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Endometrial cancer at recurrence: To re-sequence or not to re-sequence

In this month's issue of *Gynecologic Oncology Reports*, Gordhandas et al. describe their exploration of molecular processes underpinning distant metastases in two patients with endometrial cancer and lung recurrences. As part of this study, investigators performed whole exome sequencing of primary and metastatic tumors to compare somatic mutations and mutational signatures. This was complemented by immunohistochemical analysis of β-catenin and mismatch repair proteins, as well as MLH1 promoter methylation assessment and microsatellite instability testing. The authors found that both endometrioid endometrial cancer cases demonstrated a branched evolution with clonal shifts during the metastatic process whereby subclonal hotspot *CTNNB1* alterations became more dominant clonal mutations. In both cases, the carcinomas acquired additional mutations during the metastatic process. The authors postulated that specific *CTNNB1* alterations may be more likely to drive metastases, and that additional study is warranted to identify the specific alterations that most increase the risk for tumor spread (Kurnit, 2017).

These small but detailed studies are important landmarks as we advance our understanding of the interplay between molecular features and clinical behavior of endometrial cancer. In the wake of the 2023 International Federation of Gynecology and Obstetrics (FIGO) guidelines, there has been increasing focus on how molecular subtyping could be used to risk stratify patients with endometrial cancer; however, this is likely just the tip of the molecular iceberg (Berek, 2023). Certainly, there is a need for increased understanding of how molecular alterations influence patient prognosis, given observed heterogeneity in the clinical behavior of tumors within each molecular subtype (McMeekin, 2007; Stasenko, 2020). As Gordhandas et al. suggest, certain molecular alterations may identify patients who could benefit from more aggressive surveillance.

Beyond simply risk stratifying patients, the ultimate goal of molecular testing should be to improve patient outcomes, either by tailoring interventions or de-escalating therapy. While early-stage, low-grade endometrial cancer is largely curable with surgery alone, historically relied upon cytotoxic therapies have limited therapeutic benefit in advanced or recurrent disease (Davidson, 2016). In fact, some of the greatest advances in endometrial cancer outcomes have been biomarker-informed. For example, patients with mismatch repair-deficient tumors demonstrated marked improvements in survival with incorporation of immunotherapy, and patients with endometrial cancer overexpressing HER2/neu have improved survival with trastuzumab or trastuzumab deruxtecan (Eskander, 2023; Meric-Bernstam, 2024). Significant work remains to better understand which signaling cascades can be effectively and safely targeted, such as the Wnt/β-catenin pathway described by Gordhandas et al. (Urick and Bell, 2019). Challenges that must be overcome include a lack of available therapies and trials; financial and geographic barriers to accessing care with a strong bias of molecular testing toward resource-rich environments; and nascent understanding of the contextual importance of mutations and their functional consequences in tumor biology. Progress is underway, with one investigation reporting a 47% clinical benefit rate in a group of patients with endometrial cancer who enrolled in clinical trials based on tumor genetic features (Soumerai, 2018).

As Gordhandas et al. demonstrate in their case report, the molecular landscape of a tumor is dynamic. An extensive body of literature has demonstrated that distinct patterns of molecular alterations and shifts accompany tumor progression (Dessources, 2020; Ashley, 2019; Mota, 2022). Just as the tumor evolves, treatment strategies must also evolve to target shifting oncogenic drivers. While repeat biopsy and parallel sequencing can be performed, as was done in this case report, "liquid biopsy" of circulating tumor DNA represents a promising strategy for better understanding dynamic changes in the tumor landscape and for more accurately representing the often heterogenous intra- and inter-tumoral landscape. For example, in both lung and colorectal cancers, serial cell-free DNA analysis monitors for acquired resistance in patients who receive epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (Misale, 2012; Francaviglia, 2019). In endometrial cancer, preliminary studies have demonstrated that cell-free DNA could be used to monitor response to immune checkpoint inhibition, with emergence of alterations associated with immunotherapy resistance, such as truncating *B2M* alterations, in patients who progress on treatment (Manning-Geist, 2022).

Finally, given the findings from this study that recurrent, metastatic tumors acquire additional mutations during the metastatic process, this study supports the idea to perform molecular tests on not only the primary tumor but also recurrent, metastatic sites. The tumor from Case 1 was found to have the molecular subtype class of TP53 wild-type, copy number-low/no specific molecular subtype (NSMP) of the primary tumor with a subclonal *CTNNB1* mutation, but the recurrent lung metastasis showed that this subclonal *CTNNB1* gain-of-function hotspot mutation (p.G34V) became clonal. Additionally, the tumor from Case 2 was found to have a molecular subtype of MMRd, and the recurrent lung and brain metastasis had acquired *CTNNB1 p.G34E* hotspot mutation. Thus, these cases highlight that endometrioid endometrial cancers can harbor subclonal *CTNNB1* mutations that become clonal at the metastatic sites. Additionally, there may be certain hotspot *CTNNB1* mutations that have a greater effect than others as seen in this study.

While this month's featured article is a small study, it highlights promising issues related to the molecular drivers of endometrial cancer including: the importance of molecular data in prognostication, how

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alterations can be leveraged in treatment decisions, and how longitudinal molecular data can and should be used in treatment decisions. The future of molecular analysis for endometrial cancers will be one that allows us to better individualize care and develop treatments based on these molecular findings.

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