Submitted: 05 September, 2022 Accepted: 20 October, 2022 Published: 15 December, 2022 DOI:10.22514/ejgo.2022.051

EDITORIAL

European Journal of Gynaecological Oncology

Molecular markers and endometrial cancer

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Keywords

Endometrial cancer; Molecular markers; Precision medicine

Endometrial cancer (EC) is the most common gynecological tumor in industrialized countries [1, 2]. To date, molecular markers have become increasingly important in the management of this type of tumor, to help in early detection, risk stratification, prognosis and response to treatment of patients with EC [3]. New technologies allow molecular profiling of EC, bringing different diagnostic and therapeutic approaches into clinical practice, especially for patients in the recurrent and metastatic settings [4]. Combining these novel aspects with the standard ones (evaluation of lymphovascular space invasion, LVSI; histologic grading; FIGO stage), the result can become extraordinary in terms of personalized management [5].

Starting from the evidence reported by The Cancer Genome Atlas (TCGA), the subsequent ProMisE classification have been proposed to classifying four EC groups: (i) *POLE* (ultra-mutated), (ii) microsatellite instable (MSI-H/MMRd—hypermutated), (iii) copy number high (CNH)/*TP53* abnormal, and (iv) copy number low (CNL)/TP53 wild type [6, 7]. This molecular approach improves personalized medicine and tailored treatment, as confirmed in several studies summarized below [8–12]. *POLE* mutated tumors are characterized by good prognosis, on the contrary p53 abnormal tumors are associated with poor outcomes [8–10]. These results were confirmed analyzing data of the PORTEC-1 and PORTEC-2 trials [11]. Similarly, the a retrospective analysis of the randomized Adjuvant Chemoradiotherapy Versus Radiotherapy Alone in Women with High-Risk Endometrial Cancer (PORTEC-3) trial investigated high-risk EC patients and the impact of prognosis for each molecular subgroup, concluding that the biomolecular pattern has an important prognostic value in these patients (again confirming good results for *POLE*-mutated patients and a worse outcome for EC with p53 abnormal disease, with the MSI and non-specific mutational patterns groups having an intermediate outcome), and that adjuvant chemoradiotherapy should be proposed to patients affected by EC with p53 abnormal expression [12].

The most recent European Society of Gynecological Society/European Society for Radiotherapy and Oncology/European Society of Pathology (ESGO/ESTRO/ESP) 2021 guidelines for the management of endometrial tumor recommends defining risk class and choosing the best therapeutic strategy in EC patients considering molecular classification [13]. Furthermore, molecular classification is included in the last edition of the World Health Organization (WHO) classification of the female tumors, the National Comprehensive Cancer Network (NCCN) [14].

Moreover, other biomolecular markers and immune checkpoint are being studied in EC and they are promising. L1

cell adhesion molecule (L1CAM) is a strong predictor for poor disease free survival and overall survival in endometrial cancer FIGO stage I–II; furthermore, there is a correlation between L1CAM overexpression and worst clinic-pathological characteristic and distant recurrence [15]. Programmed cell death 1 (PD1) has two ligands PDL1 and PDL2 and is an inhibiting receptor protein of lymphocytes, which plays critical roles in keeping working immunological self-tolerance. The prognostic role of this ligand has just begun to be investigated in EC, to confirm whether this approach may lead to potential positive outcome using immune therapy [16].

To date, many efforts are paving the way of non-invasive early-detection of circulating biomarkers for EC [17]. In this field, a recent analysis used the Immuno-oncology panel and the Target 96 Oncology III panel to detect specific cancer-related serum protein; the result of this study allowed to identify the specific identikit of early-stage endometrioid EC patients, different from controls patients (positive analysis of Gal-1, Gal-9, MMP7, COL9A1, and FASLG serum levels) [18]. A 11-gene panel on G3 endometrioid EC (*TP53*, *MLH1*, *MSH2*, *MSH6, PMS2, EPCAM, PIK3CA, CTNNB1, KRAS, PTEN,* and *POLE*) for molecular classification confirmed a new possibility of treatment decisions, based on molecular classification in high-grade EC [2, 9, 10].

Interestingly, in the recent years several studies are focusing on prevention and early-diagnosis of EC. Studies are focusing on identify early signatures suggestive for the risk of developing EC in the high-risk population [19, 20]. Preliminary data supported those combined mutations of specific DNA-methylated genes might be considered as promising useful biomarkers for EC. Those biomarkers might be detected in cervical scrapings [19, 20].

This type of approach is radically changing the management of cancer patients and improving molecular tools is essential stratify the risk to guide surgery, adjuvant therapy, and cancer therapeutic approach for women with EC. The molecular-integrated risk profile is a useful tool to determine and to choose the best treatment for patients with advanced disease, and the goal is to make all laboratories autonomous in the future, reducing costs and differences. Meanwhile the molecular assessment which requires more expensive techniques (for example next generation sequencing, NGS) could be reserved for the most delicate and/or uncertain cases. Further prospective studies are necessary to confirm that molecular profiling might be useful to tailor adjuvant treatment even in the early stage.

AUTHOR CONTRIBUTIONS

AG—Conceptualization; OD, GB, ASL, AT—writing—original draft preparation; DC, MGS—writing—review and editing; EV, VC, LM—visualization; AG—supervision. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGEMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest. AG is serving as one of the Guest Editor of this journal. We declare that AG had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to EH.

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How to cite this article: Ottavia D'Oria, Giorgio Bogani, Enrico Vizza, Vito Chiantera, Ludovico Muzii, Maria Giovanna Salerno, *et al*. Molecular markers and endometrial cancer. European Journal of Gynaecological Oncology. 2022; 43(6): 1-3. doi: 10.22514/ejgo.2022.051.