

Abstract

Title: HER2 IHC Discordance Across Serial Prostate Cancer Biopsies

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Background. HER2 is re-emerging as a therapeutic target in prostate cancer as HER2-directed antibody–drug conjugates enter pan-tumor and HER2-low development. No prostate-specific HER2 IHC scoring system exists, and clinical practice relies on criteria developed for breast and gastroesophageal cancers. It remains unclear whether HER2 expression changes across serial biopsies and whether such changes reflect tumor biology, specimen heterogeneity, or assay variability. We examined changes in HER2 IHC scores between serial biopsies in a predominantly Black/African American cohort and explored associations between HER2 status and clinicopathologic features.

Methods. We analyzed 51 patients with HER2 IHC scores (0/1+/2+/3+) available from first and second biopsies. Changes were evaluated at three prespecified binary thresholds: 0 versus $\geq 1+$, 0–1+ versus 2–3+, and 0–2+ versus 3+. Paired differences were assessed using the exact McNemar test with Tango 95% confidence intervals. Changes in ordinal distribution were evaluated using the Stuart–Maxwell test and mean-score analysis, and agreement between biopsies was measured using Cohen κ . Exploratory analyses examined predictors of conversion from 0 to $\geq 1+$, survival, and associations of HER2 status with age, stage, Gleason score, PSA, biopsy interval, biopsy site, and treatment.

Results. The proportion of patients with HER2 $\geq 1+$ increased from 39.2% on the first biopsy to 70.6% on the second (paired difference, +31.4%; 95% CI, +16.0 to +46.2; $P=0.0004$). Mean HER2 score increased from 0.57 to 1.10 ($P=0.002$). However, this increase was driven almost entirely by changes at the 0-to-1+ boundary. Among 31 tumors initially scored HER2 0, 18 (58%) were subsequently scored $\geq 1+$. Changes at higher-expression thresholds were not statistically significant (2–3+, 15.7% to 29.4%; $P=0.065$; 3+, 2.0% to 9.8%; $P=0.219$). Agreement between biopsies was poor (unweighted $\kappa=0.18$; linear-weighted $\kappa=0.29$), with discordance across HER2 categories in 57% of cases. The median biopsy interval was 14 weeks. Among patients initially HER2 0, no candidate variable, including age, PSA, Gleason score, stage, biopsy interval, or treatment, was associated with conversion, likely reflecting limited sample size. HER2 status on the first biopsy was associated with AJCC stage ($P=0.007$) and Gleason score ($P=0.014$).

Conclusions. HER2 IHC scores increased between serial biopsies, largely because tumors initially classified as HER2 0 were subsequently scored 1+. Although this finding was consistent across multiple statistical approaches and observed in untreated patients, the change was limited to the 0-versus-1+ boundary, the least reproducible distinction in HER2 IHC. Given the short median biopsy interval and poor overall agreement, these findings cannot distinguish biological upregulation from measurement variability or specimen heterogeneity. HER2 status may therefore be unstable across serial prostate cancer samples, and a single biopsy may under-detect HER2-low disease. Prostate-specific scoring criteria and central or duplicate IHC review are needed before serial HER2 testing can reliably inform HER2-directed treatment.

Funding Acknowledgements

This study received no specific external funding.

Conflicts of Interest Disclosure Statement

The authors declare no conflicts of interest related to this study.