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ENDOMETRIAL CANCER: ADVANCES IN DIAGNOSIS AND FUTURE PERSPECTIVES

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Abstract: Endometrial cancer (EC) is one of the most common gynecological neoplasms in developed countries, with an increasing incidence attributed mainly to obesity. Although usually diagnosed at an early stage, the biological heterogeneity of the disease poses increasing challenges to clinical practice. Traditionally classified into two histological types, EC has come to be understood from a more precise molecular perspective with the introduction of The Cancer Genome Atlas (TCGA) classification, which identifies four molecular subgroups with distinct prognostic and therapeutic implications.
This study, through a narrative review of recent literature, analyzes advances in the diagnosis of EC, including the use of molecular biomarkers, imaging tests (such as transvaginal ultrasound and contrast-enhanced magnetic resonance imaging), and substitute immunohistochemical markers. The importance of molecular stratification for personalized therapeutic decisions is highlighted, especially in young patients with preserved reproductive desire. The feasibility of the genomic approach in clinical practice, through accessible techniques, represents a decisive step towards precision medicine.

INTRODUCTION

Endometrial cancer (EC) is currently one of the most prevalent gynecological neoplasms in middle- and high-income countries, ranking seventh among female cancers globally and fourth in Europe, with an incidence ranging from 12.9 to 20.2 cases per 100,000 women. (Oaknin et al., 2022; Sobel; Simpson; Ferguson, 2021) Although its mortality rate remains relatively low—estimated at between 2.0 and 2.7 per 100,000—there has been a worrying increase in the number of deaths, with an average annual increase of 1.9%, largely attributed to the growing prevalence of obesity, one of the main risk factors for the most common form of the disease. (Oaknin et al., 2022)

Early diagnosis of EC is facilitated in many cases by the clinical manifestation of abnormal uterine bleeding, especially in the postmenopausal period, which contributes to detection in the early stages, when the neoplasm is still confined to the uterus in about 80% of cases. (Sobel; Simpson; Ferguson, 2021) Despite this, the biological heterogeneity of the disease and changes in epidemiological patterns require new diagnostic approaches. Classic risk factors include obesity (with an increase of up to 273% in incidence in women with a BMI > 30), high blood pressure, diabetes mellitus, hyperinsulinemia, and prolonged exposure to unopposed estrogen with , often associated with nulliparity, polycystic ovary syndrome (PCOS), and prolonged use of tamoxifen. (Dellino et al., 2023; Oaknin et al., 2022)

Traditionally, EC is classified into two histological types: type I, which is low grade and associated with a good prognosis, and type II, which is high grade, usually diagnosed at an advanced stage and responsible for about 70% of deaths associated with the disease. (Sobel; Simpson; Ferguson, 2021) However, this binary model is being progressively replaced by an approach based on molecular profiles, as proposed by *The Cancer Genome Atlas* (TCGA), which introduces a more accurate and prognostic genomic classification. This transition reflects the need for personalized medicine, capable of guiding therapeutic management in a more effective and individualized manner. (Dellino et al., 2023)

An emerging and increasingly relevant aspect is the diagnosis of EC in young women, many of whom are of childbearing age and wish to preserve their reproductive capacity. About 5% to 10% of cases are hereditary, as in Lynch syndrome, where there is microsatellite instability and an increased risk of colon, ovarian, and endometrial tumors, with onset at an early age. (Oaknin et al., 2022; Uccella et al., 2022) In these patients, the standard treatment—total hysterectomy with bilateral salpingo-oophorectomy—poses a challenge, as it compromises fertility. The adoption of conservative strategies, such as hormone therapies with oral or intrauterine progestogens, the use of GnRH analogues, metformin, and hysteroscopic resection techniques, has shown viability in well-selected cases, provided they are associated with rigorous follow-up. (Uccella et al., 2022)

Thus, recent advances in the molecular understanding of endometrial cancer, coupled with the need for an individualized approach—especially in young women—reinforce the importance of improving diagnostic and prognostic strategies. New tools, such as the molecular markers proposed by the TCGA, enable more accurate risk stratification and favor personalized therapeutic decisions, reconciling oncological efficacy and fertility preservation. (Dellino et al., 2023) This article aims to critically review diagnostic advances in endometrial cancer and discuss its future prospects in light of precision medicine.

METHOD

This work is a narrative literature review that aims to gather and critically analyze the most recent evidence on advances in the diagnosis of endometrial cancer, as well as discuss future prospects for clinical practice. The search was conducted in the PubMed database using the following English keywords: *"Endometrial Cancer," "Diagnosis,"* and *"Treatment."*

Articles published in the last five years (from 2020 to 2025), available in full and written in English, that addressed diagnostic aspects of endometrial cancer—including screening methods, biomarkers, imaging tests, histopathological techniques, and technological innovations—were included. Priority was given to original studies, systematic reviews, scientific society guidelines, and articles with a relevant impact on gynecological oncology practice.

Duplicate articles, publications outside the thematic scope, studies focused exclusively on experimental therapies unrelated to diagnosis, and works not available in the PubMed database or in a language other than English were excluded from the analysis.

Data selection and analysis followed criteria of relevance, timeliness, and methodological quality, with the aim of providing a reliable and critical synthesis of the available evidence, contributing to the understanding of trends and challenges in the diagnosis of endometrial cancer.

RESULTS AND DISCUSSION

In recent decades, advances in the molecular and clinical understanding of endometrial cancer (EC) have significantly reshaped the diagnosis, risk stratification, and therapeutic prospects of the disease. The transition from an exclusively histopathological classification to an integrated model with molecular profiles represents a decisive milestone in current oncological practice. Initially established by Bokhman, the dualistic classification divided EC into type I (mainly endometrioid, low grade, and estrogen-dependent) and type II (non-endometrioid histologies, high grade, and more aggressive behavior). (Oaknin et al., 2022) This division, although still useful, has shown limitations in terms of reproducibility and prognostic accuracy, prompting the adoption of systems based on more refined genomic characteristics.

The classification proposed by The Cancer Genome Atlas (TCGA) project revealed four distinct molecular subgroups: ultra-mutated POLE, dMMR (mismatch repair deficient), p53-abn (with TP53 mutations), and NSMP (molecular profile without specific characteristics). This new taxonomy showed a strong correlation with clinical behavior and therapeutic response, highlighting, for example, the excellent prognosis of POLEmut tumors and the aggressive course of p53-abn cases, regardless of histological type. (Dellino et al., 2023)

The introduction of surrogate markers through immunohistochemical techniques (p53, MLH1, PMS2, MSH2, and MSH6), associated with focal sequencing of the exonuclease domain of DNA polymerase epsilon (POLE), has enabled the practical implementation of molecular classification in routine laboratory practice, with great clinical applicability. (Oaknin et al., 2022) Multicenter studies have demonstrated that the application of this simple molecular algorithm allows for more accurate prognostic stratification than traditional classification, even in tumors classified as intermediate grade or undifferentiated histology. (Uccella et al., 2022)

With regard to diagnostic imaging, transvaginal ultrasound (TVUS) remains a fundamental tool, especially in the screening of symptomatic patients. A cutoff point of ≥ 4 mm for endometrial thickness has high sensitivity (94.8%) and negative predictive value (99%) for EC, despite low specificity (46.7%). (Dellino et al., 2023) In cases with suspected deep myometrial invasion, contrast-enhanced magnetic resonance imaging (CE-MRI) has been shown to be the most accurate modality, allowing not only the assessment of the depth of invasion but also the prediction of the extrauterine extent of the neoplasm.

Classic prognostic variables, such as histological grade (G3), lymphovascular space invasion (LMSI), depth of myometrial invasion, presence of lymph node metastases, and tumor size greater than 2 cm, remain relevant. Among these, substantial LVIS (≥ 4 vessels affected per slide) showed a significant negative prognostic impact, even when evaluated on slides stained only with hematoxylin and eosin (H&E), without the need for immunostaining. (Sobel; Simpson; Ferguson, 2021)

In addition, expression of the adhesion molecule L1CAM was associated with an increased risk of recurrence and worse clinical outcome, particularly in tumors with p53-abn or NSMP patterns, highlighting its potential predictive value and as a marker of tumor aggressiveness. (Oaknin et al., 2022)

The results described above highlight the conceptual transformation of endometrial cancer, which has been shifting from an approach focused exclusively on histology to a multifactorial classification structure, in which the molecular profile plays a decisive role in prognosis and therapeutic decisions. The traditional dichotomy between types I and II, although still present in clinical practice, has proven insufficient to capture the biological complexity of the disease, as evidenced by the heterogeneity observed even between grade 1 and 2 endometrioid carcinomas.

The TCGA proposal, by incorporating genomic parameters such as mutational burden and alterations in key genes (POLE, TP53), represents a qualitative leap toward precision medicine. This classification allows the identification of subgroups with distinct prognoses, guiding more individualized therapeutic strategies. For example, evidence that POLEmut tumors have excellent outcomes, regardless of adverse histological factors, raises the possibility of reducing or even omitting adjuvant treatment, a hypothesis currently under investigation in the PORTEC-4a clinical study. In contrast, p53-abn tumors, even when confined to the uterus or with endometrioid histology, behave similarly to serous carcinomas, with documented benefit from the use of adjuvant chemotherapy. (Oaknin et al., 2022)

The clinical applicability of this new approach depends directly on the routine incorporation of molecular classification in anatomopathological reports. The adoption of basic immunohistochemical panels (MMR and p53), combined with focal sequencing for POLE, makes this proposal feasible even in centers with limited laboratory resources and also offers a valuable opportunity for screening for hereditary syndromes, such as Lynch syndrome. (Dellino et al., 2023)

Despite advances, significant challenges remain. The absence of universal standardization on which cases must be molecularly classified and the lack of structure in some services hinder the full implementation of this approach. It is therefore recommended to prioritize molecular classification in high-grade cases, non-endometrioid histologies, or more advanced stages, where the clinical implications are more relevant.

Another point of discussion is imaging assessment and its integration into the diagnostic algorithm. Although TVUS is widely used for screening patients with abnormal uterine bleeding (AUB), its accuracy depends heavily on the cutoff point adopted and the examiner's experience. The identification of a thickened endometrium (> 4 mm) requires histological confirmation, but should not be interpreted in isolation as indicative of malignancy. Functional magnetic resonance imaging, with advanced techniques such as DCE-MRI, stands out as the gold standard for assessing myometrial invasion, a critical factor for staging and prognosis. (Dellino et al., 2023)

Finally, the incorporation of emerging biomarkers, such as L1CAM, reinforces the idea that the future of endometrial cancer management will depend on an integrated approach based not only on tumor morphology, but also on its molecular signature and biological behavior. The growing adherence to molecular classification, combined with the refinement of imaging techniques and the selective use of adjuvant therapies, signals a step forward toward more accurate, effective, and less costly care for patients with EC.

CONCLUSION

There has been a transition in the approach to endometrial cancer (EC) diagnosis, from a previously histopathological model to an integrated model that incorporates molecular profiles, classic prognostic parameters, and high-precision imaging resources. The Cancer Genome Atlas (TCGA) has demonstrated superiority in risk stratification, predicting the biological behavior of the disease, and also guiding specific therapeutic interventions, such as the possibility of reducing treatment intensity in cases with a better prognosis, such as POLEmut tumors.

The practical feasibility of this approach through immunohistochemistry and focal sequencing reinforces the importance of its progressive implementation in clinical routine, including as a screening tool for hereditary syndromes. In addition, the integration of imaging methods, such as transvaginal ultrasound and contrast-enhanced magnetic resonance imaging, aids in identifying tumor stage and size, contributing to safer surgical decisions and adaptation to each patient.

However, challenges remain in standardizing the criteria for molecular classification and expanding access to diagnostic technologies in different settings. In the future, the treatment of EC should move toward more consolidated precision medicine, in which diagnosis will be based on a combination of histological, genomic, and biomolecular characteristics, ensuring better therapeutic targeting and, consequently, better oncological outcomes and quality of life for patients.

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