HER2 Heterogeneity: Why Single-Block Testing May Miss Gastric Cancer Treatment Targets

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Accurate assessment of HER2 status is critical for guiding targeted therapy in various solid tumors, including gastric and gynecologic cancers. However, the inherent heterogeneity of tumors can complicate biomarker evaluation, potentially leading to misclassification and suboptimal treatment strategies. This article explores recent findings on HER2 heterogeneity and its implications for clinical practice.

KEY TAKEAWAYS

- The Pivot: Intratumoral HER2 heterogeneity is a significant factor, with single-block testing potentially underestimating HER2 expression in gynecologic cancers.
- The Data: Dual-block assessment reclassified 13.5% of gynecologic tumors from HER2-0 to HER2 expression, improving detection sensitivity.
- The Action: Clinicians should consider the impact of tumor heterogeneity on biomarker testing, particularly for HER2, to optimize patient selection for targeted therapies in gastric and gynecologic malignancies.

The Challenge of HER2 Assessment in Gynecologic Cancers

The emergence of HER2-targeted antibody-drug conjugates (ADCs) has underscored the importance of precise HER2 status evaluation across various solid tumors. However, gynecologic cancers, which present substantial clinical challenges, particularly in advanced stages, often have limited treatment options and poor prognoses. Accurate HER2 assessment is essential for patient stratification for these targeted therapies. A recent study investigated intratumoral HER2 heterogeneity in gynecologic cancers to refine detection accuracy and improve patient selection for HER2-targeted treatments1.

Investigating Intratumoral HER2 Heterogeneity

Researchers conducted a retrospective analysis of 416 patients with gynecologic malignancies. The study utilized immunohistochemistry (IHC) testing on separate dual formalin-fixed paraffin-embedded (FFPE) tumor blocks. HER2 expression was scored according to ASCO/CAP gastric criteria. Intratumoral heterogeneity was defined as discordant IHC scores between the two blocks. Statistical analyses, including McNemar's test and multivariate logistic regression, were employed to identify discordance and clinical predictors1.

Key Findings: Underestimation of HER2 Expression

The study revealed that HER2 IHC scores across all gynecologic tumors were distributed as 0 (49.5%), 1+ (33.9%), 2+ (15.6%), and 3+ (1.0%). HER2 overexpression was most frequently observed in uterine serous carcinoma, uterine endometrioid carcinoma, and ovarian clear cell carcinoma within the cohort. Significantly, intratumoral discordance was

identified in 20.7% of all cases. The highest rates of discordance were found in uterine (23.9%, 21/88), ovarian (21.4%, 39/182), and cervical (18.2%, 26/143) tumors1.

The dual-block assessment demonstrated that most discrepancies involved incremental shifts in HER2 expression, primarily from 0 to 1+ or from 1+ to 2+. This enhanced detection approach led to the reclassification of 13.5% of tumors initially reported as HER2-0 to a state of HER2 expression. These findings suggest that relying on a single tumor block may frequently underestimate true HER2 expression, potentially impacting eligibility for HER2-targeted therapies1.

Broader Implications for Gastric Cancer Biomarker Testing

The issue of tumor heterogeneity is not unique to gynecologic cancers. Gastric cancer (GC) is also recognized as a highly heterogeneous disease, exhibiting variations in both histological presentation and genetic characteristics. Recent advancements in the treatment of metastatic and unresectable GC necessitate accurate biomarker testing for patient management. Predictive biomarkers such as HER2, programmed death-ligand 1 (PD-L1), mismatch-repair (MMR) proteins, claudin 18.2, and fibroblast growth factor receptor 2b (FGFR2b) are commonly evaluated using immunohistochemistry2.

However, the expression levels of these biomarkers can vary significantly across different tumor areas. The accuracy of biomarker diagnosis can be influenced by factors such as sample quantity, location, and collection method. Tumor heterogeneity can be categorized into spatial heterogeneity (variations within the primary tumor or between primary and metastatic sites) and temporal heterogeneity (changes over time). This inherent variability presents substantial challenges for accurate biomarker-based diagnosis and the prediction of therapeutic responses in gastric cancer2.

Clinical Implications

The findings from the gynecologic cancer study underscore a critical consideration for clinicians: intratumoral HER2 heterogeneity is common and can lead to underestimation of HER2 expression when only a single tumor block is assessed1. This has direct relevance for gastric cancer, where HER2 status is a key determinant for trastuzumab-based therapies. If a significant proportion of tumors are misclassified as HER2-negative due to sampling limitations, patients who could benefit from targeted ADCs or other HER2-directed treatments might be overlooked.

Why this matters for clinical practice today: For patients with gastric or gynecologic cancers, particularly those with advanced or recurrent disease, accurate HER2 status is paramount for treatment selection. The data suggest that a single biopsy or tumor block might not fully capture the HER2 landscape of a tumor. Clinicians should consider the potential for intratumoral heterogeneity, especially when initial HER2 results are negative or equivocal, and explore options for re-biopsy or multi-site sampling if clinically appropriate and feasible. This vigilance could help identify more patients who may benefit from HER2-targeted therapies, ultimately improving treatment outcomes.

Limitations and Next Steps

The gynecologic cancer study was a retrospective, single-center analysis, which may limit the generalizability of its findings. While dual-block assessment improved detection sensitivity, the optimal number and location of blocks for comprehensive HER2 evaluation still require further investigation. Future research should explore the clinical impact of reclassifying HER2 status based on dual-block assessment on patient outcomes and response to HER2-targeted therapies. Additionally, studies are needed to develop standardized protocols for managing tumor heterogeneity in biomarker

testing across different cancer types, including gastric cancer, to ensure consistent and accurate patient stratification for targeted treatments1,2.

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