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Sentinel Lymph Node Mapping with Pathologic Ultrastaging: A Valuable Tool for Assessing Nodal Metastasis in Low-Grade Endometrial Cancer with Superficial Myoinvasion

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Abstract

Objective—To report the incidence of nodal metastases in patients presenting with presumed low-grade endometrioid adenocarcinomas using a sentinel lymph node (SLN) mapping protocol including pathologic ultrastaging.

Methods—All patients from 9/2005-12/2011 who underwent endometrial cancer staging surgery with attempted SLN mapping for preoperative grade 1 (G1) or grade 2 (G2) tumors with <50% invasion on final pathology, were included. All lymph nodes were examined with hematoxylin and eosin (H&E). Negative SLNs were further examined using an ultrastaging protocol to detect micrometastases and isolated tumor cells.

Results—Of 425 patients, lymph node metastasis was found in 25 patients (5.9%) on final pathology—13 cases on routine H&E, 12 cases after ultrastaging. Patients whose tumors had a DMI <50% were more likely to have positive SLNs on routine H&E ($p < 0.005$) or after ultrastaging ($p = 0.01$) compared to those without myoinvasion.

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Conflict of Interest Statement

Mario M. Leitao, Jr is a consultant for Intuitive Surgical. There are no other disclosures to report.

Conclusions—Applying a standardized SLN mapping algorithm with ultrastaging allows for the detection of nodal disease in a presumably low-risk group of patients who in some practices may not undergo any nodal evaluation. Ultrastaging of SLNs can likely be eliminated in endometrioid adenocarcinoma with no myoinvasion. The long-term clinical significance of ultrastage-detected nodal disease requires further investigation as recurrences were noted in some of these cases.

Keywords

sentinel lymph node mapping; ultrastaging; micrometastasis; low-grade endometrioid carcinoma; isolated tumor cells; endometrial cancer staging

Introduction

Endometrial carcinoma continues to be the most common gynecologic malignancy in the United States, with an estimated 49,560 new cases and 8,190 related deaths in 2013 [1]. Although the majority of women will present with clinically uterine-limited disease, approximately 10% of patients will have pelvic lymph node metastasis despite favorable tumor characteristics [2]. The status of metastatic disease to regional lymph nodes is one of the most important prognostic indicators for overall survival in these patients [3–6]. Appropriate identification of nodal disease is needed to guide adjuvant therapy, and lymph node assessment continues to be the standard of care in the surgical staging of endometrial cancer [7]. The International Federation of Gynecology and Obstetrics (FIGO) staging system of uterine corpus malignancies changed from a clinically based method to a surgical one in 1988, incorporating nodal status. However, routine lymph node assessment still varies widely among different institutions and surgeons, especially in tumors presumed to be low grade [8].

The lack of consensus regarding whether to comprehensively surgically stage patients presenting with grade 1–2 (G1/G2) endometrial carcinoma is attributed to several factors: the low incidence of nodal metastases, the overall excellent prognosis of these women with low-grade tumors confined to the uterus, and the seemingly insignificant survival effect of lymphadenectomy, as reported from two recent, large randomized control trials. These two trials have shown that in unselected endometrial cancer patients, pelvic lymphadenectomy itself does not confer a therapeutic survival advantage. Instead, it can be associated with increased morbidity without improved disease-free or overall survival [9,10]. In both trials, adjuvant therapy was at the discretion of the treating physician and did not differ depending on lymph node status.

Mariani et al. identified a potential group of patients who were expected to have a low risk of nodal metastases and in which the morbidity of lymphadenectomy could be avoided. They defined such low-risk patients based on the combination of the following intraoperative features: G1/G2 tumors, <50% myometrial invasion, <2 cm tumor diameter and no lymphovascular invasion (LVI) [11]. Unfortunately, this process of identifying low-risk cases does not easily extrapolate to the majority of other institutions where the use of intraoperative uterine risk factor assessments is highly variable and unreliable. Other studies have found that the preoperative grade is upgraded in 15–20% of cases on final histology [12], and up to 24% of patients may be upstaged on final pathologic examination of grade or myometrial invasion [13]. Additionally, relying on intraoperative frozen section is also not consistently reliable, as several studies have shown that this correlates poorly with final pathologic assessment [14–16]. Classifying patients as “low risk” based on preoperative and/or intraoperative uterine factors alone may lead to as many as 25% of patients being understaged and, therefore, potentially undertreated or overtreated with adjuvant therapies [17]. Conversely, performing a full pelvic and paraaortic lymphadenectomy on all patients

will subject many of them to an unnecessary, extensive procedure. It should also be emphasized that in the Gynecologic Oncology Group (GOG) LAP II trial, among the approximately 7% node-positive endometrioid carcinoma cases reported by Milam in 2012, 60% had G1/G2 tumors, 48% had <50% myoinvasion, and 23% had tumors smaller than 2 cm. It was only when all three of these factors were simultaneously present in a patient that the risk of nodal metastasis became negligible (0.8%) [18].

Sentinel lymph node (SLN) mapping attempts to accurately identify lymphatic drainage to select lymph nodes that are most likely to harbor disease, while also reducing the morbidity associated with systemic lymphadenectomy [19]. SLNs have been shown to be three times more likely to contain metastatic disease than non-SLNs [20]. Applying an SLN algorithm in endometrial cancer staging surgery that involves a side-specific lymph node dissection in cases of failed mapping and biopsying any suspicious lymph nodes, may allow appropriate lymph node assessment without exposing all patients to the morbidity of a complete bilateral lymphadenectomy [21]. Inherent in the SLN concept is the additional pathologic assessment via serial sectioning with ultrastaging in order to discover low-volume metastatic disease. The clinical significance of finding ultrastage-detected-only tumor cells in SLNs is not yet known. The primary objective of this study was to report the incidence of nodal metastasis using our institution's SLN mapping protocol and pathologic ultrastaging in patients presumed to have "low-risk" endometrial carcinoma..

Methods

Patient and Tumor Characteristics

SLN mapping for endometrial cancer was initiated at our institution in 2005. After obtaining Institutional Review Board approval, the prospectively maintained endometrial cancer database was used to identify all patients from September 2005 to December 2011 who had undergone surgical staging that included attempted SLN mapping and biopsy. All endometrial cancer patients consented for surgery were explained our institution's method of SLN mapping and biopsy prior to their procedure. Patients were aware that additional pelvic lymph nodes may be removed if SLNs were not identified, if enlarged lymph nodes were present, and/or if the surgeon thought further sampling of lymph nodes was indicated. Para-aortic or complete lymphadenectomy was performed as per surgeon's discretion and experience with the institution's SLN mapping protocol [22]. All modalities of surgical assessment were included.

Electronic medical records, operative and pathology reports were used to obtain any initially missing demographic, operative, and pathologic details. Laterality of SLNs was determined by reviewing operative and pathology reports. Presumed "low-risk" endometrial cancer patients in this study were defined as those who had a preoperative FIGO G1/G2 endometrial carcinoma and who had <50% myometrial invasion on final pathology. All preoperative biopsies were reviewed at our institution prior to surgery. Intraoperative frozen section to determine grade, depth of myometrial invasion (DMI), LVI, and tumor size is not routinely performed at our institution, as pelvic lymph nodes are routinely assessed using our SLN mapping protocol. Thus, final pathologic assessment of myometrial invasion was used as a substitute for intraoperative DMI evaluation as other studies have reported high correlation between intraoperative assessment of DMI to final DMI [23,24]. We excluded any patients with a final DMI $\geq$ 50%.

Sentinel Lymph Node Injection and Mapping Algorithm

Lymphatic mapping consisted of injecting blue dye into the cervix during the exam under anesthesia. All patients received cervical injections with blue dye: 1 mL superficial (1–2

mm) and 1 mL deep (1–2 cm) at the 3 and 9 o'clock positions, for a total of 4 mL. As per our previously reported SLN mapping protocol [25], blue nodes were dissected and labeled as SLNs. Any suspicious or grossly enlarged nodes per surgeon's assessment were removed and sent separately as non-SLNs. All demographic, clinicopathologic, SLN mapping details, and pathology results were obtained from the patients' electronic medical records. Adjuvant chemotherapy and/or radiation was recommended and given as per physician discretion.

Pathologic Ultrastaging of Sentinel Lymph Nodes and Evaluation of Non-Sentinel Lymph Nodes

As part of our institution's investigation in SLN mapping for endometrial cancer, a standardized method of pathologic ultrastaging and reporting findings was also initiated in 2005 [26]. Both SLNs and non-SLNs are routinely sectioned once and stained with hematoxylin and eosin (H&E). Our ultrastaging pathology protocol for SLNs is implemented if the SLN is negative on initial H&E staining. Ultrastaging re-evaluates the presumed negative SLN at two additional levels, 50 μ m apart, with an extra H&E stained slide and immunohistochemistry (IHC) using the anti-cytokeratin AE1:AE3. Ultrastage-detected disease included both micrometastases (MMs) and isolated tumor cells (ITCs), as defined in the breast cancer literature by the American Joint Committee on Cancer (AJCC). Macrometastasis in lymph nodes were defined as tumor cells >2.0 mm; MMs were defined as a focus of metastatic cancer >0.2 mm and $\leq$ 2.0 mm; and ITCs were defined as microscopic clusters and single cells measuring $\leq$ 0.2 mm. SLNs containing MMs and ITCs had evidence of microscopic tumor cells on both IHC and H&E that were only discovered after additional sectioning was performed. Cytokeratin-positive cells (CKPCs) were noted as such if only single, rare cytokeratin-positive stained cells were present on IHC but not seen on H&E staining. For this study, SLNs containing only CKPCs were not considered positive for metastatic disease and were not included in the low-volume, ultrastage-detected category.

Non-SLN status was reported based on routine pathologic processing of all lymph nodes except for SLNs, while SLN status reflected results after ultrastaging of all submitted SLNs. Final lymph node status was considered negative if both SLNs and non-SLNs contained no metastatic cells; positive if either SLNs or non-SLNs contained metastatic tumor cells during standard H&E assessment; and positive for ultrastage-detected metastatic disease if only MMs or ITCs were found during pathologic ultrastaging of presumed negative SLNs and all other lymph nodes were negative. Statistical analyses were performed using SPSS software (version 21.0). The Chi square or Fisher's exact test was used to compare nominal data as appropriate, and the Mann Whitney-U test was used to compare medians for continuous data.

RESULTS

Four hundred sixty-six patients with preoperative G1/G2 endometrioid adenocarcinomas who underwent surgical staging with SLN mapping and biopsy were identified. Forty-one patients were excluded for having tumors with a final DMI $\geq$ 50%, leaving a total of 425 patients with preoperative G1/G2 endometrioid tumors with <50% DMI who underwent surgical staging with attempted SLN mapping and biopsy. Preoperative endometrioid grade was determined from endometrial sampling via office biopsy in 232 patients and dilation and curettage in 193 patients. Patient and tumor characteristics are summarized in Table 1. Among the 425 patients, the median age at the time of surgery was 58 years (range, 34–87), and the median BMI was 29 kg/m² (range, 16–69). Surgical staging was performed via a minimally invasive approach in 357 patients (84%). Final tumor histologies included serous carcinoma in 5 (1.2%), clear cell carcinoma in 1 (0.2%), carcinosarcoma in 1 (0.2%), and undifferentiated carcinoma in 3 (0.7%) patients. Five preoperative G1/G2 endometrioid

cases were upgraded to G3 endometrioid tumors on final pathology evaluation. Including the non-endometrioid histologies that were upgraded to G3 disease on final pathology, final G1, G2, and G3 tumors were found in 302 (70.1%), 108 (25.4%), and 15 (3.5%) patients, respectively. At least one SLN was detected in 348 (81.9%) of the 425 eligible patients: 218 mapped bilaterally, 130 mapped unilaterally. No myometrial invasion was found in 241 patients (56.7%), while 184 (43.3%) had <50% myoinvasion.

Of the 130 patients who mapped unilaterally, 251 total SLNs were sampled, with a median SLN of 1 (range, 0–9). In contrast, 1020 total non-SLNs were removed in these patients, with a median non-SLN of 4 (range, 0–55). Seventy-seven patients (18.1%) did not have successful mapping of at least one SLN. Among these unmapped patients, the median BMI was 35 (range, 21–69); 17 patients were overweight (BMI, 25–29), 29 were obese (BMI, 30–39), and 22 were extremely obese (BMI, 40–54). Alternatively, the median BMI for patients who had at least one SLN identified was 29 (range, 18–49). Patients who failed SLN mapping with blue dye were more likely to have a higher BMI ($P<0.001$) than those patients who had at least one SLN identified.

Lymphovascular invasion was present in 58 patients (13.6%) and absent in 367 (86.4%). A total of 1117 SLNs were biopsied, with a median of two SLNs assessed per patient (range, 0–12). Of the SLNs biopsied, 42 (3.8%) were positive (19 during standard H&E, 23 during ultrastaging evaluation). A total of 2739 non-SLNs were also biopsied, with a median of two non-SLNs assessed per patient (range, 0–55). Of the non-SLNs biopsied, 4 (0.15%) were positive. SLNs were statistically more likely to contain metastatic disease than non-SLNs in this select cohort of patients ($P<0.001$). Patients with tumors having a DMI <50% were more likely to have positive SLNs either on routine H&E ($p<0.005$) or after ultrastaging ($p=0.01$) compared to those tumors with no myoinvasion. Additionally, tumors with LVI were more likely to have positive SLNs either on routine H&E ($p<0.005$) or after ultrastaging ($p<0.005$). The presence of metastatic tumor cells in SLNs was not statistically dependent on preoperative or final tumor grade ($p=0.47$).

Among the 425 low-risk patients who underwent attempted SLN mapping during surgical staging, 25 (5.9%) were found to have metastatic disease in their lymph nodes. This included 11 patients (2.6%) on initial H&E evaluation of their SLNs. After ultrastaging of presumed negative SLNs was performed, 3 (0.7%) patients were found to have MMs in their biopsied SLNs and 9 (2.1%) patients were found to have ITCs in their SLNs. In addition, 2 patients (0.5%) were found to have metastatic disease in their non-SLNs, which were biopsied because one patient did not map bilaterally and the other only mapped unilaterally. Of the 15 patients, who had their tumors upgraded to G3 disease on final pathology; one patient with G3 endometrioid carcinoma was found to have ITCs in her biopsied SLNs. Ultrastaging also found 8 patients with CKPCs in their respective SLNs. These were considered negative nodes as only rare, isolated cytokeratin cells were found on IHC staining alone.

Table 2 classifies the different types of nodal metastases with respect to the patient's preoperative tumor grade and final DMI. Table 3 describes these same nodal diseases using their final pathology grade and DMI. As frozen sections were not obtained intraoperatively on the SLNs biopsied, Table 3 shows the results that are available to clinicians when making their adjuvant treatment recommendations.

Some form of adjuvant therapy was administered to 119 patients (28%), while 306 (72%) did not receive any adjuvant treatment. Table 4 describes the 25 patients with nodal disease, their respective uterine tumor characteristics, adjuvant treatments, and disease statuses. All patients who had macrometastases found on initial H&E evaluation of their SLNs were

recommended adjuvant treatment. Adjuvant treatment was also offered to those patients with ultrastage-detected MMs in their SLNs, with a discussion that there was no randomized evidence to strongly support treating ultrastage-detected nodal disease. In patients who only had ITCs in their SLNs, a discussion of optional adjuvant treatment was done on a case by case basis. Most patients who met high intermediate risk criteria as described in GOG 99 [27] were offered adjuvant treatment. As this study represents the history of SLN mapping and biopsy results at our institution, the adjuvant treatments varied.

With a median follow-up of 18.4 months (range, 0.9–70.3), 11 patients recurred in this presumed low-risk group of endometrial cancer patients (Table 5). Recurrence sites included the vaginal cuff (4), pelvis (1), lung (1), paraaortic retroperitoneum (1), abdominal peritoneal cavity (1), abdominal wall (1), and inguinal region (2). In this recurrent group, there were 3 patients who were found to have only ultrastage-detected metastatic disease in their SLNs. One patient was a 70-year-old woman with an endometrioid G1 tumor, <50% DMI, and LVI who had only MMs in her SLNs. She was advised to receive concurrent chemotherapy and radiation; however, she declined any further treatment. She recurred in her liver and had peritoneal carcinomatosis approximately 18 months after surgery. The second patient was a 49-year-old woman with an endometrioid preoperative G1, final G2 tumor with <50% DMI, LVI, and only ITCs in her biopsied SLNs. She was offered concurrent chemotherapy and radiation, but opted to only have pelvic radiation. She recurred in her paraaortic lymph node approximately 27 months after surgery. The third patient was a 61-year-old woman with an endometrioid G1 tumor, <50% DMI, and LVI who also only had ITCs in her SLN. This patient received brachytherapy and chemotherapy, but recurred in her pelvis approximately 16 months after surgery.

Discussion

Surgical staging for low-risk endometrioid endometrial cancers remains controversial because the overall incidence of nodal metastases is low and the overall prognosis of these patients is good [28]. Lymphadenectomy alone has not been associated with a survival benefit, as reported in randomized trials. Lymphadenectomy, however, is associated with side effects, including lower extremity lymphedema and lymphocysts, which may negatively impact a patient's quality of life. Thus, some practitioners have decided to use intraoperative frozen section results to determine whether a patient requires lymphadenectomy, while others have abandoned lymphadenectomy altogether for presumed low-risk patients. This may be problematic as up to 24% of patients may be upstaged from intraoperative frozen section to final pathology. Rather than not evaluating lymph nodes in a presumed low risk endometrial cancer patient, another approach is to implement an SLN mapping protocol with pathologic ultrastaging so that the most likely nodes to contain metastatic disease are assessed. In this cohort of patients with preoperative G1/G2 tumors and final DMI <50%, SLN mapping, biopsy, and pathologic ultrastaging helped identify 6% of patients with nodal metastasis that would have otherwise been missed if no nodes were assessed. Two additional patients were found to have nodal metastasis when side-specific lymphadenectomy was performed for failed mapping on one side of the pelvis, further emphasizing the need to utilize an SLN algorithm in endometrial cancer staging.

There are several limitations of this present study inherent in its retrospective design. This is a uniquely grouped cohort of presumed low-risk endometrioid patients using preoperative grade and final pathology DMI. Because frozen sections are not routinely used to determine which patients need lymph node assessment at our institution, intraoperative DMI, tumor diameter, or LVI was not available for all patients. Additionally, this is a single-institution study where attempted SLN mapping, biopsy, and pathologic ultrastaging assessments have become the routine method of endometrial cancer surgical staging. Thus, with time, most

surgeons have become familiar with the cervical injection method, common locations of blue SLNs, dissection methods, and how to proceed with failed mapping by applying our SLN mapping algorithm. Our dedicated gynecologic pathologists have also become experts in ultrastaging SLNs as well as locating and identifying MMs and ITCs within them.

SLN mapping failure with blue dye may occur for various reasons: improper cervical injection technique; blood-stained retroperitoneum, making the blue node difficult to visualize; lymph node(s) potentially congested with tumor cells, thus limiting the node's ability to take up blue dye; and excess adipose tissue, making the identification of the blue SLN difficult. Many of these factors are difficult to quantify; however, we found that patients who failed SLN mapping with blue dye were statistically more likely to have higher BMIs than those who had successful mapping. As our institution has a high referral population, the median BMI in this study was reflective of the patients who are treated and may differ from median BMIs at other institutions. This may limit the applicability of using blue dye for SLN mapping for some institutions. There have been recent studies demonstrating the feasibility and improved bilateral SLN mapping using indocyanine green cervical injections [29,30]. Further investigations in using alternative injection agents may assist in identifying SLNs in those patients with higher BMIs.

The wide range of SLNs and non-SLNs biopsied per patient reflect the historic learning curve of SLN mapping at our institution; as surgeons became more comfortable with the cervical injection and dissection technique, SLNs were better identified. Additionally, the increased detection of metastatic disease in SLNs compared to non-SLNs may be due to several factors. Targeted dissection of lymph nodes that are sentinel rather than traditional random lymph node sampling may help isolate and identify those nodes that are more likely to harbor metastatic disease. Additionally, the ultrastaging of SLNs allows for closer inspection of lymph nodes initially presumed negative by H&E stain. This additional pathologic examination of SLNs contributes to SLNs increased likelihood of detecting both macro- and micrometastatic disease.

Although the incidence of nodal disease is low in patients with presumed favorable uterine tumor characteristics, it is not zero. Interestingly, in our cohort, only 1 patient had her tumor upgraded to G3 endometrioid on final pathology, and she was found to have ITCs in her biopsied SLNs. In this select cohort of patients, nodal metastases (both H&E positive and ultrastage-detected) were noted more frequently in those patients with some degree of myometrial invasion (<50%) and in those tumors that had evidence of LVI.

Many gynecologic oncology surgeons have adapted one institution's uterine intraoperative frozen section criteria to determine whether a patient should undergo any lymph node assessment despite the potential risk of upstaging on final pathologic exam. As many institutions may not have the consistent detailed frozen section evaluation that confirms tumor grade, diameter, DMI, and LVI, we propose that applying an SLN algorithm and ultrastaging assessment (when there is myoinvasion or LVI in the hysterectomy specimen) may help identify those patients who have occult nodal disease. As with any new procedure, it requires a dedicated effort and there is a learning curve [22]. However, this SLN mapping technique is not an insurmountable new technique. With the cervix as the site of injection, it gives physicians relatively easy access to the main uterine lymphatic drainage system. It also allows lymph node sampling to be targeted to those nodes that are most likely to harbor disease [31]. Collaboration with the gynecologic pathologist is also essential in evaluating the few lymph nodes that are deemed sentinel as there may be evidence of MMs or ITCs that may change adjuvant therapy. The role and routine performance of SLN ultrastaging in cases with no myoinvasion on final hysterectomy pathology is uncertain because the yield of detecting metastasis in the latter group appears to be very small.

While this study is limited by its retrospective nature, the findings of recurrent disease in patients who only had MMs or ITCs in their SLNs is thought provoking. Longer follow-up in these “low-risk” patients is needed to better assess the clinical significance of finding ultrastage-detected lymph node disease. With the overall low incidence of MMs and ITCs, the paradigm shift towards treating intermediate- and high-risk early-stage endometrial cancer patients with adjuvant therapy, and the overall good prognosis of these presumed early-stage patients, it will likely be difficult to detect a survival advantage. A multi-institutional randomized control trial is needed to assess the SLN mapping algorithm, SLN pathologic ultrastaging, and adjuvant treatment options for these MMs and ITCs.

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Research Highlights

- SLN mapping with ultrastaging can detect microscopic nodal disease.
- Pathologic ultrastaging may not be necessary in uterine tumors without myoinvasion.

Table 1

Patient and tumor characteristics of all presumed low-risk endometrial carcinoma cases undergoing attempted SLN mapping and biopsy (N=425)

Characteristics	N (%)
Age at diagnosis, years	
Median (range)	58 (34–87)
BMI, kg/m ²	
Median (range)	29 (16–69)
Type of surgery	
Laparotomy	68 (16.0)
Laparoscopy	148 (34.8)
Robotic-assisted	209 (49.2)
Preoperative Histology	
Endometrioid	425 (100)
Final Histology	
Endometrioid	415 (97.6)
Non-endometrioid	10 (2.4)
Preoperative Grade	
Grade 1	323 (76.0)
Grade 2	102 (24.0)
Final Tumor Grade	
Grade 1	302 (70.1)
Grade 2	108 (25.4)
Grade 3	15 (3.5)
Final DMI	
None	241 (56.7)
< 50%	184 (43.3)
Lymphovascular invasion	
No	367 (86.4)
Yes	58 (13.6)
Cases with +LNs	25 (5.9)
Positive SLN (H&E)	11 (2.6)
Ultrastage-detected (MMs or ITCs only)	12 (2.8)
Positive non-SLN	2 (0.5)
Total # SLNs biopsied	1117
Total positive SLNs	42 (3.8)
Total +SLNs (H&E)	19

Characteristics	N (%)
Total +SLNs (ultrastaging)	23
Median # SLNs biopsied per pt (range)	2 (0–12)
Total # non-SLNs biopsied	2739
Total positive non-SLNs	4 (0.15)
Median # Non-SLNs biopsied per pt (range)	2 (0–55)

BMI: body mass index; DMI: depth of myometrial invasion; +LNs: positive lymph nodes; H&E: hematoxylin & eosin; MMs: micrometastases; ITCs: isolated tumor cells; SLNs: sentinel lymph nodes; #: number

Table 2

Incidence of nodal disease by preoperative grade and final depth of myometrial invasion

Final DMI	Preop Grade 1	Preop Grade 2	Total
DMI none	H&E 0	H&E 1	3/241 (1.2%)
	MMs 1	MMs 0	
	ITCs 1	ITCs 0	
	n = 193	n = 48	
DMI <50%	H&E 8	H&E 4	22/184 (12.0%)
	MMs 2	MMs 0	
	ITCs 7	ITCs 1	
	n = 130	n = 56	
Total	19/323 (5.9%)	6/104 (6.9%)	25/425 (5.9%)

DMI: depth of myometrial invasion; H&E: positive on standard hematoxylin & eosin staining; MMs: micrometastases found during ultrastaging of SLNs; ITCs: isolated tumor cells found during ultrastaging of SLNs

Table 3

Incidence of nodal disease by final tumor grade and depth of myometrial invasion

Final DMI	Final Grade 1	Final Grade 2	Final Grade 3	Total
DMI none	H&E 0	H&E 1	H&E 0	3/241 (1.2%)
	MMs 1	MMs 0	MMs 0	
	ITCs 1	ITCs 0	ITCs 0	
	n=194	n = 42	n = 5	
DMI <50%	H&E 8	H&E 4	H&E 0	22/184 (12.0%)
	MMs 2	MMs 0	MMs 0	
	ITCs 4	ITCs 3	ITCs 1	
	n = 108	n = 66	n = 10	
Total	16/302 (5.3%)	8/108 (7.4%)	1/15 (6.7%)	25/425 (5.9%)

DMI: depth of myometrial invasion; H&E: positive on standard hematoxylin & eosin staining; MMs: micrometastases found during ultrastaging of SLNs; ITCs: isolated tumor cells found during ultrastaging of SLNs

Table 4

Lymph node biopsy results, uterine tumor characteristics, and adjuvant treatments of 25 presumed low-risk endometrioid cancer patients found to have nodal metastases

Year of surgery	Age	Preop Grade	Final Grade	DMI	LVI	Wash	Adjuvant Treatments (description)	Type of (+)LN	Total (+) SLNs / Total SLNs	Total (+) non-SLNs / Total non-SLNs	Status	Recurrence Site
2007	61	1	1	<50 %	y	-	Chemo + pelvic RT	HE	2/2	0/16	NED	
2007	54	2	2	<50 %	n	-	Chemo only	HE	6/7	2/21	NED	
2008	41	1	1	<50 %	y	+	Chemo + pelvic RT	HE	3/3	0/9	NED	
2009	48	1	3	<50 %	y	+	Chemo + pelvic RT	ITCs	1/2	0/24	NED	
2009	75	2	2	<50 %	y	-	Chemo + pelvic RT	ITCs	1/2		NED	
2009	55	1	1	<50 %	n	-	Chemo + pelvic RT	HE	3/4	0/4	NED	
2009	66	1	1	None	n	-	Chemo only	MMs	1/10		NED	
2009	65	1	1	<50 %	y	-	Chemo +pelvic RT	ITCs	1/2		NED	
2009	52	1	1	<50 %	y	-	Chemo + pelvic RT	MMs	4/6		NED	
2009	74	1	1	<50 %	y	-	None (declined all)	ITCs	1/6		NED	
2009	73	2	2	<50 %	y	-	Chemo + pelvic RT	HE	1/3		NED	
2009	60	1	1	<50 %	y	-	Pelvic RT (declined chemo)	HE	2/5	0/6	NED	
2009	71	1	1	<50 %	y	-	Chemo + IVRT	HE		1/22	NED	
2009	55	1	1	None	n	-	None (declined hormone blockade)	ITCs	1/3		NED	
2009	49	1	2	<50 %	y	-	Pelvic RT (declined chemo)	ITCs	1/9		AWD	PALN
2010	69	2	1	<50 %	y	+	Chemo only	HE	1/2	0/19	NED	
2010	66	1	1	<50 %	y	-	Chemo only	HE	0/2	1/15	NED	
2010	61	1	1	<50 %	y	-	Chemo + pelvic RT	HE	1/5	0/1	NED	
2010	35	2	2	None	y	-	Chemo + pelvic RT	HE	1/2	0/18	NED	
2011	65	2	2	<50 %	y	-	None (declined all)	HE	1/1	0/11	NED	
2011	63	1	2	<50 %	y	-	Chemo + pelvic RT	HE	1/2		NED	
2011	59	1	1	<50 %	y	-	Chemo + IVRT	ITCs	1/3		NED	
2011	70	1	1	<50 %	y	+	None (declined all)	MMs	1/3	0/20	AWD	Liver & peritoneum

Year of surgery	Age	Preop Grade	Final Grade	DMI	LVI	Wash	Adjuvant Treatments (description)	Type of (+)LN	Total (+) SLNs / Total SLNs	Total (+) non-SLNs / Total non-SLNs	Status	Recurrence Site
2011	65	1	2	<50 %	n	–	Pelvic RT + IVRT	ITCs	1/2		NED	
2011	61	1	1	<50 %	y	–	Chemo + IVRT	ITCs	1/1		AWD	Pelvis

SLN: sentinel lymph node; DMI: depth of myometrial invasion; LVI: lymphovascular invasion; Wash: washings; Type of (+)LN: type of positive lymph node; HE: hematoxylin & eosin; MMs: micrometastases found during ultrastaging of SLN(s); ITCs: isolated tumor cells found during ultrastaging of SLN(s); IVRT: intravaginal radiation therapy; RT: radiation therapy; NED: no evidence of disease; AWD: alive with disease; PALN: paraaortic lymph node

Blue highlighted boxes indicate those cases who had positive lymph nodes detected upon examination of SLN(s) on routine H&E or by ultrastaging

Yellow highlighted boxes indicate those lymph nodes or patients who had positive lymph nodes detected upon examination of non-SLN(s) on routine H&E

Table 5

Sites of recurrence in presumed low-risk endometrioid cancer patients

Year of Surgery	Age	SLN mapping	Preop Grade	Final Grade	DMI	LVI	Wash	Type of +LN	Total (+) SLN/Total SLNs	Total (+) non-SLN/Total non-SLNs	Adjuvant txm't	Status	Recurrence Site	Recurrence from surgery (months)
2006	57	Failed b/l	2	2	<50%	n	–	None		0/16	Chemo + IVRT	AWD	Groin	67.8
2008	52	Bilateral	1	1	<50%	y	–	None	0/3	0/9	IVRT	AWD	Lung	35.2
2009	68	Bilateral	1	1	None	n	–	None	0/3	0/9	None	AWD	Vaginal Cuff	7.1
2009	49	Bilateral	1	2	<50%	y	–	ITC	1/9		Pelvic RT (declined chemo)	AWD	PALN	27.4
2009	64	Bilateral	2	2	None	n	–	None	0/2	0/5	None	AWD	Liver	31.7
2010	59	Bilateral	1	1	None	n	–	None	0/4		None	AWD	Vaginal Cuff	6.6
2010	57	Unilateral	1	1	None	n	–	None	0/2		None	AWD	Vaginal Cuff	4.1
2010	62	Failed b/l	1	1	<50%	n	–	None		0/6	None	AWD	Vaginal Cuff	15.0
2010	55	Bilateral	1	2	<50%	n	–	None	0/5		IVRT	AWD	Vaginal Cuff	14.1
2011	70	Bilateral	1	1	<50%	y	–	MM	1/3	0/20	None (declined any)	AWD	Liver & Peritoneum	17.9
2011	61	Unilateral	1	1	<50%	y	–	MM	1/1		Chemo + IVRT	AWD	Pelvis	16.4

SLN: sentinel lymph node; DMI: depth of myometrial invasion; LVI: lymphovascular invasion; Wash: washings; Type of (+)LN: type of positive lymph node; b/l: bilateral; MMs: micrometases found during ultrastaging of SLN(s); ITCs: isolated tumor cells found during ultrastaging of SLN(s); IVRT: intravaginal radiation therapy; RT: radiation therapy; AWD: alive with disease

Blue highlighted boxes indicate those cases who had positive lymph nodes detected upon examination of SLN(s) on routine H&E or by ultrastaging