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The effect of isolated tumor cells on adjuvant treatment decisions for patients with endometrial cancer: A retrospective case series

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A B S T R A C T

Objective: Sentinel lymph node biopsy (SLNB) for endometrial cancer staging may identify isolated tumor cells (ITCs). Although guidelines do not classify nodes with ITCs as positive, earlier papers reported that a significant proportion of gynecologic oncologists treat ITCs as they would positive nodes. The objective of this study was to examine practice patterns and determine if the presence of ITCs in endometrial cancer affects adjuvant treatment decision-making.

Methods: This was a retrospective series of patients with endometrial adenocarcinoma stages I to IIIB who underwent surgical staging with SNLB from July 2016 to January 2022 at three hospitals. The primary outcome of interest was the receipt of adjuvant treatment. Chi-square, Mann-Whitney *U* test, and logistic regression were used with significance set at $p < 0.05$.

Results: Of seven hundred thirty-four patients included, ITCs were identified in 41 patients (5.6 %). Deep myometrial invasion (61.0 % vs 20.5 %, $p < 0.001$) and lymphovascular invasion (58.4 % vs 17.7 %, $p < 0.001$) were more common in patients with ITCs than in those with negative lymph nodes. Patients with ITCs were more likely to receive adjuvant treatment (30 of 41, 73.2 % vs 289 of 693, 41.7 %, $p < 0.001$). When controlling for age, stage, histology, grade, and lymphovascular space invasion, ITCs were not associated with an increased likelihood of adjuvant therapy receipt.

Conclusions: Although patients with ITCs were more likely to receive adjuvant treatment, this was accounted for by other clinical and histological factors. Clinicians were likely to make decisions based on established risk factors, and more data are needed on the role of ITCs in the landscape of molecularly based decision making.

1. Introduction

Endometrial cancer is the most common gynecologic cancer, with an annual global incidence of over 400,000 cases (Sung et al., 2021). In the United States, both the incidence and mortality are growing, with 67,880 projected new cases in 2024 leading to 13,250 deaths (Siegel et al., 2024). Standard management for surgical staging of patients with endometrial cancer is total hysterectomy with bilateral salpingo-oophorectomy with lymph node assessment, which may include sentinel lymph node biopsy (SLNB). In selected patients, adjuvant therapy with vaginal brachytherapy (VBT), external beam radiation therapy (EBRT), chemotherapy, or some combination of the three has been shown to significantly reduce the rate of recurrence (Creutzberg et al., 2000; Keys et al., 2004; Nout et al., 2010).

Indocyanine green (ICG) is a dye used to map lymphatic channels in endometrial cancer, and has a sensitivity of 97.2 % and negative predictive value of 99.6 % for metastatic disease (Rossi et al., 2017). Standard lymph node pathological analysis involves sectioning the node and performing a hematoxylin and eosin (H&E) stain to identify metastases. Sentinel lymph nodes necessitate pathological analysis with ultrastaging, which consists of additional sectioning and staining with H&E and immunohistochemistry (IHC) to examine for low volume disease, such as micrometastases or isolated tumor cells (ITCs) (Kim et al., 2013).

Current conceptualization of metastasis describes circulating tumor cells that migrate through the blood stream and extravasate into a target organ (Fares et al., 2020). Such tumor clusters either become dormant or develop into a metastatic colonization, depending on a variety of tumor and immune signaling factors. ITCs resulting from circulating tumor cells have been described in breast cancer. Early studies in breast cancer suggested ITCs were associated with decreased recurrence free survival, and that these patients would benefit from adjuvant therapy (de Boer et al., 2009; Liikanen et al., 2018), while others demonstrated no adverse effect (Houvenaeghel et al., 2014; Ahmed et al., 2014). Breast cancer patients with ITCs are more likely to receive adjuvant therapy (Liikanen et al., 2018). However, European Society of Medical Oncology

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guidelines for breast cancer treatment do not upstage patients to node positive disease based on ITCs and recommend basing adjuvant treatment on other tumor and patient characteristics. The National Comprehensive Cancer Network guidelines do not mention ITCs in their most recent statement (Gradishar et al., 2024; Loibl et al., 2024).

Under current International Federation of Gynecology and Oncology (FIGO) guidelines, ITCs do not upstage patients to node positive disease; however, the presence of ITCs are noted in the staging as N0(i +) (Berek et al., 2023). This aligns with NCCN guidelines, which also acknowledges the importance of ongoing investigation into the management of ITCs in early-stage endometrial cancer (Abu-Rustum et al., 2023). Two early and influential studies reported no difference in short-term outcomes for patients with ITCs, suggesting that adjuvant treatment should be utilized for longstanding risk factors only (Plante et al., 2017; Backes et al., 2021). Despite this, in 2019, 21.3 % of surveyed gynecologic oncologists thought that ITCs should be treated as node positive (Chambers et al., 2019).

The current landscape is more complex. There remain no prospective studies yet reported, however several larger retrospective and database studies have suggested differences in outcomes with and without adjuvant therapy for patients with ITC as a solitary risk factor (Cucinella et al., 2023; Matsuo et al., 2024). We evaluated current practice patterns to determine if the presence of ITCs affects adjuvant treatment decisions in real-world practice.

2. Methods

2.1. Patient Selection

This was a retrospective series of all patients with endometrial cancer from July 2016 to January 2022 at three hospitals within one healthcare system, including one tertiary academic medical center and two satellite hospitals. Approval from the Institutional Review Board was obtained for this study. All patients underwent hysterectomy with or without bilateral salpingo-oophorectomy with sentinel lymph node biopsy for surgical staging of pathologically confirmed endometrial adenocarcinoma. Patients without sentinel lymph node biopsy were excluded. Pathological characterization was based on final pathology reports following hysterectomy. Patients with sarcoma and atypical endometrial hyperplasia were excluded. Surgeries were performed by one of seventeen gynecologic oncologists. Patients were identified by International Classification of Diseases 10th Revision (ICD-10) code C54.1 associated with endometrial cancer, and hysterectomy as identified by Current Procedural Terminology (CPT) codes. Patients with stages I to IIIB by 2009 FIGO stage were included; patients with lymph node positive disease (stage IIIC) or metastatic disease (stage IV) were excluded.

2.2. Variables

Demographic data including race, ethnicity, insurance status, and body mass index (BMI) were collected. Operative reports were reviewed to determine hysterectomy route, whether sentinel nodes were attempted and successfully mapped, sentinel node location, and whether full lymph node dissection was completed. Pathology and cytology reports were reviewed for histology, cytology, grade, extent of myometrial invasion, lymphovascular space invasion (LVSI), pathologic stage, lymph node positivity (macrometastases or micrometastases), and presence of ITCs. Deep myometrial invasion was defined as $\geq$ 50 %. The Cancer Staging Manual of the American Joint Committee on Cancer defines ITCs as tumor cell clusters $\leq$ 0.2 mm at the largest diameter. Micrometastases are defined as groups of cells $>$ 0.2 mm in diameter and $\leq$ 2 mm (Todo et al., 2016). Because lymph nodes with micrometastases are classified as positive and staged as at least IIIC, these patients were excluded from our study. When available, mismatch repair (MMR) status (intact, deficient, or methylated), p53, and HER2 status was recorded. For patients who underwent comprehensive molecular tumor profiling, *POLE*, microsatellite instability, and tumor mutational burden was recorded, along with actionable mutations associated with targeted therapeutics (Arend et al., 2021).

The primary outcome of interest was receipt of any adjuvant treatment. Adjuvant treatment decisions were made in discussion with a multidisciplinary tumor board of gynecologic oncologists and radiation oncologists. Treatment recommendations were based on consensus driven decision making. The ultimate treatment was determined through shared decision making with the gynecological oncologist and the patient. Treatment records were reviewed to determine whether patients underwent adjuvant treatment – VBT, EBRT, or chemotherapy – along with the treatment and dosage received.

Subset analyses were conducted to characterize treatment patterns by stage and risk categories. High-risk patients were those with non-endometrioid histology, grade 3 stage IB cancer, or stage IIIA or IIIB. High-intermediate-risk was defined by the GOG-99 criteria based on age and the following three pathologic risk factors: presence of deep myometrial invasion, grade 2 or 3, and the presence of LVSI. Patients who did not meet criteria for high-risk or high-intermediate-risk groups formed the low-risk group, for which surveillance is recommended (Keys et al., 2004).

2.3. Statistical Methods

Patients were categorized in the negative lymph node group if they had negative lymph node findings on ultrastaging and pathological analysis of at least one sentinel lymph node. Patients were included in the ITC group if they had at least one lymph node with isolated tumor cells. Percentages were calculated and comparisons between the two groups were performed using the chi-squared test for categorical variables and a Mann-Whitney *U* test for continuous variables. Logistic regression was performed to determine predictors associated with adjuvant therapies. P-values less than 0.05 were considered statistically significant. SPSS version 28 was used for statistical analysis.

3. Results

Of 1225 patients planned for hysterectomy for endometrial cancer, 734 met inclusion criteria and 491 were excluded (Fig. 1). One hundred twenty patients had positive lymph nodes and 118 patients did not have endometrial adenocarcinoma on final pathology and were excluded. Of the 987 patients with stage I through stage IIIB endometrial adenocarcinoma, full lymph node dissection of both hemipelves was performed in 120 patients (12.2 %). Sentinel node mapping was attempted in 820 patients (83.0 %). Of the 820 patients with attempted sentinel node mapping, at least one node was mapped in 734 patients (89.5 %), forming the study population. Six hundred sixteen patients of 820 (75.2 %) had nodes mapped in both hemipelves. ITCs were found in 41 of the 734 patients with at least one mapped hemipelvis (5.6 %).

There were no differences in age, BMI, race, ethnicity, insurance, or route of surgery between the ITC and the negative node group (Table 1). Deep myometrial invasion was identified in 20.5 % (n = 142) of the of the negative lymph node group, as compared to 61.0 % (n = 25) of the ITC group ($p < 0.001$). LVSI was identified in 17.7 % (n = 123) of the negative lymph node group compared to 58.4 % (n = 24) of patients in the ITC group ($p < 0.001$). There was no difference in the proportion of grade 1 cancers and endometrioid histology between the two groups.

Overall, patients in the ITC group were more likely to receive adjuvant treatment compared to the negative lymph node group (30 of 41, 73.2 % vs 289 of 693, 41.7 %, $p < 0.001$). The ITC group was more likely to receive VBT (19 of 41, 46.3 % vs 210 of 693, 30.3 %, $p = 0.031$) and EBRT (8 of 41, 19.5 % vs 47 of 693, 6.8 %, $p = 0.003$). However, the ITC group was not more likely to receive chemotherapy or multimodal therapy than the negative lymph node group (Table 2).

Similar to the overall analysis, stage I patients with ITCs were more likely than stage I patients with negative lymph nodes to receive

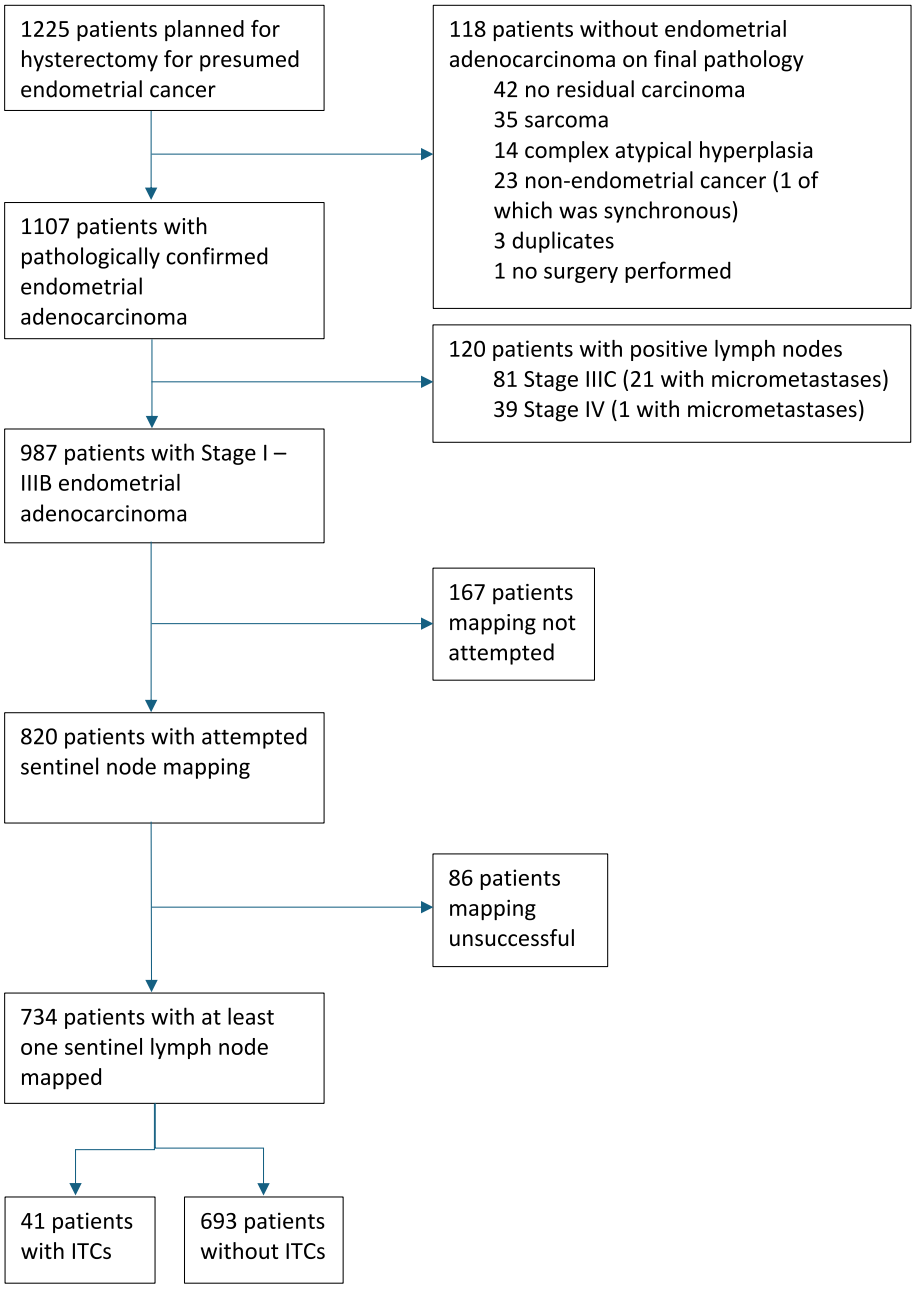

Fig. 1. Flow chart of inclusion and exclusion criteria Flow chart depicting patient characteristics that were criteria for exclusion. The two main groups used for statistical analysis were the 41 patients with isolated tumor cells (ITCs) and the 808 patients in the negative lymph node (LN) group.

adjuvant therapy (20 of 30, 66.7 % vs 236 of 633, 37.3 %). The analysis did not remain significant when patients were divided by substages – stage IA patients with ITCs were not more likely than stage IA patients with negative lymph nodes to receive adjuvant therapy. Similarly, there was no difference in treatment likelihood between ITC and negative lymph node groups within stage IB patients and stage II patients. All patients with stage IIIA disease (n = 27) were recommended adjuvant therapy; one patient did not undergo adjuvant treatment due to patient preference. Stage IIIB patients (n = 6) were all recommended adjuvant therapy. Three patients received treatment, one declined, one had rapid progression of disease, and one was lost to follow-up.

Patients were stratified into low risk, high-intermediate risk, and high risk groups. Eleven of 41 (26.8 %) ITC patients were low risk, compared to 407 of 693 (58.7 %) negative lymph node patients ($p < 0.001$). Among low risk patients, those with ITCs were not more likely to receive adjuvant treatment compared to patients with negative lymph nodes (3 of 11, 27.3 % vs 56 of 407, 13.8 %, $p = 0.204$). Seventeen of 41 (41.5 %) of ITC patients were high-intermediate risk compared to 92 of 693 (13.3 %) negative lymph node patients ($p < 0.001$). ITC patients in this group were not more likely to receive adjuvant treatment (16 of 17, 94.1 % vs 73 of 92, 79.3 %, $p = 0.148$). Thirteen of 41 (31.7 %) of ITC patients were high-risk, compared to 194 of 693 (28.0 %) of negative lymph node patients ($p = 0.608$). Within the high-risk group, ITC patients were not more likely to receive adjuvant treatment (11 of 13, 84.6 % vs 160 of 194, 82.5 %, $p = 0.844$). Of high-risk patients, two (15.4 %) patients with ITCs and 34 (17.5 %) patients with negative lymph nodes did not receive treatment ($p = 0.844$). In this group, 23 patients (63.9 %) declined treatment and 13 (36.1 %) were not recommended treatment, primarily due to medical comorbidities. In the high-intermediate-risk group, one (5.9 %) ITC patient and 19 (20.7 %) negative lymph node patients did not receive treatment ($p = 0.148$). Of these patients, six (30.0 %) declined treatment and 14 (70.0 %) were not recommended

Table 1
Patient and tumor characteristics of those with negative lymph nodes and those with isolated tumor cells.

	Negative lymph nodes N = 693	Isolated tumor cells N = 41	P-Value
Age (Median, IQR)	64 (57–71)	66 (60–70)	0.363
Body mass index (kg/m^2)	30.9 (25.7–37.0)	30.5 (26.1–35.7)	0.685
Race			0.871
White	415 (59.9)	23 (56.1)	
Black	101 (14.6)	6 (14.6)	
Asian	50 (7.2)	3 (7.3)	
Other	97 (14.0)	8 (19.5)	
Unknown	30 (4.3)	1 (2.4)	
Ethnicity			0.428
Non-Hispanic	329 (47.5)	16 (39.0)	
Hispanic	29 (4.2)	1 (2.4)	
Unknown	335 (48.3)	24 (58.5)	
Insurance			0.645
Private	274 (39.5)	13 (31.7)	
Medicaid	93 (13.4)	7 (17.1)	
Medicare	320 (46.2)	20 (48.8)	
Uninsured	5 (0.7)	1 (2.4)	
Unknown	1 (0.1)	0 (0)	
Year of surgery			0.625
2016	37 (5.3)	0 (0)	
2017	77 (11.1)	6 (14.6)	
2018	91 (13.1)	5 (12.2)	
2019	101 (14.6)	5 (12.2)	
2020	146 (21.1)	12 (29.3)	
2021	183 (26.4)	9 (22.0)	
2022	58 (8.4)	4 (9.8)	
Route of surgery			0.616
Laparoscopic	16 (2.3)	0 (0)	
Robotic	670 (96.7)	40 (97.6)	
Open	7 (1.0)	1 (2.4)	
Stage			<0.001
IA	527 (76.0)	13 (31.7)	
IB	106 (15.3)	17 (41.5)	
II	29 (4.2)	6 (14.6)	
IIIA	22 (3.2)	5 (12.2)	
IIIB	6 (0.9)	0 (0)	
Unknown Stage	3 (0.4)	0 (0)	
Grade			0.862
1	376 (54.3)	25 (61.0)	
2	121 (17.5)	6 (14.6)	
3	162 (23.4)	8 (19.5)	
Not applicable	34 (4.9 %)	2 (4.9 %)	
Histology			0.818
Endometrioid	530 (76.5)	32 (78.0)	
Non-endometrioid	163 (23.5)	9 (22.0)	
Mismatch repair status			0.283
Intact	503 (72.6)	33 (80.5)	
Deficient	39 (5.6)	1 (2.4)	
Methylated	125 (18.0)	4 (9.8)	
Not performed/unknown	26 (3.8)	3 (7.3)	
Lymphovascular space invasion			<0.001
None	542 (78.2)	14 (34.1)	
Present	123 (17.7)	24 (58.5)	
Indeterminate	28 (4.0)	3 (7.3)	
Myometrial invasion			<0.001
None	289 (41.7)	3 (7.3)	
<50 %	261 (37.7)	13 (31.7)	
≥50 %	142 (20.5)	25 (61.0)	
Indeterminate	1 (0.1)	0 (0.0)	

Selected patient and tumor characteristics in patients with negative lymph nodes as compared to those with isolated tumor cells. The continuous variables of age and body mass index are shown as median and interquartile range (IQR) with significance calculated using the Mann-Whitney *U* test. Discrete variables are listed as number and percentage of patients in each subcategory with significance calculated using the chi squared test.

Table 2
Adjuvant treatment for patients with negative lymph nodes and those with isolated tumor cells.

	Negative Lymph Node N = 693	Isolated tumor cells N = 41	P-Value
Any treatment			<0.001
No	404 (58.3)	11 (26.8)	
Yes	289 (41.7)	30 (73.2)	
Vaginal brachytherapy			0.031
No	483 (69.7)	22 (53.7)	
Yes	210 (30.3)	19 (46.3)	
External beam radiation therapy			0.003
No	646 (93.2)	33 (80.5)	
Yes	47 (6.8)	8 (19.5)	
Chemotherapy			0.212
No	562 (81.1)	30 (73.2)	
Yes	131 (18.9)	11 (26.8)	

Number and percentage of patients with negative lymph node and patients with isolated tumor cells who received each type of adjuvant treatment.

treatment. Reasons for which high-risk and high-intermediate-risk patients declined treatment included concerns about toxicity, and financial or social barriers to accessing care.

Eight of 41 (19.5 %) patients with ITCs had greater than one lymph node with ITCs. These patients were not more likely than those with just one ITC positive node to receive treatment (5 of 8, 62.5 % vs 25 of 33, 75.7 %, p = 0.753).

There were no differences in p53 status (p = 0.587) or MMR status (p = 0.283) between the ITC and lymph node negative group. The rate of next generation sequencing was low for the entire study population; overall, 42 patients (5.7 %) had next generation sequencing performed, of which only one had ITCs.

A regression analysis for adjuvant treatment receipt was performed (Table 3). ITCs were associated with receiving adjuvant therapy (OR 3.81, 95 % CI 1.88–7.73) on univariate analysis. Age, stage, non-endometrioid histology, grade, and LVSI were associated with receiving adjuvant therapy on univariate analysis. A multivariate regression accounting for all the above variables was performed in which ITCs were not independently associated with an increased likelihood of receiving adjuvant therapy (OR 1.92, 95 % CI 0.67–5.49). Compared to endometrioid histology, non-endometrioid histology was associated with receipt of adjuvant therapy (OR 2.72, 95 % CI 1.31–5.66). Using grade 1 as the reference, grade 2 (OR 5.47, 95 % CI 3.12–9.58) and grade 3 (OR 25.51, 95 % CI 12.45–52.26) were associated with increased likelihood of adjuvant therapy. Compared to no LVSI, present LVSI (OR 2.21, 95 % CI 1.19–4.12) was associated with receipt of adjuvant therapy.

A sensitivity analysis was performed to evaluate the effect of ITCs on the receipt of each adjuvant treatment. The presence of ITCs led to an increase in VBT and EBRT on univariate analysis, but not multivariate analysis. ITCs did not impact the use of chemotherapy on either univariate or multivariate analysis.

4. Discussion

In this study, we examined adjuvant treatment practice patterns in the presence of ITCs at three institutions. Of patients with stage IA through IIIB endometrial cancer who underwent sentinel lymph node

Table 3
Regression analysis for receipt of adjuvant treatment.

	Unadjusted OR	95 % CI	Adjusted OR	95 % CI
Age	1.07	1.05–1.08	1.03	1.00–1.05
Isolated tumor cells	3.81	1.88–7.73	1.92	0.67–5.49
Stage				
IA	Reference		Reference	
IB	10.70	6.56–17.47	15.06	8.04–28.22
II	40.62	9.63–171.32	76.55	15.93–367.79
IIIA	64.00	8.61–475.72	46.61	5.32–408.04
IIIB	2.46	0.49–12.33	0.35	0.05–2.38
Unknown stage	1.23	0.11–13.67	1.10	0.04–27.17
Non-endometrioid histology	10.82	6.99–16.74	2.72	1.31–5.66
Grade				
1	Reference		Reference	
2	3.54	2.31–5.41	5.47	3.12–9.58
3	26.58	15.96–44.25	25.51	12.45–52.26
Not applicable	19.75	7.95–49.06	13.18	3.93–44.21
Lymphovascular space invasion				
Absent	Reference		Reference	
Present	5.93	3.92–8.99	2.21	1.19–4.12
Indeterminate	2.67	1.28–5.56	2.46	0.92–6.61

Univariate logistic regression was performed for each variable to calculate the unadjusted odds ratio (OR) and 95% confidence interval (CI) for the receipt of any adjuvant treatment. Multivariate regression with all variables was performed to find the adjusted ORs.

biopsy for cancer staging, ITCs were found in 5.6 % of patients and were associated with deep myometrial invasion and LVSI. Patients with ITCs were more likely to receive adjuvant therapy than patients with negative lymph nodes. However, when controlling for age, stage, histology, grade, and LVSI, the presence of ITCs did not affect clinician treatment decisions. Stage higher than stage IA, grade greater than 1, non-endometrioid histology, and presence of LVSI were significantly correlated with receipt of adjuvant therapy.

The rate of ITCs in this study was 5.6 %, similar to other studies which report ITC rates of 3–10 % (Backes et al., 2021). In our cohort, ITCs were most common in stage I patients with grade 1, endometrioid histology. Factors found to be associated with ITCs were LVSI and deep myometrial invasion. LVSI was present in 58.5 % of patients with ITCs and deep myometrial invasion was present in 61.0 %. In the literature, 33–68 % of patients with ITC had LVSI (Plante et al., 2017; Castellano et al., 2021). LVSI is an established independent risk factor for nodal metastasis (Jorge et al., 2016), which may explain its association with ITCs. In another study of stage I-II patients with at least one risk factor for recurrence, myometrial invasion was significantly associated with ITC and micrometastases ($p = 0.028$) (Todo et al., 2016).

Despite its association with disease factors associated with recurrence, data remains mixed on whether ITCs are prognostic for recurrence. The first retrospective review reported was a single institutional study which showed progression free survival at three years for patients with ITCs was 95.5 %, similar to patients with node negative (87.6 %) and micrometastastic disease (85.5 %) and higher than patients with macrometastasis (58.5 %, $p = 0.0012$) (Plante et al., 2017). Other multi-institutional retrospective studies suggest that ITCs do not confer additional risk, as adjuvant treatment did not significantly affect recurrence free survival in patients with ITCs and low risk tumor characteristics (Backes et al., 2021; Ghoniem et al., 2021).

More recent literature has reported conflicting results, particularly for patients with ITCs and no other indication for adjuvant therapy. A large international multicenter retrospective study evaluated low-risk patients who did not undergo post-operative treatment. In this study, patients with ITCs had worse recurrence-free survival compared to node negative patients (85.1 % vs 90.2 %, $p < 0.01$), despite similar overall survival rates (96.8 % vs 94.9 %, $p = 0.80$) (Cucinella et al., 2023). A National Cancer Database (NCDB) study had similar results, with adjuvant therapy in low-risk patients with ITCs associated with statistically improved short-term overall survival (100 % vs 95.9 %, $p = 0.03$) (Matsuo et al., 2024). Prospective data is needed to clarify the optimal management of low-grade endometrial cancer with ITCs.

Given the limitations of the current evidence, it is not surprising that the management of ITCs is an area of interest. In 2019, 21.3 % of surveyed gynecologic oncologists thought that ITCs should be treated as node positive (Chambers et al., 2019). In a recent Surveillance, Epidemiology, and End Results (SEER) database study of patients with early-stage endometrial cancer, patients with ITCs were more likely to receive adjuvant therapy (81.8 % vs 31.7 %, $p < 0.001$) compared to a node-negative group adjusted for similar background tumor factors (Matsuo et al., 2022). This suggests that clinicians may adjust recommendations for adjuvant therapy based on ITCs. This contrasts with the low-risk group of our study, in which patients with ITCs were not more likely to receive adjuvant therapy (27.3 % vs 13.8 %, $p = 0.204$).

In our cohort, there were high-risk and high-intermediate-risk patients who did not receive adjuvant therapy, although treatment is usually indicated for these patients. There were also low-risk patients, both with and without ITCs who received treatment, although treatment is usually not indicated. This highlights that physicians may weigh clinical factors not included in guidelines when making treatment decisions. In other cases, patients declined the recommended treatment for various reasons including concern for toxicity, financial burden, or progression of disease.

As the molecular landscape of endometrial cancer becomes better integrated into practice, more information may be elucidated regarding the role of ITCs in tumorigenesis. The Cancer Genome Atlas (TCGA) classified endometrial cancer into four subtypes driven by molecular changes and with prognostic implications, which reflects the trend towards relying on molecular characteristics to inform treatment decisions (Cancer Genome Atlas Research N et al., 2013). Currently, studies are ongoing to determine the role of molecular subtypes in the adjuvant treatment of endometrial cancer (van den Heerik et al., 2020; Consortium RR, 2022). Moreover, the 2023 FIGO staging incorporates new information regarding pathological and molecular factors and continue to note the presence of ITCs without incorporating into staging (Berek et al., 2023). The guidelines reiterate the prognostic significance of ITCs remains unclear.

This study has several strengths including the patient population available for inclusion. The three hospitals included in the study are in areas with different demographics and resources, contributing to diversity in the patient population and increasing the generalizability. Further, strict inclusion criteria and review of individual operative and pathology reports increases rigor and provides insight into individual treatment decisions.

There were also several limitations to the study. It is important to note the potential bias arising from the three hospitals existing within the same healthcare system, resulting in alignment of provider treatment attitudes and limiting the generalizability of the study population. Further, only 41 patients with ITCs were identified, resulting in a small sample size that limited statistical power, especially for subgroup analyses. As the study attempted to analyze clinician treatment decision based on chart review, variables may have been factored into the decision-making process that were not recorded and therefore unable to be analyzed. The outcome of interest was of the receipt of adjuvant treatment, which differs from recommendations for adjuvant treatment. Only six percent of patients had tumor molecular testing by next generation sequencing, as this was only approved for advanced and recurrent endometrial cancer during the time period included in this study. However, this may be similar to real world test utilization, wherein stage I, low grade patients are less likely to obtain molecular profiling.

5. Conclusion

Although patients with ITCs were more likely to receive adjuvant treatment, this was accounted for by other clinical and histological factors. Despite the lack of prospective evidence on the role of adjuvant therapy in patients with ITCs, clinical practice patterns align with the current treatment guidelines and do not reflect additional treatment for ITCs alone. This hypothesis generating study underscores the need for additional data to understand the associations between ITCs and outcomes in endometrial cancer.

CRediT authorship contribution statement

Camryn Kenkel: Writing – original draft, Visualization, Investigation, Formal analysis. **Sarah S. Lee:** Writing – review & editing, Methodology, Conceptualization. **Naaman Mehta:** Investigation. **Jude Nawlo:** Investigation. **Edward Jimenez:** Writing – review & editing, Supervision. **Leslie R. Boyd:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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