Sentinel lymph node biopsy in breast cancer and melanoma
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Chapter VIII
General discussion
Breast cancer

Sentinel lymph node biopsy in women with breast cancer accurately assesses the progress of the disease. The procedure is associated with a lower morbidity rate than axillary lymph node dissection, and it has become accepted as the standard practice for the management of patients with breast cancer. Through refinements of the pathological examination, the detection of (micro) metastases in the sentinel lymph node has been improved, resulting in a better assessment of the disease status. The pathologist has fewer nodes to process (usually one to three lymph nodes) and can therefore invest more resources and time in thorough analysis. The identification of extra-axillary sentinel lymph nodes further improves disease evaluation.

Despite its widespread application, a consensus has not yet been reached on the way sentinel lymph node detection and biopsy should be carried out in breast cancer patients. Several areas remain controversial. These include both technical issues, such as:

- the best tracer,
- the preferred location of injection (intratumoural, peritumoural, intradermal, subdermal, subareolar), and
- the value of lymphoscintigraphy

as well as pure medical uncertainties including:

- the need to resect extra-axillary sentinel lymph nodes,
- the clinical relevance of sentinel lymph node positivity based on immunohistochemical staining with cytokeratin,
- the value of sentinel lymph node biopsy in ductal carcinoma in situ,
- sentinel lymph node biopsy following neoadjuvant chemotherapy, and
- the value of completion axillary lymph node dissection.

This last question is addressed by the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial,1,2 the National Surgical Adjuvant Bowel and Breast Project (NSABP) B-322 and the European Organization for Research and Treatment of Cancer (EORTC 10981-22023) AMAROSa trial3. The ACOSOG Z0011 trial randomly selects women undergoing breast-conserving therapy with low-volume axillary disease in the sentinel lymph node for treatment with completion axillary lymph node dissection or else observation. NSABP B-32 randomly selects women for treatment with a sentinel lymph node biopsy followed by a standard level I and II axillary dissection or with a sentinel lymph node biopsy without dissection unless metastatic disease is noted by HE examination.

The main objective of the AMAROS trial is to prove equivalent local/regional control for patients with proven axillary lymph node metastasis by sentinel lymph node biopsy if treated with axillary radiotherapy instead of axillary lymph node dissection, with reduced morbidity. A second objective is to investigate whether adequate axillary...
control can be obtained by not subjecting patients with a negative sentinel lymph node to axillary lymph node dissection.

It remains unclear whether isolated tumour cells or micrometastases (lymph node metastases larger than 0.2 mm, but not larger than 2 mm) detected with HE staining or special stains represent an adverse prognostic indicator and whether axillary lymph node dissection should be carried out in all such cases. Therefore the prognostic significance of micrometastases in the sentinel lymph node identified by immunohistochemistry is being evaluated prospectively in the NSABP B-32 trial.\(^2\)

The European ALMANAC\(^b\) trial randomly selects breast cancer patients for either conventional treatment of the axilla and or for sentinel lymph node biopsy. This trial seeks to determine the impact of sentinel lymph node biopsy on morbidity and quality of life.\(^4\) Similar trials are in progress in Germany, Italy and France.\(^5\)

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**Melanoma**

The accuracy of the sentinel lymph node biopsy method for assessing and determining a prognosis for melanoma patients has been validated in multicenter trials and by multiple research groups in the USA, Europe and Australia.\(^6\) In a recent update, within a group of 300 patients treated at the UMCG the five-year recurrence-free survival in sentinel lymph node-negative and -positive patients was 79 and 57\% respectively (P<0.05). The disease-specific survival at five years was 86 and 71\% respectively (P<0.05).\(^7\)

Although this procedure has become increasingly popular, its therapeutic value is not yet proven. Two major studies are underway examining the therapeutic efficacy of early regional lymph node dissection in patients with metastatic disease in a sentinel lymph node. The Multicenter Selective Lymphadenectomy Trial-I (MSLT-I) is a randomized prospective study, which aims to determine the therapeutic benefit of sentinel lymph node biopsy and the true accuracy of the technique on a large scale. This trial, in which the UMCG participates, was initiated by Morton. MSLT-I was designed to compare two treatments: wide excision of the primary melanoma site plus sentinel lymph node biopsy and wide excision plus postoperative nodal observation. The accrual of patients to MSLT-I was completed in March 2002 with a total of 2001 patients taking part. Interim analysis has demonstrated that sentinel lymph node biopsy accurately evaluates the regional nodal basin.\(^8\)\(^-\)\(^10\) Interim evidence suggests that in a subset of patients (with melanoma 1.2 to 3.5 mm Breslow thickness) with occult sentinel lymph node metastasis, early regional lymph node dissection prolongs survival compared with delayed regional lymph node dissection when metastasis become clinically evident.\(^9\) The final results on the overall therapeutic use of sentinel lymph node biopsy will not be available until the final analysis is completed. This is dependent on longer follow-up, allowing for more
In a second trial, MSLT-II, the benefits of regional lymph node dissection when the sentinel lymph node contains tumour, are investigated. This trial will determine whether early regional lymph node dissection based on sentinel lymph node status provides a therapeutic advantage over care based on postoperative ultrasonographic monitoring of the nodal basin. The trial also investigates the clinical significance of reverse transcriptase-polymerase chain reaction positivity in paraffin-embedded sections of microscopically tumour-negative sentinel lymph nodes. UMCG’s Division of Surgical Oncology is one of the MSLT-II centers.

The Sunbelt Melanoma Trial is a multicenter, randomized prospective study that is analyzing the role of adjuvant interferon-α2b for patients with minimal nodal metastasis in the sentinel lymph node. Another area of research in this trial is focused on the validity of molecular staging. Interim analysis has established a low rate of postoperative complications associated with sentinel lymph node biopsy as compared to complete regional lymph node dissection.\(^{11}\)

Although evidence of therapeutic effectiveness cannot be confirmed until the outcome of these ongoing trials is known, sentinel lymph node biopsy clearly improves the evaluation of regional lymph nodes for prognosis purposes and may enhance the selection of patients for adjuvant therapy. However, given our current limitations in adjuvant therapy, it is unclear whether knowing the tumour status of the regional lymph nodes can contribute to a survival advantage. Unfortunately adjuvant interferon showed no benefit in stage IIb/III melanoma.\(^{12,13}\)

It has been suggested that it is inappropriate to perform sentinel lymph node biopsy routinely in melanoma patients, because there is still no clinical trial evidence that this procedure is of therapeutic value.\(^{14-16}\) For this reason the sentinel lymph node procedure is reserved for melanoma patients who want to be as informed as possible about their prognosis, according to the Dutch national guideline ‘Melanoma’ (3rd revision).\(^{17}\)

The sentinel lymph node biopsy procedure has been criticised on the basis of isolated reports that in-transit metastasis rates are increased.\(^{18,19}\) However this increase was not apparent in two large series.\(^{20,21}\) Many comments by international authors point out that the presumption by Thomas and by Estourgie that sentinel lymph node biopsy would lead to an increased rate of in-transit metastasis may not be true.\(^{22-25}\) Analysis indicates that regional lymph node surgery does not increase the risk of in-transit metastasis. Rather, primary tumour biology alone seems to determine that risk.\(^{26}\)

### Other malignancies

The value of sentinel lymph node biopsy has also been studied in several other malignancies.\(^{27-30}\) The diagnostic usefulness of sentinel lymph node biopsy has been established in penile and vulvar cancer as well, but its therapeutic value remains unproven.
Preliminary studies suggest that sentinel lymph node biopsy is also technically feasible in patients with Merkel cell, high-risk cutaneous squamous cell, colorectal, anal, prostate, urinary bladder, testicular, oral and oropharyngeal squamous cell cancer. Further studies with larger populations and longer follow-up are essential to better delineate the advantages of sentinel lymph node biopsy in the assessment and treatment of these malignancies. In the management of patients with thyroid, lung, gastric, cervical, uterine and ovarian cancer the clinical value of sentinel lymph node biopsy appears less promising.

**New developments**

Now that the concept of sentinel lymph node imaging has been firmly established, future developments deal with providing answers to clinical questions and technical improvements. The trials mentioned above will provide answers to the clinical questions. Technical improvements in the procedures mainly focus on improving spatial resolution of the gamma-camera images, e.g. combining single photon emission computed tomography (SPECT) with computer tomography (CT), in the new generation of SPECT-CT scanners. Early reports appear to improve the yield of the procedure. Another improvement in resolution could be gained from using positron emission tomography (PET) for sentinel lymph node imaging. However, adequate tracers with half-lifes sufficiently long enough to allow intra-operative imaging e.g. 24 hours after tracer administration, are currently not available. Sentinel lymph nodes can also be depicted using new magnetic resonance imaging (MRI) techniques, but this application does not allow probe guided surgery. Possibly new MRI techniques can be of value to determine the metastatic nature of a lymph node. However, whether this method will ever be able to detect the micrometastatic disease enabled by the sentinel lymph node biopsy, is unlikely.

In conclusion, sentinel lymph node biopsy is now considered best practice in breast cancer patients and in melanoma patients, who want to be informed about the stage of their disease, e.g. prognosis. However to date, the effect on tumour recurrence and survival rates in patients with breast cancer and melanoma is still unknown. Despite rapid advances in the molecular characterization of cancer, sentinel lymph node biopsy is likely to remain an important part of patient management, as it allows the most aggressive clones of the tumour (those that have metastasized) to be examined. Future management is likely to involve a combination of surgical and molecular techniques.
References

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