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Editorial

ProMisE on the horizon: molecular classification of endometrial cancer in young women

While the global incidence and mortality from most solid tumors have declined or plateaued in the last thirty years, endometrial cancer remains one of the only malignancies in which both incidence and deaths are on the rise [1]. In the United States alone, the rate of new uterine cancer cases has increased 1% per year and the mortality rate has risen 1.9% annually. In 2018, this amounted to 63,230 new cases and 11,315 deaths [2]. With a growing obesity epidemic and a strong correlation between increasing weight and endometrial cancer risk, these sobering statistics are only expected to worsen [3]. Perhaps this is, in part, related to the many biological subtypes and molecular alterations found in endometrial cancer and that a "one size fits all" approach to treatment has not lead to improved outcomes. Despite this, clinical research funding, output, and subsequent treatment success has somewhat lagged behind that of other women's cancers [4]. Although approximately 75% of women diagnosed with endometrial cancer have early-stage disease and overall favorable survival rates, clinical outcomes for women with high-risk histologies, advanced-stage at diagnosis, or disease recurrence leave much to be desired [4]. Additionally, 15% of new endometrial cancer cases are diagnosed in young, premenopausal women—a trend also anticipated to increase. Even in cases were cure is possible, the loss of reproductive potential in younger women diagnosed with an endometrial malignancy is a devastating consequence of treatment. Given these disturbing trends, a reinvigorated research effort focused on endometrial cancer prevention and on identifying those with cancer who are most likely to benefit from definitive surgical and adjuvant therapies are needed.

One strategy to improve outcomes in this setting is to more accurately identify those at the highest risk of recurrence or treatment failure through contemporary tumor classification systems. Traditional classification protocols use histopathology to stratify tumors into separate categories with differing behavior and prognosis. Specifically, Bokhman's classification schema, using clinical and endocrine features to sort endometrial cancers into two cohorts (i.e, Type 1 and Type 2) [5], and more recently, the World Health Organization system of grade and histology categorization, have been utilized to characterize endometrial cancer subtypes for purposes of both clinical care and research. The current systems require minimal tumor testing and rely primarily on pathology review. However, there are limitations to this approach including inter-observer variability and inconsistencies in histologic and grade categorization [6,7]. To reduce these discrepancies and increase the prognostic value of the classification system, current research is focused on identification and validation of endometrial cancer molecular classification protocols.

New molecular methods have already begun to revolutionize tumor classification protocols and identify those women who will most profit from specific targeted treatments or immunotherapies. The Cancer Genome Atlas (TCGA) project provided the first comprehensive molecular analysis of endometrial cancer [8]. This landmark effort classified endometrial cancer into four prognostic subgroups: POLE ultra-mutated, microsatellite instable, microsatellite stable/copy number low and serous-like/copy number high. Notably, the study identified a previously unrecognized subgroup of POLE ultra-mutated tumors with a superior prognosis irrespective of other high-risk tumor characteristics [8] and an additional subgroup of microsatellite instable tumors that are quite responsive to checkpoint inhibitor therapies [9]. However, the TCGA technique is time consuming, costly, and requires specialized tissue handling and processing. Thus, it is not practical for routine clinical care. In the race to develop a diagnostically accurate and more clinically feasible molecular classification system, two approaches have emerged. The ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer) algorithm employs mutation and protein expression analyses to assign tumors to one of four subgroups: mismatch repair deficient, POLE mutated, p53 abnormal, and p53 wild type. ProMisE subgroup assignment is sequential, first delineating the MMR-deficient cases, then POLE, and finally aberrant p53 staining; the remaining tumors are categorized as p53 normal [10–12]. Similarly, the TransPORTEC initiative has identified four prognostic subgroups, p53-mutant tumors, microsatellite instable tumors, POLE proofreading-mutant tumors, and a group with no specific molecular profile [13]. In both series, prognostic signatures emerged by stratifying endometrial cancer tumors by these molecular criteria. Ongoing studies to validate the findings and to explore a molecular approach to risk stratification and treatment decision-making are in progress.

In this month's issue of *Gynecologic Oncology*, Britton et al [14] present a study on ProMisE molecular subtyping of tumors from young women (< 50 years of age) with endometrial cancer [13]. Care of this population presents unique challenges due to issues relating to fertility preservation, retention of ovaries, and long-term treatment toxicity. Under-treatment in an attempt to allow for fertility or ovarian preservation may introduce excess oncologic risk, while over-treatment may subject patients to loss of fertility, lifelong treatment side effects, as well as an elevated risk of secondary malignancy in some cases. Thus, accurate risk stratification is vital for these young women. Building on the prior work by Talhouk et al [4], 257 young study subjects who had hysterectomies performed for endometrial adenocarcinoma were studied. Clinicopathologic and outcomes data were gathered and formalin-fixed paraffin-embedded blocks were used for analysis.

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Immunohistochemistry for PMS2, MSH6 and p53 and sequencing of POLE exons 9-14 was performed. The most frequently identified ProMisE subtype was p53 wildtype (64%), followed by MMR deficient (19%), POLE (13%) and p53 abnormal (4%). The distribution of molecular subtypes was consistent to that observed in previously published, non-age stratified cohorts with the exception of less p53 abnormal staining observed in the younger cohort of the current study. Noteworthy associations between ProMisE subtype and clinicopathologic characteristics included: 1) p53 wildtype designation and age less than 35, 2) p53 abnormal designation and age 41-49 years, 3) MMR deficient and advanced stage, and 4) POLE mutation and aggressive molecular features. Notably, no association between synchronous ovarian primary tumors and a ProMisE subtype was observed. A subset of 189 study subjects was also divided into three clinical risk groups: high estrogen (55%), Lynch-like (10%), or neither (35%). Lynch-like was associated with advanced stage, high-grade, and non-endometrioid subtypes. The study also compared the association of molecular subtype and clinical risk group. The distribution of ProMisE subtypes within clinical risk groups differed markedly, with 80% of the high estrogen cohort found to be p53 wildtype, 78% of the Lynch-like subtype was MMR deficient, and more than twice the expected number of POLE mutated tumors (23%) in the neither clinical category. Most notably, the ProMisE subtypes were associated independently with disease-specific (DSS) and overall survival (OS), whereas the clinical risk groups were not associated with survival.

With this initial test cohort and prior studies by this research team, Britton et al [14] have made a compelling case for consideration of endometrial cancer molecular subtyping via the ProMisE method. Although women undergoing conservative treatment and fertility preservation were not specifically studied, the authors have set the stage for a potential paradigm shift away from solely using histologic classification and clinical data to guide treatment recommendations and towards a molecular subtyping model which may more accurately predict DSS and OS in this patient population. The methods are rapid, feasible, and appear cost contained, thus overcoming a previous practical barrier to successful implementation of a molecular categorization system. However, prospective and larger studies in a racially diverse, young endometrial cancer patient population undergoing conservative management have not been performed to date, and are necessary to validate ProMisE in this setting. Given there are no reliable biomarkers of hormonal treatment response or outcome in young women with endometrial cancer undergoing uterine-sparing treatments, it will be critical to assess the utility of ProMisE in predicting which patients are the safest candidates for conservative treatment.

Still in its infancy, ProMisE is a clinically relevant and feasible molecular subtyping framework designed with the intent of improving risk stratification of endometrial cancer. In addition to those TCGA-like markers proposed within the existing platform, there are other relevant endometrial cancer markers and actionable mutations, such as ARID1A, TSC2, CTNNB1, and HER2, that may also be considered in a contemporary molecular diagnostic paradigm [15,16]. A truly valuable molecular subtyping platform must not only be predictive of outcome, but identify tumors that may respond to specific existing treatments and help molecularly stratify tumors to allow for exploration of new drug development targets. In the coming decade, our challenge will be to transform a molecular subtyping model of endometrial cancer from a prognostic to a predictive tool, integrated into day-to-day decision-making and clinical trials. Realizing the “promise” of tumoral molecular signatures and mutational diagnostics in endometrial cancer care, with the goal of tailoring therapies, reducing over- and under-treatment, and improving survival may be closer than we think.

Author contribution

Both authors contributed to researching and writing the article.

Conflicts of interest

Dr Fader reports an honorarium from Merck.
Dr Wethington has nothing to disclose.

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