

Wednesday, 17 March 2004

16:00–17:15

## PROFFERED PAPERS

## Sentinel node – technique, diagnosis and management

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ORAL

## The impact of preoperative breast biopsy on the risk of sentinel lymph node metastases: analysis of 2502 cases from the Austrian Sentinel Node Biopsy Group

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**Background:** Preoperative breast biopsy might cause disintegration of tumour cells and tumour cell spread. The sentinel lymph node is examined more precisely and therefore tumour cell spread in a lymph node is detected more frequently. The purpose of this study was to investigate the impact of preoperative biopsy on the rate of metastases to the SLN of patients with primary breast cancer.

**Methods:** We report the results of 2502 patients with primary breast cancer who were operated and a sentinel node biopsy was performed. The association of preoperative biopsy with the risk of SLN metastases was examined by regression analyses and tested for possible confounding well known factors for axillary node metastases.

**Findings:** 1892 Patients were available for final analyses. 1048 (55.4%) patients had a preoperative diagnosis done by fine needle aspiration or core biopsy. 642 (33.9%) patients had a positive SLN when conventional H&E and IHC staining was performed. Patients with preoperative breast biopsy showed a 1.37 fold (95% CI, 1.13–1.66) increased relative risk for SLN metastases on univariate analysis but this result was not persistent when analysis was adjusted for other relevant factors for axillary node metastases RR 1.06 (95% CI, 0.83–1.34). In addition, subgroup analyses of the risk for occult micro metastases to the SLN (detected by IHC only) on H&E negative cases, did as well not reveal an accessory risk for preoperative biopsy RR 1.04 (95% CI, 0.67–1.60).

**Conclusions:** Preoperative breast biopsy does not cause artificial tumour cell spread to the SLN so – we assume – has no impact on survival or disease free survival.

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## Non-Sentinel lymph node involvement in breast cancer patients with a micrometastatic sentinel lymph node: Results of the Austrian Sentinel Node Study Group

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**Background:** The impact of micrometastatic sentinel lymph node(s) on disease free and overall survival in breast cancer patients is still debated, as is whether a axillary lymph node dissection (ALND) is mandatory in case of a micrometastatic sentinel node (SN). The purpose of this study was to identify a subset of breast cancer patients with a micrometastatic SN, in whom ALND may be omitted.

**Patients:** Data from 2037 successfully performed SN biopsies from the Austrian SN study group data bank were analysed.

**Results:** The SN was negative in 1360 patients (67%) and positive in 677 patients (33%). 423 of 677 patients (62%) had macrometastases, 254 of 677 (38%) had micrometastases in the SN. 158/254 (62%) were found by H&E examination, whereas 96/254 (38%) were found by immunohistochemistry. Non-SN(s) were involved in 205/414 patients (49.5%) with a macrometastatic SN but only in 49/220 patients (22.3%) with a micrometastatic SN (IHC detected micrometastasis 19.2%, H&E detected micrometastasis 23.8%). Univariate and multivariate analysis of patient and tumor parameters found the incidence of non-SN metastases significantly related to the size of the SN micrometastasis ( $p=0.028$ ). There was no such significance found with the other factors analysed (patient age, tumor size, histology, histological differentiation, receptor

status, tumor quadrant, department performing the SN biopsy, distance of micrometastasis to lymph node surface and location of micrometastasis in the SN). The micrometastasis in the SN was missed by frozen section in 167/232 patients (72%) who then required a secondary axillary dissection (in macrometastatic SN the metastasis was missed in only 9% of the patients). In 34 of 254 patients with a SN micrometastasis no ALND was performed. After a median follow up of 22 months there was one axillary recurrence and the patient underwent salvage axillary dissection.

**Conclusion:** In patients with a micrometastatic SN tumor involved non-SNs are found in 22%, with the incidence of finding a positive non-SN being significantly correlated to the size of the micrometastasis.

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## Discrepancies in current practice of pathological evaluation of sentinel lymph nodes in Europe

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The European Working Group for Breast Screening Pathology (EWGBSP) evaluated aspects of the current practice of sentinel lymph node (SLN) pathology in breast cancer via a questionnaire-based survey, in order to recognise major issues that the European Guidelines for Mammography Screening should address in the next revision.

A questionnaire was circulated by mail or electronically by the members of the EWGBSP in their respective countries. Replies from pathology units dealing with SLN specimens were evaluated further.

Of the 382 responders, 240 European pathology units were dealing with SLN specimens. 60% of these units carry out intraoperative assessment, most commonly consisting of frozen sections. Most units slice larger SLNs into pieces and only 12% assess these slices on a single haematoxylin and eosin (HE) stained slide. 71% of the units evaluated routinely use immunohistochemistry in all cases negative by HE. The terms micrometastasis, submicrometastasis, and isolated tumour cells (ITC) are used in 93%, 22% and 71%, respectively, but have a rather heterogeneous interpretation. Molecular SLN staging was reported from only 10 units (4%). Most institutions have their own guidelines for SLN processing, but some countries have also well recognised national guidelines.

Pathological examination of SLNs throughout Europe varies considerably and is not standardized. The European Guidelines should focus on standardizing examination. They should recommend techniques that identify metastases >2 mm as a minimum standard. Uniform reporting of additional findings may also be important, because micrometastases and ITC may in the future be shown to have some clinical significance.

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## Relative value of blue dye and isotope in sentinel node localization for breast cancer in a multicentre trial

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**Background:** Among the advocates of blue dye, isotope, or combined dye-isotope mapping of the sentinel lymph node(SLN) for breast cancer, there is no universal consensus as to which technique is optimal. The objective of this study was to examine the relative contribution of blue dye and radioisotope to identifying both the SLN and the positive SLN.

**Methods:** In the validation phase of the ALMANAC multicentre trial, 842 patients underwent sentinel node biopsy using a combined technique of blue dye and isotope mapping with preoperative lymphoscintigraphy according to a standardised protocol. SLN biopsy was followed by standard axillary treatment in all patients.

**Results:** Of the 815 patients with adequate data on method of localisation, 33 (4.0%) were failed localisations. This figure would increase to 117 (14.4%) if blue dye alone had been used, or if the isotope alone had been used.

Of the 782 patients who were successfully localised using both agents, 506 were true negatives. Of the 276 with positive axillae, 258 were correctly identified and 18 (6.5%) were false negatives. Also, of these 276 patients, an additional 7 (2.5%) would be false negatives if blue dye alone was used, or an additional 12 (4.3%) if the isotope alone was used.

Dye, isotope, and combined success rates

Patients	Success in identifying sentinel lymph node					
	Dye success		Isotope success		Combined success	
	n	%	n	%	n	%
All patients (n=815)	698	85.6	698	85.6	782	96
Success in identifying positive sentinel lymph node						
All pts with +ve axilla (n=276)	251	90.9	246	89.1	258	93.5

**Conclusion:** The success and accuracy of SLN mapping in breast cancer is optimized by the combined use of blue dye and isotope. Using a single localising agent would more than triple the failed localisation rate, and also lead to an appreciable increase in the clinically more serious false negatives.

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# **Reproducibility study of lymphoscintigraphy: excisional biopsy of breast lesions changes drainage patterns**

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A previous study established a 100% reproducibility of preoperative lymphoscintigraphy using intralesional tracer injection in patients with their primary breast cancer still present. The purpose of the current study was to validate the sentinel node procedure in patients after prior excisional biopsy by means of determining the reproducibility of lymphoscintigraphy before and afterwards.

**Methods:** Twenty patients scheduled for excisional biopsy of a breast lesion were investigated. Informed consent was obtained from all patients. The same investigator performed two scintigraphic studies in each patient. The day before surgery, <sup>99m</sup>Tc-nanocolloid was injected into the tumor. Anterior, lateral, and – if needed – oblique images were obtained after twenty minutes, two hours and four hours. Lymphoscintigraphy was repeated after a minimum of two weeks post-operatively. The radioactive tracer was then injected around the biopsy cavity but otherwise the procedure was identical.

**Results:** Preoperative lymphoscintigraphy visualized at least one sentinel node in all twenty patients. Discrepancy in the drainage patterns was seen in fourteen out of the twenty patients (70%). A change in drainage pattern to the axilla after excisional biopsy of the breast lesion was seen in nine patients (45%): an original sentinel node could not be visualized in six patients whereas additional hot spots were visualized in the other three.

Drainage to the internal mammary chain was preoperatively seen in ten of the twenty patients. After excisional biopsy, only two of these patients showed the same drainage pathways. The location of a hot spot changed to another intercostal space in six patients whereas in two patients, no hot spot was visualized in the internal mammary chain the second time around.

**Conclusions:** Compared to preoperative drainage from the actual breast lesion, post-excisional lymphoscintigraphy shows a different drainage pattern in 45% of the patients with axillary sentinel nodes and in 80% of the patients with internal mammary sentinel nodes. This implies that sentinel node biopsy should be performed prior to excisional biopsy to ensure optimal sensitivity.

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POSTER HIGHLIGHT

# **EORTC 10981–22023 trial. AMAROS: after mapping of the axilla: radiotherapy or surgery? Trial update**

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**Background:** The EORTC-AMAROS trial is a phase III randomised non-inferiority trial comparing a complete axillary lymph node dissection versus radiotherapy to the axilla in sentinel node biopsy positive patients, whereas sentinel node negative patients will be followed for the endpoints of the study as well. The main objective of the trial is to prove equivalent local/regional control for patients with proven axillary lymph node metastasis by sentinel node biopsy with reduced morbidity if treated with axillary radiotherapy instead of axillary lymph node dissection. The involved patients will have an operable invasive breast cancer of over 5 mm and less than 3 centimetres, without clinically suspected regional lymph nodes. Quality control constitutes an important part of the trial design.

**Methods:** Before the participating centre is allowed to enter patients, at least 30 sentinel node procedures have to be performed, with a minimum of 27 patients with accurate sentinel node identification and not more than one false negative. After 30 cases, the participating centre will be site visited and all the cases will be reviewed. If quality criteria are fulfilled, the participating team can enter patients in the trial. The quality of radiotherapy will be controlled before participation by evaluation of a dummy run.

**Current status:** The trial started in February 2001 and has randomised 825/3485 patients till September 15<sup>th</sup>. At the moment 14 institutions are recruiting patients actively, another 7 centres will participate in the near future.

**Interim results:** Sentinel node biopsy results show that 37% is positive and 61% is negative. Due to the quality control, identification rates in the participating centres are excellent (98%).

**Prospects:** With the introduction of Remote Data Capture, paper case report forms will be replaced by webforms. Access will be on the EORTC.be website without any special software necessary. The advantages are less administration, a better accuracy of data and a faster process of data.

**More information:** [www.amaros.nl](http://www.amaros.nl)

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POSTER HIGHLIGHT

# **Multifocality is not a contraindication to sentinel node biopsy in breast cancer**

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**Background:** Multifocal breast cancer has been suggested as a contraindication for sentinel node biopsy. However, recent studies have demonstrated that the lymphatic drainage of the entire breast coincides with drainage of the tumour bed, regardless of the quadrant. This should mean that the presence of multifocal tumour should not affect the lymphatic drainage. The purpose of this study was to evaluate the feasibility and accuracy of sentinel node biopsy in patients with multifocal breast cancer using a peritumoural injection technique for SLN mapping.

**Methods:** In the ALMANAC multicentre trial validation phase, we took sentinel node biopsy samples from 842 patients with node negative, invasive breast cancer with use of a blue dye and radiolabelled colloid mapping technique at the peritumoural injection site. All patients underwent standard axillary treatment after sentinel node biopsy. 75 of the 842 patients had multifocal lesions on histopathologic examination. The following analysis is restricted to patients with multifocal or multicentric lesions.

**Results:** A mean number of 2.4 SLNs were identified in 71 of 75 patients (identification rate: 94.7%). Thirty one patients had a positive SLN, 40 a negative SLN. Standard axillary treatment confirmed the SLN to be negative in 37 of 40 patients, whereas three patients revealed positive non-sentinel lymph nodes (false-negative rate: 8.8%). Overall SLN biopsy accurately predicted axillary lymph node status in 68 of 71 patients (95.8%).

**Conclusion:** SLN biopsy accurately staged the axilla in multifocal breast cancer and may become an alternative to complete axillary lymph node dissection in node negative patients with multifocal breast cancer.

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POSTER HIGHLIGHT

# **Routine internal mammary sentinel node (IM-SN) biopsy in breast cancer is clinically relevant**

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**Background:** Routine internal mammary sentinel node (IM-SN) biopsy is feasible and allows for more accurate nodal staging, by identifying patients with worsened prognosis, as based on the presence of metastases in the IM-chain. Thus, adjuvant therapeutic strategies can be tailored accordingly, to gain survival advantage in this subgroup.

**Material and methods:** Within an ongoing prospective clinical study 720 consecutive clinically T<sub>1-3</sub>N<sub>0</sub> breast cancer patients underwent lymphatic mapping, using peritumoural injection of 370 MBq <sup>99m</sup>Tc nanocolloid and intradermal injection of 0.8 ml patent blue dye. IM-SN biopsy was attempted in all cases showing IM-hotspots on the preoperative scan.

**Results:** Lymphoscintigraphy showed axillary SNs in 97% (701/720) and additional IM-SNs in 21% (152/720). Routine IM-SN biopsy was successful in 67% (102/152), revealing overall 22.5% (23/102) internal mammary metastases. Five of these patients had no axillary metastases. All IM-SN positive patients received adjuvant chemotherapy, changing systemic therapeutic strategies in four out of five axillary node-negative patients, i.e. in 17% (4/23) of this group. Additionally, all IM-SN positive patients received adjuvant parasternal radiotherapy. In all, IM-SN biopsy changed adjuvant treatment in 15% (23/152) of patients with visualized IM-hotspots and in 22% (23/102) of patients with successful IM-SN biopsy, illustrating its clinical relevance.

Complete follow up of all IM-SN positive patients now ranges from 2 to 75 months (median 43, mean 37), showing no deaths and one event of distant metastases, diagnosed 7 months after surgery.

**Conclusion:** Routine IM-SN biopsy detects otherwise occult metastases in 15% of breast cancer patients with visualized lymph drainage patterns to the IM-nodes, enabling tailored adjuvant treatment strategies in order to improve overall survival in this poor prognosis subgroup.