Sentinel node biopsy. Evolving from melanoma to breast cancer
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Although the procedure of lymphatic mapping and sentinel lymphadenectomy is said to be one of the major developments in surgical oncology in this decade\textsuperscript{1,2}, many aspects still need to be refined. A survival benefit of sentinel node biopsy for patients with melanoma has yet to be shown. Now that longer follow-up is available of patients who underwent sentinel node biopsy for melanoma, the sensitivity is found to be lower than initially expected. The relatively high rate of failure in patients with breast cancer needs to be resolved. Indications for the procedure also have to be further defined. Which patient (sub)groups are the most suitable candidates?

**MELANOMA**

**LONG-TERM OUTCOME**

Sentinel node biopsy was developed to avoid elective lymph node dissection in patients with clinically localised melanoma\textsuperscript{3}. The main aim is to improve the prognosis of these patients. The Multicenter Selective Lymphadenectomy Trial may give the answer to this question. But why would this trial bring forward a survival benefit of sentinel node biopsy that could not clearly be found for elective lymph node dissection\textsuperscript{4-8}? First of all, the number of patients entered will be 1600, which is more than in the previous randomised trials investigating elective lymph node dissection. This increases the power of the trial and allows proper
subgroup analysis. Second, lymphoscintigraphy is performed in all patients. This was not the case in the trials investigating elective lymph node dissection. It may improve the accuracy of staging because lymphatic drainage is in general unpredictable and because lymph nodes are frequently found outside the axilla, groin or neck. Sentinel node biopsy has the advantage that lymph node dissection is reserved for a subset of patients who are more likely to benefit.

The absolute gain in survival will be low. An estimated 80% of patients with melanoma will not benefit from sentinel node biopsy because they have no lymph node metastases. About 9% of patients with both nodal and distant disease at the time of sentinel node biopsy will undergo early lymph node dissection but this will have no impact on the course of the distant disease. Approximately four of the remaining eleven patients with only lymph node metastases at the time of diagnosis can also be cured if dissection is performed at a later stage. The remaining seven patients may be cured by early lymph node dissection. With a false-negative rate around 10% as in the series of The Netherlands Cancer Institute (Chapter 3), this number will be decreased to six out of each 100 patients. Thus, six out of each 100 patients may benefit, which is 30% of the 20 patients undergoing lymph node dissection.

Possible long-term effects of sentinel node biopsy are increased entrapment of tumour cells that are "in-transit" between the primary tumour and the regional lymph node basin (Chapter 3). Also, unpredictable lymphatic spread due to alterations in lymph flow patterns and hematogenic spread may be favoured. Furthermore, the rate of regional recurrence after selective lymph node dissection may increase because of contamination of the area around a tumour-positive sentinel node. Diagnosis and treatment of regional recurrences may be more difficult in a previously mapped basin. The rate of long-term morbidity such as lymphedema is yet unknown. Early complications are usually mild and occur in 9% of patients (Chapter 3). Other consequences of sentinel node biopsy are increased costs of the diagnostic process in institutions where a wait-and-see policy is standard of care. Furthermore, the number of patients diagnosed as being node-positive
will increase with about 10% because the sentinel lymph nodes are examined more thoroughly with serial sections and staining for S-100 and HMB-45. The Multicenter Selective Lymphadenectomy Trial may resolve several of these issues.

What should be done if the Multicenter Selective Lymphadenectomy Trial fails to show a survival benefit? It would be wise to stop performing lymphatic mapping in patients with melanoma. It is however unlikely that the technique will be left. The concept of sentinel node biopsy is appealing to both patients and physicians. Sentinel node biopsy provides important prognostic information. A patient with a tumour-free sentinel node can be reassured. Patients with a tumour-positive sentinel node can be entered in adjuvant therapy trials. In the United States, accrual for the Multicenter Trial has slowed down considerably because patients refuse to be randomised and request to undergo the procedure (Morton, personal communication). The debate on elective lymph node dissection, that has been going on for 20 years now, may then just shift to sentinel node biopsy.

**WHO ARE THE MOST SUITABLE CANDIDATES?**

Breslow thickness is a possible criterion to select patients for sentinel node biopsy. At present, the lower limit to perform a sentinel lymphadenectomy varies between 0.75 mm and 1.5 mm Breslow thickness, while most investigators do not set an upper limit. The Multicenter Selective Lymphadenectomy Trial may lead to identification of a subgroup of patients who benefit from sentinel lymphadenectomy, defined by Breslow thickness or other prognostic variables. Interesting conclusions in this regard were drawn in a report on a mathematical model that was generated to predict sentinel node involvement based on Breslow thickness and age. These two factors emerged after a multivariate analysis using a stepwise logistic regression model including age, gender, Clark level, Breslow thickness, presence of ulceration, location and number of nodal basins. In individual patients, this model can be used for counselling purposes regarding the likelihood
of metastatic disease in the sentinel nodes. It can also be used routinely to identify subgroups of patients, who will have the most to gain from the procedure.

The results of sentinel node biopsy in the head and neck region seem less favourable than in other regions (Chapter 5), although the experience is limited. Some adjustments of the protocol may improve performance. Using a small volume (0.1-0.2 ml in stead of 0.4 ml) and a lower dose (30-40 MBq in stead of 60-70 MBq) of the tracer could improve the quality of the scintigraphy images: this reduces the blur at the injection site and decreases the flow rate, the uptake of radioactivity per node and the total number of nodes that become radioactive. A smaller amount of blue dye can be injected (0.3-0.5 ml in stead of 1 ml) to prevent swift staining of multiple second-echelon nodes and to prevent a long-lasting discolouration of the skin at the injection site. A second injection can be given during the course of the operation if necessary. Concentrating patients with melanoma in the head and neck in a few high-volume centres may be a way to achieve sufficient accuracy.

Better non-invasive staging procedures, both for regional and systemic disease, may also further refine the selection of patients for sentinel node biopsy. Currently available non-invasive regional staging procedures are ultrasound examination, combined with aspiration cytology, CT scanning, MRI and positron emission tomography (PET). Some promising results have been published from ultrasonography. Up till now, monoclonal antibodies for the detection of regional metastases also lack sensitivity. Multimarker and molecular reverse transcriptase polymerase chain reaction (RT-PCR) techniques have been developed to detect malignant melanoma cells in the blood. The presence of specific tumour markers for melanoma, such as the new sensitive immunoluminometric assay, Sangtec® 100 (S-100), seems to be a useful prognostic parameter for hematogenic spread. For the more distant future it even may be anticipated that sentinel lymphadenectomy could become a redundant procedure, when more sophisticated tumour markers and
improved techniques will become available to detect circulating tumour cells in the blood.

ISSUES TO BE RESOLVED

Although lymphoscintigraphy is a well established procedure in lymphatic mapping and plays a crucial role in localising sentinel nodes preoperatively, little is known about its reproducibility. Kapteijn et al.32 studied 25 patients, in whom two scintigraphic studies were performed in an identical manner with a two to four week interval. In three patients (12%), there was a difference in the number of sentinel nodes depicted on the first and second scans. The number of unidentified sentinel nodes can be reduced by combining lymphoscintigraphy and mapping with patent blue (Chapter 4)33,34. However, efforts should be made to achieve optimal reproducibility of lymphoscintigraphy, both to increase the reliability of the method and to avoid removing (too many) non-sentinel nodes from the lymphatic basin.

Another question is: is it always necessary to clear the entire lymphatic basin after the removal of an involved sentinel node? In the series reported so far, additional involved nodes were found in 10 to 30% of the definitive specimens1,3,35-37. An interesting observation in this regard was made by the group of Reintgen38. In a series of 88 patients, they found that all those with involved nodes beyond the positive sentinel node(s) had a primary melanoma thickness of greater than 1.5 mm. The same was found in the series of patients described in Chapter 3 of this thesis14. These results suggest that the disease in sentinel-node-positive patients with a primary tumour of less than 1.5 mm in thickness may be confined to the sentinel node and that they, therefore, not necessarily require further lymph node dissection.

Sentinel node biopsy can be used to select patients for adjuvant therapy trials. The survival benefit of interferon alfa-2b found by Kirkwood et al.39 is encouraging but needs to be confirmed in other studies. Other treatment schedules should be evaluated that are less toxic.
than the regimen prescribed by Kirkwood et al. When lymphatic mapping does not improve prognosis for patients with melanoma, the procedure will probably continue to be performed in the light of adjuvant therapy trials.

The clinical relevance of the RT-PCR technique for examination of sentinel nodes has to be elucidated\textsuperscript{40,41}. RT-PCR detects tyrosinase messenger RNA which is a marker for the presence of melanoma cells in sentinel lymph nodes. In one report, patients with RT-PCR positive and histologically negative sentinel nodes had a recurrence rate of 13%, compared to 2% in RT-PCR negative patients\textsuperscript{41}. This suggests that RT-PCR may be of practical value in melanoma staging and could also become a selection criterion for entering patients in adjuvant treatment schedules.

\section*{BREAST CANCER}

\section*{LONG-TERM OUTCOME}

The main goal of sentinel node biopsy in patients with breast cancer is to prevent unnecessary lymph node dissection. The concept has been shown to be a reliable staging method in several groups\textsuperscript{42-45}. Controversies exist, however, on many technical aspects of the technique. It is still unknown what combination of tracer dose, volume and particle size, which time schedule for injection, imaging and operation and which site of injection results in the highest reliability and reproducibility. Quality control remains important when the technique is introduced in an inexperienced group. Krag et al. showed in a multi-centre validation study that the false-negative rate ranged from zero to almost thirty per cent with the same protocol\textsuperscript{46}. False-negative biopsies may lead to undertreatment of patients and decreased regional control and survival\textsuperscript{47,48}. It is too early to introduce the sentinel node biopsy as standard of care\textsuperscript{45,49}.
Long-term outcome could be evaluated in a prospective randomised trial. Such a multi-centre trial (the ALMANAC trial) has been initiated by Mansel et al. in the United Kingdom, randomising patients between conventional treatment of the axilla and sentinel node biopsy. Axillary clearance is performed in case of a tumour-positive sentinel node. Relevant endpoints of such a trial include local control, survival, morbidity, quality of life and economic aspects. Similar trials are in progress in Sweden, Italy and the United States (NSABP-B32). Large numbers of patients are needed to find a difference in prognosis between the groups. One may even question whether a prospective study is necessary for the implementation of a new diagnostic procedure.

A possible advantage of sentinel node biopsy over routine axillary clearance is that sentinel node biopsy may improve staging. The one or two sentinel nodes can easily be examined more thoroughly by the pathologist than the ten to twenty nodes recovered from an axillary dissection specimen. Some 10% of patients may be upstaged\textsuperscript{50-52}. What this means in terms of indications for adjuvant treatment and in terms of survival will probably become evident in the future\textsuperscript{53,54}.

Another advantage of lymphatic mapping is that individual variation in lymphatic drainage patterns is incorporated in the staging process. Sentinel nodes may be located in level III in the axilla, in the interpectoral fossa, lateral in the breast, supraclavicular or in the internal mammary chain (Chapter 10 and 11). Biopsy of sentinel nodes outside level I and II in the axilla will refine the indications for adjuvant irradiation, adjuvant chemotherapy and hormone treatment strategies. Because retrieval of internal mammary nodes is technically difficult and has limited clinical impact, biopsy of those nodes may be reserved for study purposes in high-volume institutions.

**WHO ARE THE MOST SUITABLE CANDIDATES?**

The validity of lymphatic mapping and sentinel lymphadenectomy has been shown best for early palpable breast cancer. Further research is
required to find the optimal technique after excision of the primary tumour because conflicting data have been found\textsuperscript{44,46,55,57}. The same applies to using the method in patients with non-palpable malignant breast lesions. Multifocal disease may remain a contra-indication for sentinel node biopsy (Chapter 7). Ductal carcinoma in situ could be an interesting indication\textsuperscript{57,58}. Patients with palpable nodes can be enrolled if the nodes are tumour-negative with ultrasound examination and fine needle aspiration cytology (Chapter 7).

Just like in melanoma, improvements in imaging techniques for the clinically uninvolved axilla, such as sonography combined with aspiration cytology\textsuperscript{59}, CT scanning\textsuperscript{60}, MRI\textsuperscript{61} and PET\textsuperscript{62}, may decrease the number of patients who have to undergo sentinel lymphadenectomy in the future. Tumour deposits smaller than 3 mm can unfortunately not be detected by these imaging techniques. Ultimate refinement in the detection of micrometastases may come from the search for specific tumour-seeking agents, such as monoclonal antibodies\textsuperscript{63}. Lack of selectivity of these agents, however, is still a limiting factor. The same holds true for the tumour tracer sestamibi\textsuperscript{64}. Other possible developments, such as greater insight into the prognostic characteristics of the primary tumour, or the finding of a reliable tumour marker in the blood, could eventually make lymph node status less important as a prognosticator\textsuperscript{65}.

**ISSUES TO BE RESOLVED**

The procedure of lymphatic mapping and sentinel lymphadenectomy is more difficult to perform in patients with breast cancer than in patients with melanoma (Chapter 7). Drainage of the tracers from the breast parenchyma is less efficient than drainage from the skin (Chapters 8 and 9). Further research may aim at establishing optimal tracer type, dose, volume and concentration to increase uptake in the sentinel node. Sentinel nodes may then be visualised more often with lymphoscintigraphy, may appear sooner after injection and intraoperative identification will then be easier.
Subdermal\textsuperscript{44,66}, intradermal\textsuperscript{67} or subareolar\textsuperscript{68} injection have been advocated. The theoretical rationale for these techniques is that the mammary gland develops as an appendix of the skin. These injection techniques may facilitate sentinel node identification\textsuperscript{67} because the uptake in the lymph nodes is increased. Borgstein et al. showed in 35 patients that a radiopharmaceutical injected around the tumour and blue dye injected intradermally, both drained to the same axillary nodes\textsuperscript{69}. On the other hand, different nodes are sometimes visualised when both techniques are used for lymphoscintigraphy in the same patient\textsuperscript{70,71}. Drainage to internal mammary chain nodes is frequently seen with parenchymal injection (Chapter 10) and this is not the case with injection in or underneath the skin for breast cancer\textsuperscript{72} or for melanoma\textsuperscript{10}. Veronesi et al. have now changed their technique and inject the tracers in the breast parenchyma if the tumour is located deep in the breast\textsuperscript{72}. Besides this, concern has been expressed that intradermal injection may lead to a blue tattoo, caused by retarded dissipation of the dye from the injection site\textsuperscript{73}. Breast oedema after partial mastectomy, axillary node dissection and postoperative irradiation could be promoting factors for this suggested sequel\textsuperscript{74}. Reintgen et al. and Giuliano et al. recommend that subdermal or intradermal injection should be avoided\textsuperscript{45}.

Another issue of lymphoscintigraphy is the choice of the radiopharmaceutical. The ideal tracer is taken up into sentinel nodes a short time after injection and is efficiently retained in the first draining node(s) without overflow to second-echelon nodes. The amount of activity that stays behind at the injection site should be minimal to prevent interference with probe measurements in the axilla. The radioactive label \(^{99m}\text{Tc}\) comes close to the ideal label, but it is not clear which particle size is optimal for the colloid. Antimony sulphur colloid, human serum albumin and sulphur colloid were compared in patients with truncal melanoma\textsuperscript{75}. There was no significant difference in the number of drainage basins identified. Further comparative studies with regard to the number of depicted sentinel nodes and non-sentinel nodes are desirable to establish the best radiopharmaceutical. Future research should also be directed at development of a more selective tracer: modifications of surface characteristics may increase uptake in macrophages in the sentinel nodes.

\textit{DISCUSSION}
How many cases should be enough for a learning phase? The surgeon has to master the blue dye technique and the gamma probe detection and has to learn about the limitations of lymphoscintigraphy (Chapter 4). Bass et al. showed that in a single institution an average of 23 cases per surgeon was needed to achieve a 90% identification rate and 53 cases for a 95% identification rate. One should be aware that these numbers are not sufficient to calculate the false-negative rate reliably. If the incidence of node-positive patients is 30%, only seven out of 23 will have lymph node metastases. The false-negative rate will be 14% if only one case is missed and 0% if none is missed. The learning curves of surgeons implementing this technique will reflect not only their technical expertise but also the overall effectiveness of the multidisciplinary team they are working in. Nuclear medicine physicians and pathologists play an important role in the procedure. Some hospitals do not have a department of pathology or nuclear medicine, which complicates communication and logistics. The number of patients needed to achieve a 90% identification rate and a false-negative rate of less than 5% may vary per institution.

Another interesting issue is whether all sentinel node positive patients need completion axillary node dissection. Chu et al. found that the incidence of tumour-positive nodes beyond the sentinel node increased with increasing size of the metastases in the sentinel node and with the size of the tumour. They suggest that axillary node dissection may not be necessary if there is only micrometastasis in the sentinel node or if the tumour is less than 5 mm in diameter. Patients with a positive sentinel node could also be irradiated on the axilla. This is the subject of an upcoming EORTC trial organised by Van der Velde and Rutgers et al. from the Netherlands (the AMAROS trial). It is interesting to know whether treatment of the axilla is necessary at all when micrometastases are present. Such a trial has recently been organised by Giuliano and Cox et al. on behalf of the American College of Surgeons Oncology Group, randomising patients with micrometastatic involvement of a sentinel node between either lymph node dissection or no treatment of the axilla.
OTHER TUMORS

Lymphatic mapping and sentinel node biopsy have been described for staging several other tumours than melanoma and breast cancer. Horenblas et al.\(^7\) have recently reported a large series of patients with penile carcinoma and they achieved good results. Promising results have also been reported for vulvar carcinoma\(^78-80\).

Other common tumours for which the technique may be of value are gastrointestinal and pulmonary cancers\(^81-85\). The lack of easy and reliable follow-up procedures to monitor non-dissected lymph node areas in case of a negative sentinel node forms a major problem in these patients.

The application of sentinel node biopsy for squamous cell carcinoma of the head and neck is interesting but needs further research\(^86-89\). The same is true for Merkel cell carcinoma\(^89,90\), thyroid carcinoma\(^89,91,92\), cutaneous lymphoma\(^93\), uterine and cervical carcinoma\(^94,95\) because the experience in these patient groups is limited.

CONCLUDING REMARKS

The procedure of lymphatic mapping and sentinel lymphadenectomy is valuable for staging patients with melanoma. However, it is necessary to prove whether the early detection and excision of clinically occult lymph node metastases leads to improved regional control and increased survival. Acute and long-term side effects have to be evaluated. The impact of adjuvant treatment at the early stage of lymphatic metastasis also has to be investigated prospectively. Sentinel node biopsy remains an experimental procedure in patients with melanoma until a survival benefit is proven or an effective adjuvant therapy regimen is available for patients with involved nodes.
Sentinel lymphadenectomy is of value in the staging and early regional treatment of patients with breast cancer. Several technical issues remain to be resolved. It is desirable to adopt a uniform method of performing the procedure around the world. Improvement of non-invasive imaging techniques for detection of regional lymph node metastases will probably decrease the number of patients that will have to undergo sentinel lymphadenectomy. Lymphatic mapping will decrease morbidity after surgery for breast cancer and will decrease the cost of primary treatment without jeopardising regional control and survival.
REFERENCES


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