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Newsletter

Molecular Classification for Endometrial Carcinoma

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1st Quarter 2023

Endometrial cancer is the most common gynaecologic malignancy in developed countries. Most cases arise in the postmenopausal period, with a mean age at presentation of 60 years, and 67% of cases present at an early stage.

From a pathophysiologic perspective, endometrial carcinomas have been traditionally divided into 2 types:
Type 1: includes endometrioid and mucinous carcinoma.

- These lesions are associated with long-term elevated oestrogen levels, which lead to persistent proliferative stimulation of the endometrium.

Type 2: includes serous, clear cell, undifferentiated carcinoma and carcinosarcoma.

- These tumours have a lesser association with unopposed oestrogen exposure.
- Serous carcinoma is characterised by early alterations in TP53 oncogene.

From a biologic and clinical perspective, the classification of endometrial carcinoma is evolving towards a molecular-based grouping.

Molecular / cytogenetics description

Determination of the tumour histologic type is critical for patient risk stratification and management. However, there is poor inter-observer reproducibility in tumour type and grade even among expert pathologists.[1]

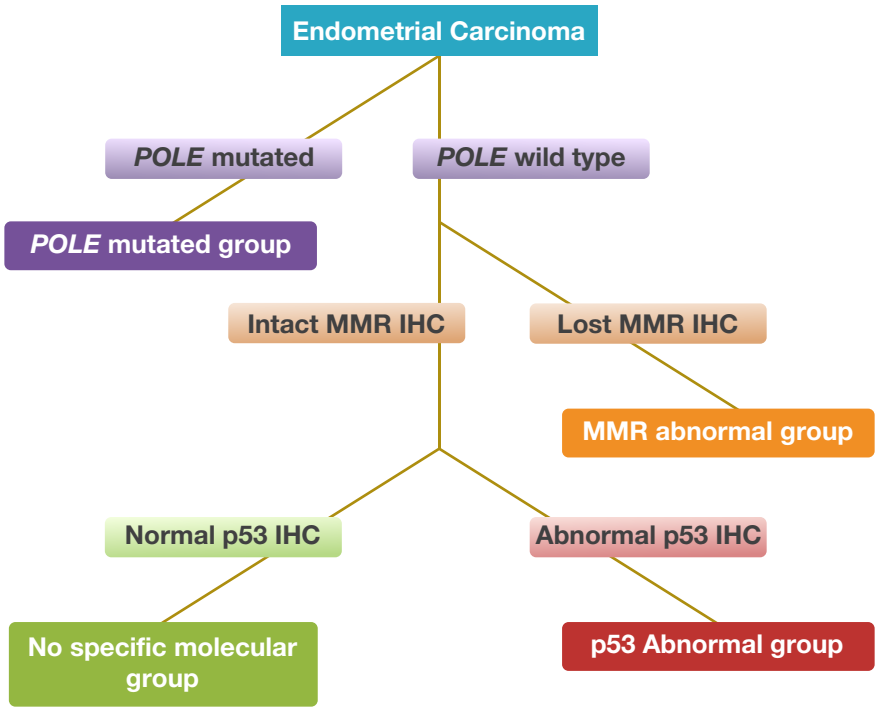
Recent studies have provided a comprehensive characterisation of the genomic profiles of endometrial carcinoma. In 2013, The Cancer Genome Atlas (TCGA) Research Network published an integrated genomic characterisation of endometrial carcinoma based on genomic data from array and sequencing based technologies.[2]

It proposed a classification that separates endometrial carcinomas into 4 groups:

- Copy number - high (frequently involving mutations of TP53); this group includes the vast majority of serous carcinomas and 25% of high-grade endometrioid tumours.
- Copy number - low (frequently involving mutations of PTEN, PIK3CA, ARID1A and KRAS); this group is mostly composed of low-grade endometrioid carcinomas.
- Microsatellite instability hypermutated (frequently involving alterations of mismatch repair protein genes).
- Polymerase ε (POLE) ultramutated; this group is mostly composed of endometrioid cancers, which despite having a dramatically increased transversion mutation frequency and newly identified hotspot mutations in the POLE gene (which encodes the central catalytic subunit of DNA polymerase epsilon), appear to have a better prognosis than other groups.[3,4]

Molecular-based classification correlates with clinical outcomes: survival rates are best in POLE mutated tumours, followed by copy number - low, microsatellite instability and copy number - high carcinomas.[2] The molecular fingerprint can better assist in patient risk stratification and management.

The **PROMISE algorithm** (see following page) is based on POLE mutational analysis and immunohistochemistry (IHC) for p53 and mismatch repair (MMR) proteins (MLH1, MSH2, MSH6 and PMS2) as a valid surrogate to determine the molecular group.[5]



Lancet Laboratories offers an NGS Endometrial Tumour Panel in our Molecular Pathology Laboratory that can be performed on all newly diagnosed endometrial carcinomas:

- *The European Society of Medical Oncologists recommends that molecular classification of endometrial carcinomas (EC) should be carried out on all specimens regardless of histological type.*[6]
- *Prioritisation of molecular classification should be done for cases where results are relevant to guiding adjuvant treatment recommendations. It applies particularly to those classified as being high grade or at high stage (>FIGO stage II), as the clinical consequences for these patients will be most pronounced.*
- *ECs that have not (completely) been molecularly classified should be designated as EC not otherwise-specified (ECNOS) and continue the use of the histology-based classification system.*
- *Molecular classification is done through well-established IHC staining for p53 and MMR proteins (MLH1, PMS2, MSH2, MSH6) in combination with Endometrial Tumour Panel sequencing. Please contact the laboratory if Endometrial Tumour Panel (D805) sequencing is required on an EC sample.*

References:

1. Han G, et al. Reproducibility of histological cell type in high-grade endometrial carcinoma. Mod Pathol 2013; 26(12): 1594 – 1604.
2. Cancer Genome Atlas Research Network, Kandoth C, et al. Integrated genomic characterization of endometrial carcinoma Nature 2013; 497(7447): 67 – 73.
3. Billingsley CC, et al. Polymerase (POLE) mutations in endometrial cancer: clinical outcomes and implications for Lynch syndrome testing. Cancer 2015; 121(3): 386 – 394.
4. Church DN, et al. Prognostic significance of POLE proofreading mutations in endometrial cancer. J Natl Cancer Inst 2014; 107(1): 402.
5. Talhouk A, et al. A clinically applicable molecular-based classification for endometrial cancers. Br J Cancer 2015; 113(2): 299 – 310.
6. Oaknin A, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2022; 33(9): 860 – 877.

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corporate branding/newsletters/sa/2024/N00275 cpt molecular classification for endometrial carcinoma a4 eng duplex 170gsm leo mrch2024.cdr | rev001

ITEM CODE: N00275