Eriksson

Sentinel lymph node (SLN) biopsy has emerged as an alternative staging approach in women with assumed early-stage endometrial carcinoma. Through image-guided surgery and pathologic ultrastaging, the SLN approach is introducing “precision medicine” to the surgical management of gynecologic cancers, providing a comprehensive evaluation of high-yield lymph nodes. This approach improves the surgeons’ ability to detect small-volume metastatic disease while reducing intraoperative and postoperative morbidity associated with lymphadenectomy. Although the majority of clinicians in Europe and the USA have recognized the value of SLN biopsy in endometrial carcinoma and introduced this as part of clinical practice, there is ongoing debate regarding its role in very low-risk patients as well as in patients at high risk of nodal metastasis. The significance of low-volume metastasis is not fully understood, and there is no consensus in regard to how the presence of isolated tumor cells should guide adjuvant therapy. Standardized protocols for histopathologic evaluation of SLNs are lacking.

Keywords: endometrial cancer ; sentinel lymph node ; lymphadenectomy

1. Introduction

1.1. History of Sentinel Lymph Node Concept

More than a century ago, the surgeons William Halsted and Herbert Snow hypothesized that cancer spread in an orderly fashion, initially to regional lymph nodes and thereafter to more distant sites. They subsequently advocated for lymph node dissection in patients with melanoma and breast cancer [1][2]. The evolution of the initiation and acceptance of SLN mapping has been unique to each disease site, due to multiple variations in demographic and clinico-pathologic characteristics.

In gynecologic cancers, SLN mapping was first implemented in the setting of vulvar carcinoma. Vulvar tumors are easily accessible to injection of tracer, and the lymphatic drainage is well described following lymphatic channels to one or both groins. SLN biopsy in endometrial carcinoma was first reported by Burke and colleagues in 1996 [5]. In this pilot study, they injected isosulfan blue dye sub-serosally into the myometrium of 15 women with high-risk endometrial carcinoma and were able to identify uptake of dye in nodes in 67% (10 of 15) of cases. Several other observational studies followed, exploring injection sites and selection of dye, as well as oncologic and patient reported outcomes.

1.2. Sentinel Lymph Node Injection Site

Three main injection techniques have been evaluated for SLN mapping in endometrial carcinoma: cervical, hysteroscopic and laparoscopic fundal injection [6][7][8]. Cervical injection is preferable and has been adapted by the majority of surgeons due to its feasibility and high detection rates [9]. Some para-aortic lymph nodes may be reached only via the infundibulo-pelvic ligament pathway, which are not commonly accessible via the superficial cervical injection, and there is concern that some isolated para-aortic lymph node metastases are missed due to this. This is mainly of concern in patients with high grade and deeply invasive tumors, where isolated para-aortic metastasis has been reported in as many as 16% of patients [10]. These reports are from the pre-SLN era, prior to image-guided surgery and the introduction of pathologic ultrastaging and may thus have missed metastatic nodes in the pelvis. When retrospectively performing pathologic ultrastaging of patients with previously confirmed negative pelvic lymph nodes and isolated para-aortic metastasis, Multinu and colleagues found the prevalence of isolated para-aortic metastasis in their cohort to be reduced from 2.5% (10/394) to 1.8% (7/394) [11].

The Multicenter Italian Trials in Ovarian cancer (MITO) study group recently published the results from their prospective randomized controlled trial on hysteroscopic peritumoral injection versus cervical injection of indocyanine green (ICG) for sentinel node detection in endometrial carcinoma, where the primary endpoint was para-aortic detection rate [12]. The hysteroscopic injection route detected more para-aortic SLNs than the cervical injection route, however this difference did

not reach statistical significance. The bilateral pelvic mapping rate was 60% in the hysteroscopic injection group versus 85% in the cervical injection group. This study supports the use of cervical injection with ICG for SLN biopsy in surgical staging of endometrial carcinoma. Surgeons should however consider the potential drawbacks of cervical injection on para-aortic SLN detection in women with higher risk of para-aortic metastasis.

2. Oncologic Outcomes

Although the diagnostic accuracy of SLN mapping and biopsy is well-established, oncologic outcomes comparing SLN biopsy to comprehensive lymphadenectomy have not been investigated in prospective randomized trials, for any histologic subtype. It is generally accepted that SLN biopsy is sufficient for nodal assessment and without detriment to patients with negative SLNs due to the excellent NPV of this approach. Plante and colleagues explored the risk of metastasis in remaining non-SLNs in patients with a positive SLN, evaluating 268 women with apparent early-stage endometrial carcinoma [13]. They found that when the size of the SLN metastasis was ≤2 mm, the risk of having another positive lymph node was 5%, conversely, when the size of the SLN metastasis was >2 mm, the risk of having another positive lymph node was 60.8%. Histologic type, grade, depth of myometrial invasion, LVSI, cervical stromal invasion and CA-125 were not predictive. By this information, SLN biopsy should not influence oncologic outcomes significantly in women with SLN micrometastasis or ITCs. Although two randomized clinical trials have not demonstrated a survival benefit to lymphadenectomy in endometrial carcinoma [14][15], the therapeutic effect of removing metastatic nodes remains a controversial topic. There is ongoing debate, whether patients with high-risk endometrial carcinoma should undergo comprehensive lymphadenectomy, and by the same token if patients with positive SLNs should undergo completion lymphadenectomy. The Endometrial Cancer Lymphadenectomy Trial (ECLAT) started recruitment in March 2018 and may answer this question. The primary aim of this trial is to ascertain whether or not systematic pelvic and para-aortic lymphadenectomy have a significant impact on overall survival in patients with endometrial carcinoma FIGO Stages I or II and high risk of recurrence; this includes FIGO IB or II all histologic subtypes and FIGO IA endometrioid G3 or non-endometrioid endometrial carcinoma. In total, 640 patients will be randomized. In arm A, a total hysterectomy, bilateral salpingo-oophorectomy and in case of serous or clear cell histology an omentectomy will additionally be performed. In arm B, systematic pelvic and para-aortic lymphadenectomy up to the level of the left renal vein will additionally be performed. Final results from the ECLAT trial are not expected until 2029 [16].

Our knowledge regarding oncologic outcomes after SLN biopsy is limited to retrospective observational studies (**Table 1**). Historic cohorts from the Mayo Clinic and Memorial Sloan Kettering Cancer Center were compared to evaluate oncologic outcomes comparing SLN mapping and selective lymphadenectomy in women with endometrial carcinoma at low risk of nodal metastasis [17]. Of 1135 cases identified, 642 (57%) were managed with an SLN approach and 493 (43%) with a lymphadenectomy approach. Metastasis to pelvic LNs was detected in 5.1% and 2.6% of patients, respectively, and to para-aortic LNs in 0.8% and 1.0%, respectively. The three-year disease-free survival rates were 94.9% and 96.8% respectively, suggesting that both approaches are reasonable in detecting nodal metastasis with similar oncologic outcomes. When comparing oncologic outcomes in patients with deeply invasive endometrioid endometrial carcinoma there was no association between type of nodal assessment and recurrence or overall survival [18]. The same group compared oncologic outcomes after lymph node assessment by a SLN algorithm (118 cases) vs. comprehensive pelvic and para-aortic lymphadenectomy (96 cases) in patients with serous and clear cell endometrial carcinoma, and found that overall survival (OS) was not compromised with the SLN algorithm [19]. The study found that SLN may be associated with a decreased recurrence-free survival in this population, but similar OS in node-negative cases despite the majority receiving chemotherapy [19].

Table 1. Oncologic outcomes of patients with endometrial carcinoma having undergone SLN mapping.

Study	Study Population	Nodal Assessment	*n*	Metastatic Nodes	*p*-Value	DFS	*p*-Value	OS	*p*-Value
Eriksson [17]	Endometroid Myoinvasion < 50%	SLN LND	642 493	5.1% pelvic 2.6% pelvic	0.03	94.9% 96.8% (3-year)	nr	97.4% 95.4% (3-year)	0.07
Schlappe [18]	Endometrioid Myoinvasion > 50%	SLN LND	82 94	33.3% pelvic 14.8% pelvic	0.005	78.7% 77.7% (3-year)	nr	91.8% 77.6% (3-year)	nr

Study	Study Population	Nodal Assessment	*n*	Metastatic Nodes	*p*-Value	DFS	*p*-Value	OS	*p*-Value
Schlappe [19]	Serous & Clear Cell	SLN LND	118 96	22% pelvic 20% pelvic	0.83	69% 80% (3-year)	0.32	88% 77% (3-year)	0.06
Schiavone [20]	Carcinosarcoma	SLN LND	48 88	17.5% nr	na	23 mo 23.2 mo	0.7	nr	na
Basaran [21]	Serous Carcinoma	SLN LND	79 166	26.5% 29.5%	0.63	58.8% 64.9% (2-year)	0.48	89.1% 83.9% (2-year)	0.85

SLN, sentinel lymph node; LND, lymphadenectomy; DFS, disease-free survival; OS, overall survival; mo, months; na, not applicable; nr, not reported.

3. Conclusions and Future Perspectives

Sentinel lymph node biopsy is increasingly used as an alternative to lymphadenectomy in surgical staging of women with endometrial carcinoma. The approach has gained significant acceptance and is applied in many centers. There is robust evidence regarding the accuracy of SLN biopsy for nodal staging in all risk-categories of endometrial carcinoma, however, prospective data on oncologic outcomes are lacking. The significance of low-volume disease identified by ultrastaging remains unknown. Future research should focus on understanding the optimal clinical management of this sub-group of patients. Standardized histopathological, and possibly molecular assessment protocols of SLNs is lacking. Reaching a consensus regarding histopathologic evaluation is important as the SLN approach is gaining acceptance and becoming more widespread. Oncologic outcomes, particularly in women at high risk of nodal metastasis, is lacking, and should be the focus of prospective trials. Any trial investigating the SLN approach should include patient reported outcomes.

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