Published in final edited form as:

Curr Obstet Gynecol Rep. 2016 December ; 5(4): 279–285. doi:10.1007/s13669-016-0178-7.

Sentinel Lymph Node Mapping in Patients with Endometrial Carcinoma: Less Can Be More

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Abstract

Purpose of review—The role and extent of lymphadenectomy for endometrial carcinoma has been debated for over 30 years. Many clinicians argue that there is therapeutic value for lymphadenectomy in patients deemed to be “at risk”, a designation not universally defined, despite the lack of randomized data supporting this argument. However, lymphadenectomy is associated with morbidity, including lower extremity lymphedema. Sentinel lymph node (SLN) mapping is emerging as a viable alternative to comprehensive lymphadenectomy in the surgical staging of patients with endometrial cancer.

Recent findings—Nodal disease status is an important prognostic and predictive factor. Surgical staging with lymphadenectomy remains an important part of the treatment of patients with newly diagnosed endometrial carcinoma despite the dispute regarding its therapeutic value. Many clinicians have argued for abandoning lymphadenectomy altogether; however, this too is not ideal, as it may lead to under-treatment due to inadequate staging or over-treatment with toxic therapies.

Summary—SLN mapping has emerged as a viable compromise between a comprehensive lymphadenectomy and no lymph node sampling in the surgical staging of these patients, and may lead to reduced morbidity risks. In this review, we present the currently available data in this area of research, as well as our experience with SLN mapping.

Keywords

sentinel lymph node; sentinel lymph node mapping; lymphadenectomy; endometrial cancer

Introduction

Endometrial carcinoma is the most common malignancy of the gynecologic reproductive tract, and most often diagnosed at an early stage [1,2] Surgery is the preferred initial treatment in the majority of patients diagnosed with endometrial carcinoma [2]. Total hysterectomy with or without removal of the ovaries is considered standard without much

Conflict of Interest: Mario M. Leitao, Jr. declares no conflict of interest.

Compliance with Ethics Guidelines: Human and Animal Rights and Informed Consent: This article does not contain any studies with human or animal subjects performed by any of the authors.

debate [2]. Preservation of the uterus with medical management may be attempted in highly select patients desiring future fertility [3]. The role and extent of surgical nodal assessment has been debated for over 30 years, since the publication of the results from Gynecologic Oncology Group (GOG) study 33 [4].

Risk of nodal metastasis and lymphadenectomy controversies

GOG 33 demonstrated that nearly a quarter of patients with disease clinically confined to the uterus had extra-uterine spread detected after surgical staging, with 11% having nodal disease [4]. The risk of nodal spread was correlated with multiple factors, including tumor grade and depth of myoinvasion. All patients in GOG 33 were required to have undergone a comprehensive lymphadenectomy extending from the pelvic to the para-aortic nodal basins up to the level of the renal vessels bilaterally. Comprehensive lymphadenectomy became the standard in large part because of the findings of GOG 33. However, GOG 33 was not meant to support the routine use of such a procedure, but rather, it was a clinicopathologic study to assess the risk of extra-uterine spread and recurrence in a cohort of patients who all underwent lymphadenectomy [5]. Comprehensive lymphadenectomy became “standard” practice without ever having been tested in a randomized fashion.

Retrospective studies have suggested that there may be a therapeutic benefit associated with the extent of lymphadenectomy in cases felt to be “intermediate” or “high” risk [6-9]. Chemotherapy and/or radiation therapy use was not uniform in all of these studies [6-9]. There are a few key points to keep in mind regarding the “therapeutic” value of lymphadenectomy. First, the ability to actually detect nodal metastasis before or during surgery is poor. Various algorithms are used to determine whether an individual patient is at high enough risk for nodal spread necessitating a lymphadenectomy. An often-used algorithm is one that has been extensively reported by surgeons from the Mayo Clinic [10]. The prevalence of nodal metastasis using this algorithm is still only 14% in “at-risk” endometrioid and 35% in non-endometrioid endometrial carcinomas, which is consistent with many other similar reports [10]. In other words, at least 65% of patients who are subjected to the morbidity of pelvic and para-aortic lymphadenectomy will not have nodal disease. It is quite difficult to believe that removing 50-60 normal pelvic and aortic nodes will make any single patient remain disease-free or live longer. The value of an extensive lymphadenectomy beyond just merely identifying metastasis in those 14-35% of cases with microscopic nodal disease remains unanswered.

Second, the upper limit of para-aortic lymphadenectomy has always been determined to be the renal veins. This is an arbitrary limit and not anatomic. The lymphatic channels do not end at the renal veins but continue above them. It is likely that there will be microscopic supra-renal nodal disease in cases with nodal disease detected in the high para-aortic nodes. One would think that the “therapeutic” benefit of lymphadenectomy would be to remove all microscopic disease in node-positive cases. If this is true, then one could reasonably argue that the lymphadenectomy should be extended supra-renally.

Third, recently published results from randomized trials failed to demonstrate a survival advantage for lymphadenectomy [11,12]. In the largest trial (A Study in the Treatment of

Endometrial Cancer [ASTEC]), 1408 women were randomized to hysterectomy alone or hysterectomy plus pelvic lymphadenectomy [12]. There was no difference in recurrence-free, disease-specific, or overall survival between the two groups. There have been many criticisms of this trial. Para-aortic lymphadenectomy was not performed in these trials. Many of the enrolled cases may have been low risk for nodal disease. The extent and uniformity of pelvic lymphadenectomy has also been questioned, since the median number of excised pelvic nodes was 12, ranging from 1-59. Adjuvant chemotherapy was not used in any of the cases, including the node-positive ones and, in many, neither was radiation therapy. However, the results of these randomized trials have led many to propose abandoning lymphadenectomy in all cases and using only uterine features to make decisions concerning adjuvant therapy. A problem with this approach is that it could lead to significant overtreatment of patients with toxic and costly additional therapies. It could also lead to undertreatment in some, since there is always a risk of nodal spread, albeit low, in the cases felt to be at low risk.

Predictive value of nodal status

The presence of nodal disease is prognostic [13]. It is also predictive of the need for adjuvant therapy. Adjuvant radiation therapy in some early-stage endometrial carcinomas may decrease local recurrence but has no impact on overall survival [14,15]. Vaginal brachytherapy results in the same impact on local recurrence, with decreased morbidity, compared with external beam radiation therapy [15]. There is no proven value for adjuvant chemotherapy for patients with well-staged (node-negative) stage I endometrial cancer. The presented, but not yet published, GOG 249 trial, which compared external beam pelvic radiation therapy alone versus vaginal brachytherapy followed by carboplatin and paclitaxel, failed to demonstrate any survival benefit with the use of adjuvant chemotherapy compared with radiation therapy in early-stage endometrial carcinoma. However, adjuvant chemotherapy will confer a survival benefit in patients with International Federation of Gynecology and Obstetrics (FIGO) stage III and IV disease based on results from GOG study 122 [16]. A post-hoc analysis of GOG 122 noted that the total number of pelvic or para-aortic nodes removed in stage III cases was not associated with outcome [17]. The GOG has completed enrollment for a trial assessing the added value of concurrent chemoradiotherapy, but the results from this trial are not yet available.

There is increasing evidence to shed significant doubts on the therapeutic value of comprehensive lymphadenectomy. However, the surgical assessment of nodal status remains important, as it does have clinical and prognostic implications. Until recently, a comprehensive lymphadenectomy was the only method to accurately assess for nodal metastasis despite the above-mentioned unclear therapeutic benefit. Lymphadenectomy does increase operative time and morbidity. The impact of lymphadenectomy on the development of lower extremity lymphedema is of concern. Yost and colleagues noted a 23% risk of lymphedema and patient-reported lower extremity lymphedema after surgery for endometrial cancer, resulting in a negative impact on patients' quality of life [18].

Sentinel lymph node technique and detection rates

Sentinel lymph node (SLN) mapping has emerged as a potential and viable medium to adequately stage these patients without the added, and often unnecessary, morbidity of comprehensive lymphadenectomy. We initiated a pilot study assessing SLN mapping in endometrial cancer in 2005, and it has since become our standard approach. Multiple techniques have been reported. Various compounds have been used, including blue dyes (i.e., isosulfan blue, patent blue, or methylene blue), indocyanine green (ICG), and technetium-99 (Tc99) either alone or in combination. The route of injection has also been described using various methods: cervical injection, hysteroscopic injection, and subserosal fundal injection either alone or jointly. Our institutional standard is to use ICG and cervical injection only, without Tc99, as we feel this is the most convenient, cost-effective, and reproducible approach [19]. We inject the cervix at the 3- and 9-o'clock positions with 1mL of dye into the stroma and also submucosally after the patient is prepped and draped and prior to abdominal entry. We prefer not to use Tc99 because it is expensive, causes patient discomfort, and is inconvenient, as it often requires an additional appointment with the nuclear medicine department, where the injection is performed while the patient is awake. Intraoperative injection of Tc99 has been reported, but it is not feasible at all institutions and still introduces an added expense [20].

A meta analysis of 26 studies reported an acceptable SLN detection rate using cervical injection only [21]. Cervical injection will map the lymphatics of the pelvis to the level of the inferior mesenteric artery (IMA) based on lymphatic anatomy. A cervical injection will not map the para-aortic nodal regions between the IMA and renal veins. However, the risk of isolated para-aortic nodal metastasis in this basin in endometrial carcinomas felt to be “at risk” per Mayo criteria is only 2% [22]. It is also plausible that in these 2% of cases identified through routine pathologic nodal assessment, additional findings would be detected in the nodes below the IMA if an ultrastaging protocol were to be used. For now, we accept that there is a potential 2% risk of missing nodal disease in these cases.

The goal of SLN mapping is to identify SLNs in each hemipelvis up to the IMA (i.e., bilateral mapping). The bilateral SLN detection rate at our institution using blue dye (with or without Tc99) is approximately 50% [19]. This is comparable to what is reported in the literature, in which bilateral SLN detection rates with blue dye and Tc99 range from 27-69% [21]. The only prospective study on SLN mapping in endometrial carcinoma to date (SENTI-ENDO) also reported a 62% bilateral SLN detection rate using blue dye and Tc99 [23]. Recently, near-infrared (NIR) imaging using a fluorophore dye, ICG, has resulted in much higher bilateral detection rates. Successful bilateral mapping is now achieved in 85% of cases at our institution using ICG alone and remains at 54% with blue dye [24].

Obesity directly impacts SLN detection rates. Our study showed bilateral SLN detection rates of 92% in patients with BMI <30 kg/m², 85% for BMI 30 kg/m² but <40, and 69% for BMI ≥ 40 kg/m² using ICG compared with 56%, 54% and 25%, respectively, using blue dye [24]. NIR imaging using ICG only via cervical injection is preferred if available to the surgeon. Our protocol is to use an ICG concentration of 1.25 mg/mL, meaning 25 mg of

powdered ICG is diluted with 20 mL of sterile water. Otherwise, blue dye only is an acceptable alternative.

SLN mapping algorithm

SLN mapping for endometrial carcinoma involves the use of an algorithm, which was published by our group and is supported by the National Comprehensive Cancer Network (NCCN) (Figure 1) [19]. The algorithm involves a careful inspection of all peritoneal surfaces upon entering the abdomen. The identification of SLNs is unnecessary in the presence of gross metastatic intraperitoneal disease. The pelvic retroperitoneal spaces are dissected, with identified SLN(s) resected. Any enlarged, suspicious nodes should be removed irrespective of whether they mapped. If an SLN is not identified in a hemipelvis up to the IMA, then a side-specific lymphadenectomy should be performed. In our study, the false-negative rate if only mapped nodes were removed was 23%, compared with 3% when the algorithm was applied [19]. The false-negative predictive value (using all cases in which SLN mapping was performed) was 0.5% [19]. The negative predictive value noted in the SENTI-ENDO trial was also reassuring at 97% [23]. The false-negative cases in this study were non-endometrioid cases with >50% myoinvasion, with nodal disease encountered in pelvic basins that did not map. Therefore, our algorithm would have detected these cases. This accuracy is comparable, if not improved, compared with SLN mapping results in other malignancies.

Pathologic SLN ultrastaging protocol

The proper pathologic processing of SLNs is important when introducing SLN mapping into practice. Figure 2 depicts our ultrastaging algorithm for SLNs [25]. All resected nodes undergo routine hematoxylin and eosin (H&E) staining. If nodal disease is detected, then no further processing is needed. The SLNs undergo ultrastaging in cases that are node-negative on initial H&E stain. Additional sections 50µm apart are obtained with immunohistochemical (IHC) stains for AE1:AE3 performed, as well as H&E stains. **Macrometastases** are defined as tumor clusters and/or cells in lymph nodes measuring more than 2 mm. **Micrometastases** are defined as microscopic clusters and single cells measuring between 0.2 mm and 2 mm. **Isolated tumor cells (ITCs)** are defined as microscopic clusters and single cells measuring <0.2 mm. Tumor cells must be seen on both IHC and corresponding H&E stains to be considered as either micrometastases or ITCs. Cells seen only on IHC staining are considered cytokeratin-positive (CK+) only, and we do not consider these as evidence of metastatic disease. Ultrastaging will detect additional nodal disease not seen on original H&E sections [25].

There is a caveat to the above pathologic ultrastaging protocol. Ultrastaging detected additional low-volume metastases (i.e., micrometastases or ITCs) in only 2 (0.8%) of 241 cases with endometrioid histology of any grade and with no myoinvasion [26]. Currently at our institution, the hysterectomy specimen is processed and assessed for histology and depth of invasion on final processing, not frozen section. The retrieved nodes are processed in a routine fashion. Ultrastaging in node-negative cases is then not performed if the final histology is endometrioid without myoinvasion (any grade).

Outcomes using an SLN algorithm and the role of “backup” lymphadenectomy

Integration of an SLN algorithm into our practice resulted in fewer lymph nodes being removed and shorter operative times, without compromising staging accuracy [27]. The rate of comprehensive lymphadenectomy decreased from 65% to 23% during the first 3 years we implemented SLN mapping into routine clinical practice. The median operative time decreased by approximately 40 min (from 218 to 176.5 min), and the median number of nodes retrieved also decreased from 20 to 7. However, the proportion of stage IIIC cases identified remained the same. The decrease in number of nodes removed should have a positive impact on the risk of lower extremity lymphedema, although this has not been objectively assessed. We are currently initiating a trial assessing patient-reported lymphedema in this cohort of cases.

We recently published the results of a collaborative retrospective study between Memorial Sloan Kettering Cancer Center (MSK) and the Mayo Clinic comparing our SLN algorithm to a historic selective lymphadenectomy (LND) approach in patients with endometrioid histology of any grade and with myoinvasion of <50% [28]. In brief, based on Mayo criteria, a lymph node dissection is not performed in low-risk cases (tumor grade 1 or 2, <50% myoinvasion, and ≤ 2 cm in tumor diameter). In our SLN cohort, 93% of cases had pelvic nodes excised, compared with 58% in the LND cohort. The median number of pelvic nodes excised was significantly lower, with 6 in the SLN cohort and 34 in the LND cohort. Despite this, nodal metastasis was detected in 5.1% cases in the SLN cohort compared with 2.6% in the LND cohort. Similarly, less para-aortic nodes were excised in the SLN cohort, but the rate of nodal disease was still the same (0.8% vs 1%). The 3-year disease-free survival rate was 94.9% in the SLN cohort compared with 96.8% in the LND cohort, and this was not significant. The 3-year disease-specific survival rate was 100% and 98.8%, respectively. This provides reassuring support in favor of an SLN algorithm for endometrioid adenocarcinomas of any grade with limited (<50%) myoinvasion.

The findings in endometrioid carcinomas with $\geq 50\%$ myoinvasion and in clear cell and serous carcinomas with any degree of myoinvasion were presented at the Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer in 2015 but have not yet been published. In summary, the findings were similar in terms of detecting nodal disease with fewer median nodes excised. The survival outcomes are still undergoing in-depth analysis.

There have not been any randomized trials directly comparing an SLN mapping algorithm with comprehensive lymphadenectomy. However, based on our experience to date and that of others reported in the literature, it seems that the false-negative rate of SLN mapping in experienced hands is acceptable, and an extensive lymphadenectomy can be avoided. A prospective trial of 268 endometrial carcinoma cases undergoing SLN mapping and completion lymphadenectomy noted that nodal disease was found in non-SLNs in only 0.6% of cases if SLNs were negative bilaterally [29]. This provides even greater support for SLN mapping only in cases that map bilaterally and are found to not have disease in the SLNs. This same study demonstrated that the risk of non-SLNs having disease was 5% in cases

with either micrometastases or ITCs in the SLNs. The authors concluded that additional lymphadenectomy may also not be warranted in these cases. Nodal metastases in non-SLNs were found in 61% of cases with macrometastases in the SLNs. At many institutions, similar cases will receive some form of systemic adjuvant therapy since the publication of the data of GOG 122. An important unanswered question is whether a completion lymphadenectomy in cases found to have macrometastases in SLNs will offer any further survival advantage compared with adjuvant therapy alone. This brings us back to the question of the “therapeutic” benefit of lymphadenectomy. Our approach is to not complete the lymphadenectomy, and we feel these patients need systemic therapy as part of their treatment. This is also one of the reasons we do not perform intraoperative frozen section on SLNs for endometrial carcinomas. However, this is controversial, and only a randomized trial will truly answer this question.

Low-volume SLN metastases

The detection of low-volume metastases (i.e., ITCs and micrometastases) has also prompted questions regarding their significance and role with adjuvant therapy. We recently reported the findings in a series of 844 patients who had been managed with our SLN mapping algorithm [30]. The cohort included all histologies and grades, the majority of which were low-grade endometrioid with myoinvasion of less than 50%. Overall, 10.8% of the cases were found to have nodal disease: ITCs (2.7%), micrometastasis (2.5%), and macrometastasis (5.6%). The 3-year recurrence-free survival rate for ITCs (86%) and for micrometastasis (86%) appeared similar to that of node-negative cases (90%). The 3-year recurrence-free survival rate for those with macrometastases was 71%. These findings suggest that low-volume metastases have a similar outcome with that of node-negative disease. However, the vast majority of these low-volume cases did receive adjuvant therapy. Adjuvant chemotherapy with or without radiation therapy was administered in 87% of the ITC cases and 81% of the micrometastatic cases. Whole pelvic radiation therapy alone was administered in another 8.7% of ITC cases and 4.8% of micrometastatic cases. Therefore, it is difficult to know whether our findings reflect the natural history of these low-volume cases or the impact of adjuvant treatment.

There are some data and points to consider regarding the potential prognostic and predictive significance of low-volume metastases, but we cannot make any definitive statements regarding this topic at this time. Low-volume metastases must all be seen on an H&E stain, as we have defined it. Therefore, it is quite plausible that such low-volume metastases have always been seen by chance through routine pathologic nodal processing prior to the introduction of SLN ultrastaging protocols. Tumor cells found in nodes prior to SLN mapping were all likely determined to be positive, and patients were treated as if having stage IIIC disease without any discussion. It would be interesting to apply SLN ultrastaging nomenclature and definitions to lymph nodes that were called positive through routine processing to determine how many of these would now be re-classified as micrometastases or ITCs.

Less importance has been placed on low-volume SLN disease in patients with breast cancer recently. Primary tumor features are now frequently used in the decisions to recommend

adjuvant therapy, making low-volume SLN findings less important in breast cancer. However, the presence of micrometastases and ITCs in typically “low-risk” breast cancers that did not receive any adjuvant therapy has been reported to be associated with a worse outcome. Tan and colleagues identified 368 patients with breast cancer treated at MSK from 1976 to 1978 who were node-negative after a full axillary lymph node dissection and standard nodal pathologic evaluation [31]. All of these patients underwent nodal re-evaluation using a current pathologic SLN ultrastaging protocol. None had received any form of adjuvant therapy, including hormonal therapy, and all had 20-year follow-up. Nodal disease was discovered in 23% of these cases after ultrastaging, including macrometastatic disease in 5 cases. The presence of these newly detected low-volume metastases was associated with worse survival. Similarly, the presence of low-volume SLN metastases in untreated “favorable” breast cancer cases identified in the Netherlands Cancer Registry was significantly associated with a worse outcome [32]. The use of adjuvant therapy in cases with low-volume SLN metastases significantly improved survival.

The aforementioned data are interesting and may or may not be applicable to endometrial carcinomas. Todo and colleagues recently reported their analysis of 61 endometrial carcinomas with risk factors for nodal spread but were diagnosed as node-negative for metastases at initial routine pathologic evaluation [33]. Paraffin-embedded blocks were then processed using an SLN ultrastaging protocol. Micrometastases and ITCs were identified in 9 cases (15%). The presence of micrometastases and ITCs was an independent risk factor for extrapelvic recurrence with an HR of 17.9 (95% CI, 1.4, 232.2). The recurrence-free and overall survival rates for micrometastases/ITCs were 56% and 71%, respectively, compared with 84% and 92% in the node-negative cases, respectively. These differences were not statistically significant due to the small sample size, which also limits the interpretation of these results. However, this small series is quite interesting and should be attempted and validated by other investigators.

Conclusion

SLN mapping is emerging as a viable, more precise, and potentially less morbid option to comprehensive lymphadenectomy in the surgical staging of patients with endometrial carcinoma. Many questions remain unanswered. There is potential for randomized trials to answer some of these questions, but the resources for conducting such trials are always a rate-limiting step. Continued research can help address the many questions surrounding SLN mapping.

Acknowledgments

Funding: This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

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Figure 1. The Memorial Sloan Kettering Cancer Center sentinel lymph node mapping algorithm for patients with endometrial and cervical cancers

With permission from: Barlin JN, Khoury-Collado F, Kim CH, Leitao Jr MM, Chi DS, Sonoda Y, et al. The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: beyond removal of blue nodes. *Gynecol Oncol* 2012;125:531-535.

Figure 2. Memorial Sloan Kettering Cancer Center's pathologic ultrastaging protocol for sentinel lymph nodes

With permission from: Kim CH, Soslow RA, Park KJ, Barber EL, Khoury-Collado F, Barlin JN, et al. Pathologic ultrastaging improves micrometastasis detection in sentinel lymph nodes during endometrial cancer staging. *Int J Gynecol Cancer* 2013;23:964-970.