Isolated Tumour Cells in Early Endometrial Carcinomas: A New Concept With Controversial Therapeutic and Prognostic Impact

Authors:	Youbi Zakaria Ahmed[1] 1. University Hospital Centre of Montreal (CHUM), Quebec, Canada *Correspondence to zakaria.youbi@gmail.com

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Endometrial cancer is the most common gynaecologic malignancy in high-income countries due to increased life expectancy. Approximately 8,100 endometrial cancer cases were reported in Canada in 2022, and almost 1,500 of these will die from this disease.[1] Due to the significant morbidity and mortality of endometrial cancer, several studies are underway, taking into account technological advances in molecular biology and therapeutics. The Cancer Genome Atlas (TCGA) identified four subgroups with different prognoses (*POLE* hyper-mutated, mismatch repair deficient, p53 abnormal, and non-specific molecular profile), which require treatment regimens to be adapted.[2]

Node mapping is an important step that conditions the treatment, and consequently the overall survival.[3] It is essentially surgical, with pelvic and para-aortic selective lymph node dissection. Lymph node involvement is a proven factor of poor prognosis, and, therefore, finding out its status is an essential step during staging surgery, because it conditions, with other risk factors, the utility of adjuvant treatments by radiation therapy and/or chemotherapy.[4,5] However, a lymph node dissection is often responsible for infections, haemorrhages, and especially compressive complications due to the lymphoceles.[6]

To remedy this considerable morbidity, several randomised trials and meta-analyses have been performed, and demonstrated the benefit of the sentinel node biopsy technique (SLN) in early endometrial cancer.[7,8] Better sensitivity was attributed to this new technique, and negative predictive value and false negatives were lower.[9] In the multicentre trial by Rossi et al.,[9] SLN followed by pelvic+/-para-aortic lymphadenectomy had only 3% false negatives, with fewer post-operative complications.

Currently, SLN is considered a validated option for surgical treatment of endometrial cancer recommended by most scientific societies, including the European Society of Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP).[10-12]

The concept of isolated tumour cells (ITC) has appeared since the validation of the sentinel biopsy as an alternative to pelvic lymph node dissection in early endometrial cancer treatment. The American Joint Committee on Cancer (AJCC) defined it, for the first time, in 2002.[13] It is present in approximately 5.9% of endometrial and serous subtypes, according to the largest published cohort.[13] The Memorial Sloan Kettering Cancer Center (MSKCC), New York City, USA, established its own definition, which is the presence of a small volume metastatic lymph node (size: ≤0.2 mm), different from micro-metastatic involvement (size: >0.2–≤2.0 mm).[13] Several studies have shown that ultra-staging has increased the detection of lymph node volume between 20–65%.[14]

To pathologically detect the cancer, haematoxylin and eosin staining and cytokeratin AE1/AE3 staining are used on two 5 µm sections.[9,13,14] Two instances of ITCs can be individualised: a single cluster of cells or several clusters sized ≤0.2 mm, the prognostic significance of which is still not elucidated.

The risk of lymph node involvement is estimated to be less than 5% in Stage I. Adjuvant treatment with chemotherapy and/or radiotherapy did not improve locoregional or overall recurrence-free survival according to the PORTEC and GOG trials. [15-16] Several retrospective studies have evaluated the therapeutic and prognostic value of this concept, but no Phase III study has been performed to date. Its impact in the choice of adjuvant treatment remains controversial. In the MSKCC study, published by St Clair et al.,[14] of 844 patients, 23 had ITC (2.7%) in SLN, 21 had micro-metastasis (2.5%), and 47 had macro-metastasis (5.6%). Adjuvant chemotherapy was administered to 19 out of 23 patients (83.0%) with ITCs, and two patients (8.7%) had pelvic radiotherapy. Recurrence-free survival at 3 years was 90% (±1.5) for patients who were node negative, 86% (±9.4) for ITCs, 86% (±9.7) for micro-metastatic, and 71% (±7.2) for macro-metastasis (p<0.001). These results show a better survival rate with ITCs, and allowed the investigators to question the use of adjuvant treatment in this subgroup of patients.[14]

Another large study, published by Plante et al.,[17] evaluated the role of adjuvant treatment in the management of 519 patients with early endometrial cancer, 31 of whom had ITCs positively identified by SLN. Of these, 11 received adjuvant chemotherapy with or without whole pelvic radiotherapy, 10 patients received whole pelvic radiotherapy, and 10 others received no adjuvant therapy or vaginal brachytherapy only. To note, ITCs are not retained as node positive in this study. After 29 months of median follow-up, the 3-year progression-free survival was similar for the patients with ITCs (95.5%), who were node negative (87.6%), and had micro-metastasis (85.5%), but statistically better than patients with macro-metastasis (58.5%; p=0.0012). Only one patient with ITC recurred (stage IB, 7 cm carcinosarcoma), despite adjuvant treatment, while none with endometrioid histology recurred (0 out of 28), and none of the patients with ITC who did not receive adjuvant treatment or vaginal brachytherapy recurred (0 out of 10). The conclusion of this prospective trial affirms the better outcome of patients with positive SLN-ITCs. However, the indication for adjuvant treatment must take into account other high-risk uterine factors, as well as the histological type of endometrial cancer, and not just the presence of ITCs. Thus, patients in this group probably derive little benefit from the addition of adjuvant therapies.[7]

Ghoniem et al.[18] had demonstrated in its multi-institutional study that patients with Grade I endometrioid carcinoma without lympho-vascular extension, or of unknown status, and with a low-volume metastasis on the SLN, had a better prognosis even without adjuvant treatment.[18]

To date, no randomised trial has been published demonstrating the benefit in local control or overall survival of adjuvant treatment with pelvic radiotherapy. The discussion of all cases on a tumour board is essential, and strongly recommended, and other risk factors of recurrence should be integrated, particularly myometrial invasion and lympho-vascular space infiltration, which indicate vaginal brachytherapy and/or post-operative pelvic radiotherapy. The proposed treatment, according to the experts, for endometrioid carcinomas Grade I Stage IA without myometrial invasion and without lympho-vascular extension, or with focal extension, is observation, but some centres continue to irradiate the pelvis in view of the paucity of the literature.

At the author's centre, all observations of endometrial cancer are presented to a tumour board, and the centre has retained a local consensus that pelvic radiotherapy should be used if there are ITCs on several clusters, but they should always have a volume of <0.2 mm. In the presence of a single cluster, simple observation is necessary in the absence of other high-risk factors, and adjuvant pelvic radiotherapy is necessary when there are high-risk factors.

Therefore, several questions need to be answered, and randomised trials should be conducted to evaluate lymph node dissection or pelvic irradiation in case of single ITCs or multiple, in order to identify the risks of lymph node recurrence, loco-regional recurrence, and overall survival. Its integration with the new molecular classification: *POLE* mutated, mismatch repair deficient, p53 abnormal, and non-specific molecular profile, remains to be demonstrated for a better management of this patient entity.

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