Available online at www.sciencedirect.com
SciVerse ScienceDirect
EJSO 39 (2013) 266–272
EJSO the Journal of Cancer Surgery
www.ejso.com

Does increased tumor burden of sentinel nodes in breast cancer affect detection procedure?

A.S. Kohl Schwartz [a,*], C. Leo [a], K. Rufibach [b], Z. Varga [c], D. Fink [a], N. Gabriel [a]

[a] Department of Gynecology, University Hospital of Zurich, Switzerland
[b] Division of Biostatistics, Institute of Social and Preventive Medicine, University of Zurich, Switzerland
[c] Institute of Surgical Pathology, University Hospital of Zurich, Switzerland

Accepted 17 December 2012
Available online 12 January 2013

Abstract

Numerous studies have shown that sentinel lymph node biopsy (SLN) has a high level of detection sensitivity. Successful detection procedure depends on the amount of radioactivity and accumulation of blue dye in the SN. Our aim was to relate the differences observed in intraoperative SN presentation to tumor burden, characteristics of the primary tumor and patient attributes.

Our retrospective analysis included 369 patients undergoing SLN in the Department of Gynecology of the University Hospital of Zurich within five years. Data was collected from the patients (age, BMI), the primary tumor (size, grading, hormone receptors, HER2 status) and the SNs removed (counts per second [cps], blue dye, size of nodular metastasis, extracapsular involvement, number of SNs excised).

Because patients typically had more than one SN, a linear mixed-effects model was used to account for the clustering within one patient.

SNs presented with significantly lower radioactivity in elderly (-1.8%/year, $p < 0.001$) and obese patients (-3.9%/kg/m2, $p = 0.006$) as well as in G3 primary tumors ($p = 0.002$). Radiocolloid accumulation decreased with increasing metastasis size (-6.1%/mm, $p = 0.006$).

In conclusion the detection procedure of SNs is mainly affected by the patient's age and BMI and by nodular metastasis' size. Phagocytotic activity in the lymph node may increase radiotracer accumulation, showing the highest tracer signals in micrometastatic SNs. In large SN metastasis the lymph flow appears obstructed, reducing the axillary drainage and therefore making detection procedure difficult.

Keywords: Breast cancer; Sentinel lymph node biopsy; Failed localization; Tumor burden

Introduction

Sentinel node biopsy (SLN) is an established standard procedure in the operative care of early, clinically node-negative breast cancer. As a result, the presence of axillary lymph node metastases can be accurately assessed. In numerous studies, the detection sensitivity for SLN is reported to be 90–95%.[1–5] Intraoperatively, however, it can be difficult to detect sentinel nodes (SNs). This difficulty is due to marked differences in the presentation of SNs, which is dependent on the amount of radioactivity and the accumulation of blue dye. Patient characteristics, such as older age and higher body mass index (BMI), have been demonstrated to influence the flow of radiocolloid and blue dye and are known to diminish the detection rate of SLNs.[6–8] However, the influence of tumor-specific factors such as tumor size[9] and grading[8,10] on the axillary drainage is not conclusive. Except for the study of Goyal et al. the effect of the tumor burden within the SN on the axillary drainage has not been extensively analyzed.[11] Therefore, the aim of our study was to relate the differences observed in intraoperative SN presentation to tumor burden, characteristics of the primary tumor (tumor size, grading, hormone receptor status and HER2 status), and patient attributes (age, BMI). The study is limited to the intraoperative presentation during SLN, identification rates were not analyzed.

Patients and methods

Patients

Data from all 369 women undergoing SLNs in the Department of Gynecology of the University Hospital of

* Corresponding author. Department of Gynecology, University Hospital of Zurich, Frauenklinikstrasse 10, 8091 Zurich, Switzerland. Tel.: +41 (0) 44 255 5200; fax: +41 (0) 44 255 4433.
E-mail address: sentinel@kohl.ch (A.S. Kohl Schwartz).

0748-7983/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejso.2012.12.016

Zurich from 07/2005 to 12/2009 were retrospectively analyzed in agreement with our ethics committee. Indications for SLN were uni- and multifocal tumors ≤5 cm (<cT3) in size. Patients with DCIS (ductal carcinoma in situ) only, multicentric tumors and patients status post treatment with neoadjuvant chemotherapy were excluded.

Sentinel node mapping

Our protocol consisted of co-application of a radiopharmaceutical and blue dye. The afternoon before surgery, in median 19 h, (17–24 h) before incision time, 75 MBq of 99mTc-Nanocoll® from GE healthcare was injected peritumorally and subdermally. In case of non-palpable lesions, the radiotracer was applied in the periareolar region. The intraoperative SN detection was based on radioactivity and blue dye mapping. Diluted patent blue dye V was injected peritumorally and the lymphatic flow was activated by a gentle massage of the tumor area. Using a gamma probe, the radioactivity in the following areas was measured and recorded: the tumor; the supraclavicular, infraclavicular and parasternal regions; at the edge of the mammary gland; and over the hot spot in the axilla. The lowest count was used as a background count. For SLN, all lymph nodes − radioactivity-positive and/or blue or suspiciously palpable − were removed and their ex vivo count "*cpsex-vivo*" measured and recorded. In our analysis, we included all hot (more than 10-fold the background count)[12] and/or blue SNs. If neither a blue nor hot node was found, the node with the highest radioactivity was designated as the SN.

Histological processing of the sentinel nodes

For intraoperative frozen section analysis, the SNs were sent to the Institute of Surgical Pathology, University Hospital Zurich, Switzerland. The intraoperative processing of SNs was performed according to the following internal protocol[13,14]: 1) all SNs were longitudinally bisected (or sectioned in 2-mm slices if the SLN had a diameter of more than 5 mm) and primarily assessed with a stereomicroscope; 2) each cut section surface of the SN slices was stained with intraoperative print touch cytology and immediately analyzed under the microscope.

If the cut section surface of the SN was clearly involved or was highly suspicious for malignancy or if the print touch cytology revealed malignant cells, then one single frozen section of the SN was performed and analyzed. In all other cases, SNs were submitted to paraffin embedding and complete histological sectioning as follows: paraffin blocks were completely step-sectioned (200 μm steps) with one hematoxylin-eosin (H&E) stained and one unstained slide at each step. No residual lymph node structures remained in the paraffin block. If no tumor could be detected on the H&E slides, all unstained slides were subjected to pancytokeratin immunohistochemistry (Lu5, 1:250, Roche, Basel, Switzerland) using standard immunohistochemical protocols and Ventana Benchmark autostainer platforms (Ventana, Tucson, AZ, USA).

SNs that were found to be positive (pN1) in one of the intraoperative methods described above were fixed with formalin, embedded in paraffin and stained with an H&E stain. Additional cytokeratin immunostaining was performed in selected cases if considered necessary.

If detection of the SN was impossible, an axillary lymph node dissection (ALND) was performed. In some cases, a secondary ALND was necessary due to an upgrade in the histopathologic diagnosis. The histopathologic results of the primary tumor and the SNs were recorded. If the SLN was negative, the lymph nodes were classified as *negative SN in all negative axilla,* corresponding to pN0 (sn). Lymph nodes with isolated tumor cells were considered negative (pN0, i+, sn) (ASCO guidelines[15]). If the SLN was positive, the affected nodes were classified as *positive SN*. If the lymph node metastasis was between 0.2 mm and 2 mm, it was classified as a *micrometastatic SN,* corresponding to pN1mi. Lymph node metastases larger than 2 mm were classified as *macrometastatic SN*, corresponding to pN1. Additional negative sentinel lymph nodes adjacent to a *positive SNs* were classified as *negative SN in axilla with positive SN.* See Fig. 1.

Database

Patient data (e.g., BMI, age), intraoperative findings (e.g., cps count, blue dye staining) and the results of pathological evaluation were all documented in our breast cancer database, acknowledged by EUSOMA (the European Society of Mastology).

Statistical analysis

Because patients were typically found to have more than one SN (clustered data), we had to account for this clustering within patients.[16] To account for the dependency within potential multiple observations within each patient when analyzing the continuous response "*cpsexvivo,*" we used a multiple linear mixed-effects model with a patient-specific random intercept. To better meet the assumptions of a linear mixed-effects model, all models for *cpsexvivo* are computed for the log of this variable. To account for the dependency when analyzing the binary response "blue," we used a generalized linear mixed-effects model with a patient-specific random intercept. These are marginal models, and interpretation of estimated odds ratios is on a subject-specific level. Generalized linear mixed models with random intercepts, as we computed them, are equivalent to extracting standard errors from a generalized least squares (GLS) model, assuming a compound symmetry correlation structure. We did not perform a correction for multiple testing in these exploratory analyses, i.e., all statistical tests were performed at a significance