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Slow and steady wins the race: precision medicine for low risk endometrial cancer

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In general, women with early stage, low grade endometrioid endometrial cancer can be cured with surgery alone. If patients experience recurrence outside of the vagina, however, their likelihood of death is as high as patients with stage IV disease.[1] Historically, histologic characteristics, such as depth of myometrial invasion and lymphatic/vascular space invasion, and clinical characteristics, such as age, have been used to triage patients at highest risk for recurrence and who might benefit from adjuvant therapy.[2] However, all gynecologic oncologists can identify more than a few endometrial cancer patients from their practice who inexplicably suffered from recurrence despite favorable characteristics at diagnosis. This is a clear area of unmet need.

Given limitations of clinicopathologic features, researchers are searching for molecular features to identify patients who will have poor outcomes. A number of molecularly relevant biomarkers evaluated previously include estrogen regulation genes,[3] DNA ploidy,[4] mismatch repair deficiency,[5] and homologous recombination deficiency.[6] Next generation sequencing has also been used to identify potential prognostic biomarkers, including *CTNNB1*, *TP53*, and *POLE*.[7 8] Recently, complex algorithms have been proposed based on findings of The Cancer Genome Atlas, the best developed of which include ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer)[9] and PORTEC (Post Operative Radiation Therapy in Endometrial Carcinoma)-4a.[10] However, none of these has yet impacted clinical practice and the care of women with endometrial cancer.

In this issue of the *International Journal of Gynecologic Cancer*, Stasenko and colleagues[11] performed molecular evaluation, including microsatellite instability and deep next generation sequencing, to determine features associated with recurrent low grade, early stage endometrial cancer. One of the clear strengths of the current study was the narrow inclusion criteria limiting patients to only those of lowest risk: grade 1 endometrioid histology without myometrial invasion or lymphatic/vascular invasion. However, this same strength also plagues many similar single-institution, retrospective studies. These stringent criteria are only met by a relatively small number of patients, even at large volume centers. This is further compounded by limitations of accessing and sequencing old tumor blocks, many of which contain only a small amount of tumor at the outset. This is exemplified in the current paper where 211 had microsatellite instability testing but only 36 underwent full genomic profiling. The number of patients required to detect the impact of mutations (whose effects are not all or none) on a rare outcome is already high. When we then evaluate for increasingly complex combinations of mutations and clinical characteristics that are more reflective of real-world practice, this already large number becomes astronomical.

We strongly agree with the authors' recommendation that future prospective evaluations should be undertaken. Retrospective data are intriguing and hypothesis-generating, but until these molecular markers are evaluated in a prospective manner, it is unlikely treatment algorithms will change. Additionally, simply identifying a high-risk marker is not adequate—an effective treatment must then be identified for at-risk patients. Whether the ideal treatment will include traditional strategies, combining radiation and cytotoxic chemotherapy, or a completely novel therapy approach remains to be seen and will similarly require prospective evaluation. We eagerly anticipate results from PORTEC-4A and other prospective, molecularly driven, clinical trials under development with the hope that, as a field, we can develop and validate new treatment algorithms for women with low risk endometrial cancer.

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