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Review Article

Sentinel lymph node mapping and staging in endometrial cancer: A Society of Gynecologic Oncology literature review with consensus recommendations

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HIGHLIGHTS

- SLN mapping compared to staging lymphadenectomy in EC may reduce morbidity.
- Literature-based recommendations for the inclusion of SLN assessments are presented.
- History and various techniques of SLN mapping in endometrial cancer are described.
- Pathology and clinical outcomes from SLN assessment are reviewed.
- Controversies and future directions for research in SLN assessment are discussed.

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ABSTRACT

The emphasis in contemporary medical oncology has been “precision” or “personalized” medicine, terms that imply a strategy to improve efficacy through targeted therapies. Similar attempts at precision are occurring in surgical oncology. Sentinel lymph node (SLN) mapping has recently been introduced into the surgical staging of endometrial cancer with the goal to reduce morbidity associated with comprehensive lymphadenectomy, yet obtain prognostic information from lymph node status. The Society of Gynecologic Oncology's (SGO) Clinical Practice Committee and SLN Working Group reviewed the current literature for preparation of this document. Literature-based recommendations for the inclusion of SLN assessment in the treatment of patients with endometrial cancer are presented. This article examines:

- History and various techniques of SLN mapping in endometrial cancer
- Pathology and clinical outcomes from SLN assessment
- Controversies and future directions for research in SLN assessment in endometrial cancer.

Contents

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1. Introduction

Endometrial cancer is the most common gynecologic cancer in North America, and worldwide there are approximately 320,000 cases diagnosed annually. Following the Federation of International Gynecology and Obstetrics (FIGO) adoption of surgical staging in 1988, pathology that includes information about the primary tumor as well as lymph node status has guided prognosis and use of adjuvant therapies. Surgical staging is associated with risks of lymphedema, lymphocysts, cellulitis, and damage to nearby nerves. Sentinel lymph node (SLN) assessment has been proposed as a more "targeted" alternative to complete pelvic lymphadenectomy in an effort to secure information about lymph node status for treatment planning, yet minimize collateral damage. The purpose of this article is to review the current literature regarding SLN assessment in endometrial cancer and to improve outcomes for women with this disease.

2. History of endometrial cancer surgical staging

The value of staging patients with cancer lies in the ability to assess prognosis, plan therapy, and facilitate communication between health care providers. Surgical staging also serves as a research tool to assess treatments among patient groups and for stratification in clinical trials. Prior to 1950, staging endometrial cancer was quite variable between institutions and expert gynecologists. Following the success of standardized staging for cervical cancer in the 1950s, FIGO assumed responsibility of the Annual Report from the Health Organization of the League of Nations. The first FIGO staging system for endometrial cancer was predicated on two criteria alone. Stage I patients had tumor clinically confined to the uterus, and stage 2 patients had disease that had spread beyond the uterus [1]. FIGO staging of uterine carcinoma has since undergone multiple strategic revisions, most notably in 1962 with expansion to a four-stage system, and in 1988 with a change from clinical to surgical staging [1]. Over the past 60 years, FIGO staging progressively evolved to reflect the significant scientific breakthroughs in understanding the histopathology and associated risks of recurrence associated with various risk factors in endometrial cancer. The staging system now includes tumor grade, depth of myometrial invasion, local and regional spread, lymph node metastasis, and distant metastasis.

The addition of lymph node status to FIGO staging followed the publication of the results of Gynecologic Oncology Group (GOG) study 33 [2] and ultimately contributed to the controversy regarding the clinical significance of lymph node metastasis today. The addition of routine lymphadenectomy led to a significantly increased number of clinical stage I uterine cancers that were upstaged to stage III. However, the risk of lymph node metastasis in early-stage, low-grade tumors is relatively low, and the potential morbidity from routine lymphadenectomy may outweigh population-based clinical benefits. While GOG 33 demonstrated an overall risk of metastasis in pelvic and aortic lymph nodes of 9% and 6%, respectively, well-differentiated tumors had a risk of 3% and 2%, and tumor confined to the endometrium conferred an even lower risk of metastasis at 1% [2].

Multiple studies have attempted to evaluate the impact of routine lymphadenectomy on survival. Some studies support lymphadenectomy for all patients [3], others in higher grade disease only [4], and others report that the determining factor may be the number of nodes removed [5]. All of these trials were retrospective in nature and led to two large randomized European trials. Benedetti Panici et al. [6] identified approximately 10% more cases of nodal metastasis with the inclusion of lymphadenectomy. However, despite the increased detection of metastasis, there was no survival advantage and a significantly higher rate of lymphedema was documented in staged patients [6]. These observations were consistent with the results of the ASTEC trial, which also showed no survival benefits and an increase in lymphedema [7]. These trials were criticized for lacking a standardized lymphadenectomy protocol, as well as for inconsistencies in adjuvant therapy. Nonetheless, these phase 3 trials legitimately called into question the role of routine lymphadenectomy in endometrial cancer.

Mariani et al. [8] defined a "low-risk" population in whom staging lymphadenectomy may be safely omitted. Based on the histologic criteria from GOG 33 as well as their own historical cohort of patients treated for endometrial cancer, low risk was defined as grade 1 or 2 disease, <50% myometrial invasion, and tumor diameter <2 cm. These criteria were then used in a prospective observational study that demonstrated patients with low-risk disease (approximately 30% of all the endometrial cancers treated at the Mayo Clinic) had a <1% risk of having a positive lymph node or nodal recurrence, compared to a 16% risk of lymph node involvement for endometrioid adenocarcinoma that did not meet these criteria [8]. The Mayo Clinic low-risk group represents a clinically significant number of women who may be able to avoid staging lymphadenectomy. However, the diagnosis depends on intraoperative frozen section, a practice that has variable levels of reported accuracy [9,10] and may potentially lead to understaging some high-risk cases. In contrast, patients with high-grade histologies (endometrioid grade 3, clear cell, serous, and carcinosarcoma) have a 20–40% risk of lymph node involvement [8,11].

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