Symposium: Breast Cancer

Current European Studies of Sentinel Lymph Node Biopsy for Breast Cancer

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The paradigm shift in the assessment of the axilla in breast surgery has evoked specific clinical issues. In a population where breast cancer is diagnosed early and service screening mammography is applied, the chance for a woman to be free of lymph node metastases is approximately 60%. Currently, there are three ongoing and one published randomized series on sentinel node lymphadenectomy in Europe, comprising more than 100 patients. These studies address the important issues of morbidity, quality of life and long-term outcome measures such as survival and recurrence. [Asian J Surg 2004;27(4):291-3]

Introduction

Publications on sentinel lymph node biopsy (SLNB) for breast cancer have concluded that it is feasible and accurate after appropriate training. There is still variability regarding techniques and methods for localizing the sentinel node(s), but these facts have not substantially altered the results in the larger published series.

SLNB was quickly adopted in the 1990s and, at the first Sentinel Node Congress in Amsterdam in 1998, it became clear that after a learning phase, many centres began adopting SLNB as part of clinical practice.

To the author’s knowledge, there are very few national studies that have explored the diagnostic and clinical pathways with SLNB in a sequential manner. On the contrary, many breast centres have recorded and published their experience in the various steps of SLNB. Denmark has a national database for breast cancer management, the Danish Breast Cancer Cooperative Study Group (DBCG). The guidelines that describe indications for SLNB and auditing are clearly stated.1 To date, most centres that perform breast surgery in Denmark offer SLNB and, thus, report to the DBCG. There is, however, no national trial ongoing.

In Sweden, the introduction of SLNB and the formation of the Swedish Breast Surgery Section almost coincided, and since 1997, trials on feasibility, audit and validation have followed. More or less complete coverage of all SLNB in Sweden is registered (L. Bergkvist, personal communication, December 2003). Centres that meet the prerequisites with documented and successful learning experience have participated in a study where 2,000 selected patients underwent SLNB with or without axillary clearance for assessment of axillary recurrence. From the three studies performed so far, the detection rate increased after the audit phase from 94% to 97% (L. Bergkvist, personal communication, December 2003).2

In the UK, only centres that have enrolled in the national randomized trial perform SLNB.

The different specific variables that have been the focus of the larger European trials have included imaging techniques, histopathological assessment of sentinel nodes, assessment and consequences of micrometastases, axillary morbidity, quality of life, therapeutic consequences of a positive sentinel node, and health economics.3–9 The European Working Group for Breast Screening Pathology recently published a review on current data and recommendations for guidelines.10

This review will focus on the work that has emerged from European centres that have conducted randomized trials. At
the time of writing, a MEDLINE search was made for randomized clinical trials published in English (between 1997 and September 2003). There were 10 hits, three of which were European. Two of these studies dealt with labelling and injection techniques, comprised 20 and 80 patients, and therefore will not be mentioned in detail.11,12 The third study was a validation study of SLNB versus routine axillary dissection.13 The other cited references have been selected to be representative of the current ongoing research in the field.

There are currently three ongoing randomized European multicentre trials.

**European randomized trials**

**ALMANAC**

To date, SLNB in the UK is limited to a few centres as the method has not been approved as standard treatment. The Axillary Lymphatic Mapping Against Axillary Clearance (ALMANAC) trial is funded by the UK Medical Research Council.14 It is a multicentre trial that consists of two phases, one audit phase where organized training occurs and where identification of the sentinel node should be 90% and the false-negative rate should be less than 5% after 40 cases have been performed. Once these requirements are fulfilled, centres can join the randomized trial, which includes all patients with planned axillary surgery to either have SLNB or standard treatment. The histopathological diagnosis of the sentinel node is made from paraffin sections. The primary endpoints of the study are axillary morbidity and quality of life, but the study also compares health economic issues between the different procedures. With longer follow-up, the study will also address the issue of axillary recurrence.

**SLNB versus routine axillary dissection in breast cancer**

This study involved a single institution. The primary endpoint of the study was the predictive status of the sentinel node compared to axillary status in patients who underwent full axillary clearance after SLNB. Secondary endpoints were quality of life, axillary recurrence and survival. The trial included low-risk patients (i.e. patients with tumours < 2 cm) who were eligible for breast conservation therapy. Of 649 eligible patients, 516 were included. The histopathological assessment was extremely thorough and included frozen-section analysis with approximately 60 sections per node at intervals of 100 μm. The results showed an overall accuracy of 96.9%.13 The false-negative rate was 8.8%. With 4 years’ follow-up, no axillary recurrence had occurred.

**Micrometastases in sentinel nodes (IBCSG 23-01)**

In this multicentre trial, the prognostic significance of micrometastases will be assessed, as this issue remains highly controversial. More than 60% of low-risk patients are free of axillary metastases. A labour-intensive technique in which numerous lymph nodes are examined shows that the actual rate of micrometastases increases. The clinical importance of micrometastatic spread in the sentinel-node setting is unknown and different views prevail. The endpoints of the current study are disease-free survival and overall survival.

Patients with unifocal breast cancer less than 3 cm in greatest diameter with proven micrometastases after SLNB are randomized to proceed with axillary clearance or observation. The study implies meticulous histopathological examination of the sentinel node with the technique described above. Some 1,900 patients are needed for evaluation of the endpoints.15

**AMAROS**

The After Mapping of the Axilla Radiotherapy Or Surgery (AMAROS) study is a multicentre international phase III trial to assess treatment of the axilla.16 Randomized patients with tumours of less than 3 cm will undergo SLNB. Patients with negative SLNB will be observed without further treatment, whereas patients with positive SLNB will either undergo axillary lymphadenectomy or receive radiation to the axilla. The principal aim of the trial is to assess morbidity between the different treatments. A secondary endpoint will be morbidity after SLNB only. To answer these questions, some 3,400 patients should be included. Possible reasons for the rather modest accrual are the study design that combines surgery and radiation therapy. The radiotherapy guidelines were studied in a trial where participating centres were asked to provide a radiotherapy plan according to the AMAROS study protocol. The findings led to enhanced protocol compliance and several adjustments were made by the participating centres.17

**Conclusions**

SLNB has gained widespread popularity in Europe, although it is not yet a recognized treatment in the UK. In three Scandinavian countries, there are national guidelines and auditing of the procedure. There are currently three randomized trials published in the English literature: two multicentre studies and one single-institution study. These studies, in combination with other randomized trials outside Europe, will provide evidence-based information that will serve as guidelines for modern breast cancer treatment.
References

1. http://www.dbcg.dk/