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Molecular Landscapes of Endometrial Cancer – Is it Time to Change our Clinical Practice?

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Introduction

Endometrial cancer is a common gynaecological malignancy, the fourth most common one in United States [1]. Most women with endometrial cancers fare well with treatment. There are two groups of endometrial cancers. Type I endometrioid are seen in obese women and are related to excess estrogens. Type II primarily serous tumors are seen in non-obese women and have a poorer prognosis. The cornerstone of treatment for management for endometrial cancers is surgical staging. Endometrioid early stage tumors are usually treated with adjuvant radiation, whereas, advanced stage and serous tumors are given chemotherapy in the adjuvant setting [2,3].

Worldwide, scientists are intrigued with thoughts regarding poorer outcomes for some women as compared to others. A pertinent question needs to be answered – Can we make some additions in the diagnostic workup of women with endometrial cancers and bring about some innovations in their treatment options?

The Way Forward

"*Everything in the world began with a yes. One molecule said yes to another molecule and life was born.*" - *Clarice Lispector*

The Cancer Genome Atlas (TCGA) in 2013 addressed this issue and gave the world the most comprehensive molecular study on endometrial cancers [4]. This included whole genome sequencing, exome sequencing and microsatellite instability (MSI) assays. 232 endometrioid and serous endometrial cancers were classified into four groups based on molecular information - POLE ultramutated, MSI hypermutated, copy-number (CN) low and CN high. These correlated with progression free survival.

Cancer centres across the globe have felt the need for reproducible categorization to standardize management of endometrial cancers. Tumors are categorized based on biologically relevant features. Histological segregation of endometrial cancers into type I and II is inadequate. Mismatch repair (MMR) mutations and p53 IHC testing and interpretation can be easily performed in most oncopathology departments. Women with Lynch syndrome will benefit from such testing. In young women with early endometrial cancers desirous of fertility, molecular classification could help in categorization of MMR or p53 and such detection could help in the decision of radical treatment rather than a fertility sparing approach. Women with p53 mutations have poorer prognosis.

What to Test?

POLE testing, MSI assay and p53 testing are needed to classify endometrial tumors – the molecular way [5]. The MSI assay is now substituted by immunohistochemistry on four MMR proteins MLH1, MSH2, MSH6 and PMS2. This is more cost effective and readily available. Testing for MMR proteins has additional advantage of identifying women who may benefit from genetic testing for Lynch syndrome. CN status was defined by three genetic loci: *FGFR* (4p16.3), *SOX17* (8q11.23), and *MYC* (8q24.12). These loci were able to identify all the CN-high cases. In addition, aberrant/abnormal (abn) p53 by genetic testing or IHC for complete loss or overexpressing (2+) was able to separate CN-high (p53 abn) from CN-low (normal p53) subtypes.

Looking Beyond the Usual

The integration of molecular classification of endometrial cancer and its impact on current clinical care is yet to be determined. Many questions remain answered. Can we understand the natural history of endometrial cancers based on this molecular classification? Can poorly differentiated tumors be managed in a different manner? What is the occurrence of various molecular subtypes of endometrial cancers in different populations? Does the detection of a p53 aberrant endometrial tumor improve clinical outcome? Can adjuvant therapy be avoided in the favourable POLE mutated endometrial tumors?

Prospective trials are needed to address these questions. The time has arrived to look beyond histology, grade and stage of endometrial cancers. Molecular classification of endometrial cancers can be a real game changer!

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Conflict of Interest

There appears no potential conflict of interest or the appearance of a conflict of interest for this work.

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