Thursday, 23 March 2006 14:15–16:00

SCIENTIFIC SESSION

Sentinel node procedure and beyond

227 Invited

What is a positive sentinel node?

G. Cserni. *Bacs-Kiskun County Teaching Hospital, Pathology, Kecskemet, Hungary*

The axillary nodal status is considered the most important prognostic factor in breast cancer. Sentinel node (SN) biopsy allows a meticulous search for metastatic deposits, but also increases the heterogeneity in methods advocated for nodal staging. *Histological methods* have obvious bearing on metastasis identification. This is not independent of *metastasis size*; nodal involvement identified only by step sectioning or immunohistochemistry (IHC) is generally of low volume. Positive and negative results can, in theory, be trusted only if a systematic search for a given size metastasis is carried out. With the new *TNM definitions*, the lower end of nodal involvement (isolated tumor cells – ITC) should not be considered metastasis, therefore the definition of metastasis has also bearing on the identification of a positive SN. It seems that the categories of micrometastasis and ITC are rather heterogeneously used, and this brings up *the pathologist* as a further factor bearing on the identification of an SN as positive. Low volume nodal involvement can often be missed by routine microscopy even if IHC is used. It was also found that the ITC and micrometastasis TNM categories are suboptimally reproducible. Further concerns, such as artificial transport of tumor cells into the SNs, cytokeratin positivity of reticulum cells may also influence positivity of an SN, and care should be taken to *avoid false-positive SN diagnoses*.

After all these confusing issues, *a practical approach* should be given, even if this is not acceptable to all. Until evidence for the opposite emerges, an SN should be considered positive if metastases are detected in it by histology. A metastasis should be considered a nodal involvement >0.2 mm in its largest dimension. A target size should be identified, and SNs, as the most likely sites of nodal metastases should be searched systematically to find (nearly) all of the targeted metastases. The European guidelines for SN assessment have set 2 such target sizes, acknowledging that health care systems differ: it is stated that all metastases >2 mm should be identified as a minimum, and optimally all micrometastases should also be sought for. IHC may facilitate this latter task and is therefore not discouraged, but is not considered mandatory either. The role of IHC may be greater in lobular carcinomas, where I personally recommend its use for HE-negative SNs. Finally, an SN should be considered positive if the pathologist says it is positive.

228 Invited

Sentinel node biopsy and beyond

R. Mansel. *University of Wales College of Medicine, University Department of Surgery, Cardiff, United Kingdom*

Sentinel node biopsy (SNB) for breast cancer now has a large body of observational data with individual series of several thousand patients. The method has a very high predictive rate for a negative axilla. The recent ASCO technology guidelines suggest that the technique has become standard of care in many institutions in the USA but the introduction in Europe has been slower and more patchy. There remain questions about the best methodology for the procedure, but it is clear that the combined technique has a higher localisation rate compared with the dye alone method. The largest RCT comparing the combination with dye alone showed the former method to be more succesful.

Major questions relating to micrometastases and local recurrence rates in the long term remain to be resolved, but it is clear that the technique will be used in the majority of clinically node negative early breast cancer patients in the future. All the 3 published RCTs all of which come fromm Europe show major advantges in terms of morbidity for SNB. The Almanac trial from the UK, the largest to date demonstrates economic gains in shorter hospital stays (around 2 days less) and earlier return to work.

However all these gains are dependent on high localisation rates, which limit larger axillary procedures in the majority of women. The important factor is training and validation. The formal and validated NEW START programme in the UK has given success rates of 98% in SNB naive surgeons after a 30 case validation training set using a standardised combination method. This unique programme delivers training in the local breast unit by an experienced tutor.

Translation of the trial data to the general population should bring lower morbidity and lower costs in the surgery of early breast cancer.

229 Invited

How safe is a sentinel node biopsy?

V. Galimberti. *European Institute of Oncology, SENOLOGY, Milan, Italy*

Sentinel node biopsy (SNB) has quickly become a standard means of assessing axillary status in breast cancer. It has the merit of being less invasive than the once-obligatory complete axillary dissection, and has been shown to accurately stage the axilla. However some residual concerns remain regarding various aspects of the safety of the technique.

Of the invasive breast cancer patients who received SNB at our Institute from 1996 to 2000, we investigated 953 consecutive patients who received no further axillary treatment since the sentinel nodes were negative by extensive pathological examination.

After a maximum follow up of 7 years (median 38 months) there were 55 unfavourable events but only three cases of overt axillary metastasis -- all re-treated by complete axillary dissection. Local morbidity occurred in 2% of cases, in 6 of which limited anaesthesia of the lower aspect of the ipsilateral arm.

Ten years after the introduction of SNB in breast cancer, the above experience and the experience of other centers now provide sufficient clinical data to warrant the conclusion that the procedure is not only as effective as complete axillary dissection in staging the axilla, but is also oncologically safe in that the rate axillary recurrences using the procedure is less than expected. The local morbidity rate is also exceptionally low.

230 Invited

Update of the sentinel node trials

E.J.T. Rutgers. *The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam*

Sentinel node biopsy as staging procedure in early breast cancer is considered standard of care. Therapeutic implications has to come from randomised clinical trials. Five large randomized trials are initiated. In Europe, the Milan study was the first to publish its results, the ALMANAC trial reported functional assessment and quality of life data, and the EORTC 10981–22023 AMAROS trial is still ongoing and included already. Across the Atlantic, the ACOSOG Z0011 and NSABP B-32 trials are conducted.

In the single centre Milan study 516 patients with primary breast cancer and a tumour of $\leqslant$ 2 cm were randomly assigned either to SLNB and ALND or to SLNB followed by ALND only if the sentinel node contained metastases [2]. Patients were included from March 1998 to December 1999. A positive sentinel node was found in 34% of all patients. In the patients who underwent SLNB and ALND the false negative rate of the SLNB was 9%; the overall sentinel node identification rate was close to 99%. Patients who underwent SLNB only demonstrated less pain and better arm mobility than those who also underwent ALND. So far, no cases of overt axillary metastases were encountered in the SLNB only group.

The multi-centre ALMANAC trial from the United Kingdom was preceded by an audit phase of the technique as performed by the participating surgeons. When this first stage was succesfully completed, surgeons entered the second stage: the randomized clinical trial comparing SLNB with standard axillary treatment (ALND or nodal sampling). Data from the early validation phase showed a sentinel node identification rate of 90% preoperatively, and 98% intraoperatively, with a false-negative rate of 7% [3]. This study also included comprehensive and repeated quality of life assessments. Eight hundred and twenty-nine patients completed functional assessment and anxiety inventories at baseline and during follow-up [4]. There were significant differences between treatment groups favouring the SLNB group throughout the 18 months assessment. Approximately twice as many patients who underwent standard axillary treatment compared to SLNB reported substantial arm swelling (14% versus 7%) or numbness (19% versus 9%). These findings are corroborated by results from a smaller randomized trial of 298 patients [5].

The third large European randomized clinical trial is the 10981–22023 AMAROS trial which randomizes sentinel node positive patients between ALND versus radiotherapy to the axilla. Eligible are patients with an operable invasive breast cancer between 5 mm and 30 mm, without clinically suspected regional lymph nodes. SLNBs are performed by the combined technique. Surgical and radiotherapy quality control constitutes an important part of the trial design. Main objective of the trial is to prove equivalent axillary control for sentinel node positive patients with reduced morbidity if treated with axillary radiotherapy instead of ALND. As of March 2006, over 2300 (66%) patients have been included by 30 institutes. SLNB results demonstrated 34% positive and 64% negative sentinel nodes leading to an overall identification rate of 98%.

Unfortunately, one of the two large American sentinel node trials has been suspended because of low accrual: the ACOSOG trial Z0011 was designed to address the question of further treatment to the axilla in, on H&E staining, sentinel node positive patients. So far, 595/1900 (31%) patients were randomly assigned to radiation of the breast only, without specific treatment of the axilla, or to radiation of the breast accompanied with ALND.

The NSABP B-32 has a similar design as the Italian study: SLNB followed by ALND versus SLNB and ALND only if tumour is found in the SLNB. Primary endpoints of this multi-centre study are the long term control of regional disease, disease-free and overall survival of patients who underwent a SLNB alone and its morbidity compared with ALND. This study has completed accrual with 5611 patients randomized between May 1999 and February 2004. Preliminary results demonstrated an overall sentinel node identification rate of 97%, 26% of whom were sentinel node positive and a 10% false negative rate [6].

In the previous St. Gallen consensus discussion meeting [7], it was concluded that sentinel lymph node biopsy (SLNB) is considered standard for lymphatic staging in patients with invasive breast cancer <3 cm, and no clinical involvement of ipsilateral axillary lymph nodes. Although there is not yet data on the effect of SLNB on long-term survival of patients with breast cancer, the available evidence from randomized clinical trials demonstrates that this technique is safe and accurate if performed by experienced surgeons.

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231 Proffered Paper Oral

Improved outcome of breast cancer patients with internal mammary lymph node metastases by use of tailored treatment

E.M. Heuts, F.W.C. Van der Ent, K.W.E. Hulsewé, P.A.M. Heeren, A.G.M. Hoofwijk. *Maaslandziekenhuis Sittard, Surgery, Sittard, The Netherlands*

Introduction: Staging of the internal mammary (IM) nodal basin is not performed routinely and subsequent treatment generally is not influenced. The IM lymph node status is, however, a major independent prognostic factor in breast cancer. If positive, prognosis is less favourable.

Since the introduction of the sentinel node procedure for staging in breast cancer, we routinely perform IM sentinel node biopsy as visualized on lymphoscintigraphy, in order to improve nodal staging and to adjust adjuvant treatment accordingly.

Patients and Methods: Between April 1997 and July 2004, a total of 794 consecutive patients with stage T_{1-3} breast cancer were enrolled into a prospective study on SN biopsy. Adjuvant treatment algorithms were according to Dutch national guidelines. In case of IM metastases internal mammary radiotherapy was added and systemic treatment was adjusted when appropriate. Data with regard to demographics, diagnostic procedures, therapy and follow up were gathered from all patients. Patients treated after July 2004 were excluded from this study to permit at least one year of follow-up.

Results: Data from 788 patients were available for follow-up, six patients were lost for follow-up.

A total of 425 patients proved to have no lymph node metastases (group 1), 336 patients had axillary metastases (group 2) and 27 patients had IM metastases (group 3). Mean follow-up was 46 months. Overall survival was 94% in group 1, 85% in group 2 and 87% in group 3, respectively. Disease free survival was 90% in group 1, 81% in group 2 and 86% in group 3. The differences between group 2 and group 3 were statistically not significant.

Discussion: With positive IM nodes a survival disadvantage is expected. However, after adjuvant local treatment (parasternal radiotherapy) and adjusting chemotherapy in therapeutic schedules, treatment outcome of patients with proven IM nodal metastases, after a mean follow-up of 46 months, was comparable to patients with axillary metastases only.

Conclusion: Our results suggest that high risk patients with IM metastases benefit from improved staging and tailored adjuvant treatment algorithms.

232 Proffered Paper Oral

Recurrences and survival after sentinel node biopsy with mandatory axillary node dissection versus sentinel node biopsy followed by axillary node dissection only for positive sentinel nodes – a retrospective analysis of 3159 cases from the Austrian Sentinel Node Study Group

U. Denison[1], P. Konstatiniuk[2], C. Peters-Engl[1], P. Schrenk[3], S. Woelfl[4], S. Roka[5], O. Riedl[5], S. Poestlberger[6], D. Hecke[6], A. Haid[7]. [1]*General Hospital Hietzing and Neurologisches Zentr, Gynecology and obstetrics, Vienna, Austria;* [2]*Univ. Hospital, Graz, Austria;* [3]*AKH, Surgery II, Linz, Austria;* [4]*AKH, Pathology, Lnz, Austria;* [5]*Univ. Hospital, Surgery, Vienna, Austria;* [6]*Hospital Barmherzige Schwestern, Linz, Austria;* [7]*Genreal Hospital, Surgery, Feldkirch, Austria*

The purpose of this analysis was to determine the influence of sentinel node biopsy followed by axillary node dissection only in cases of positive sentinel nodes as opposed to sentinel node biopsy (SNB) with obligatory axillary dissection in all cases, on axillary lymphnode recurrence, disease free survival and over all survival.

3564 patients are registered in the Austrian sentinel node data base. 3159 patients with unilateral, unicentric, non metastatic invasive breast cancer were analysed for axillary recurrence. 50 sentinel node biopsies with obligatory axillary dissection (phase I) (n658) were obligatory before performing SNB as standard procedure (phase II).

Blue dye, technetium^{99} or a combination of both were applied to identify the sentinel node.

473 out of 658 SNB were identified in phase I with a false negative rate of 6.4%. The median follow up in phase I is 50.1 (±28.3) months, in phase II 29.5 (±19.3) months

The axillary recurrence rate was 1% in phase I and 0.3% in phase II: There was no significant difference in disease free and over all survival although the follow up time interval is still short.

The SNB became standard in many breast cancer centres in Austria. The axillary recurrence rate is very low. The impact of axillary dissection or irradiation of the axilla after pos SNB is still unclear.

233 Proffered Paper Oral

Determination of axillary sentinel lymph node status in primary breast cancer by prospective use of immunohistochemistry increases the rate of micrometastases and intratumour cells without prognostic information

L. Rydén[1], P. Jönsson[1], L. Sjöström[2], G. Chebil[2]. [1]*Dept of Surgery, Helsingborg, Sweden;* [2]*Dept of Pathology, Helsingborg, Sweden*

Background: Axillary node status is today determined by the sentinel lymph node (SLN) biopsy avoiding axillary lymph node diseection (ALND) in patients without metastatic involvement. In patients with SLN micrometastases the risk of non SLN metastases is about 15% making ALND standard procedure, whereas in patients with intratumour cells (ITC) the risk for additional nodal involvement is not defined.

Patients and Methods: 174 patients with invasive breast cancer <3 cm were enrolled consecutively during 2001–2002. SLN's were examined by frozen section perioperatively and on formalinfixed, paraffine-embedded tumours using hematoxylin and eosin (H&E) as well as immunohistochemistry (IHC) with cytokeratin antibodies for definitive histopathological diagnosis. Patients with macrometastases (>2 mm in size), micrometastases (>0.2 mm ⩽2 mm) and ITC (⩽0.2 mm) in SLN had ALND enabling examination of axillary nodes in all patients irrespective of SLN tumour burden. The follow-up was 3 years (0–4years).

Results: Macrometastatic SLN was found in 29 patients and could be diagnosed by H&E in all cases, micrometastatic SLN was identified in 16 patients (3 diagnosed by IHC) and ITC in 6 patients (4 diagnosed by IHC).