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Molecular classification in endometrial cancer — are we ready?

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Ten years have passed since the revolutionary publication of molecular classification of endometrial cancer [1].

Since that time its prognostic significance has been validated in several studies [2–6]. There is no doubt that the molecular classification carries a significant prognostic information for endometrial cancer patients and differentiate at least four distinct tumors with non-similar prognosis: Polymerase epsilon muted (POLEmut), P53 abnormal (p53abn), Mismatch Repair Deficient (MMRd) and Non-specific molecular profile (NSMP). Patients with POLEmut profiles have an excellent prognosis, whereas patients with p53abd tumors have a poor prognosis. The classification was first published for endometrioid type endometrial cancer, however, can also be extrapolated for non-endometrioid endometrial cancer.

The molecular classification has been integrated in the European guidelines since 2020 [7] and recently has been added to the Polish Guidelines for Endometrial Cancer Management.

Apart from the prognostic value, molecular classification can guide adjuvant treatment. MMRd patients are found to be good candidates for checkpoint inhibitors. In a recurrent setting, immune checkpoint inhibitors showed remarkable results with response rate between 43% and 57% in MMRd tumors [8,9]. P53 abnormal serous tumors are currently tested for PARP-I and HER2 targeted therapies with promising results [10, 11]. Finally, NSMP tumors can be treated with hormonal therapy [11].

Important prospective clinical trials by the PORTEC group are ongoing to assess the role of molecular profile-based radiation therapy [11, 12]. The same group have recently published a retrospective study on the impact of molecular profile-based adjuvant chemotherapy in high risk endometrial [13].

Finally, an important epidemiological impact cannot be neglected. Universal use of the molecular classification can help to extract patients that are at familiar risk of cancer. Patients with MMRd tumors that are not related to the promotor methylation should be consulted by a clinical geneticist. Approximately 3 % of endometrial cancer patients will be diagnosed of Lynch Syndrome [14]. Recent publications show a possible familiar association with pathological POLE mutations [15].

In practice, the correct assignation to one of the molecular subtypes requires four tests: MMR immunohistochemistry, p53 immunohistochemistry, POLE mutation testing. This strategy termed Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) was created by an international group of experts. It identifies four molecular subtypes that are analogous but not identical to the four genomic subtypes described in TCGA [4].

There are several approaches to perform the diagnostic tests. Most authors propose to perform the POLE test first [16]. Others opt for more economical way and start with p53, MMR immunohistochemistry and perform POLE mutation testing only in complex cases. However, this last approach misdiagnoses the "so-called" multiple classifiers. The major limitation is testing for POLE mutation, because it is expensive and not available in every center and reference institutions cannot manage all endometrial cancer patients.

Therefore, should all endometrial cancer patients have molecular testing at first diagnosis? Should we wait for the result of ongoing prospective studies? What we know so far is firmly convincing and enough to say that the benefit of molecular classification is clear. The molecular classification should be offered to all endometrial cancer patients.

Conflict of interest

All authors declare no conflict of interest.

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