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Research Article

Characterization of Patients with Endometrial Cancer and Low-Volume Nodal Disease

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Abstract

Background: Isolated tumor cells (ITCs) are deposits measuring ≤0.2 mm, whereas micro metastasis (MM) measures >0.2 to ≤2 mm. The significance of these findings in endometrial cancer remains controversial. We sought to determine whether patient and disease characteristics correlate with ITCs/MM on sentinel lymph node (SLN) biopsy for endometrial cancer staging. **Methods:** We carried out an IRB-approved retrospective chart review of all women with endometrial cancer who underwent SLN biopsy during staging at two medical centers between 2013 and 2018. **Results:** A total of 472 patient charts met inclusion criteria. Among women included, 5.7% (n = 27) had ITCs/MM. The median age of women with ITCs/MM was 64 years and median BMI was 33.8. Neither was found to be related to ITCs/M. Lymphovascular space invasion (LVSI) was present in 73% (n = 19). Compared to patients without LVSI, those with LVSI were more likely to have ITCs/MM (OR = 7.61, 95% CI 3.00–19.32). Compared to patients with superficial invasion of the myometrium, those with a greater myometrial invasion were more likely to have ITCs/MM (OR = 6.37, 95% CI 1.90–21.37). **Conclusion:** ITCs/MM are relatively rare in women undergoing SLN biopsy for endometrial cancer. Additional data are needed to clarify risk factors and associated patient outcomes.

Introduction

Endometrial cancer is the most common gynecologic malignancy in the developed world, with over 60,000 new cases diagnosed annually in the United States alone. [1] Sentinel lymph node (SLN) biopsy has revolutionized the surgical staging of this prevalent disease. Prior to the development of this technique, patients with endometrial cancer routinely underwent comprehensive pelvic lymphadenectomy, potentially with removal of additional nodes in the paraaortic region, to detect nodal metastasis. [2] While lymphadenectomy is known to increase the detection of metastatic disease in patients with endometrial cancer, multiple studies have found increased morbidity associated with the procedure and no improvement in overall or disease-free survival.[3, 4] Recognizing an area for improvement, the first SLN biopsy for the surgical staging of endometrial cancer was reported by Burke et al. in 1996 [5]. Since then, studies comparing SLN biopsy with comprehensive lymphadenectomy have demonstrated not only a decrease in complications, but also similar or superior detection of nodal metastasis and similar survival outcomes associated with SLN biopsy [6-10]. As such, SLN biopsy has replaced routine lymphadenectomy in many institutions.

The superior detection of nodal metastasis is largely attributable to a pathology technique used to evaluate SLNs called ultrastaging. Traditional pathologic review of nodes obtained from lymphadenectomy involves examination of a bivalved specimen. Ultrastaging involves gross sectioning of a SLN, following by serial sectioning to obtain micron level segments throughout the node. Ultrastaging not only aids in superior detection of nodal gross metastasis; it also has led to an increase in the identification of isolated tumor cells (ITCs) and micrometastases (MM). ITCs are defined as tumor deposits measuring £ 0.2 mm, whereas MM are defined as metastatic deposits measuring > 0.2 mm to ≤ 2 mm. The prevalence of these low-volume nodal disease findings is estimated to range from 3-10% based upon studies of women with endometrial cancer undergoing SLN biopsy.[6-11]In breast cancer literature, for which SLN biopsy has been longer utilized and better studied, MM have been correlated with worse 5-year survival rates compared to node negative disease, while no difference in outcome has been associated with ITCs compared to node negative disease. [12] In endometrial cancer, the significance of low-volume disease as it relates to patient outcomes and therapy remains unclear.[6-13] One study by Plante et al. revealed no statistically significant difference in 3-year disease-free survival between patients with node negative, ITC positive, and MM positive disease, concluding that adjuvant therapy should not be offered solely on the basis of node positivity.[14] The largest investigation of ITCs by Backes et al. found that of 175 patients with endometrial carcinoma and ITCs, recurrence rates were low (5.1%) and adjuvant therapy was not statistically associated with an improvement in recurrence free survival.[11] Conversely, a study by Todo et al. suggested worse survival and recurrence rates associated with both ITCs and MM, though this study was limited by small sample sizes.[15]

While research regarding the prognostic value of low volume nodal disease and need for adjuvant therapy is ongoing, there is also more to be discovered regarding patient characteristics and predictors for the presence of ITCs and MM on SLN biopsy. A recent study found ITCs to be associated with larger tumor size and increasing depth of myometrial invasion compared to node negative disease. [16] We sought to add to the available knowledge by determining whether certain patient and disease characteristics correlate with the finding of ITCs or MM on SLN biopsy performed for endometrial cancer staging.

Material and Methods

A retrospective chart review was performed of all women over the age of 18 who underwent SLN mapping and biopsy during surgical staging for endometrial cancer at the University of Rochester Medical Center and Women & Infants Hospital of Brown University between 2013 and 2018. IRB approval was obtained at each institution. Further study criteria necessary for inclusion were endometrioid histology, successful SLN biopsy without full lymphadenectomy in which pathology confirmed presence of nodal tissue, and availability of access to records.

All cases were identified by the Departments of Pathology and Divisions of Gynecologic Oncology. Medical record numbers provided by the departments were used to access only pertinent data from patients' electronic medical records. Information of interest included demographic variables (age, race, ethnicity, menopausal status, body mass index (BMI), major medical problems, known genetic mutations), pathologic variables (histology, grade, presence or absence of lymphovascular space invasion (LVSI), depth of invasion, tumor size, tumor location, positivity of SLN, number and location of SLN, SLN MM vs metastasis, SLN ITCs, MSI tumor status) and outcome variables (surgical complications, disease recurrence, vital status), when available. Data extracted from chart review were managed using the HIPAA-compliant REDCap system hosted by the University of Rochester Wilmot Cancer Institute.

The primary patient characteristics of interest for this study included age and BMI. The primary disease characteristics of interest included disease grade, LVSI, and depth of myometrial invasion. Secondary variables of interest for this study were outcome-related and included disease recurrence and mortality.

Descriptive characteristics of the sample were displayed as medians with ranges for continuous variables or frequencies with proportions for categorical variables. The independent, or adjusted, association of baseline characteristics with either or both ITCs and

MM relative to negative SLNs were estimated using a logistic regression model with a Firth correction for sparse data. [17] Odds ratios (OR) are presented with 95% confidence intervals (CI). Analyses were conducted using SAS software (v 9.4, SAS Institute, Cary NC).

Results

In total, 576 patient charts were reviewed. Of these, 64 were excluded due to non-endometrioid histology, 38 were excluded for SLN biopsy failure, and 2 were excluded for incomplete records, leaving a total of 472 cases eligible for inclusion in the study. Within the study population, 27 patients (5.7%) were identified to have either ITCs or MM without macrometastasis upon pathologic evaluation of identified SLNs, including 10 with ITCs and 17 with MM. Macrometastasis (tumor deposits >2 mm) was identified in 15 patients (3.2%). Characteristics of these patients are found in Table 1.

	Negative	**Macrometastases**	**ITC or MM**
Total	**n (%)**	**n (%)**	**n (%)**
	430 (91)	15 (3)	27 (6)
Age (median (range))	62 (29-90)	65 (39-91)	64 (54-92)
< 50	43 (10)	1 (7)	0 (0)
50-69	281 (65)	7 (47)	19 (70)
≥ 70	106 (25)	7 (47)	8 (30)
BMI (median (range))	35.4 (16.5-64.5)	29.1 (22.9-46.0)	33.8 (21.3-53.0)
≤ 25	43 (10)	2 (13)	2 (7)
25-30	78 (18)	6 (40)	7 (26)
30-40	172 (40)	6 (40)	13 (48)
≥ 40	137 (32)	1 (7)	5 (19)
Race			
White	405 (94)	15 (100)	27 (100)
Black	9 (2)	0 (0)	0 (0)
Asian	7 (2)	0 (0)	0 (0)
Pacific Islander	3 (1)	0 (0)	0 (0)
Unknown	6 (1)	0 (0)	0 (0)
Stage			
IA	333 (77)	0 (0)	7 (26)
IB	67 (16)	0 (0)	3 (11)
II	12 (3)	0 (0)	0 (0)
IIIA	15 (3)	0 (0)	0 (0)
IIIB	2 (0)	0 (0)	0 (0)
IIIC1	0 (0)	14 (93)	17 (63)
IVB	1 (0)	1 (7)	0 (0)
FIGO Grade			
1	293 (69)	7 (50)	9 (33)

2	108 (25)	4 (29)	13 (48)
3	27 (6)	3 (21)	5 (19)
Unknown	2	1	0
Lymph vascular space invasion			
Present	62 (15)	13 (87)	19 (73)
Absent	366 (86)	2 (13)	7 (27)
Unknown	2	0	1
Depth of myometrial invasion			
Inner third	286 (69)	2 (13)	4 (15)
Middle third	83 (20)	4 (27)	11 (41)
Outer third	46 (11)	9 (60)	12 (44)
Unknown	15	0	0

Table 1: Characteristics of Patients with Negative SLNs vs Macro Metastasis vs ITCs or MM only on SLN Biopsy. Percentages that do not add up to 100 are a Result of Rounding.

The primary patient characteristics of interest were age and BMI. Race was also of interest, though the vast majority of patients (95%) were white, therefore limiting analysis. Patient age among women with ITCs or MM ranged from 54 to 92 years, with a median age of 64. By comparison, the median age of women with negative SLNs was 62. BMI ranged from 21 to 53 among women with ITCs or MM, with a median of 33.8. The median BMI for women with negative SLNs was 35.4. There was no statistical association identified between the presence of ITCs or MM and either age (OR 1.02, 95% CI 0.97-1.07) or BMI (1.02, 95% CI 0.96-1.08). This was true for ITCs alone, MM alone, or ITCs or MM combined, as shown in Table 2.

Characteristic	Odds Ratio	95% CI	P-value*
Outcome = ITC vs negative SLN (n=421, 19 excluded for missing data)			
Age	1.03	0.97, 1.10	0.3145
BMI	1.03	0.95, 1.11	0.5092
Figo Grade (2 vs 1)	1.09	0.28, 4.27	0.9005
Figo Grade (3 vs 1)	0.86	0.12, 6.01	0.8748
LVSI (Yes vs No)	9.31	2.55, 33.96	0.0007
Myometrial Invasion (middle vs inner)	1.51	0.34, 6.70	0.5865
Myometrial Invasion (outer vs inner)	3.46	0.76, 15.89	0.1101
Outcome = MM vs negative SLN (n=427, 20 excluded for missing data)			
Age	1.00	0.94, 1.05	0.9847
BMI	1.01	0.94, 1.09	0.8136
FIGO Grade (2 vs 1)	2.96	0.88, 9.96	0.0643
FIGO Grade (3 vs 1)	3.14	0.67, 14.57	0.2062
LVSI (Yes vs No)	5.52	1.80, 16.95	0.0016
Myometrial Invasion (middle vs inner)	8.92	1.67, 47.80	0.0131

Myometrial Invasion (outer vs inner)	11.54	1.99, 66.85	0.0047
Outcome = ITC or MM vs negative SLN (n=437, 20 excluded for missing data)			
Age	1.02	0.97, 1.07	0.4805
BMI	1.02	0.96, 1.08	0.5855
FIGO Grade (2 vs 1)	1.98	0.75, 5.23	0.1668
FIGO Grade (3 vs 1)	1.77	0.47, 6.59	0.3963
LVSI (Yes vs No)	7.61	3.00, 19.32	<0.0001
Myometrial Invasion (middle vs inner)	3.90	1.24, 12.28	0.0201
Myometrial Invasion (outer vs inner)	6.37	1.90, 21.37	0.0027

Table 2: Adjusted patient and disease associations with ITC, MM, or either. After adjusting for age, BMI, grade, and myometrial invasion, LVSI is significantly associated with ITCs. After adjusting for age, BMI and grade, LVSI and myometrial invasion are independently associated with MM.

Estimated OR (95% CI) and significance test from Firth corrected logistic regression model.

The primary disease characteristics of interest included tumor grade, LVSI and depth of myometrial invasion. Tumors among women with ITCs or MMs were most commonly FIGO grade 2 (48%), and about 67% were FIGO grade 2 or grade 3. LVSI was present in 73% of women with ITCs or MM. Furthermore, 44% of women with ITCs or MM had disease invade into the outer third of the myometrium (Table 1).

Compared to patients without LVSI, patients with LVSI had higher odds of SLNs positive for ITCs or MM at the time of surgical staging (OR = 7.61, 95% CI 3.00–19.32) (Table 2). Increasing depth of myometrial invasion also increased the odds of ITCs or MM (OR = 6.37, 95% CI 1.90–21.37 for outer third invasion vs inner third invasion, and OR = 3.90, 95% CI 1.24-12.28 for middle third invasion vs inner third invasion). These trends were identified for ITCs or MM combined as well as for MM alone, but only LVSI was statistically associated with ITCs alone. There was no statistical association between any low volume nodal disease group (ITCs alone, MM alone, or ITC or MM combined) and FIGO grade (OR = 1.77, 95% CI 0.47-6.59 for FIGO grade 3 vs 1 and OR = 1.98, 95% CI 0.75-5.23 for FIGO grade 2 vs 1).

Follow-up information was only available for 250 of the University of Rochester patients in the study, and of those, only 13 had ITCs or MM.

Discussion

Low volume nodal disease, encompassing both ITC and MM, identified on SLN biopsy for endometrial cancer staging remains a relatively rare finding. The prevalence in this study was 5.7%, which is consistent with the prevalence of 3-10% reported in prior literature. [6-11] The scarcity of ITCs and MM make them difficult to study, especially as it pertains to outcomes. Nonetheless, there is more to learn about the associations and implications of these disease findings and further efforts are needed to fill gaps in knowledge and guide management.

While the patient characteristics of age and BMI, as well as the disease characteristic of tumor grade, were not statistically associated with the presence of ITCs or MM, the disease characteristics of LVSI and increasing depth of myometrial invasion were correlated. Interestingly, while LVSI was associated with ITCs alone, MM alone, and ITCs or MM combined, depth of myometrial invasion was only associated with MM alone and ITCs or MM combined. This suggests that the weight of association with MM is likely the reason for the association in the combined group. The decision to treat patients with endometrial cancer and MM with adjuvant therapy is considered less controversial than the decision to treat those with ITCs, in large part due to evidence of poor outcomes associated with MM in other cancers given the limited concrete data in the endometrial cancer population. [12, 18-20] Our finding of an association between MM, but not ITCs, and the known high-risk disease feature of depth of invasion is suggestive that MM may pose a greater risk than ITCs in the endometrial cancer population, though MM and depth of invasion cannot be independently assessed in regards to outcome in our study. Other studies have found MM to be an independent risk factor, and one even found that treatment of MM improved outcomes in endometrial cancer when controlled for histopathologic features such as depth of invasion, supporting its consideration when deciding upon adjuvant therapy. [21, 22].

The association between ITCs and MM and LVSI in this study was largely unsurprising, especially considering high rates of LVSI detected in those with low volume nodal disease in the

literature. [11] Logically, it seems that LVSI should be essential for tumor cells to spread and be identified within lymph nodes. Patients with MM are typically treated regardless of LVSI, but given the findings of the current study showing a statistical correlation with LVSI and ITCs, for patients with ITCs where LVSI is not identified in the tumor, ITCs could be considered a high-risk feature, as LVSI is per the Gynecologic Oncology Group (GOG). [23] This would support consideration of ITCs when assessing treatment options. However, the entire clinical context would be important to consider, especially in light of some reports of excellent outcomes in endometrial carcinoma with ITCs without adjuvant treatment, and reports that small LVSI may not benefit from adjuvant therapy. [14-24, 25] Further outcomes-based studies are needed. While we were interested in disease recurrence rates and mortality rates for those with ITCs or MM compared to those with negative SLNs, due to a very small number of patients with low volume disease and follow-up data available, we were unable to address this question. Further investigation, likely across a larger number of institutions as in the investigation by Backes et al., is needed to expand upon outcomes associated with ITCs or MM. [11]

A strength of this study was the collaborative efforts between two major institutions, allowing data sharing and a larger study population than either institution would have been able to produce independently. However, due to the relative scarcity of low-volume nodal disease overall, low sample sizes of patients with ITCs or MM continues to be a limitation of research on this topic. The small study population also precluded the ability to differentiate MM from ITCs, as well as the ability to draw conclusions, especially regarding outcomes. The study was also limited by the date range of the available shared dataset, with the most recent cases from 2018. Another limitation was a lack of racial diversity amongst patients. The vast majority of patients within this study were white, as were all of the patients with ITCs or MM, weakening external validity. Collaboration between centers may increase the racial and ethnic diversity of patients studied and thus strengthen generalizability. In conclusion, ITCs and MM are a relatively rare finding in women with endometrial cancer. It remains unknown whether ITCs or MM significantly affect long-term recurrence and mortality, and therefore whether their identification should influence treatment. Multi-institutional collaboration with long-term follow-up will be essential to the advancement of knowledge regarding ITCs and MM in endometrial cancer moving forward.

Conflict of Interest

The authors have no conflicts of interest to disclose with the exception of Richard Moore, who is supported by research grants from the Department of Defense and Angle plc, and has received additional support from Fujirebio Diagnostics, Inc. and GlaxoSmithKline.

Author Contributions: Kaylee Underkofler: Conceptualization; Methodology; Investigation; Data Curation; Writing-Original Draft; Review; and Editing.

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Myla Strawderman: Methodology; Formal Analysis; Writing-Review and Editing

Katina Robison: Resources; Supervision; Writing- Review

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