Molecular Pathology and Liquid Biopsies in Endometrial Cancer

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Introduction

Endometrial cancer (EC) represents the most prevalent gynecologic malignancy, with rising incidence among postmenopausal women [1]. It is the fourth most common cancer in women and the fifth most common cause of cancer death [2]. Diagnosing EC requires invasive procedures such as endometrial biopsy but have limitations. There is an unmet need for minimally invasive, cost-effective modalities that detect, monitor, and predict EC progression and therapeutic response.

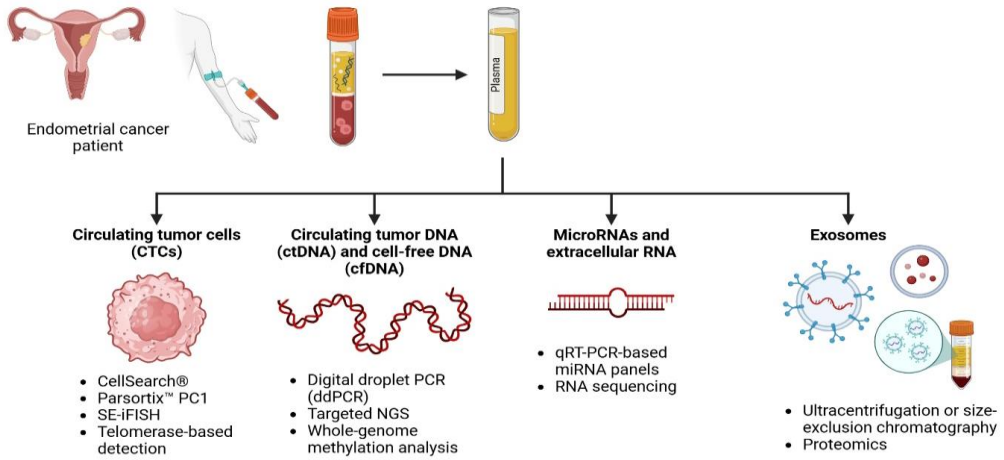
Liquid biopsies offer a non-invasive approach studying tumor's genetic and epigenetic landscape [3]. They have the potential to overcome limitations of tissue sampling by capturing tumor heterogeneity and clonal evolution, essential in EC management.

Diagnostic Refinements and Emerging Roles for Pathologists

ECs categorized into two types, type I, 70%, low-grade, endometrioid; type II, high-grade, estrogen-independent. However, this classification has proved simplistic in describing many subtypes of EC. The Cancer Genome Atlas (TCGA) revolutionized stratification defining four new genomic subgroups. [4].

These refinements highlight molecular diagnostics enabling stratification, integrating liquid biopsy approaches interrogating tumor-derived DNA, RNA, and cells [5]. Molecularly guided management remains less developed. As management incorporates molecular signatures alongside tissue evaluation, pathologists play a role in bridging histopathologic interpretation with assays such as liquid biopsies.

Liquid Biopsy: Technologies and Biomarkers



Molecular Profiling: Mutation Panels and Methylation

One major focus of liquid biopsies in EC is their ability to detect specific mutations in the ctDNA. Studies have found that alterations in *PTEN*, *PIK3CA*, *KRAS*, and *CTTNB1* are among the most common mutations in EC [4]. A study showed that up to 94% of patients will have at least one of these oncomutations detected by NGS panel [6]. Another study demonstrated that each marker's methylation level was significantly higher in EC patients. This method was also able to detect early-stage cancers with sensitivity and specificity around 90%. Furthermore, more accurate methylation tests have been developed recently, targeting other genes like *ZSCAN12*, *GYPC*, *RASSF1A*, and *HOXA9 [7]*.

Clinical Applications

Human epididymis protein 4 (HE4) in a meta-analysis was identified to yield a high specificity (91%), moderate accuracy (AUC 0.84), low sensitivity (65%), and high diagnostic Odds Ratio (19.46) [8]. Another marker, thyroid transcription factor-1 (TTF-1) in CTCs, was associated with high grade tumors, lymph node and vascular infiltration, and metastasis.

Correlation between quantity of CTCs/ ctDNA and predicting tumor aggressiveness and patient prognosis is also a very useful tool. Positive CTC count (15% of patients) was correlated to higher cervical invasion, larger tumors, worse disease stage, worse survival expectancy, deep myometrial invasion, and lymph node positivity [9].

Future Directions

While histopathological findings can be essential to the diagnosis of cancer, it alone is not able to anticipate disease relapses or treatment resistance. Hence, it would be most useful to integrate surgical, histopathological, and liquid biopsy data to provide the best patient outcomes.

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