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Human epidermal growth factor receptor-type 2 status and tumor heterogeneity in invasive breast carcinomas: clinical pathological impact

Karla Calaça Kabbach Prigenzi¹, Lucas de Figueiredo Barbosa¹, Lisandra Gonzalez Porta Nova¹, Adilson Monteiro dos Santos Filho¹, Ana Luiza da Cruz¹, Angela Flávia Logullo Waitzberg¹

¹Universidade Federal de São Paulo, Escola Paulista de Medicina – São Paulo (SP), Brazil.

Objective: To assess the human epidermal growth factor receptor-type 2 (HER2) expression spectrum in primary invasive breast carcinoma, focusing on its heterogeneity and correlation with pathological factors, given its impact on prognosis and therapy resistance. **Methods:** A retrospective study reanalyzed HER2 immunohistochemistry slides from patients with primary invasive breast carcinoma diagnosed and treated at the São Paulo Federal University Hospital, from 2019 to 2023. Clinical data, including age, laterality, tumor size, and Breast Imaging Reporting and Data System (BI-RADS), were collected. The HER2 slides were reviewed by three observers, following the ASCO-CAP 2018 guidelines. Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS), version 26.0. **Results:** The study included 353 patients, with a mean age of 58 years. Of those, 191 (54.1%) cases were left-sided and 162 (45.9%) were right-sided. BI-RADS categories 4 and 5 were the most common. Among 164 patients with follow-up, 14 deaths occurred. Pathologically, 304 (86.1%) cases were of no special type, and 26 (7.4%) were of invasive lobular carcinomas. HER2 status showed 296 (83.9%) negative, 42 (11.9%) positive, and 15 (4.2%) HER2 2+. Regarding negative cases, 235 were HER2 0+ and 61 were HER2 1+. HER2 intratumoral heterogeneity was present in 66 cases (18.7%), with 34 (51.5%) showing 1+ as the primary score. HER2 positivity and intratumoral heterogeneity were associated with higher mortality ($p=0.003$ and $p=0.001$, respectively). HER2-positive tumors were larger than HER2-negative ones (31.3 vs. 25.6 mm; $p=0.012$), while intratumoral heterogeneity did not correlate with tumor size ($p=0.165$). **Conclusion:** We conclude that intratumoral heterogeneity is prevalent in HER2 expression and should be addressed in pathology reports, since it may play an additional role in tumor progression and drug response, especially in the antibody-drug conjugates scenario.

Keywords: breast neoplasms; ErbB-2 receptor.