

## Letter to the Editor

### Micrometastases in axillary nodes: Out of the reckoning?

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Dear Editor,

The treatment of breast cancer has seen a paradigm shift towards minimally invasive surgery with large randomized trials<sup>[1,2]</sup> conclusively establishing sentinel lymph node biopsy (SLNB) in node negative patients as the standard of care. SLNB has in turn led to an increase in the detection of micrometastasis and isolated tumor cells as a result of more thorough and exhaustive evaluation of a smaller number of nodes. The study looking at immunohistochemistry (IHC) detection of micrometastases in node-negative patients by Choudhury *et al.*<sup>[3]</sup> brings to the fore yet another debate in the surgical management of breast cancer.

Of 178 patients who underwent a mastectomy at the author's institute, 32 (17.9%) were negative for axillary lymph node metastasis. On further IHC evaluation of these 32 cases, 6 (18.75%), and 4 (13%) cases were positive for axillary lymph node metastases by cytokeratin (CK) and epithelial membrane antigen (EMA) staining respectively. A statistically significant correlation is also established between the sentinel nodes identified by the surgeon and the detection of these micrometastases by CK and EMA IHC. All the patients detected with micrometastases received adjuvant chemotherapy and barring two who were lost to follow-up, the rest were disease-free at a median follow-up of 56 months. The numbers are very small, but it definitely opens up the Pandora's Box again.

Clinical significance of detection and treatment of micrometastatic disease in the axilla has been widely studied and debated with controversial results. In the NSABP B-32 trial<sup>[4]</sup> despite a statistically significant detriment in overall survival (OS) of 1.2% in the group with occult metastases, the investigators ruled out the routine use of IHC for the detection of micrometastatic disease.

Similarly in the MIRROR study,<sup>[5,6]</sup> the group with micrometastases had worse disease-free survival (DFS) outcomes and axillary recurrence rates, but these reached statistical significance only in the group that did not receive adjuvant therapy. In one of the landmarks trials on nodal micrometastases, ACOSOG Z0010 occult metastases were detected in 349 (11%) of 3326 cases.<sup>[7]</sup> However, no significant association was noted between IHC detected occult metastases and DFS or OS at a median follow-up of 6.3 years and the 5 year OS and DFS rates were comparable between IHC positive and negative sentinel node groups. Another important trial, the International Breast Cancer Study Group 23-01 randomized women with micrometastatic disease in the sentinel node to SLNB alone versus completion axillary lymph node dissection.<sup>[8]</sup> Even though the trial closed early due to low accrual and failure to attain the projected event rates, both groups at a median follow-up of 5 years had similar axillary recurrence, DFS and OS rates indicating no clinical significance of micrometastases on outcome. Furthermore, in a meta-analysis<sup>[9]</sup> by de Boer *et al.* despite a poorer DFS and OS associated with micrometastases and

isolated tumor cells, this significance was lost on multivariate analysis.

The data on micrometastatic disease must also be viewed in the light of trials such as ACOSOG Z11, wherein macrometastatic positive nodes left behind in the axilla did not impact survival in breast cancer patients<sup>[10]</sup> and AMAROS<sup>[11]</sup> where axillary clearance and axillary radiotherapy after a positive SLNB yielded comparable axillary control rates. Even as lymph node examination becomes more and more thorough with the advent of a host of investigations like imprint cytology, IHC staining, and even reverse transcription polymerase chain reaction, we are yet to fully define the actual prognostic implication of micrometastases. National Comprehensive Cancer Network guidelines<sup>[12]</sup> do not recommend the routine use of IHC for detection of axillary nodal disease and till we are confident of the way ahead, it might be best to let sleeping dogs lie!!!

(Continue on page 69...)

(Letter to the editor continue from page 66...)

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