Advancing endometrial cancer management in the era of molecular classification: insights into pattern of recurrence

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Received 23 March 2024
Accepted 27 March 2024
Published Online First 8 April 2024

► http://dx.doi.org/10.1136/ijgc-2023-005165

To cite: De Vitis LA, Multinu F. *Int J Gynecol Cancer* 2024;**34**:667–668.

Following the landmark study of the Cancer Genome Atlas, the classification of endometrial cancer into four groups has reshaped its management: (1) POLE mutated, (2) mismatch repair deficient, (3) p53 abnormal, and (4) no specific molecular profile. Since then, molecular classes have been incorporated into international guidelines and clinical algorithms.[1 2] Recently, the International Federation of Gynecology and Obstetrics included the classification in its updated staging system.[3] Nevertheless, numerous questions remain unanswered, one of which pertains to whether molecular classification can predict the recurrence pattern of endometrial cancer.

This month's lead article by Aznar et al addresses this question.[4] They conducted a single center retrospective analysis of 658 endometrial cancer patients categorized by molecular classification. Among them, 122 (18.5%) experienced relapses, which were categorized by site of recurrence into vaginal, pelvic, peritoneal, nodal, and distant. As anticipated, the p53 abnormal classification presented the highest rate of relapse (53.7%), with the majority of recurrences being distant (28.4%) and peritoneal (21.1%). The no specific molecular profile and mismatch repair deficient classifications showed similar recurrence rates (14.5% and 12.4%, respectively), but no specific molecular profile, despite the excellent prognosis, recurred more frequently on distant locations (10.3%), whereas mismatch repair deficient recurrences tended to be locoregional (ie, vaginal, pelvic, and nodal) (9.4%). Only one (2.1%) recurrence of the POLE mutated classification was detected at the para-aortic lymph node, thus reflecting excellent oncologic outcomes.

Interestingly, in the multivariable analysis adjusting for clinical and histopathologic parameters, the p53 abnormal classification remained a significant risk factor for peritoneal and vaginal recurrences, while both the p53 abnormal and no specific molecular profile classifications proved to be independent predictors of distant recurrence.

These findings could have significant implications for adjuvant treatment management. In accordance with the results of PORTEC-3 (Randomized Trial of Radiation Therapy With or Without Chemotherapy for Endometrial Cancer), p53 abnormal endometrial cancers might benefit more from systemic chemotherapy, thereby reducing the risk of distant metastasis, while mismatch repair deficient cancers may require local treatments, such as radiotherapy, to minimize recurrence in vaginal, pelvic, and lymph node regions.[5] The no specific molecular profile category, representing the largest molecular class, showed heterogeneous behavior even within this study, highlighting the need for further stratification into smaller subgroups. Recent evidence suggests that a number of biomarkers, such as hormone receptors, may be useful for this purpose.

In addition to treatment selection, follow-up strategies can be tailored to molecular classes. While p53 abnormal cancers may need more rigorous follow-up and imaging focused on detecting distant and peritoneal metastases, POLE mutated cases can probably be monitored at longer intervals, reducing patients stress.

Endometrial cancer, whose incidence is rising in tandem with the increase in associated risk factors, will pose a significant burden in the foreseeable future. Hence the paper by Aznar et al, along with recent literature on molecular biomarkers, will aid the gynecologic oncology community in better managing this rapidly evolving disease. Nonetheless, further studies and higher levels of evidence are crucial before this novel approach can be universally adopted, as advocated by scientific societies and experts. To date, prospective studies are limited, although many are underway and will hopefully confirm the existing body of evidence.

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Contributors All authors contributed to the writing and approval of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

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