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Improved frozen section examination of the retroareolar margin for prediction of nipple involvement in breast cancer

Jose Roberto Piatto
University of São Paulo, Brazil

Introduction: Development of the nipple-sparing mastectomy (NSM) technique has constituted a significant advance in the surgical treatment of selected cases of breast cancer. The most important aspect of areolar complex preservation is the exclusion of carcinoma involving the nipple. The retroareolar surgical margin is usually sampled and subjected to an intraoperative evaluation by frozen section examination in order to avoid a second procedure. However, this method is not standardized resulting in variable rates of false-negative results. Here, a new technique is proposed for the intraoperative study of the retroareolar margin. This ex vivo study was conducted by performing a simulated NSM procedure for patients undergoing total mastectomy to assess the impact of these measures on the accuracy of retroareolar frozen section examination.

Materials and Methods: Between September 2012 and April 2014, we studied 158 mastectomy specimens from patients undergoing total mastectomy for breast cancer at the Cancer Institute of the State of São Paulo. Inclusion criteria were stage Tis-T3 tumors, multifocal and multicentric breast carcinoma, unicentric carcinoma not suitable to quadrantectomy. Patients submitted to neoadjuvant chemotherapy were also included. To obtain the entire sample area, the terminal retroareolar milk duct bunch was isolated. Fragments approximately 1.5 cm in length were excised and sectioned in parallel at the base of the nipple using a cold bistoury. Three transverse histological sections (4 mm each) at 200 mm intervals that included the entire isolated fragments were subjected to frozen section examination. The sections were stained with hematoxylin-eosin (H&E) and were evaluated. The remainder of each fragment was embedded in paraffin and 4 mm sections were subsequently stained with H&E and examined.

Results: A total of 158 mastectomy specimens involving mammary carcinoma of no special type were examined. These included 15 (9.5%) *in situ* stage tumors, 36 (22.8%) stage I tumors, 71 (44.9%) stage II tumors, and 36 (22.8%) stage IIIA tumors. Paraffin examinations identified 25 retroareolar fragments compromised by carcinoma, resulting in 16.1% prevalence. Of the frozen sections examined, 2/158 (1.3%) had false-negative results and 5/158 (3.1%) had false-positive results. For the former two cases, the corresponding paraffin examinations detected low-grade carcinoma *in situ* and a residual cell cluster with a diameter less than 1 mm. The latter was found in a mastectomy specimen from a patient that underwent neoadjuvant chemotherapy. For the three cases involving false-positive results, the corresponding paraffin examinations revealed no atypical ductal hyperplasia present, one sclerosing intraductal papilloma and one nipple syringomatous adenoma. Statistical analysis revealed that the frozen section examinations performed had a sensitivity rate of 92.0% and a specificity rate of 96.2%. In addition, the positive predictive value (PPV) was 82.1%, the negative predictive value (NPV) was 98.4%, and the accuracy was 95.4%.

Conclusion: The frozen section examination technique described here detected nipple involvement in breast cancer with greater accuracy than the frozen section usually performed by most surgeons.