Low-volume lymphatic metastasis (isolated tumor cells) in endometrial cancer: management and prognosis

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CASE PRESENTATION

A 58-year-old patient G₁P₁ presented with intermittent postmenopausal vaginal bleeding that started in August 2016. She underwent an office endometrial biopsy with her local gynecologist, which revealed a Federation of Gynecology and Obstetrics (FIGO) grade 1 endometrioid endometrial carcinoma. She was then referred for further evaluation and treatment. At the time of presentation in February 2017, the patient reported persistent mild vaginal bleeding. She denied any other symptoms. Past medical history was significant for hypertension and hypothyroidism. Surgical history was significant for tonsillectomy. Family history was significant for breast cancer in a paternal aunt. Her body mass index was 37 kg/m². Bimanual pelvic examination revealed a mobile uterus and no other abnormalities. This patient had a CT scan of the abdomen and pelvis performed by her local gynecologist, which showed a uterus measuring 8.5×6×5 cm; there was no evidence of extrauterine metastases. For patients with low-grade cancer at our institution, we do not routinely perform pre-operative CT scans. For patients with high-grade endometrial cancer, we perform preoperative CT scan of the chest, abdomen, and pelvis.

We discussed with the patient that the first step towards management of her endometrial cancer would be surgical staging. This includes a total hysterectomy, bilateral salpingo-oophorectomy, and bilateral sentinel pelvic lymph node excision. We discussed the possibility of requiring a full pelvic node dissection if the sentinel nodes were not detected bilaterally. We discussed that we will plan to perform

this via a minimally invasive approach. Risks, benefits, and alternatives to surgery were discussed. She was also made aware that she might require adjuvant treatment based on the final surgical stage.

Dr Mariani: Would you comment on surgical approach and consideration for open versus minimally invasive. In addition, would your recommendation be different if the patient had presented with a type II endometrial cancer?

The Gynecology Oncology Group (GOG) LAP2 trial was a large randomized study that compared laparoscopy and laparotomy for women with clinical stage I to IIA endometrial cancer.¹ Women who underwent laparoscopy had fewer moderate to severe post-operative adverse events with no difference in 5-year recurrence rates and overall survival. In a subgroup analysis evaluating type 2 endometrial cancers, there was no difference in oncologic outcomes. The Laparoscopic Approach to Cancer of the Endometrium (LACE) trial was another large study comparing open versus minimally invasive hysterectomy in patients with endometrial cancer and found no difference in disease-free survival and overall survival for women who underwent laparoscopy as compared with those who underwent laparotomy.² Based on these trials, there is no evidence that minimally invasive surgery worsens oncologic outcomes in endometrial cancer. Multiple retrospective studies also support these findings. Therefore, minimally invasive surgery should be the treatment of choice in endometrial cancer.

The patient underwent robotic hysterectomy, bilateral salpingo-oophorectomy, and bilateral sentinel

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Figure 1 Hematoxylin and eosin (A, B) Endometrial FIGO grade 1 endometrioid adenocarcinoma.

pelvic lymph node biopsy on March 16, 2017. There was no evidence of any enlarged pelvic lymph nodes at the time of surgery. Operative time was 173 min and estimated blood loss was 75 mL. There were no intra-operative or post-operative complications. The patient was discharged on post-operative day 1. Final pathology demonstrated a 2.4 cm FIGO grade 1 endometrioid type endometrial carcinoma invading 2 out of 22 mm myometrium. There was no evidence of lymphovascular invasion. A total of four sentinel lymph nodes were removed. Two right sentinel lymph nodes, located along the external iliac artery, were identified and removed. One right sentinel pelvic lymph node had isolated tumor cells identified both on hematoxylin and eosin (H&E) and on keratin-stained sections. Two left sentinel pelvic lymph nodes, removed from the obturator fossa, were negative for malignancy. Peritoneal cytology was negative for cancer.

Dr Narasimhulu: What is the value of routine cytology in patients undergoing surgery for endometrial cancer?

Women with positive cytology and risk factors such as non-endometrioid histology, high-grade, lymphovascular space invasion, deep myometrial invasion, and uterine serosal involvement have a high risk of distant failure. Women with positive cytology as the only sign of extrauterine disease have a lower risk of recurrence if they do not have these risk factors. These findings have been demonstrated in multiple retrospective studies.^{3,4} This is why we continue to perform cytology even though it is no longer part of staging.

Drs Swanson and Schoolmeester: Please provide details on pathological findings

The hysterectomy specimen showed a well-differentiated endometrial proliferation with glandular architecture and invasion into underlying myometrium (Figure 1A,B). The tumor cells had uniformly low-grade features as shown by mild to moderate atypia, minimal pleomorphism, and inconspicuous nucleoli. The findings were diagnostic of endometrioid carcinoma, FIGO grade 1. Mismatch repair protein immunohistochemistry demonstrated loss of MLH1 and PMS2 and retention of MSH2 and MSH6. Further testing found loss of MLH1 protein expression was probably due to somatic/epigenetic inactivation of MLH1, resulting in promoter hypermethylation. The tumor cells were identified on H&E in one of four sentinel lymph nodes as single cells and in small clusters and stained positively for keratin AE1/AE3, representing isolated tumor cells (Figure 2A,B).

Dr Narasimhulu: Please provide details as to whether performing mismatch repair protein evaluation should be routine and what are the clinical implications of these findings?

About 31% of all endometrial cancers are mismatch repair deficient, the majority of which are sporadic and commonly due to MLH1 promoter hypermethylation.⁵ Approximately 2–3% of patients with endometrial cancer have Lynch syndrome, an autosomal dominant inherited cancer susceptibility syndrome. It is important to identify patients with Lynch syndrome in order to screen for other cancers and identify family members at risk. Patients with mismatch repair deficiency are also candidates for immunotherapy in the setting

Figure 2 Hematoxylin and eosin (A) shows a lymph node with isolated tumor cells, highlighted by keratin AE1/AE3 immunohistochemical stain (B).

Case study

of advanced or recurrent disease. For these reasons, performing mismatch repair protein evaluation should be routine for patients with endometrial cancer.

Dr Narasimhulu: Please describe the definition of isolated tumor cells and micrometastasis

Pathologic ultrastaging is an important part of the sentinel lymph node assessment algorithm. This has led to the detection of more low-volume metastasis than with the traditional pathologic evaluation of lymph nodes. Low-volume metastases are classified based on the size of the largest tumor in the lymph nodes: they are called isolated tumor cells when ≤ 0.2 mm and micrometastasis when the size is between >0.2 and ≤ 2 mm. Approximately half of all sentinel lymph node metastasis are low-volume metastases.⁶ Many of these might not have been detected if not for the pathologic ultrastaging.

The size of lymphatic metastases correlates with the risk of additional non-sentinel pelvic and para-aortic lymph node dissemination, with greater risk for macrometastasis.^{7,8} Some patients have low-volume metastasis with more than one cluster of tumor cells, each of which are ≤ 0.2 mm, while some have only one cluster of tumor cells. The prognostic significance of more than one deposit of low-volume metastasis is not known at this point.

Strategies for pathologic ultrastaging, including the number of level sections examined by H&E staining, the depth of sectioning into the tissue block, the interval between sections, and the use of immunohistochemistry to identify tumor cells not noted on H&E alone, all vary among institutions. The Memorial Sloan Kettering algorithm consists of an initial evaluation by H&E, and if negative, two adjacent 5 μ m sections (one H&E and one cytokeratin AE1/AE3) cut from each paraffin block at each of two levels 50 μ m apart.⁹

Frozen section has low sensitivity (41–50%) in detecting metastases in the lymph nodes.¹⁰ The size of the lymphatic metastasis is the most important factor related to its detection at frozen section. In addition, identification of positive sentinel nodes by frozen section does not change our intra-operative approach. However, frozen section is useful to identify the absence of lymph node tissue in the sentinel node biopsy specimen ('empty node'). Therefore, frozen section can be used to identify empty nodes and reduce the occurrence of inadequate staging. Of note, the frozen section evaluation should not be to determine whether there is evidence of disease but rather to determine if there is actual lymph node tissue in the packet.

Dr Narasimhulu: What is the risk of recurrence in patients with low-volume metastasis? How does this compare with the risk of recurrence among patients with macrometastasis?

Several groups have published studies on the outcomes of patients with low-volume metastasis in the sentinel lymph nodes. Most patients have been treated with adjuvant chemotherapy and/or radiation. When treated, their survival is similar to patients with negative nodes, and prognosis is improved in comparison with patients with macrometastasis in the lymph nodes.^{6,11} In a retrospective study including 844 patients, the 3-year recurrence-free survival was 90% for node-negative patients, 86% for patients with isolated tumor cells, 86% for micrometastasis, and 71% for macrometastasis.⁶ There are subsets of patients with isolated tumor cells and low-risk disease (stage I low-grade endometrioid endometrial cancer) who seem to do well without adjuvant treatment

or brachytherapy only.^{6,12} However, one should be careful with the interpretation of the available data, because the numbers are small, the follow-up is still limited, and there is a suggestion that disease in patients with low-volume metastasis may recur late.¹³ Todo et al performed ultrastaging on patients who underwent complete lymphadenectomy and reported that the median time to recurrence for women with isolated tumor cells or micrometastases was 49 months.¹³

Dr Narasimhulu: What would you recommend for further workup of this patient?

It is important to point out that the sentinel lymph node evaluation algorithm specifies that any enlarged lymph nodes have to be removed. This patient already had a pre-operative CT scan of the abdomen and pelvis which ruled out loco-regional and distant metastatic disease. Therefore, no additional imaging is required at this point. In the absence of pre-operative imaging, it is our practice to obtain a CT scan of the abdomen and pelvis for patients with isolated tumor cells or micrometastases.

Dr Mariani: What were your treatment recommendations for this patient?

At our institution, we review all patients with isolated tumor cells at tumor board. This gives us an opportunity to review the slides with our pathology colleagues to confirm the diagnosis of isolated tumor cells. We also evaluate other uterine pathologic risk factors. This patient had none. She had a grade 1 tumor with 9% myometrial invasion and no lymphovascular invasion. We planned for observation. Our recommendation is based on limited published data on very small cohorts of patients with grade 1 and 2 endometrioid endometrial cancer who received no adjuvant treatment or brachytherapy only and who have had no recurrences during a still limited follow-up time.^{6,14} We had a discussion with the patient to make her aware of the very limited data available in the literature and the uncertainty related to this decision.

Dr Mariani: Would you treat the patient differently if she had other uterine risk factors?

Aloisi et al reported that the recurrence rate was lower for women with isolated tumor cells in pelvic lymph nodes (12/71, 17%) than for those with micro/macrometastasis (50/135, 37%) with median follow-up of 32 months.¹⁵ A total of 69 of 71 patients with isolated tumor cells in this series received adjuvant therapy with chemotherapy, external beam radiation, or both. Of the 12 patients with isolated tumor cells that recurred, histology was as follows: eight were non-endometrioid or grade 3 tumors, two were grade 2 endometrioid, and two were grade 1 endometrioid. For this reason, when patients with grade 3 or non-endometrioid tumors have isolated tumor cells, we treat them as stage IIIC disease with a combination of pelvic radiation and chemotherapy with carboplatin and paclitaxel for six cycles.

Dr Mariani: Would you treat the patient differently if she had micrometastasis rather than isolated tumor cells?

Currently, we consider patients with micrometastases as stage IIIC disease and recommend a combination of pelvic radiation and chemotherapy with six cycles of carboplatin and paclitaxel. At our institution, we administer external radiation between cycle 3 and cycle 4 of the chemotherapy in a 'sandwich' fashion. This is

different from the sequencing used in the large endometrial cancer trials. We observed that chemotherapy was well tolerated (94.9% completed more than four chemotherapy cycles) and local control was not compromised despite delaying radiation until after three cycles of chemotherapy.¹⁶ For comparison, when chemotherapy was administered following pelvic radiation, only 71% of patients in the Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) 3 trial and 75% of patients in the GOG 258 trial completed four cycles of chemotherapy.

Dr Mariani: Is there any role for completion pelvic lymphadenectomy?

We know that there is a 34.8% risk of additional metastases in other pelvic and para-aortic lymph nodes when the sentinel lymph nodes are positive.⁸ However, this risk seems to be relatively low (5%) in the presence of low-volume metastases in the sentinel nodes.⁸ Multinu et al recently combined the data from two institutions (Mayo Clinic and the Memorial Sloan Kettering Cancer Center), comparing different nodal assessments for endometrial cancer.¹⁷ The authors included 104 patients with non-bulky stage IIIC endometrial cancer (patients with isolated tumor cells were not included). Of these, 48 patients had systematic pelvic and para-aortic lymphadenectomy and 56 patients were treated applying the sentinel lymph node algorithm. The risk of progression was not significantly different between the two cohorts (HR=1.27; 95% CI 0.60 to 2.67). The authors observed a lower risk of para-aortic progression (HR=0.27; 95% CI 0.05 to 1.42) in the lymphadenectomy group; however, this was not statistically significant, and did not translate into an improvement in overall survival. In this study, the most important and independent predictor of poor prognosis was the presence of aggressive biologic characteristics of the tumor (high grade, type II histology, or depth of myometrial invasion). Also, administration of combined adjuvant therapy (chemotherapy combined with radiotherapy) decreased the rate of recurrences. From these data,¹⁷ it appears that, even in patients with lymphatic metastases, the risk of pelvic recurrence or survival was not significantly improved by removal of non-sentinel nodes. Therefore, it is even less likely that completion lymphadenectomy would help in patients with isolated tumor cells in the sentinel nodes. However, most patients in the study received adjuvant treatment, as they had positive lymph nodes, and the administration of combined adjuvant treatment with radiation and chemotherapy was an important predictor of improved oncologic outcome.

At this time, we consider that there is no evidence supporting completion lymphadenectomy. There is the uncertainty of missing microscopic lymphatic occult metastatic residual disease in the pelvis if the patient does not receive any external radiation or chemotherapy. However, this risk is reasonably low (5%) in the presence of isolated tumor cells and low-grade tumor.⁷ In addition, two randomized studies have failed to demonstrate a survival benefit of pelvic lymphadenectomy in patients with early-stage endometrial cancer.

Dr Mariani: What about performing para-aortic lymphadenectomy?

According to historical Mayo Clinic data, approximately two-thirds of patients with positive pelvic lymph nodes have para-aortic dissemination. Thus, if we do not target the para-aortic area, potential

metastatic disease might be missed. However, the risk of para-aortic dissemination is significantly low (11.1%) in patients with microscopic lymph node metastases and no uterine risk factors.⁷ Also, it is true that in the study by Multinu et al we observed a non-significant trend for a higher rate of para-aortic recurrences in the sentinel lymph node cohort, but this did not translate into a survival advantage.¹⁷ This finding emphasizes that a large fraction of para-aortic recurrences are associated with concomitant distant dissemination,¹⁵ which is unlikely to be controlled by a radical treatment of the para-aortic area with surgery and radiation.

Therefore, we suggest that additional treatment of the para-aortic area with surgery and/or radiation is very unlikely to provide an improvement of oncologic outcomes in our patient, due to the very low estimated risk of para-aortic dissemination. Also, even when microscopic para-aortic dissemination is found, a radical treatment of the para-aortic area with surgery and/or radiation, though possibly preventing a para-aortic recurrence, is unlikely to provide a survival advantage.

Dr Mariani: What is the plan for surveillance in this patient?

There are no specific guidelines for surveillance of patients with isolated tumor cells. However, at the Mayo Clinic, if a patient with isolated tumor cells is receiving only vaginal brachytherapy or observation, we recommend surveillance with CT scans of the abdomen and pelvis every 6 months, to possibly detect early recurrences. This recommendation is based on group consensus at our institution, but prospective data are still lacking.

CLOSING SUMMARY

The concept of isolated tumor cells in endometrial cancer is relatively new and more studies are needed to determine optimal management of these patients. The incidence of isolated tumor cells is low (5.9% in a large cohort of patients with clinical stage I serous or endometrioid endometrial cancer).¹⁸ Pooling data from multiple institutions is important to improve our understanding of this entity.

At the Mayo Clinic, when we started caring for patients with isolated tumor cells, most women received adjuvant treatment (chemotherapy or external radiotherapy or both). We are now offering observation to those women who are otherwise low risk (grade 1 endometrioid, without lymphovascular space invasion, and no other evidence of disease outside of the uterine corpus—apart from isolated tumor cells in the sentinel nodes). This is what has been recommended for our patient. However, available data in the literature are still very limited, and more studies are required before providing definitive recommendations.

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REFERENCES

- 1 Walker JL, Piedmonte MR, Spirtos NM, *et al.* Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group study LAP2. *J Clin Oncol* 2009;27:5331–6.
- 2 Janda M, Gebiski V, Davies LC, *et al.* Effect of total laparoscopic hysterectomy vs total abdominal hysterectomy on disease-free survival among women with stage I endometrial cancer: a randomized clinical trial. *JAMA* 2017;317:1224–33.
- 3 Mariani A, Webb MJ, Keeney GL, *et al.* Assessment of prognostic factors in stage IIIA endometrial cancer. *Gynecol Oncol* 2002;86:38–44.
- 4 Havrilesky LJ, Secord AA, O'Malley DM, *et al.* Multicenter analysis of recurrence and survival in stage IIIA endometrial cancer. *Gynecol Oncol* 2009;114:279–83.
- 5 Bonneville R, Krook MA, Kautto EA, *et al.* Landscape of microsatellite instability across 39 cancer types. *JCO Precis Oncol* 2017;2017:PO.17.00073:1–15.
- 6 Plante M, Stanleigh J, Renaud M-C, *et al.* Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: does adjuvant treatment matter? *Gynecol Oncol* 2017;146:240–6.
- 7 Zanfagnin V, Huang Y, Mc Gree ME, *et al.* Predictors of extensive lymphatic dissemination and recurrences in node-positive endometrial cancer. *Gynecol Oncol* 2019;154:480–6.
- 8 Touhami O, Trinh X-B, Gregoire J, *et al.* Predictors of non-sentinel lymph node (non-SLN) metastasis in patients with sentinel lymph node (SLN) metastasis in endometrial cancer. *Gynecol Oncol* 2015;138:41–5.
- 9 Casarin J, Multinu F, Pasupathy K, *et al.* Frozen section for detection of lymph nodes after cervical injection with indocyanine green (ICG) for sentinel lymph node technique in endometrial cancer staging. *Ann Surg Oncol* 2018;25:3692–8.
- 10 Pristauz G, Bader AA, Regitnig P, *et al.* How accurate is frozen section histology of pelvic lymph nodes in patients with endometrial cancer? *Gynecol Oncol* 2009;115:12–17.
- 11 St Clair CM, Eriksson AGZ, Ducie JA, *et al.* Low-volume lymph node metastasis discovered during sentinel lymph node mapping for endometrial carcinoma. *Ann Surg Oncol* 2016;23:1653–9.
- 12 Backes FJ, Felix AS, Grégoire J, *et al.* Sentinel lymph node (SLN) isolated tumor cells (ITCs) in otherwise stage I/II endometrioid endometrial cancer: to treat or not to treat? *Gynecol Oncol* 2018;149:7–8.
- 13 Todo Y, Kato H, Okamoto K, *et al.* Isolated tumor cells and micrometastases in regional lymph nodes in stage I to II endometrial cancer. *J Gynecol Oncol* 2016;27:e1.
- 14 Goebel EA, St Laurent JD, Nucci MR, *et al.* Retrospective detection of isolated tumor cells by immunohistochemistry in sentinel lymph node biopsy performed for endometrial carcinoma: is there clinical significance? *Int J Gynecol Cancer* 2020;30:291–8.
- 15 Aloisi A, Casanova JM, Tseng JH, *et al.* Patterns of FIRST recurrence of stage IIIC1 endometrial cancer with no PARAAORTIC nodal assessment. *Gynecol Oncol* 2018;151:395–400.
- 16 Narasimhulu DM, Block MS, Weaver AL, *et al.* Chemotherapy before radiation for women with stage IIIC endometrial cancer receiving combined adjuvant chemotherapy and radiation. *Gynecol Oncol* 2020;159:227–8.
- 17 Multinu F, Ducie JA, Eriksson AGZ, *et al.* Role of lymphadenectomy in endometrial cancer with nonbulky lymph node metastasis: comparison of comprehensive surgical staging and sentinel lymph node algorithm. *Gynecol Oncol* 2019;155:177–85.
- 18 Mueller JJ, Pedra Nobre S, Braxton K, *et al.* Incidence of pelvic lymph node metastasis using modern FIGO staging and sentinel lymph node mapping with ultrastaging in surgically staged patients with endometrioid and serous endometrial carcinoma. *Gynecol Oncol* 2020;157:619–23.