





Isolated tumor cells in low-risk endometrial cancer: are we ready for treatment decisions in 'isolation'?

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Low-volume disease in the lymph nodes is categorized as either micrometastases or isolated tumor cells. Does the presence of isolated tumor cell impact the decision on adjuvant treatment or not? Neither the FIGO 2009 staging nor the recently updated FIGO 2023¹ staging incorporates isolated tumor cells as part of the routine staging of patients with endometrial cancer. Additionally, ESGO treatment guidelines² do not include isolated tumor cells as a factor in their treatment strategy decision. This is based on earlier literature that identified no prognostic implications associated with isolated tumor cells.

Gómez-Hidalgo et al carried out a meta-analysis to explore the incidence of low volume disease in the lymph nodes following lymphatic mapping and to identify patterns in post-operative care. The study encompassed eight investigations involving 286 participants, of which 99 had isolated tumor cells. Adjuvant therapies were administered to 72% of the participants, and those with low volume disease exhibited a heightened relative risk of recurrence (relative risk (RR) 1.34, 95% confidence interval (CI) 1.07 to 1.67). The study unfortunately did not provide conclusive insights into the potential association between isolated tumor cells and heightened recurrence rates. This limitation arises from the inherent constraints associated with the article's design and scope. What's more, in that study cases with isolated tumor cells were associated with uterine factors that lead to increased risk of recurrence.³ Backes et al published a retrospective multicenter study investigating stage I/II endometrioid endometrial cancer with isolated tumor cells detected via sentinel lymph node mapping.⁴ The study included 175 patients with isolated tumor cells, with 49% of the patients being stage IA, 39% stage IB, and 12% stage II. Treatment distribution included 43% who received no adjuvant or brachytherapy alone, 12% who underwent external beam radiation, and 45% who received chemotherapy. A total of 5.1% of patients experienced recurrences. The occurrence of extravaginal recurrences was comparable between patients who did and did not receive chemotherapy (5.2% vs 3.8%, $p=0.68$). On adjusting for stage, lymphovascular space invasion,

and grade, it was found that chemotherapy and pelvic radiotherapy were not significantly associated with recurrence-free survival (hazard ratio (HR) 0.63, 95% CI 0.11 to 3.52; and HR 0.90, 95% CI 0.22 to 3.61, respectively). Additionally, neither the type of lymph node dissection nor the method of isolated tumor cell detection showed any association with recurrence-free survival. Overall, in the majority of published studies, adjuvant treatment is administered largely depending on uterine risk factors.

With the introduction of sentinel lymph node mapping, isolated tumor cells are increasingly identified in routine practice. This has sparked a debate about whether adjuvant treatment should be administered when isolated tumor cells are the only known risk factor in a patient or whether it increases the patient's risk of recurrence with other known risk factors. Based on data from Matsuo et al investigating National Cancer Institute's Surveillance, Epidemiology and End Result Program,⁵ it was shown that isolated tumor cells were more prone to receiving adjuvant treatment (81.8% vs 31.7%, $p<0.001$). Comparable correlations were noted within the low-risk category, encompassing stage IA, grade 1, and two endometrioid tumors (78.4% vs 9.2%, $p<0.001$).

In this month's issue of the International Journal of Gynecological Cancer, Cucinella et al conducted this multicenter retrospective study comparing the prognosis of patients with negative nodes versus those with isolated tumor cells in sentinel lymph nodes who are considered low risk; namely FIGO 2009 IA cases with endometrioid grade 1 or 2.⁶ From 15 centers worldwide, 494 patients (42 isolated tumor cells and 452 node negative) were included. Twenty-one recurrences (4.3%) were identified, including in five patients with isolated tumor cells and 16 patients with negative lymph nodes. Six vaginal recurrences (one isolated tumor cells, five negative nodes) and 15 non-vaginal recurrences (four isolated tumor cells, 11 node negative) were documented. Median follow-up was 2.3 years and 2.6 years for isolated tumor cells and node negative patients, respectively. The study found that isolated tumor cells, grade 2, and lymphovascular space invasion were all associated with

worse recurrence-free survival in the univariate analysis. Even when considering patients with negative lymphovascular space invasion, the presence of isolated tumor cells was still associated with higher non-vaginal recurrence (HR 4.47, 95% CI 1.21 to 16.6, $p=0.03$).

The authors ought to be congratulated for their efforts in investigating these important questions and for precisely defining strict inclusion criteria. A few factors should be considered before full conviction that adjuvant treatment should be given for isolated tumor cells in low-risk endometrioid endometrial cancer. Why was an increased risk of isolated tumor cells not identified in previous literature? This could be due to a small sample size effect. Will molecular features play a role in this? It is known that a certain degree of low grade endometrioid cases are deficient mismatch repair (dMMR), and that these patients are known to more easily metastasize to lymph nodes. Could dMMR cases also be likely to have isolated tumor cells? If so, that would also explain why these patients did not have inferior overall survival, since dMMR cases are susceptible to radiation. How will age interfere with these factors? Age has always been a factor in risk stratification. Since the overall survival is not inferior, does that mean the cases are salvageable and adjuvant therapy can be spared until recurrence? Lastly, the study was divided into three time periods, 2012–14, 2015–17, and 2018–19, with the percentage of isolated tumor cells significantly higher in the last time period (4.3%, 3.8%, 21.9%, $p<0.01$). Could this have anything to do with a learning curve of identifying isolated tumor cells? And if identification of these circumstances is a problem, how could it be further implemented in the future or extrapolated to other centers around the world?

Ultimately, what conclusions can we draw from this data? Currently the author's group are conducting prospective studies to decide what is best when making recommendations in the low grade endometrioid endometrial cancer with isolated tumor cells. How do isolated tumor cells interplay with the other multiple risk factors of endometrial cancer? These are among the questions that still need further exploration and

we will only achieve this goal by collaboration among institutions with expertise in quality control for sentinel mapping and sentinel lymph node ultrastaging. Until then, we must focus on uterine factors and molecular profiling of endometrial tumors to make the most educated decision for our patients.

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