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Title: Monosomy of Chromosome 17 in Breast Carcinoma During Interpretation of Her-2/neu Gene Amplification.

Submission Body:

Background: Recent guidelines (ASCO/CAP 2013) addressed and get guide to appropriate Her-2/neu test scoring. Among uncommon patterns of Her-2 abnormalities, monosomy of chromosome 17 may affect the interpretation of Her-2/neu amplification. Its prevalence ranges from 1% up to 38% of breast carcinoma. We sought to evaluate the impact of monosomy of chromosome 17 to interpretation of Her-2/neu gene status.

Design: 201 breast carcinoma were reviewed at genomic level for Her-2/neu gene amplification. FISH analysis was performed by using double probes (LSI/CEP) (Abbott). Absolute gene copy number was scored per each probe. Her-2 FISH test was repeated on serial tissue sections, ranging in thickness from 3 to 20 µm. Ratio was initially scored and subsequently corrected by monosomy after control tests using the aCGH method to overcome false interpretation due to nuclear truncation. Her-2 immunotests (Hercept Test) was performed on all cases.

Results: 26/201 cases were amplified (13%). Single signals per CEP17 were revealed in 7/201 (3,5%) cases. Five out of 7 cases appeared monosomic after matching with aCGH analysis and evidenced single signals in >60% of nuclei after second-look on FISH analysis. Among 5, one case showed amplification with a pattern 7/1 (Her-2/CEP17>2) of copies (3+ at immunotest); three cases revealed single signals per both probes (LSI/CEP=1) and one case revealed a 3:1 (LSI/CEP>2) count ratio; importantly all last 4 cases showed 0/1+ score at immunotest.

Conclusion: 1) monosomy of chromosome 17 may be observed in 3,5% of breast carcinoma; 2) the skewing of the ratio due to single centromeric 17 probe may bring to false positive evaluation of gene amplification; 3) monosomy due to biological reasons rather than nuclear truncation was observed when cut-off set to 60% of nuclei; 4) when dealing with cases showing a 3:1 ratio (Her-2/CEP) the interpretation should be “Her-2 negative”.
