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Short Communication

Molecular Classification of Endometrial Cancer and Its Impact on Management

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Abstract

The treatment for endometrial cancer is rapidly evolving with the development of molecular analysis and novel strategies. Surgical resection, cytotoxic chemotherapy, endocrine or hormonal treatment, and radiation have been the staples of treatment for decades. However, precision-based approaches for tumors are rapidly becoming part of these strategies.

For several years, around 420,242 people have been diagnosed with endometrial cancer. Among them, nearly 97,704 people die each year (Bray., *et al*. 2024, p. 229). In Morocco, endometrial cancer is the third most common gynecological cancer, according to a study conducted at the Military Hospital of Rabat. It mainly affects postmenopausal women, and its symptoms include abnormal bleeding, particularly after menopause.

Two histological types of endometrial cancer are distinguished: hormone-dependent endometrioid carcinoma with a good prognosis, and non-hormone-dependent non-endometrioid carcinoma with a poor prognosis.

Recent studies on endometrial cancer have established a new purely molecular classification comprising four tumor classes, from best to worst prognosis: ultra-mutated "POLE," hyper-mutated, low copy-number, and high copy-number.

This new classification opens up new therapeutic possibilities and improves prognosis. This section highlights a scientific literature review on molecular classification and its impact on management.

Keywords: Endometrial Cancer; Magnetic Resonance Imaging (MRI); Radiotherapy

Introduction

Endometrial cancer is a common tumor among women in developed countries. In Morocco, it is the 4th most common gynecological cancer in women, with an incidence of 3.5 per 100,000 inhabitants. Endogenous or exogenous hyperestrogenism represents the main risk factor. Other factors have also been described, such as hypertension, diabetes, hereditary factors, and obesity.

The average age of onset of endometrial cancer is 50 years. Diagnosis is often made at an early stage due to postmenopausal bleeding, which must be thoroughly investigated.

Therapeutic management depends on endometrial biopsy to determine histological type and grade, and on magnetic resonance imaging (MRI) for staging. Currently, thanks to molecular (genomic) and histological classification, new therapeutic options and improved prognoses are possible.

The new European 2021 recommendations for managing endometrial cancer are based on three European societies: ESGO (Gynecologic Oncology), ESTRO (Radiotherapy and Oncology), and ESP (Pathology). These guidelines address diagnosis, risk-group definition, and all aspects of treatment.

Discussion

TCGA molecular classification of endometrial carcinomas

It is evident that the use of traditional risk assessment alone cannot adequately stratify high-intermediate-risk patients into low- or high-risk groups for surgical planning and adjuvant treatment (Oumayma, 2023, p. 46). This limitation may lead to over- or under-treatment, affecting clinical outcomes (Gilks., *et al*. 2013, p. 874). Therefore, integrating clinicopathological and molecular biomarker data provides more accurate risk assessment and better prognosis (Salinas., *et al*. 2019, p. 20).

Due to the large number of possible markers, only a few have been included in internationally recommended guidelines for risk stratification (Oumayma, 2023, p. 78). Between 2012 and 2013, "The Cancer Genome Atlas (TCGA)" (Levine., *et al*. 2013, p. 67) introduced a new approach to endometrial carcinoma by performing pan-genomic analyses on approximately 373 cases — 307 endometrioid carcinomas, 53 serous carcinomas, and 13 mixed cases. These results provided new insights into endometrial cancer [1-3].

The analysis included:

- Whole-exome sequencing
- Transcriptome sequencing
- Genomic copy-number analysis
- Protein network analysis
- Microsatellite stability testing and methylation profiling

From this, four groups were identified:

- Tumors with inactivating somatic mutations of the POLE exonuclease gene, characterized by extremely high mutation rates ("ultra-mutated"), representing about 7% of cases and associated with a favorable prognosis.
- Tumors with microsatellite instability (MSI), often due to MLH-1 promoter hypermethylation, accounting for about 28% of cases.
- Endometrioid carcinomas with low copy-number alterations (39%), with survival rates comparable to group 2.
- High copy-number ("copy-number high" or serous-like) tumors (26%), with frequent TP53 mutations, a low mutation rate, and a poor prognosis. This group includes most serous carcinomas and some high-grade endometrioid carcinomas.

Summary

Molecular biology has revolutionized the management of endometrial cancer by enabling tumor classification based on genetic characteristics. This classification, which includes molecular subtypes such as POLE mutations and mismatch repair deficiencies (dMMR), refines prognosis, allows risk stratification, and guides treatment for each patient.

- Classification and prognosis: Molecular classification divides endometrial cancers into four main groups, offering more precise prognostic evaluation than histological classification alone.
- Subtype identification: It distinguishes molecular subtypes, such as POLE mutations or mismatch repair deficiency (dMMR).
- Treatment adaptation: Molecular data are crucial for tailoring treatment and identifying eligibility for targeted therapies, such as immunotherapy for dMMR tumors.

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