

Sentinel Lymph Node Mapping and Biopsy in Gynecological Malignancies

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In malignant tumors, lymph node metastasis is one of the most important prognostic factors for treatment decisions and survival. For many years, patients with endometrial and cervical cancer underwent extensive pelvic and para-aortic lymphadenectomy as part of their staging procedures. However, performing routine lymphadenectomy exposes patients to risks such as lymphedema, lymphocele, increased operative time, blood loss, and nerve and vascular injury with questionable survival benefit to the removal of multiple lymph nodes [1–3].

Whenever a malignancy has a known and systematic lymph node spread, injection of dye or radiocolloid to the tumor site will spread via the lymphatic channels to the regional lymph node the same way as the tumor cells do. The first lymph nodes that accumulate the tracer – sentinel lymph nodes (SLN) – can be removed for histological evaluation. If there are no metastases in these SLN, full lymphadenectomy can be avoided.

SLN mapping first gained wide acceptance as part of the surgical staging and for metastatic evaluation in melanoma and breast cancer in the 1990s. Multiple publications demonstrated a decreased rate of postoperative complications, low false negative rates with SLN mapping, and lack of a survival benefit with traditional lymphadenectomy [4,5]. This change in concept influenced the gynecologic oncol-

ogists to explore the role of SLN in vulvar cancer. Several prospective randomized studies demonstrated high detection rate with less than 2% false negative rate for SLN mapping with proper patient selection [6]. The complication rate dropped from 25–30% to approximately 5–10% for wound breakdown and lymphedema [7]. Favoring the results of these studies, SLN mapping in vulvar cancer is currently considered the standard of care for lymphatic assessment in women with apparent early-stage vulvar cancer.

In the last decade, the role of SLN has been extensively evaluated for endometrial and cervical cancer. Endometrial cancer is the most common gynecologic malignancy with more than 700 new cases diagnosed annually in Israel [8]. Lymphatic metastasis occurs in 10–15% of all patients and is the most important determinant for survival [9]. Thus, lymphatic assessment was incorporated into the surgical staging of endometrial cancer in the 1988, by the International Federation of Gynecologic Oncology (FIGO). Since then, significant controversy has existed as to the extent of lymph node removal and value of lymphatic assessment.

On the one hand, lymph-node staging is essential for selecting women for adjuvant therapy. On the other hand, especially in women with low grade endometrial cancer, lymphadenectomy did not show survival benefit [1,2,10]. Many times, the decision whether to perform lymphadenectomy was based on preoperative and intra-operative findings such as pathological differentiation and myometrial invasion. However, such criteria did not always accurately predict nodal metastases. With such a lack of consensus, the

SLN concept has gained major popularity in the last decade. The FIRES trial [11], a prospective multicenter study, compared lymphadenectomy to SLN mapping using near-infrared fluorescence imaging with indocyanine green (ICG) dye, which emits a fluorescent near-infrared signal when excited. SLN mapping had a 97.2% (95% confidence interval [95%CI] 85.0–100) sensitivity to detect node-positive disease with a negative predictive value of 99.6% (95%CI 97.9–100).

Several injection techniques have been evaluated for SLN mapping in endometrial cancer: cervical, endometrial via hysteroscopy, or direct myometrial during laparoscopy. Cervical injection is easier to perform, requires minimal additional surgical time, and results in a higher SLN detection rate [12]. It was further shown that superficial and deep injection into the cervix results in excellent penetration to uterine vessels, parametria, lower uterine segment, and cornual regions [13,14]. For these reasons, cervical injection has become the preferred technique for SLN mapping in endometrial cancer.

SLN mapping is also gaining acceptance for cervical cancer staging. In cervical cancer, the lymph node status is a major determinant for treatment. If the patient has lymph node metastasis, she will not undergo surgery and the treatment is chemoradiation. Although positron emission tomography/computed tomography (PET/CT) has a high sensitivity for lymph node metastasis of 95–97% [15] and is part of our preoperative evaluation in patients with cervical cancer, it has low predictive value in small volume lymphatic metastasis. Performing SLN mapping in cervical cancer can assist

in avoiding unnecessary lymphadenectomies or radical hysterectomies.

Since the uterus is a central organ with bilateral lymphatic drainage, SLN should be detected on both sides. In a systematic review and meta-analysis of 55 studies comprising a total of 4915 women, Bodurtha Smith et al. [12] investigated the utility of SLN mapping for endometrial cancer. They showed that cervical injection was associated with significantly higher rates of bilateral SLN detection compared with uterine injection (56% vs. 33%, $P = 0.003$). Use of indocyanine green was associated with higher rates of bilateral SLN detection than blue dye (75% vs. 51%, $P = 0.008$). The pooled sensitivity of SLN mapping for the detection of lymphatic metastases was high at 96% (95%CI 92–98).

In order to achieve this high sensitivity, adherence to some basic principles is paramount. SLN should be found on both pelvic sides. If SLN is not identified, full lymphadenectomy should be performed on that hemi-pelvis. Any suspicious or enlarged lymph nodes should be resected even if they are not the sentinel lymph node. Furthermore, an important role in the finding of lymph node metastasis in the SLN is no doubt related to an ultrastaging pathological procedure (i.e., multiple sections through the SLN, typically 50 μ m apart) and the utilization of both hematoxylin and eosin (H&E) and immunohistochemistry using anti-cytokeratin dye. SLN biopsy using the ultrastaging protocol is more sensitive than regional lymphadenectomy with conventional histopathology [16].

In this issue of the *Israeli Medical Association Journal (IMAJ)*, Namazov and colleagues [17] reported on an Israeli experience of SLN mapping during endometrial and cervical cancer surgery. Forty-six consecutive patients with early-stage endometrial or cervical cancer were enrolled and underwent SLN mapping with a near-infrared fluorescent imaging and indocyanine green integrated laparo-

scopic system. Bilateral SLN detection was achieved in 89% of patients and in seven, lymph node metastases were found. These results, even though performed on a small group of patients, show that the procedure is easily performed, with high detection rate that equals results of larger published studies.

This preliminary Israeli experience signifies a world-wide shift from radical complication-related surgeries to more conservative and patient tailored operations. In endometrial and cervical cancer, the SLN procedure with ultrastaging provides us with a more sensitive method to identify women at high risk and suggest adjuvant therapy for them.

There are still some unanswered issues: should full lymphadenectomy be conducted on patients with positive SLN? How should we treat women with micrometastases? Is the procedure acceptable in all types of endometrial histology? Should this be the standard of care for all sub-stages of early cervical cancer?

CONCLUSION

SLN mapping is feasible and accurately predicts nodal status. SLN is emerging as an alternative standard of care in the staging and management of women with endometrial and cervical cancer while avoiding unnecessary lymphadenectomies and related complications.

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