Can we use frozen section analysis of sentinel lymph nodes mapped with methylene blue dye for decision making upon one-time axillary dissection in breast carcinoma surgery in developing countries?

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Summary

Purpose: To evaluate the accuracy of intraoperative frozen section analysis (FSA) of sentinel lymph nodes (SLNs) mapped using methylene blue dye (MBD) and its usefulness for selecting patients with breast carcinomas and positive axillary lymph nodes (ALNs) for one-time axillary dissection.

Methods: 152 female patients with T1/T2 breast carcinomas and clinically negative ALNs were selected for mapping using MBD (1%) from October 2010 to December 2011. Patients underwent FSA of mapped SLNs and ALN dissection. The accuracy of SLN-FSA was tested by comparing these findings with the definite histopathology (HP) of SLNs, as well as of other ALNs. Sensitivity, specificity, positive and negative predictive values were calculated.

Results: There was a 98%-match between FSA and definite HP findings of SLNs, suggesting high accuracy of FSA in this series. None of 3 patients with false-negative SLNs on FSA had additional axillary nodal metastases. One out of 20 (5%) patients with metastases in other ALNs had “clear” SLNs, both on FSA and definite HP (false-negative). Accuracy reached 94.1%.

Conclusions: SLN-FSA enables adequate selection of patients for one-time axillary node dissection. MBD mapping technique is cheap, feasible and enables easy and precise detection of the first draining ALNs. Using FSA of SLNs mapped with MBD, patients with breast carcinoma benefit from complete surgical treatment during one hospitalization, the risk of undergoing anaesthesia twice is reduced, as well as the treatment cost, which is important in developing countries.

Key words: axillary dissection, breast cancer, developing countries, frozen section analysis, methylene blue dye mapping, sentinel lymph nodes

Introduction

ALN status determines to a great extend the need for adjuvant therapy for breast cancer and consists the most important single prognostic factor for recurrence and survival [1]. Sentinel lymph node biopsy (SLNB) has been introduced two decades ago as a useful method for staging ALNs in patients with invasive breast carcinoma [2]. Since then, the use of SLNB has become the gold standard for preoperative N0 patients [3]. Current treatment guidelines suggest completion ALND only in cases with histologically positive SLN after previous surgery [4-8]. However, the financial and administrative implications as well as potential complications for patients from two-step breast cancer surgery in developing countries should not be neglected.
The aim of this study was to evaluate the accuracy of intraoperative FSA of SLNs mapped using MBD technique and its predictive value for selecting breast cancer patients for one-step axillary nodal dissection.

Methods

Before the beginning of this research, all patients with breast cancer were treated with complete ALND according to local protocols, while SLNB was performed occasionally. In 2009, the British Association of Surgical Oncologists guidelines suggested SLNB technique as adequate approach for axillary staging. Based on these suggestions, surgeons should have a minimum of 30 cases series, with >90% SLN identification rate and <10% case negative rate [9]. Quality surgery can only be achieved with high volume practice.

This observational study was conducted at the Surgical Oncology Clinic of the Institute for Oncology and Radiology of Serbia (IORS), from October 2010 to December 2011. Female patients with T1 or T2 breast carcinomas, clinically negative ALNs and no distant metastases were selected for lymph node mapping using MBD (1%). Patients with locally advanced and inflammatory breast cancer, patients who had neoadjuvant chemotherapy, previous breast surgery for non-malignant conditions or previous axillary procedures, patients with recurrent breast cancer, as well as pregnant or lactating patients were not subjected to SLNB, since there was insufficient level of evidence for these clinical circumstances in the current ASCO recommendations [5]. Finally, patients with failure to stain any ALN during the procedure were also excluded. The revised 2009 TNM classification (7th Edn) was used for disease clinical and histopathological staging.

SLN-FSA findings were compared with the final SLN-HP and the final HP of other lymph nodes from the axillary dissected tissue (non-SLNs) was registered. Patients with non-SLN metastases and FSA-negative SLNs were specifically observed.

Statistics

The Statistical Package for Social Sciences (SPSS Inc, Chicago, Ill) version 17.0 software was used for statistical analyses. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) were calculated. Additional parameters observed in this study were number of SLNs identified and their position in the axilla (Berg’s level 1 vs Berg’s level 2). Several parameters were tested in correlation to SLNs number and location: MBD injection site (periareolar vs peritumor), MBD injection time (5 vs 10 vs 20 min before the incision of the skin) and MBD volume (0.2 vs 0.5 vs 1.0 ml), in order to try to optimize the vital dye mapping technique. Pearson’s $x^2$ test was used for this analysis and the statistical significance level was set at p=0.05.

Results

Patient characteristics

All 152 patients with breast carcinoma were females, aged from 33 to 82 years, with a mean of 56.74 years (±SD 11.53). Clinically, 101/152 (66.4%) patients had tumors not larger than 20mm in size, while 51/152 (28.1%) had tumors from 2 to 5cm in size. The majority of the patients (120/152; 78.9%) were treated with conservative operation (quadrantectomy, SLNB and ALND), and 32/152 (21.1%) had either Madden’s modified radical mastectomy (23/32; 71.9%) or nipple-sparing mastectomy with immediate breast reconstruction, SLNB and ALND (9/32; 28.1%).

Histopathology findings

The patient distribution by HP characteristics of breast carcinomas and lymph node status are shown in Table 1. The majority of tumors were of ductal type (60%, including medullary and tubular subtypes), moderately differentiated (82%), with rarely verified lymphovascular invasion (<5%) and a mean size 15.78 mm (±7.30). In total, 183 (1-4) SLNs were excised and analyzed intraoperatively. Other details regarding lymph nodes HP are given in Table 2.

Methylene blue dye mapping technique

Details regarding the technique of mapping

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<tr>
<th>Table 1. Pathological characteristics of tumors</th>
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<td>Tumor type</td>
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<td>3 (high)</td>
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<td>Lymphovascular invasion</td>
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SD: standard deviation, * IDC subtypes
and biopsy of identified SLNs are shown in Table 3. The vast majority of patients (93%) had peri-
areolar injection of MBD. In 86% of the cases a single 0.5ml dose of MBD was used. The majority
of surgeons (74%) injected MBD 5 min before the skin incision. A total of 183 SLNs were identified,
1.2 SLNs per patient (range 1-4). In 87% of the patients, SLNs were identified in the Berg’s lev-
el 1. There was no statistically significant difference between MBD injection site, time or volume
and localization of SLNs in the ipsilateral axilla or number of SLNs identified (Pearson’s x² test,
\( p > 0.05 \)).

**Sentinel lymph node biopsy and frozen section analysis - method’s accuracy**

Comparison of FSA and definite HP findings on SLNs (Table 2) showed concordance in 98% of
the patients, since there were 3 patients with false-negative SLNs on FSA (Table 3). This sug-
gests the high accuracy of FSA in this series.

The predictive value of SLN-FSA concerning the positivity of other axillary lymph nodes (non-
SLNs) was calculated. None of the 3 patients with false-negative SLNs on FSA had non-SLN metas-
tases on definite HP examination. Non-SLNs metastases were present in 20/152 (13.2%) patients.
In total, 19/20 (95%) patients were correctly identified by FSA of SLNs as true-positive (sensitivi-
ty). The specificity of the method was 93.9%. The SLNB with MBD and intraoperative FSA accura-
cely selected patients for ALND in 94.1% of the cases. A probability that non-SLN metastases were
present in patients with positive SLNs was 70.4% (PPV), while negative SLN findings predicted ab-
sence of non-SLN metastases in 99.2% of patients (NPV). There was a false negative rate of 5% ob-
erved in the study, meaning that one of the 20 patients identified on definite HP with non-SLN
axillary metastasis had “clear” SLNs, both on FSA and definite HP.

**Discussion**

Elective ALND for breast cancer was the ony adequate method for evaluation of locore-
gional status of the disease up until mid-1990s when SLNB was introduced. Since then, the use of
SLNB has increased [3], as well as variations in patient selection and mapping technique applied.

Several points regarding SLN mapping technique are matters of dispute in the literature. Trac-
ers used for SLN mapping are numerous, as well as techniques for SLNs detection. All techniques
carry certain difficulties in everyday practice (ad-
verse reactions, costs, availability, complexity).
Fluorescence-guided SLN biopsy using indocyanine green, as well as use of radioactive colloids and preoperative lymphoscintigraphy are costly and not always available. The price for Technetium is $60/g, while 50ml of MBD (1%) costs only $4.50. While series of papers report allergic reactions to vital dyes, especially patent blue V and isosulfan blue [10,11], many authors point out MBD as a safer and less expensive dye [12-14], with high efficacy for mapping. Adverse reactions after intradermal injection of MBD have been reported in the literature and involve skin and fat inflammation or necrosis [15-17]. Interference with pulse oximetry [18] and pulmonary edema [19]. There were two reports of anaphylaxis after MBD injection in female adults with breast carcinoma [20,21] and one report in a 6-year-old child with melanoma [22]. However, these adverse reactions are rare in the literature, given the frequency and the wide use of MBD. In our institution, MBD is widely used in melanomas and thyroid carcinomas [23-26] as a standard technique for SLN mapping for almost a decade and there have been no reports of any adverse reactions whatsoever. It is a hypo-allergic, low-cost vital dye demonstrating high success in lymph node staining. Disputes about the “ideal” tracer injection site and tracer type (vital dyes vs radiocolloids) for identification of “true SLN” date back to the late 1990s [28]. Our patients were operated by several surgeons at that time, and since the SLNB method had only recently been introduced in IORS, differences in the vital dye injection technique should be expected. However, these differences in MBD injection site, time and volume did not affect the location and the number of SLNs identified (Pearson x² test, p>0.05).

The SLN identification rates vary from 95 to 97% in the most recent trials [5,29]. Results from the validation phase of the ALMANAC trial show accuracy of 97.6% and sensitivity of 93.3% [30]. Both surgeon and pathologist are recognized as important factors for identification of SLNs and SLNB accuracy [31]. Several researchers [30,32] found that removal of more than one SLN might improve accuracy. In this study, 1-4 lymph nodes (1.2 per patient) were removed. A review by Chen and Wu [31] reported occult lymph node metastases in 7-33% of SLN-negative patients found by serial HP sectioning, which might suggest that multiple-level sectioning with immunohistochemistry provides more accurate lymph node staging [33]. In our Institute we perform intraoperative FSA of identified and excised SLNs for over a decade in thyroid carcinomas and melanomas. In our experience, trained pathologists can achieve high accuracy of FSA. Concordance of FSA and definite HP on SLNs in our study was seen in 98% of the cases. Three patients were wrongly identified as having “clear” SLNs on intraoperative FSA. However, they had no other axillary metastases on definite HP. Practice guidelines suggest that in cases with positive SLNs completion ALND should be performed [4,6,7]. In the literature, additional non-SLN metastases are present in approximately 50% of SLN-positive patients [34] – in our series in 63.3% (19/30) of the patients. The SLNB method with MBD and intraoperative FSA accurately selected patients for one-time ALND in 94.1% of the cases. In this way, out of the total of 152 patients, 19 (12.5%) with additional metastases outside SLNs would have had benefit of intraoperative examination of SLNs being given one-time axillary dissection. Only one patient would have been misdiagnosed as disease-free axillary lymph nodes since she had “clear” SLN both on FSA and definite HP, with metastasis in one other ALN. False-negative SLN rates vary in the relevant literature from 0-29% (lower than 13% in the majority of studies) [34]. This might explain axillary recurrences reported in SLN-negative patients with breast carcinoma in up to 1.15% [35-37]. Quality control procedures aim to achieve false-negative rates of 5% or lower [5]. False-negative rate in this study was 5%.

Several clinical trials [29,30,38,39] demonstrated that SLNB vs ALND in early breast carcinoma reduces lymphedema and arm morbidity risk, whilst shortening the postoperative hospital stay. On the other hand, there was no significant increase in locoregional recurrence or survival, not even with longer follow-up [29,38]. Verry et al. [40] suggested an analytic model to estimate the 20-year effectiveness and cost-effectiveness of SLNB vs ALND in patients with early breast carcinoma. Based on this, SLNB generated an additional 8 quality-adjusted life years and saved 883,000$ per 1000 patients over 20 years. However, it was less effective when false-negative SLN rate was over 13%.

The results of this observational study concur with data obtained by many international studies regarding accuracy of SLNB method in the staging of axillary lymph nodes. What authors would like to point out is the high accuracy of frozen section analysis in the detection of true metastases in SLNs which enables adequate selection of patients for one-step axillary dissection. Further-
more, MBD mapping technique for lymph nodes is a cheap and feasible method that enables easy and precise detection of the first draining lymph nodes in the axillary fossa. Frozen section analysis of SLNs mapped with MBD in patients with breast carcinoma leads to completion of surgical treatment in a single hospitalization. In this way, the benefits of SLNB are maintained and second procedure is avoided, with obvious advantages regarding possible complications and costs.

References

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