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A multicentric analysis and an introduction of a German prospective study to evaluate the value of sentinel node excision after neoadjuvant chemotherapy

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Introduction: Sentinel node excision (SNE) is a routine procedure in the treatment of primary breast cancer. Neoadjuvant chemotherapy (primary systemic therapy = PST) is currently used in locally advanced and inflammatory breast cancer and rather recommended for patients with tumours of unfavourable tumor biology who are likely to recieve adjuvant therapy anyway.. Nodal downstaging is reported in about 16−23% of all patients after PST. SNB after PST is not recommended as a routine procedure in national and international guidelines. We evaluated the safety and reliability of SNB with determination of detection rate and the false-negative rate after PST in a multicentric setting.

Material and Methods: retrospective analysis of 128 patients treated in 3 different centers with primary systemic therapy innational PST trials as TECHNO, PREPARE and GeparQuattro.

Results: Between 2003 and 2005 92 out of 128 patients received PST and underwent consecutive SNB after PST. The median age was 49 years. In 88 of 92 patients (96%) the sentinel was detected either by lymphscintigraphy and/or with blue dye during surgery. The remaining 4 patients received classical ALND. As SNB showed tumor-free sentinel nodes 12 patients refused to undergo further ALND. 76 patients received SNB and further ALND irrespectively of nodal sentinel node status. 30 of 92 patients showed positive lymph nodes out of which 5 patients had a negative sentinel node biopsy. Thus, the false negative rate is calculated 5/30 = 16.6%. In 74 patients Level I and II ALND was performed after SNB, 4 patients received a Level III lymph node resection, in 1 patient only Level I ALND was reported and in 1 patient no detail of complete ALND was stated.

Conclusion. The results confirm the existing studies. Compared to the adjuvant setting the results are not satisfying and need to be evaluated in a prospective trial as it is done in the German neoadjuvant SENTINA protocol (Sentinel Node excision after NeoAdjuvant therapy).

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Added value of preoperative SPECT/CT in surgery planning for internal mammary sentinel node localisation in patients with breast cancer

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Background: Accurate localisation of sentinel nodes (SNs) outside the axilla is a major concern when interpreting lymphoscintigraphy. The use of SPECT/CT for the localisation of SNs is a recent non-invasive technique. The purpose of this study is to investigate whether SPECT/CT has a an influence on surgical decision making, compared to lymphoscintigraphy alone in patients with internal mammary SN localisation.

Material and Methods: All consecutive patients from 2006 up to 2008 with a T1−3N0 breast carcinoma with internal mammary SN localisation on lymphoscintigraphy were prospectively included. Lymphoscintigraphy was followed by SPECT-CT in all patients with SNs outside the axilla. During surgery attempts were made to harvest both axillary and non-axillary SNs. The differences between the lymphoscintigraphy and the SPECT/CT with respect to the number and location of hot spots as well as the surgical and pathological results were analysed.

Results: 42 patients (mean age: 54.8 yrs) were included. In 13 patients (30.9%), the SPECT/CT provided no additional information compared to lymphoscintigraphy alone. In 3 patients (7.1%) the SPECT/CT provided a closer determination of the anatomical location of the hot spot, but without surgical consequences. In 2 patients (4.8%) the lymphoscintigraphy turned out to be more accurate than the SPECT/CT. In 1 patient (2.4%) the lymphoscintigraphy and the SPECT/CT located the SN retrosternal, but the SN appeared to be parasternal during surgery.

In the remaining 23 patients (54.8%) the SPECT/CT results had a major impact on the surgical procedure. In 4 patients (9.5%), the SPECT/CT showed 6 additional SNs. In 20 patients (47.6%) the SPECT/CT results gave substantial reason not to explore the SN as visualised on the lympho-scintigraphy: in 12 patients due to a surgically inaccessible localisation, and in 8 patients because the hotspot could not be linked to an anatomic substrate on the SPECT/CT. In one patient an extra axillary SN and an inaccessible SN was detected on SPECT/CT.

Conclusions: In the majority of patients, SPECT/CT has a considerable influence on the surgical procedure. Not only to improve localisation and to increase the number of visualized SNs, but foremost, to reduce the number of unnecessary and potentially harmful explorations. Thus, SPECT/CT has a major impact on surgical decision making compared to lymphoscintigraphy alone, in patients with internal mammary SN localisation.

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Sentinel node biopsy in ductal carcinoma in situ of the breast – results in 99 cases

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Background: Ductal carcinoma in situ (DCIS) represents a proliferation of malignant-appearing cells in the breast that have not invaded beyond the ductal basement membrane. DCIS diagnoses exclude axillary lymph node infiltration. The risk for nodal metastases in patients with DCIS is <3%. Microinvasive tumors are more frequent in association with large or high grade extensive disease. The aim of this study is to assess the requirement of sentinel node biopsy (SLNB) in DCIS management.

Material and Methods: Between December 1998 and September 2007, 970 SLNB were performed as the staging procedure for T1 and T2 breast cancer patients without palpable axillary lymph nodes. In 99 patients histologic diagnoses was DCIS, 91.9% of them non palpable mammography lesion. Diagnostic procedure for the breast disease was: Advanced breast biopsy instrumentation (ABBI) 36.4%; core biopsy under stereotactic guidance 25.3%; wire-guided open breast biopsy 18.2%; vacuum-assisted biopsy device (Mammotome®) 12.1% and other methods 8%.

SLN localization was performed by combined technique (dye and radioisotope) in 73.7% and by isotope technique in 26.3%. Breast conserving procedures were used in 73.3% of patients, mastectomy with or without associated reconstruction in the rest of cases. Histologic analysis included serial sectioning, H&E staining and IHC examination (EMA, AE1/AE3).

Results: Identification rate was 98%. Lymphatic mapping was negative in four (4%) patients, axillary positive in eighty (80.8%), internal mammary chain in one (1%), axillary and internal mammary positive in thir-teen (13.1%), intramammary in one (1%). Total number of excised sentinel nodes was 135 (1.39±0.6), 120 axillary located, 14 internal mammary and one intramammary node. Histologic exam showed micrometastatic disease in 2 (3.1%) cases, both histologic grade 3 DCIS. Complete axillary lymphadenectomy didn't found any other metastatic node. In other three patients, IHC exam demonstrated isolated tumoral cells. No additional surgical treatment was performed in these cases.

Conclusion: SLNB is a useful staging tool, which can be used in selected patients with DCIS. The disclosure of microinvasive disease is the main indication for SLNB, so large tumors treated with mastectomy or high grade DCIS could possibly benefit from its implementation.

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Sentinel lymph node biopsy for breast cancer using a new camera system for simultaneous capturing color and near-infrared fluorescence of indocyanine green

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Background: Dye and/or radioisotope (RI) methods are usually performed to detect sentinel lymphnode (SLN) of breast cancer. However, special surgical training for dye method and radiation control area for RI method is necessary. Another method, based on the near-infrared (NIR) fluorescence of indocyanine green (ICG) dye, might be considered to be a new alternative to resolve these problems of conventional dye and RI methods. It provided direct visual images of lymphatic flow over skin. However, it was difficult to detect the anatomical relationship between ICG-enhanced structures and non-enhanced surrounding tissues intraoperatively with currently available systems for capturing of monochrome images. To visualize ICG-enhanced structures against a background of vivid tissue

color, we developed a new camera for simultaneous capturing of color and NIR fluorescence.

Materials and Methods: A combination of custom-made optical filters for attenuation of visible light and enhancement of NIR fluorescence was mounted on an ultra-high sensitive color CCD image sensor (SANYO LC99169). A light source for excitation of ICG dye was made with an array of light emitting diodes (LED) at 780 nm. Since April 2007, we performed SLN biopsy in 40 patients with histologically confirmed breast cancer, tumor size $\leqslant$3 cm and clinically node negative, using this camera system. After ICG dye (1.25 mg/body) was injected subcutaneously surround areola, lymphatic flow was observed on the color monitor and the site of skin incision was decided. Simultaneously, usual combination methods of dye (indigo-carmine) and RI (99mTc-Sn colloid, 3mCi) were performed in all patients.

Results: In all of 40 patients, SLNs were identified by NIR fluorescence. This result was not inferior to those of simultaneously performed dye (39/40) and RI method (35/40). Moreover, the images, acquired using a new camera system, can be used as an intraoperative navigator.

Conclusion: Fluorescence method using our new camera system, which can simultaneously capture color and NIR fluorescence, is expected to be a new alternative to conventional dye and/or RI method.

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Factors predicting sentinel and non-sentinel lymph node metastases in patients with breast cancer

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Background: The sentinel lymph node (SLN) is the only focus of axillary metastasis in a significant proportion of patients. Factors that were associated with a negative sentinel lymph node, or negative non-sentinel lymph nodes were investigated in this study in order to omit complete axillary lymph node dissection.

Patients and Methods: Data were retrospectively reviewed for 579 consecutive patients with clinical T1/T2 N0 breast cancer who underwent SLN biopsy. Multiple sectioning and immunohistochemical (IHC) analysis were performed to evaluate the SLNs. All clinicopathologic criteria were reviewed and correlated with the metastatic involvement of sentinel and non-SLNs by using the new AJCC staging criteria that defined micrometastases (<0.2 cm) and macrometastases ($\geqslant$0.2 cm).

Results: Lymphatic mapping was performed using isosulphan blue dye alone (58.4%) or in addition to a technetium Tc 99m sulfur colloid technique (41.6%). SLN was identified in 558 patients (96%). Among those, SLN micrometastases were identified in 39 patients (18.3%) patients whereas macrometastases were detected in the remaining 174 patients (81.7%). Factors including tumor size more than 2 cm (T1, 31% vs T2, 48.7%; $p < 0.0001$) and presence of lymphovascular invasion (LVI−, 26.5% vs LVI+, 54%; $p < 0.001$), and presence of multifocal/multicentric tumors (unifocal tumor, 36.9% vs multifocal/multicentric tumors, 49.3%; $p = 0.044$) were associated with positive SLNs. Furthermore, tumor size more than 2 cm (T1, 37.3% vs T2, 53.2%; $p = 0.02$), the presence of macrometastases in SLNs (micrometastasis, 20.6% vs macrometastases, 56%; $p < 0.0001$) and extracapsular node extension (extracapsular node extension −, 30.2% vs extracapsular node extension +, 67%; $p < 0.0001$) were found as significant predictive factors of non-SLN metastases.

Conclusion: Our findings suggest that the size and the extention of metastases in SLN are important factors predicting the non-SLN metastases. Therefore, complete axillary dissections could be omitted in selected patients with T1 tumors and micrometastases without extracapsular node extention.

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Advantages of partial intraoperative pathologic evaluation of sentinel lymph node biopsy – our experience in 267 cases of breast cancer and review of the methods

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Introduction: SLN evaluation performed by total intraoperative evaluation by H&E and IHC with more than 50 section, as described by Viale and Coll. is expensive and needs time but is definitive, on the other hand microscopic examination of delayed paraffin section necessitated a second surgical approach for complete axillary dissection if the SLN is positive To avoid this reoperation and the patient stress correlated by reducing costs and time of full examination, a partial intraoperative SLN evaluation is proposed.

Patients and Methods: SLN technique was applied to a total of 238 breast cancer SLN biopsies were subjected to a rapid intraoperative partial (only four section by H&E) pathologic examination with synchronous total axillary dissection offered to patients with a positive finding. All intraoperative pathologic examination were followed by a definitive evaluation, axillary node dissection, performed with a second operative procedure within 15 day was performed in N+ pts.

Intraoperative Pathologic Evaluation: Lymph node specimens were sent fresh to the pathology laboratory. Each lymph node was cut in two parts along the longitudinal axis and grossly examined for macroscopic foci of tumor. One section was immediately frozen for intraoperative examination while the mirror section was kept for the permanent evaluation. Four intraoperative slides of the lymph node obtained were processed with hematoxylin and eosin (H&E). It take in average 20 minutes.

Permanent Pathologic Evaluation: Each half of the previously bivalved SLN specimen was fixed in 10% formalin, paraffin imbedded and all sectioned each 200 micron. All sections were stained by hematoxylin and eosin and evaluated with the technique of immunohistochemistry using a monoclonal antibody for cytokeratin.

Results: 73pts (28.52%) resulted positive at permanent pathologic SLN evaluation 39 of whom had been found positive at the intraoperative evaluation. False-negative SLNs resulted in 29 cases. Micrometastases were identified in 30 patients, 4 of whom were positive at the intraoperative pathologic evaluation. (sensitivity 16%). The presence of isolated tumor cells were reported in 12 patients and 2 of them were identified at the intraoperative evaluation. The overall sensitivity of the intraoperative detection of metastasis in our study was 57%. The specificity was 100%, Negative Predictive value was 85% and Accuracy 88%.

34/256 patients need a second operation that means 13.28%, 30 patients had only micrometastasis with non evidence of positive nodes after total axillary clearance.

Discussion: Partial intropeative evaluation if compared with the complete intraoperative evaluation, that also include immunostaining for cytokeratins using a rapid immunocytochemical assay appears to be less expensive and more rapid and in our experience only 13.28% of pt. need a second operation, if we look to the patient with macromets only 8 on 256 that is 3.0%.

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Factors predicting failure of sentinel lymph node mapping in breast cancer patients with previous axillary lymph node surgery

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Background: Previous axillary lymph node surgery is considered as a contraindication for Sentinel node (SN) mapping in breast cancer patients. We determined the feasibility and accuracy of lymphatic mapping following previous axillary surgery and evaluated parameters associated with mapping failure.

Methods: Lymphatic mapping using peritumoural injection of a radio-colloid and blue dye was attempted in 34 patients with primary (n = 7) or recurrent (n = 27) breast cancer and a history of previous axillary lymph node dissection (n = 15) or Sentinel node biopsy (n = 19).

Results: Lymphatic mapping identified a mean number of 1.6 (range 1−3) lymph nodes in 22 of 34 patients (identification rate 65%). The lymph nodes were removed from the ipsilateral axilla (n = 15), the internal mammary chain (n = 3), both the internal mammary nodes and the axilla (n = 2), the interpectoral space (n = 1) and the contralateral axilla (n = 1). 4/22 patients had a positive lymph node (two had a micrometastasis or isolated tumor cells, two had macrometastases), 18/22 patients had a negative lymph node. Axillary lymph node dissection was done in 15 of 18 patients but found no positive nodes (false negative rate = 0). A negative lymphoscintigram ($p < 0.001$) and a number of more than 10 lymph nodes removed at the time of previous axillary lymph node surgery ($p = 0.02$) were significantly associated with a mapping failure. The time between previous axillary surgery and the mapping procedure, previous chemotherapy and/or previous radiation showed a lower (not significant) identification rate.

Conclusion: Lymphatic mapping following prior axillary surgery was accurate but associated with a low identification rate. The lymphatic drainage pattern in these patients was unpredictable and the use of a radionuclide for mapping was prerequisite for a successful mapping procedure.