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Role of frozen section in sentinel lymph node biopsy for breast cancer in the era of the ACOSOG Z0011 and IBCSG 23-10 trials

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ABSTRACT

Background: Intraoperative frozen sections (FS) of sentinel lymph nodes (SLN) were evaluated to avoid the need for deferred axillary lymph node dissection (ALND) in patients with early breast cancer (EBC). However, FS has low sensitivity for detecting micro-metastases (<2 mm), resulting in patients who later undergo deferred ALND. The aim of the study was to determine the best clinical approach for selecting patients who would derive real benefit from ALND, as well as to minimize the functional and psychological damage caused by delayed surgery, and the risk of undertreating EBC patients.

Methods: This study evaluated 1453 patients with early breast cancer (EBC) who underwent SLN biopsy, FS and definitive evaluation. Causes of discrepancies between SLN biopsy and FS results and the need for further surgery were evaluated.

Results: A total of 1226 (86%) patients underwent FS; of these patients, 146 (11.9%) were false negatives. The global sensitivity of FS in detecting both macro and micrometastases was 53.7%. Although ACOSOG Z0011 criteria found that ALND could be avoided in 236 patients, 40 (17%) of these had >3 positive axillary lymph nodes. In contrast, application of the IBCSG 23-10 trial criteria, found that only three patients (3.1%) had >3 positive axillary lymph nodes.

Conclusions: FS has a low sensitivity in detecting micrometastases (19%), but a reasonable sensitivity for macrometastases (75%). Most false negatives were smaller metastases (mean 2.1 mm) and more likely in patients with infiltrating lobular carcinoma. Retrospective modelling of the IBCSG 23-10 criteria reduced the percentage of patients requiring deferred surgery from 12% to 4%. Guidelines recommend irradiation of lymph node drainage stations in patients with ≥4 axillary metastatic lymph nodes. Omission of ALND from 40% of patients who met Z0011 criteria would have resulted in their

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undertreatment. This risk decreases to 3% by omitting axillary clearing only in patients with micrometastases.

Introduction

Over the last two decades, sentinel lymph node biopsy (SLNB) followed, if metastatic, by complete axillary lymph node dissection (ALND), has become the main protocol in managing stage early breast cancer (EBC).[1,2] Lymph node status can affect postoperative treatment options, particularly for radiation therapy.[3]

Intraoperative frozen sections (FS) of sentinel lymph nodes (SLN) were evaluated to avoid the need for deferred ALND in patients with EBC. However, FS has low sensitivity, especially for detecting micro-metastases (<2 mm), resulting in a non-negligible percentage of patients who later undergo deferred ALND, leading to greater psycho-physical discomfort for patients and higher costs.[4]

Many EBC patients with positive SLN do not have additional axillary metastases identified at ALND. This led to research designed to estimate the risk of non-sentinel node metastasis, thereby avoiding unnecessary surgery in non-metastatic patients.[5] The results of the ACOSOG Z0011 trial[6–8] changed the standard approach to axillary surgery, showing that completion lymph node dissection did not alter overall survival and disease-free survival curves in patients with metastatic SLN. Two subsequent trials—IBCSG 23-108 and AMAROS—showed that ALND had little impact in EBC patients with metastatic SLN, both in patients with micrometastases (IBCSG 23-108) and when comparing ALND with radiotherapy (AMAROS).[9] Further studies attempting to confirm or refute the results of these trials resulted in different treatment options.[10–16] At institutions adopting the criteria derived from these trials, the use of both ALND and SLN FS declined, due to diminished need to determine lymph node status intraoperatively.[17,18]

This retrospective study of a prospectively collected database was performed to define the current role of FS and the current protocols for postoperative adjuvant therapies. The aim of this study was to identify the optimal clinical approach for choosing patients who would benefit from ALND, minimizing the functional and psychological damage caused by delayed surgery while also minimizing the risk of undertreating patients with EBC.

Methods

This study recruited 1453 patients with invasive breast cancer and non-palpable nodes who were treated at our institution from October 2004 to March 2017. All subjects provided written informed consent, and the study protocol was approved by the local ethics committee. All patients underwent surgery, either conservative or mastectomy, as well as SLNB. SLNs were detected by radioactivity with a gamma probe and sent during surgery to our department of pathology. In order to identify metastases while avoiding loss of fatty nodal tissue, each lymph node >10 mm was divided into two halves. In cases of total adipose involution (i.e. prevalence of fatty tissue within the lymph node), FS was not performed due to the difficulty of obtaining suitable sections. One-half of each node was evaluated by FS and haematoxylin-eosin (HE) staining. The other half of each node was embedded in paraffin and subjected to standard and immunohistochemical (IHC) staining.

SLNs with micrometastases (0.2–2 mm) or macrometastases (>2 mm) were considered positive, whereas SLNs without metastasis or with isolated tumour cells (ITC; <200 μm) were considered negative, regardless of the method used for histologic detection. Patients with positive FS underwent ALND during the same surgical procedure. Permanent sections in patients with negative FS were analysed later; if permanent sections were positive, patients underwent surgery 2 weeks later.

Through December 2011, only 15 patients with positive SLN did not undergo surgery to clear the axilla, either because they refused or because of contingent clinical characteristics (e.g. high risk, older age). After December 2011, ALND was omitted in patients with micrometastatic SLNs (<2 mm). No patient with ITCs (<200 μm) underwent axillary clearing. Patients were followed-up ≥1 year later.

Study design

The criteria of the ACOSOG Z0011 and IBCSG 23-10 trials were applied to our large series of patients with EBC treated at a single institution. Analyses included the number of patients spared ALND, the percentage of patients who underwent deferred surgery, and the risk of undertreatment.

The aim of treatment was to spare all patients who did not require ALND while reducing the risk of undertreatment, thereby minimising the percentage of patients requiring reoperations for positive SLNs.

Results

In 23 (1.58%) of the 1453 recruited patients, SLNs could not be intraoperatively identified by the probe, resulting in the necessity of performing ALND. In 24 (1.65%) patients, FS was deliberately not performed due our use of an old protocol for patients receiving neo-adjuvant chemotherapy, in which SLNB was performed before starting treatment. FS was not indicated in an additional 180 patients (12.4%), based on the

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