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Editorial

Relevance of pathologic features in risk stratification for early-stage endometrial cancer

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Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries. EC is a heterogeneous disease, regarding clinicopathological features and prognosis. In real world, management of EC patients should be tailored based on each individual patient's risk assessment, because a significant rate of recurrences occurs in tumors apparently confined to the uterine corpus.

Traditional risk classification in EC is mainly based on stage, histotype, grade, depth of myometrial invasion, and assessment of lymphovascular invasion (LVI). Worse prognosis is associated with >50% myometrial invasion, higher grade, LVI, and non-endometrioid histologic types. Depending on the estimated risk of recurrence, patients may be observed or receive adjuvant treatment after surgery. Lymph node (LN) status is an important component of stage.

Lymphadenectomy is a surgical procedure that may be associated with increased surgical morbidity and does not have relevance in overall survival. There has been interest in applying preoperative risk stratification schemes to identify patients who could benefit of LN dissection. In this issue of the journal, Daix and coworkers [1] combined pathologic analysis of the preoperative endometrial biopsy with magnetic resonance imaging for preoperative risk stratification to identify the subset of patients to perform LN dissection. Results were compared with the final pathologic report of the surgical specimen. The authors found a weak concordance between preoperative risk stratification and final histological exam. This emphasizes the importance of an accurate pathologic evaluation of preoperative biopsy and surgical specimen. Moreover, in a 37% of cases the risk of LN involvement was underestimated, thus authors suggest performing sentinel lymph node biopsy (SLNB) could improve risk stratification.

SLNB has become a good alternative of LN dissection in EC patients, with less post-operative morbidity. Application of SLNB to low-grade, clinically early-stage EC patients may be important to identify a subset of stage III that could be misinterpreted as stage I. Pathologic ultrastaging strategies are relevant to detect any possible amount of tumor cells and also to quantify tumor burden in 3 categories (macro-, micro-metastasis and isolated tumor cells). Application of molecular tests (such as One Step Nucleic Acid Amplification; OSNA) is still an evolving issue. Several retrospective and prospective studies have demonstrated

high sensitivity of sentinel lymph node status for LN assessment in stage I EC [2]. European Society of Gynaecological Oncology (ESGO)-European Society for Radiotherapy & Oncology (ESTRO)-European Society of Pathology (ESP) 2021 guidelines recommend SLNB can be considered for staging purposes in patients with low risk/intermediate risk EC, although it can be omitted in cases without myometrial invasion. Systematic lymphadenectomy is not recommended in this group [3].

Pathological features are important in EC risk stratification. The most recent World Health Organization (WHO) classification defines several histotypes of EC: endometrioid carcinoma (EEC), serous carcinoma (SC), clear cell carcinoma, mixed carcinoma, undifferentiated carcinoma, carcinosarcoma, neuroendocrine carcinomas, and other unusual types [4]. Histological type has been demonstrated as an important biologic predictor in EC. Its accurate evaluation is relevant in biopsy and resection specimens. It is noteworthy that traditional Bokhman classification (type I vs. type II) is not useful for stratification from the pathologic viewpoint, since there are overlapping features at the clinicopathological and molecular levels.

Evaluation of histopathological grade in EC is very important in both the initial biopsy/curettage and the final hysterectomy specimen. Some series reported a concordance of 35% in histopathological grade between both [5]. This discrepancy could be due to intratumoral heterogeneity and/or to be sample-dependent [6]. WHO 2020 recommended a binary grading system: low-grade (grade 1 and 2) and high-grade (grade 3) tumors [4], since it facilitates clinical decision and improves reproducibility. In fact, grades 1 and 2 EEC are managed in the same way in terms of risk stratification in some guidelines such as National Comprehensive Cancer Network and 2016 ESGO-ESTRO-European Society for Medical Oncology (ESMO) [7].

LVI has emerged as an important component of risk stratification schemes. LVI can be diagnosed when there is a tumor embolus within an endothelial-lined vessel. According to WHO 2020, focal LVI is defined as the presence of up to 3 vessels involved by neoplasm and extensive LVI when there are 4 or more vessels involved. There is scientific evidence suggesting extensive LVI is associated with adverse prognostic factors and worse outcomes when compared to EC with focal or no LVI. Extensive LVI is an indicator for the need of adjuvant treatment, as recommended in the 2016 ESGO-ESTRO-ESMO [7] and the most recent 2021 ESGO-ESTRO-ESP guidelines [3].

Finally, The Cancer Genome Atlas Research Network (TCGA)- molecular classification, based on array and sequencing technologies [8], identified 4 prognostically significant EC subtypes. Group 1 with somatic inactivating mutations in polymerase epsilon (POLE) exonuclease and very high mutation rates (ultramutated), usually high-grade EEC (7%), associated with good prognosis. Group 2 included EEC with microsatellite instability (MSI) (hypermutated) and high mutation rates (28%). Group 3 included EEC with low copy-number alterations, also designated as nonspecific molecular profile (NSMP) (39%) with an intermediated prognosis, as group 2. Group 4 (serous-like or copy-number high) (26%) composed of most SC (but also some ECC), with low mutation rate, but frequent TP53 mutations and worse prognosis. This classification can be achieved using clinically applicable surrogate tests: mutation analysis of POLE and 3 immunohistochemical markers (MSH6, PMS2 and p53) [9]. Several studies have demonstrated the prognostic value of this TCGA surrogate approach.

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The TCGA surrogate has been recently incorporated in EC risk stratification by 2021 ESGO-ESTRO-ESP guidelines [3]. It has been shown to be particularly helpful in the group of high and intermediate-high risk EC and especially in high-grade EEC, which are uniquely distributed among the 4 molecular subtypes [10]. However, it seems to be less informative in low-grade EEC, since vast majority of these are NSMP or MSI. This is relevant, because low-grade EEC account for a huge proportion of early-stage EC. In this big group, some other prognostic markers may be potentially useful, such as L1CAM expression, mutations in CTNNB1, or combination of markers.

In conclusion, appropriate pathologic assessment, including TCGA molecular-surrogate, is crucial for risk stratification in EC. Moreover, SLNB with appropriate pathologic ultrastaging, seems an important tool for accurate staging in patients with early-stage EC, to identify a subset of stage III EC that clinically present as stage I.

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