Nadine El Kassis, MD
Gynecology and Obstetrics, Gynecologic oncologic surgery
Hôtel Dieu de France, Achrafieh, Lebanon
Lecturer at Saint Joseph University, Beirut, Lebanon

Molecular Classification of endometrial cancer and its Implications

Abstract:

Endometrial cancer (EC) is the most prevalent gynecologic malignancy in the developed world. Majority of women with EC have good outcomes (80% in stage I, 5 year survival rate ~ 90%)[1]. Traditional risk group classification into type I and type II is based on post-surgical staging pathologic examination (principally histotype, tumour grade and stage). Type I is mostly hormono dependant and has a better prognosis than type II [2].

This classification has a lot of limitations because of the overlap of the two types and the heterogeneity in each one. In addition to that, Interobserver disagreement in endometrial carcinoma histotype assignment varies from 10% to 20% and reaches 26% to 37% in high-grade tumors [3].

For all these reasons and due to molecular biology advances, genomic classification of endometrial carcinoma was issued by the National Cancer Institute and National Human Genome Research Institute, in 2013 (The cancer genome atlas, TCGA) [4]. It classifies EC into 4 groups:

- **POLE (ultramutated) tumours** : endometrioid EC grades 1 to 3, with a very good prognosis
- **Microsatellite-instable (MSI [hypermutated])** : endometrioid EC grades 1 to 3, with intermediate prognosis
- **Copy-number low** (endometrioid) tumours, comprising microsatellite-stable grade 1 and 2 endometrioid cancers with low mutation rates : intermediate prognosis
- **Copy-number high** (serous-like) tumours : characterised by extensive copy number aberrations and low mutation rates, with poor prognosis.

This classification is reproducible, reliable preoperatively, helps in treatment decisions and guides clinical trials of targeted therapies. It improves as well prognostic accuracy.

This classification was then improved in the ProMisE study where the authors used molecular classifiers: MMR IHC testing (MLH1, MSH2, MSH6 and PMS2) for MSI, POLE exonuclease domain (EDM) mutations, and p53 status (determined by IHC) [5].

In conclusion, creating an integrated molecular profile adding histopathological features to molecular classification improves prognostic prediction and treatment modalities and permits the implementation of targeted therapies.

References:

1. National Cancer Institute. Physician Data Query (PDQ). Endometrial cancer treatment. 4/23/2014. Accessed at www.cancer.gov/cancertopics/pdq/treatment/endometrial/healthprofessional on January 22, 2015.

2. Genestie C, Leary A, Devouassoux M, Auguste A. Histological and molecular classification of endometrial carcinoma and therapeutical implications. Bull Cancer. 2017 Dec;104(12):1001-1012.

3. Hoang, Lien n et al .Interobserver Agreement in Endometrial Carcinoma Histotype Diagnosis Varies Depending on The Cancer Genome Atlas (TCGA)-based Molecular Subgroup. The American journal of surgical pathology, 2017, Volume 41, Number 2.

4. Douglas A. Levine & The Cancer Genome Atlas Research Network Integrated genomic characterization of endometrial carcinoma. *Nature* 2013, volume 497, pages67–73.

5. A Talhouk, M K McConechy, S Leung, H H Li-Chang, & J N McAlpine . A clinically applicable molecular-based classification for endometrial cancers *British Journal of Cancer* volume 113, pages299–310(2015)