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Editorial

New Insights into Molecular Mechanisms and Management of Endometrial Malignancies

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Endometrial pathologies are generally recognized as among the most common gynecological diseases. In developed countries, endometrial cancer (EC) is the most frequent gynecological malignancy and a significant source of neoplasm-related mortality, and ranks as the fifth most commonly diagnosed cancer in women worldwide [1]. Over the past decade, the incidence of EC has risen by 40%, accompanied by a 60% increase in associated deaths [1,2]. This evident increase in EC incidence is primarily attributed to the growing relevance of EC risk factors such as obesity and aging [3].

Researchers have recently focused on the clinical management and personalized treatment of EC. Studies have been conducted to establish more precise risk classification and to develop therapies targeting factors with oncogenic molecular pathways.

The release of The Cancer Genome Atlas (TCGA) Research Network date in 2013 marked a significant turning point. It offered comprehensive molecular, genomic, transcriptomic, and proteomic insights into EC. This milestone fundamentally reshaped the traditional classification of the disease. Indeed, for decades, risk classification in EC was primarily determined by factors such as tumor grade, histological characteristics, and the involvement of myometrial and contiguous structures. With the advent of molecular analysis based on mutations, somatic copy-number variations, genome and exome sequencing, and microsatellite instability (MSI) assays, EC has been categorized into the following four groups: Polymerase epsilon (POLE) ultramutated, MSI hypermutated, copy-number low (CNL), and copy-number high (CNH) [4]. The advantage of this refined classification is the possibility of tailoring the management and treatment of the different categories of EC based on the different prognosis of each subclass.

The main limitations of the TGCA study methodologies included complexity, unsuitability for immediate clinical application and cost. To address these challenges, the ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer) model was introduced, incorporating the guidelines from the Institute of Medicine (IOM) [5].

In EC cases with poorer prognosis, common molecular alterations often include features such as estrogen receptor (ER) positivity, catenin beta 1 (CTNNB1) mutation, progesterone receptor (PR) positivity, and L1 cell adhesion molecule (L1CAM) positivity [6,7]. After the discovery of these significant molecular characteristics, researchers have investigated other genetic alterations. These, combined with the clinicopathological characteristics, aim to provide a more comprehensive understanding of the features within the four molecular subclasses [7,8].

For example, analysis of p53-mut showed that EC featuring this mutation has an unfavorable prognosis with high risk of cancer progression. The evidence revealed that L1CAM expression is significantly expressed in this subclass of ECs. Another significant example is the MSI group, which is commonly associated with CTNNB1 mutant and carries an increased risk of distant relapse diseases [7–9].

High-risk ECs, including non-endometrioid histotypes, present assorted characteristics in terms of molecular alterations and prognosis. Evidently, more precise molecular analysis is warranted in these ECs, and could help in therapeutic management and clinical practice [7–10].

Although EC therapy is becoming increasingly personalized, the adoption of molecular characteristics in the selection of adjuvant therapy is not currently supported by strong evidence.

In fact, advanced or metastatic stages are presently the only settings in which molecular analysis is necessary to choose the correct target therapy. For example, advanced microsatellite instability hypermutated (MSI-H)/mismatch repair-deficient (dMMR) status could benefit from the target therapy. Considering that immune checkpoint-associated proteins (ICIs) are present at elevated concentrations in the tumor microenvironment, research evaluated the efficacy of monoclonal antibodies against ICI, with the aim of making cancer cells vulnerable to the immune system [7,8]. Since EC could also occur in patients in pre-menopause or in patients seeking pregnancy, molecular classification may target the tailored conservative therapy of EC precursors.

Furthermore, as endometrial diseases are increasingly diagnosed in premenopausal patients or those seeking pregnancy, molecular analysis can also guide conservative treatments, including the management of EC precursors. The role of molecular classification in predicting which molecular profile precursor has highest risk of evolution in EC

remains unclear, with scant data available in the literature. Nonetheless, preliminary results indicate that POLE and CNL mutations in endometrial atypical hyperplasia are associated with favorable oncological outcomes, in contrast to CNH and MSI-H mutations. Additionally, individuals expressing a combination of Phosphatase and TENsin homolog (PTEN)-negative/b-catenin-positive markers may face an increased risk of cancerous progression. One of the future goals could involve using molecular risk assessment to identify suitable candidates for fertility-sparing treatments among patients [11–13].

Molecular classification has significantly altered the risk stratification and clinical-therapeutic approach of patients with EC and could revolutionize the management of precancerous lesions. Furthermore, it could also tailor surgery itself, thereby reserving non-conservative or radical procedures for patients with poorer prognosis.

More studies, which could radically change the clinical-therapeutic approach of endometrial disease, are still needed to validate scientific evidence [14,15]. Among ongoing studies, RAINBO clinical trials are investigating four molecular class-directed adjuvant treatment strategies following surgery. The goal of RAINBO is to increase survival outcomes through the implementation of novel targeted therapies, thereby reducing treatment-related toxicity while improving the quality of life for patients [15].

The present work has several limitations. Currently, there is limited supporting evidence in the literature for these concepts, and in the future, additional studies will be required to validate these concepts and potentially revolutionize the management of endometrial diseases.

Author Contributions

VDD and LM designed the research study. VDD contributed to the analysis of the data and supervision. VDD and IC wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

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