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Editorial

Molecular classification of endometrial cancer: entering an era of precision medicine

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▸ See the article "Genomic landscape of advanced endometrial cancer analyzed by targeted next-generation sequencing and the cancer genome atlas (TCGA) dataset" in volume 33, e29.

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The classification of endometrial cancer has evolved beyond simple histomorphology to molecular characterization of tumors. The Cancer Genome Atlas (TCGA) project proposed 4 classes of endometrial cancer, each characterized by specific genetic alterations: *POLE*-mutated (*POLE*mut), hypermutated with microsatellite instability, copy number high, and copy number low. Since the publication of the TCGA nomenclature, a more clinically accessible alternative—but analogous—classification system has emerged: *POLE*mut, MMR deficient (MMRd), p53-aberrant (p53abn), and no specific molecular profile (NSMP). Each of these molecular subgroups has unique clinicopathologic features that may inform prognosis and treatment [1-3]. Three key studies have investigated the prognostic implications of these classifications: a Vancouver study that assessed overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) in a cohort of 152 endometrial cancer cases categorized by molecular classifier; a study by the *Trans*PORTEC consortium that examined distant metastasis rates, RFS, and OS and correlated these clinical outcomes with molecular subgroups in a cohort of 116 patients with high-risk endometrial cancer; and a NRG/GOG study that categorized 982 specimens from GOG210, "A Molecular Staging of Endometrial Cancer" (NCT00340808), by molecular class and assessed progression free survival (PFS), DSS, and OS. *POLE*mut tumors, characterized by mutations in the exonuclease domain of the *POLE* gene (a gene involved in nuclear DNA replication and repair), tend to be high-grade endometrioid endometrial cancers. Additionally, these tumors tend to have an excellent prognosis: in the Vancouver cohort, patients with *POLE*mut tumors had a significantly better RFS compared to patients with NSMP tumors (hazard ratio [HR]=0.16) [4]; in the *Trans*PORTEC cohort, there were no distant recurrences among patients with *POLE*mut tumors [5]; and in the NRG/GOG study, patients with *POLE*mut tumors had significantly better PFS, DFS, and OS (HR=0.27, 0.48, and 0.22, respectively) compared to copy number stable tumors, although these differences were not statistically significant [6]. MMRd tumors, characterized by loss of expression of 1 of 4 MMR proteins (MLH1, MSH2, MSH6, or PMS2) either through mutation or silencing of MLH1 by promoter hypermethylation, have predominantly endometrioid histology and also tend to have a favorable prognosis, evident in the Vancouver, *Trans*PORTEC, and NRG/GOG cohorts [4-6]. Tumors with p53abn tend to be high-grade and serous endometrial cancers and carry a poor prognosis: in the Vancouver cohort, p53abn tumors had a HR of 2.19 for RFS compared to p53 wild type; and in the *Trans*PORTEC group they had a HR of 6.79 for locoregional recurrence compared to NSMP

[4,5]. Finally, tumors with NSMP—in essence, those tumors who do not fall into any of the other 3 groups—tend to have endometrioid histology and are frequently estrogen receptor/progesterone receptor positive. This group also has an intermediate prognosis, with a 39% rate of locoregional recurrence and 52% 5-year RFS in the *Trans*PORTEC study [5].

This issue of *Journal of Gynecologic Oncology* features 2 papers that add to this growing body of literature regarding the molecular characterization of endometrial cancer. In Hong et al. [7], the authors performed NGS testing on 21 tissue samples from patients with stage III and IV endometrial cancer. Compared to stage I tumors, advanced stage tumors were more likely to have *TP53* and *PPP2R1A* mutations. Furthermore, in a univariate analysis, these mutations were associated with decreased survival proportion. In Yu et al. [8] sequencing and immunohistochemistry were performed on tissue specimens from 414 patients with high-grade endometrial cancer. Their study identified 2 new, possibly pathogenic, *POLE* mutations. Of the 414 patients included in the study, 43 had *POLE*mut tumors. Consistent with prior literature, the prognosis of these tumors was very good: 5-year PFS and DSS were 97.7% and 96.6%, respectively. Furthermore, PFS and DFS were not significantly affected by type of adjuvant therapy (observation, radiotherapy, chemotherapy, and chemoradiotherapy).

Both papers further emphasize the importance of molecular characterization of endometrial cancer, as accurate classification has both prognostic and therapeutic implications and, in the case of MMR testing, may identify hereditary cases of endometrial cancer. In light of the growing body of evidence supporting this classification system, the National Comprehensive Cancer Network has incorporated molecular analysis into its endometrial carcinoma algorithm. Universal testing for MMR proteins is recommended, and *MLH1* loss should be further evaluated for promoter hypermethylation to assess an epigenetic mechanism. If resources are available, additional studies for *POLE* sequencing and *p53* immunohistochemistry are encouraged [9]. Further research is needed regarding the management of patients with varying molecular profiles. For example, the role of anti-PD-1 therapy in the management of previously treated MMRd tumors is well-established [10], but the role of immunotherapy in front-line treatment of these tumors is a current area of investigation. Additionally, it is unknown whether treatment could be deescalated for those with *POLE*mut tumors or how treatment should be optimized for p53abn or NSMP tumors. Research is also needed regarding the prognostic and therapeutic implications of tumors with overlapping molecular profiles. We eagerly await the results of ongoing studies to help answer these questions.

REFERENCES

1. Yen TT, Wang TL, Fader AN, Shih IM, Gaillard S. Molecular classification and emerging targeted therapy in endometrial cancer. Int J Gynecol Pathol 2020;39:26-35.
PUBMED | CROSSREF
2. McAlpine J, Leon-Castillo A, Bosse T. The rise of a novel classification system for endometrial carcinoma; integration of molecular subclasses. J Pathol 2018;244:538-49.
PUBMED | CROSSREF
3. Jamieson A, Bosse T, McAlpine JN. The emerging role of molecular pathology in directing the systemic treatment of endometrial cancer. Ther Adv Med Oncol 2021;13:17588359211035959.
PUBMED | CROSSREF
4. Talhouk A, McConechy MK, Leung S, Li-Chang HH, Kwon JS, Melnyk N, et al. A clinically applicable molecular-based classification for endometrial cancers. Br J Cancer 2015;113:299-310.
PUBMED | CROSSREF

https://doi.org/10.3802/jgo.2022.33.e47

5. Stelloo E, Bosse T, Nout RA, MacKay HJ, Church DN, Nijman HW, et al. Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative. Mod Pathol 2015;28:836-44.
PUBMED | CROSSREF
6. Cosgrove CM, Tritchler DL, Cohn DE, Mutch DG, Rush CM, Lankes HA, et al. An NRG Oncology/GOG study of molecular classification for risk prediction in endometrioid endometrial cancer. Gynecol Oncol 2018;148:174-80.
PUBMED | CROSSREF
7. Hong JH, Cho HW, Ouh YT, Lee JK, Chun Y, Gim JA. Genomic landscape of advanced endometrial cancer analyzed by targeted next-generation sequencing and the cancer genome atlas (TCGA) dataset. J Gynecol Oncol 2022;33:e29.
PUBMED | CROSSREF
8. Yu S, Sun Z, Zong L, Yan J, Yu M, Chen J, et al. Clinicopathological and molecular characterization of high-grade endometrial carcinoma with POLE mutation: a single center study. J Gynecol Oncol 2022;33:e38.
CROSSREF
9. Abu-Rustum NR, Yashar CM, Bradley K, Campos SM, Chino J, Chon HS, et al. NCCN guidelines® insights: uterine neoplasms, version 3.2021. J Natl Compr Canc Netw 2021;19:888-95.
PUBMED | CROSSREF
10. O'Malley DM, Bariani GM, Cassier PA, Marabelle A, Hansen AR, De Jesus Acosta A, et al. Pembrolizumab in patients with microsatellite instability-high advanced endometrial cancer: results from the KEYNOTE-158 study. J Clin Oncol 2022;40:752-61.
PUBMED | CROSSREF