

EDITORIAL

Molecular markers and endometrial cancer

Ottavia D'Oria¹, Giorgio Bogani², Enrico Vizza³, Vito Chiantera⁴, Ludovico Muzii², Maria Giovanna Salerno⁵, Donatella Caserta⁶, Antonio Simone Laganà⁴, Andrea Tinelli⁷, Giacomo Corrado⁸, Andrea Giannini^{1,*}

¹Department of Medical and Surgical Sciences and Translational Medicine, PhD Course in "Translational Medicine and Oncology", Sapienza University, 00189 Rome, Italy

²Department of Maternal and Child Health and Urological Sciences, Sapienza University of Rome, Policlinico Umberto I, 00160 Rome, Italy

³Gynecologic Oncology Unit, Department of Experimental Clinical Oncology, IRCCS-Regina Elena National Cancer Unit Institute, 00144 Rome, Italy

⁴Unit of Gynecologic Oncology, ARNAS "Civico-Di Cristina-Benfratelli", Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, 90127 Palermo, Italy

⁵Department of Woman's and Child's Health, Obstetrics and Gynecological Unit, San Camillo-Forlanini Hospital, 00152 Rome, Italy

⁶Gynecology Division, Department of Medical and Surgical Sciences and Translational Medicine, Sant'Andrea University Hospital, Sapienza University of Rome, 00189 Rome, Italy

⁷Department of Gynecology and Obstetrics, Division of Experimental Endoscopic Surgery, Imaging, Minimally Invasive Therapy and Technology, Vito Fazzi Hospital, 73100 Lecce, Italy

⁸Woman, Child and Public Health Department, Fondazione Policlinico Universitario A. Gemelli, IRCCS, 00168 Rome, Italy

*Correspondence

andrea.giannini@uniroma1.it (Andrea Giannini)

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*, *CTNBN1*, *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.

REFERENCES

- [1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *A Cancer Journal for Clinicians*. 2021; 71: 209–249.
- [2] Laganà AS. Management of endometrial cancer: current insights and future directions. *Translational Cancer Research*. 2020; 9: 7685–7687.
- [3] Králičková M, Větvicka V, Laganà AS. Endometrial cancer—is our knowledge changing? *Translational Cancer Research*. 2020; 9: 7734–7745.
- [4] Li L, Chen F, Liu J, Zhu W, Lin L, Chen L, *et al.* Molecular classification grade 3 endometrial endometrioid carcinoma using a next-generation sequencing-based gene panel. *Frontiers in Oncology*. 2022; 12: 935694.
- [5] Bianco B, Barbosa CP, Trevisan CM, Laganà AS, Montagna E. Endometrial cancer: a genetic point of view. *Translational Cancer Research*. 2020; 9: 7706–7715.
- [6] Cancer Genome Atlas Research Network; Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, *et al.* Integrated genomic characterization of endometrial carcinoma. *Nature*. 2013; 497: 67–73.
- [7] Talhouk A, McConechy MK, Leung S, Yang W, Lum A, Senz J, *et al.* Confirmation of ProMisE: a simple, genomics-based clinical classifier for endometrial cancer. *Cancer*. 2017; 123: 802–813.
- [8] Bogani G, Dowdy SC, Cliby WA, Ghezzi F, Rossetti D, Frigerio L, *et al.* *European Journal of Gynaecological Oncology*. 2016; 37: 6–12.
- [9] Bogani G, Ray-Coquard I, Concin N, Ngoi NYL, Morice P, Enomoto T, *et al.* Uterine serous carcinoma. *Gynecologic Oncology*. 2021; 162: 226–234.
- [10] Bogani G, Ray-Coquard I, Concin N, Ngoi NYL, Morice P, Enomoto T, *et al.* Clear cell carcinoma of the endometrium. *Gynecologic Oncology*. 2022; 164: 658–666.
- [11] Stelloo E, Nout RA, Osse EM, Jürgenliemk-Schulz IJ, Jobsen JJ, Lutgens LC, *et al.* Improved risk assessment by integrating molecular and clinicopathological factors in early-stage endometrial cancer—combined analysis of the PORTEC cohorts. *Clinical Cancer Research*. 2016; 22: 4215–4224.
- [12] León-Castillo A, de Boer SM, Powell ME, Mileskin LR, Mackay HJ, Leary A, *et al.* Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: impact on prognosis and benefit from adjuvant therapy. *Journal of Clinical Oncology*. 2020; 38: 3388–3397.
- [13] Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, *et al.* ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. *International Journal of Gynecological Cancer*. 2021; 31: 12–39.
- [14] Köbel M, Ronnett BM, Singh N, Soslow RA, Gilks CB, McCluggage WG. Interpretation of P53 immunohistochemistry in endometrial carcinomas. *International Journal of Gynecological Pathology*. 2019; 38: S123–S131.
- [15] Vizza E, Bruno V, Cutillo G, Mancini E, Sperduti I, Patrizi L, *et al.*

- Prognostic role of the removed vaginal cuff and its correlation with LICAM in low-risk endometrial adenocarcinoma. *Cancers*. 2021; 14: 34.
- ^[16] Di Tucci C, Schiavi MC, Faiano P, D’Oria O, Prata G, Sciuga V, *et al.* Therapeutic vaccines and immune checkpoints inhibition options for gynecological cancers. *Critical Reviews in Oncology/Hematology*. 2018; 128: 30–42.
- ^[17] Benati M, Montagnana M, Danese E, Mazzon M, Paviati E, Garzon S, *et al.* Aberrant telomere length in circulating cell-free DNA as possible blood biomarker with high diagnostic performance in endometrial cancer. *Pathology & Oncology Research*. 2020; 26: 2281–2289.
- ^[18] Ura B, Capaci V, Aloisio M, Di Lorenzo G, Romano F, Ricci G, *et al.* Targeted proteomics approach for screening serum biomarkers observed in the early stage of type I endometrial cancer. *Biomedicines*. 2022; 10: 1857.
- ^[19] Liew P, Huang R, Wu T, Liao C, Chen C, Su P, *et al.* Combined genetic mutations and DNA-methylated genes as biomarkers for endometrial cancer detection from cervical scrapings. *Clinical Epigenetics*. 2019; 11: 170.
- ^[20] Huang R, Su P, Liao Y, Wu T, Hsu Y, Lin W, *et al.* Integrated epigenomics analysis reveals a DNA methylation panel for endometrial cancer detection using cervical scrapings. *Clinical Cancer Research*. 2017; 23: 263–272.

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. doi: 10.22514/ejgo.2022.051.