Advances in endometrial cancer research.

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Introduction

Endometrial cancer, the most common gynecologic malignancy in developed countries, primarily affects the lining of the uterus. Over recent years, significant strides in understanding the molecular underpinnings of endometrial cancer have propelled forward research and clinical practices, offering new hope for improved diagnosis, treatment, and outcomes. This article delves into the latest advances in endometrial cancer research, highlighting molecular genetics, diagnostic innovations, and emerging therapeutic strategies [1].

Recent genomic studies have revolutionized our understanding of endometrial cancer, revealing its heterogeneity and identifying distinct molecular subtypes. The Cancer Genome Atlas (TCGA) project categorized endometrial cancer into four molecular subtypes: POLE-ultramutated, microsatellite instability (MSI)-high, copy number low, and copy number high. This molecular classification has profound implications for prognosis and treatment strategies [2].

Characterized by mutations in the POLE gene, this subtype exhibits an exceptionally high mutational burden and a favorable prognosis. Patients with POLE-ultramutated tumors often respond well to immune checkpoint inhibitors due to the high number of neoantigens presented by these cancers. This subtype is marked by defects in the DNA mismatch repair system, leading to high mutational rates. MSI-high tumors are also good candidates for immunotherapy, specifically immune checkpoint blockade.

Typically associated with endometrioid histology and favorable outcomes, this subtype presents fewer genetic aberrations. Standard treatment approaches often suffice for these patients, although ongoing research aims to refine therapeutic options further. Often encompassing serous and high-grade endometrioid carcinomas, this subtype shows extensive genomic instability and is generally associated with poorer outcomes. TP53 mutations are prevalent, and targeted therapies against specific pathways are under investigation [3].

Advancements in diagnostic technologies have enhanced early detection and accurate classification of endometrial cancer, pivotal for personalized treatment.The development of liquid biopsy techniques, which analyze circulating tumor DNA (ctDNA) in blood samples, offers a non-invasive method for detecting genetic alterations associated with endometrial cancer. Liquid biopsies can facilitate early diagnosis, monitor treatment response, and detect recurrences with high sensitivity [4].

Positron emission tomography (PET) and magnetic resonance imaging (MRI) with novel tracers provide detailed insights into tumor biology and molecular characteristics. These imaging modalities improve staging accuracy and help guide biopsy and treatment planning. Research has identified several biomarkers, such as L1 cell adhesion molecule (L1CAM) and estrogen receptor (ER) status, which correlate with prognosis and treatment response. Integrating these biomarkers into routine diagnostics can tailor treatment plans to individual patients [5].

The therapeutic landscape of endometrial cancer is evolving rapidly, with novel approaches being explored to enhance efficacy and minimize adverse effects. Immune checkpoint inhibitors, such as pembrolizumab, have shown promise in treating MSI-high and POLE-ultramutated endometrial cancers. Ongoing trials are evaluating the combination of immunotherapy with other modalities, such as radiation and targeted therapies, to overcome resistance mechanisms and improve outcomes. Advances in understanding the molecular pathways involved in endometrial cancer have led to the development of targeted therapies. For instance, inhibitors of the PI3K/AKT/mTOR pathway, frequently altered in endometrial cancer, are under investigation. Additionally, anti-HER2 therapies are being explored for HER2-positive serous carcinomas [6].

For hormone receptor-positive endometrial cancers, hormonal therapies such as progestins, tamoxifen, and aromatase inhibitors remain cornerstone treatments. Research into the optimal sequencing and combination of hormonal agents continues to refine these approaches. Combining different therapeutic modalities holds the potential to enhance treatment efficacy. Trials exploring the combination of chemotherapy with targeted agents or immunotherapy aim to exploit synergistic effects and improve patient outcomes [7].

Despite these advances, several challenges remain in endometrial cancer research and treatment. The molecular heterogeneity of endometrial cancer complicates treatment, with varying responses to therapies and the emergence of resistance. Understanding the mechanisms driving this heterogeneity and resistance is crucial for developing effective

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treatments. While numerous potential biomarkers have been identified, validating these biomarkers in large, diverse patient cohorts is essential before they can be routinely integrated into clinical practice [8].

Implementing personalized medicine approaches requires comprehensive molecular profiling and the integration of clinical, genetic, and biomarker data. Establishing robust infrastructure and standardized protocols for such integrative analyses is a significant undertaking. Ensuring equitable access to advanced diagnostic and therapeutic options remains a challenge, particularly in resource-limited settings. Efforts to address disparities in care and enhance global health equity are vital [9].

Advances in molecular genetics, diagnostic innovations, and emerging therapeutic strategies are transforming the landscape of endometrial cancer research and treatment. A deeper understanding of the molecular underpinnings of the disease has paved the way for personalized medicine approaches, offering hope for improved outcomes. Continued research, collaborative efforts, and equitable access to care are essential to translate these advances into tangible benefits for all patients with endometrial cancer [10].

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