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Intra-operative surgical margins planification by ultrasonography − A new tool for the surgeon in conservative breast surgery

J.L. Fougo[1], F. Osorio[1], A.P. Cardoso[1]. [1]*Clinica da Mama da Boavista, Clinica da Mama da Boavista, Oporto, Portugal*

Background: The traditional techniques of subclinical breast tumors localization (ink skin marking, hook wire guided or radioisotope guided) carry some limitations for the surgeon in defining a precise resection because those techniques doesn't allow correct surgical margins delineation.

The use of the ultrasonography (US) in the operative teather, by the breast surgeon, permits a real-time localization of impalpable nodular breast lesions and the subsequent planning of surgical margins, in order to excise the smallest specimen possible with adequate clear histological radial margins.

Material and Methods: We describe and present our intraoperative technical solution of surgical resection planning using, in the operative theatre, the US to target the breast lesion and to delineate, with ink skin lines, the breast volume to excise with precision, preserving the better cosmesis.

Results: With adequate training in breast US, the described technique is easy, not invasive, not time-consuming and cheapest comparing with traditional localization techniques. It only demands a new operating room tool − the US hardware. This solution can be applied not only on impalpable breast lesions, but also on clinical palpable tumors.

During poster presentation, a video of the technique will be available online at YouTube® (www.youtube.com).

Conclusions: The preoperative use of the US by the breast surgeon is an easy, simple, not invasive and satisfactory method to localize impalpable nodular breast lesions and allows intuitive and practical surgical margins delineation, to excise an adequate histological specimen in breast conservative surgery.

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POSTER SESSION

Sentinel node − technique, diagnosis and management

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Is intra-operative frozen section assessment of sentinel lymph nodes worth our while?

Q. Lu[1], G.Y.G. Lai[1], E.Y. Tan[1], J.C. Chen[1], M.Y.P. Chan[1]. [1]*Tan Tock Seng Hospital, General Surgery, Singapore, Singapore*

Background: Sentinel lymph node (SLN) biopsy is now the standard of care for small invasive carcinomas without clinically palpable lymph nodes. Full axillary nodal dissection (ALND) is reserved for cases where the SLN is positive. Intra-operative SLN assessment therefore has the advantage of allowing ALND to be performed at the same setting. Intra-operative frozen section (FS) assessment is currently used at our institution. However there are concerns regarding its accuracy and the additional operative time required. We therefore reviewed our data to determine whether intra-operative FS prolonged operative times, and evaluated the false negative rate on FS, which would necessitate a second surgery for ALND.

Materials and Methods: A retrospective review was performed. Between 1st January 2006 to 1st July 2009, 225 patients underwent surgery with SLN biopsy. Intra-operative FS was routinely performed in those with a pre-operative diagnosis of invasive carcinoma. SLN biopsy was performed for selected cases of ductal carcinoma-in-situ (namely high grade and large tumours), but FS was not done in these cases.

Results: One hundred and forty-two patients underwent wide local excision (WLE) with SLN biopsy; FS was not done in 14 (9.9%). Eighty-three patients underwent mastectomy and SLN biopsy, FS was not done in 18 (21.7%). SLN was positive in 64 patients of 193 patients (33.2%). In the 32 patients in whom intra-operative FS was not done, none had a positive SLN. The false negative rate for intra-operative FS of SLN was 20.3% (13 of 64 patients). On histological examination of the formalin-fixed paraffin-embedded sections, these cases were found to have micrometastasis. Intra-operative FS was found to have a sensitivity of 79.7% and a specificity of 100%; positive predictive value (PV) was 100% and negative PV was 94.0%. Intra-operative FS did not significantly prolong the surgery. In the WLE group, median operative time without FS was 60min, while that of those including FS was 70min. In the mastectomy group, median operative time without FS was 92.5min compared with 95min with FS.

Conclusion: Intra-operative FS does not significantly prolong the surgery. Intra-operative FS was found to have a high sensitivity and specificity, but was inadequate for the detection of micrometastasis. FS therefore is an efficient method of assessing SLN status intra-operatively, and is useful in helping the surgeon decide whether to proceed with ALND.

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Sentinel lymph node biopsy and immunohistochemical examination of bone marrow for the detection of isolated tumour cells in early stage breast cancer

M. Solá[1], M. Margeli[2], E. Castellà[3], J.M. Gubern[4], P. Culell[5], F.J. Julian[6], V. Vallejo[1], M. Fraile[1]. [1]*Hospital Universitario Germans Trias i Pujol, Nuclear Medicine, Badalona (Barcelona), Spain;* [2]*Hospital Universitario Germans Trias i Pujol, Oncology, Badalona (Barcelona), Spain;* [3]*Hospital Universitario Germans Trias i Pujol, Pathology, Badalona (Barcelona), Spain;* [4]*Hospital Mataró, Surgery, Mataró (Barcelona), Spain;* [5]*Hospital Sant Joan de Déu, Surgery, Manresa (Barcelona), Spain;* [6]*Hospital Universitario Germans Trias i Pujol, Surgery, Badalona (Barcelona), Spain*

Background: Almost a third of breast cancer patients recur and die from the disease in spite of node-negative status. Such adverse events could be explained by early haematogenous spread of tumour cells. The aim of the present study was to correlate axillary lymph node status according to sentinel lymph node biopsy (SLNB) and isolated tumour cells (ITC) in bone marrow (BM) as well as other clinical, pathological and biochemical prognostic factors.

Material and Methods: 104 patients with operable T < 3 cm breast cancer and both clinical and sonographically negative axillary lymph nodes, were scheduled for SLNB. Lymphoscintigraphy was obtained 2 hours after intratumoral administration of 2 mCi (74 MBq) of 99mTc colloidal albumin. SLN was evaluated for the presence of tumour cells by haematoxylin-eosin staining and, if negative, by immunocytochemistry using an anticytokeratine antibody (MNF-116).

BM aspirates were also collected intraoperatively from both iliac crests and mononuclear cell layers were separated by density centrifugation. Slide preparations were then examined for the presence of ITC by anticytokeratine-antibodies (A45-B/B3) immunocytochemistry.

Relevant clinical features and known prognostic factors such as age, clinical and radiological presentation at diagnosis, tumour size, histological type and grading, lymph vascular invasion, estrogen and progesterone receptor status were correlated using univariate analysis.

Results: SNB was positive in 28% of cases. ITCs were found in the BM of 22% of the patients. Even though there were five patients with coincidental SNB and BM ITC positivity, no overall correlation was seen between the two spread pathways ($\chi^2 = 0.232$; $p = 0.63$). Similarly, no single or combined clinical or prognostic features was strongly predictive of haematogenous and/or lymphatic spread. All patients recieved chemotherapy or hormonal treatment and radiotherapy. After a mean follow-up period of 56 months (5−80 months), 8 patients had recurred, and 4 of them had died from breast cancer. No correlation between BM ITC positivity or lymph node status and recurrence has been found.

Conclusions: BM ITCs were detected by immunocytochemistry in a significant proportion of early breast cancer. Also, SNB was positive in a fair proportion of our sample. Ocurrence of BM ITC and lymph node positivity seem to obey to completely unrelated pathways. Perhaps due to the scarcity of follow-up events in a cohort of patients receiving extensive adjuvant therapy, no prognostic power could be shown for either BM ITC positivity or LN status.

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Meta-analysis of predictive factors for non sentinel lymph node metastases in breast cancer patients with a positive SLN

R. van la Parra[1], P.G.M. Peer[2], M.F. Ernst[3], K. Bosscha[3]. [1]*Gelderse Vallei Hospital, Department of Surgery, Ede, The Netherlands;* [2]*Radboud University Nijmegen Medical Center, Department of Epidemiology Biostatistics and Health Technology Assessment, Nijmegen, The Netherlands;* [3]*Jeroen Bosch Hospital, Department of Surgery, 's Hertogenbosch, The Netherlands*

Background: Over the last years, sentinel lymph node (SLN) biopsy has emerged as the minimally invasive alternative to routine axillary lymph node dissection (ALND) to stage breast cancer. Different clinicopathological variables, predictive of non sentinel node (NSN) metastases, have been identified to select those patients most likely to benefit from ALND when a positive SLN is found. The present study is a meta-analysis of the identified predictors of NSN metastases.

Materials and Methods: A Medline search was conducted which ultimately identified 56 candidate studies. Original data were abstracted

from each study and used to calculate odds ratios. The random-effects model was used to combine odds ratios to determine the strength of the associations.

Results: Fifty-six published series were included in the meta-analysis. The 8 individual characteristics found to be significantly associated with the highest likelihood (odds ratio >2) of NSN metastases are SLN metastases >2 mm in size, extracapsular extension in the SLN, >1 positive SLN, ⩽1 negative SLN, tumour size >2 cm, ratio of positive sentinel nodes >50% and lymphovascular invasion in the primary tumour. The histological method of detection, which is correlated with the size of metastases, had a correspondingly high odds ratio.

Conclusions: We identified 8 factors predictive of NSN metastases that should be recorded and evaluated routinely in SLN databases. These factors should be included in a predictive model that is generally applicable among different populations.

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Level III lymph node involvement cannot be predicted following positive sentinel node biopsy

E.K. Romano[1], C.C. Kirwan[1], M.S. Absar[2], S. Pritchard[3], M. Wilson[4], L.B. Barr[5], A.D. Baildam[6], N.J. Bundred[1]. *[1]South Manchester University Hospitals Trust, Academic Surgery, Manchester, United Kingdom; [2]North Manchester General Hospital, Breast Surgery, Manchester, United Kingdom; [3]South Manchester University Hospitals Trust, Clinical Pathology, Manchester, United Kingdom; [4]South Manchester University Hospitals Trust, Radiology, Manchester, United Kingdom; [5]South Manchester University Hospitals Trust, Oncoplastic Breast Surgery, Manchester, United Kingdom; [6]South Manchester University Hospitals Trust, Oncolpastic Breast Surgery, Manchester, United Kingdom*

Background: Following a positive sentinel node biopsy, the remaining axillary nodes are usually managed with axillary node clearance or radiotherapy. However variations in hospital radiotherapy protocols and surgeons practice mean that level III lymph nodes are not always treated, raising the concern of inadequate treatment.

Methods: A retrospective review of 605 patients undergoing sentinel node biopsy for breast cancer, following normal axillary ultrasound, to identify factors predicting for level III involvement.

Results: In total 105 (17.4%) of 605 women undergoing sentinel node biopsy had node involvement. Subsequent completion ANC was performed in 84 (80%) patients. Of patients undergoing completion ANC, 36 (34%) had further axillary node involvement. Further lymph node involvement was not predicted by standard pathological factors (oestrogen/progesterone/Her2 neu receptor status/tumour size/grade). Of patients with only micrometastasis, 7 of 22 (32%) had further axillary node involvement, whereas 10 of 26 (38%) patients with macrometastases had further nodal disease ($p = 0.6$). However 0 of 22 patients with micrometastases had level III nodal involvement and 4 of 26 (15%) with macrometastases had level III nodal involvement ($p < 0.05$). The Memorial Sloane Kettering Cancer Center (MSKCC) breast nomogram for additional node metastases had limited clinical utility. The mean (range) score to predict node involvement in node positive patients was 22% (4−95%) and node negative patients was 12% (3−40%) ($p = 0.01$). 13 (12.4%) of patients had metastatic disease in level III nodes at surgery, following a positive sentinel node biopsy. Level III involvement was not predicted by routine clinicopathological factors, and although the MSKCC breast nomogram gave higher scores for the prediction of patients with subsequent level III involvement (level III positive: 30% (5−95%); negative: 14% (3−69%) $p = 0.003$), it was not discriminatory.

Conclusion: Neither the MSKCC breast nomogram or standard clinicopathological factors predict for level III node involvement following positive sentinel node biopsy. There is a possible role for more limited axillary treatment in patients with only micrometastases, however with this current data, level III axillary node clearance must be recommended as the gold standard for positive axillary disease to avoid the risk of undertreating over 12% of patients.

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Sentinel lymph node diagnosis in breast cancer: comparison between two different molecular methods

R. Cano Muñoz[1], L. Bernet[2], M. Martinez-Benaclocha[2], F. Sevilla Chica[2], J. Medrano[3], J.P. González[4]. *[1]Hospital de la Ribera, Pathology, Alzira, Spain; [2]Hospital Lluís Alcanyís, Pathology, Xàtiva, Spain; [3]Hospital Lluís Alcanyís, Surgery, Xàtiva, Spain; [4]Hospital de la Ribera, Surgery, Alzira, Spain*

Background: Considering that the histological method for the intraoperative sentinel node (SN) study seems not to be the gold standard for its evaluation, mainly due to the different ways its study is approached, and since two new molecular methods have been recently developed to evaluate the presence of metastasis, we hereby try to evaluate the advantages and disadvantages between these two methods when used as a routine procedure.

Material and Methods: We compare our experience with the One-Step-Acid-Nucleic-Amplification (OSNA) (Sysmex®) procedure against the published data from of groups using the GeneSearch Breast Lymph Node Assay (BLNA) (Veridex LLC, Raritan, NJ®).

The first method is a one step isothermal RT-Lamp amplification for detection of Cytokeratin 19 mRNA (CK19 mRNA). The second one is a RT-PCR that detects mRNA of both Mammoglobin and CK19.

Results: In our experience, the OSNA sensibility up to date is 100% and its specificity 97.2%. The published BLN Assay results have a 95.6% sensibility with a specificity lately not specified.

BLNA, in one hand, offers a relative quantification (related to an internal control) which allows a binary result (either positive or negative). Due to this limitation, it does not differentiate between macro metastasis and micro metastasis, therefore part of the node has to be reserved for a post operative study. On the other hand, the OSNA method gives an absolute quantification of the amount of CK19 mRNA copies offering so a differentiation between micro metastasis and macro metastasis allowing to provide an intraoperative definitive result and diagnosis.

In the technical aspect, BLNA is more complex since nucleic acid extraction requires some experience in molecular handling. This is not the case with OSNA, which has a low technical complexity and high degree of automation, not requiring previous experience in molecular laboratory.

Finally, the timing of the BLNA procedure ranges from 36 to 46 minutes for one to three sentinel nodes. In our experience, OSNA takes a mean of 31 minutes to evaluate up to four sentinel nodes.

Conclusions: The OSNA procedure seems to have better sensitivity and specificity than the BLNA. The OSNA discriminate between macro-metastases, micro-metastases and isolated tumour cells (ITC) while the BLNA only offers positive and negative results. Time wise, OSNA procedure is shorter than the BLNA one.

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Complete axillary lymph node dissection versus clinical follow-up in breast cancer patients with sentinel node micrometastases. Interim analysis of the Spanish multicenter clinical trial. AATRM 048/13/2000

M. Solá[1], F.J. Julian[2], B. Ballester[3], R. Rojo[4], I. Pericás[5], A. Piñero[6], A. García[7], V. Vallejo[1], J.L. De Pablo[8], M. Fraile[9]. *[1]Hospital Universitario Germans Trias i Pujol, Nuclear Medicine, Badalona (Barcelona), Spain; [2]Hospital Universitario Germans Trias i Pujol, Surgery, Badalona (Barcelona), Spain; [3]Hospital Universitario Salamanca, Surgery, Salamanca, Spain; [4]Hospital Ramon y Cajal, Surgery, Madrid, Spain; [5]Instituto Oncológico San Sebastian, Nuclear Medicine, San Sebastian, Spain; [6]Hospital Virgen Arrixaca, Surgery, Murcia, Spain; [7]Mutua de Terrassa, Gynecology, Terrassa (Barcelona), Spain; [8]Hospital de Txagurritxo, Surgery, Vitoria Gasteiz, Spain; [9]Hospital Universitario Germans Trias i Pujol, Medicina Nuclear, Badalona (Barcelona), Spain*

Objective: To asses the impact of SN technique on the wellbeing and performance status of breast cancer patients, specifically targeting the finding of axillary micrometastatic disease.

Method: To achieve such objective, a randomized prospective clinical trial was devised with two arms. In one arm, patients with SN micrometastases are the subject of plain clinical follow-up (experimental arm). In the other arm, patients are submited for second-sugery completion ALND (control arm). All patients are intended for a two-year follow-up period.

Results: The accrual phase is completed (1st gen 2002 to 31 dec 2008). A total of 248 patients have been entered. There have been 14 withdrawals in both groups. 113 patients are being followed in the control arm, and 121 in the study arm. In the control arm, 15 completion ALND turned out positive, in 13 only with one additional (non-sentinel) lymph-node metastasis, being a micrometastases in 6 of them. In the study arm, one axillary recurrence has been observed in a single lymph-node, one year after primary surgery.

Conclusions: The follow-up phase is not completed. However, the observed data after primary surgery treatment suggest that adjuvant radio-chemotherapy might cure residuary axillary minimal disease in those patients not subbmited to completion ALND. Primary endpoints analysis, including survival and regional control will have to wait for the study follow-up to be completed.