Chapter II

Sentinel lymph node biopsy as a surgical staging method for solid cancers

Review article

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Introduction
It is generally accepted that regional lymphadenectomy is indicated in patients with clinically suspicious or pathologically proven metastases to the regional lymph nodes. A controversy exists, however, over whether early lymph node dissection in patients with clinically negative lymph nodes offers any therapeutic advantage over observation and later dissection if the patient develops clinically obvious nodal metastases. Over the past five years, the new concept of sentinel lymph node biopsy has been applied to assist in the further identification of patients for complete lymph node dissection. The sentinel lymph node is defined as the first lymph node that drains a primary tumour (Figure 1). If lymphatic drainage occurs in a step-wise fashion, this lymph node should reflect the pathological status of the remaining lymph node basin.

**Figure 1.**
The sentinel lymph node is defined as the first lymph node that drains a primary tumour.

In 1977, Cabanas originally proposed this concept in the management of patients with penile cancer. He reported that the lymphatic system of the penis drains to one lymph node (or a group of nodes), ‘the sentinel lymph node’, which is the dominant site of tumour spread from penile carcinoma. The location of this sentinel lymph node was visualized by performing lymphangiography of the dorsal lymphatics of the penis. Its location was close to the superficial epigastric vein. Patients with a tumour-positive sentinel lymph node underwent subsequent inguinal lymph node dissection.

In 1992, Morton et al. introduced the use of a vital blue dye (isosulfan blue) at the operating theatre, to visualize the lymphatic drainage from a malignant melanoma. Patent blue dye® was injected intradermally around the biopsy site of a primary melanoma and 10-20 min later, a skin incision was made in the regional lymph drainage region. Blue stained lymphatic vessels and blue stained nodes could be traced during this operation.

In 1993, Alex and Krag introduced the use of a radioactive tracer ¹⁹⁹m Technetium sulphur
colloid, injected intradermally around a primary melanoma site, followed by imaging and subsequent intraoperative use of a gamma probe to localize and extirpate the sentinel lymph node. In addition, they compared gamma-probe-guided localization to vital blue dye mapping in an animal model.\textsuperscript{2} In recent years, lymphoscintigraphy and blue dye have been used to trace the regional sentinel lymph node in many tumours. The technique and its use for malignant melanoma, breast cancer, penile cancer, vulvar cancer, Merkel cell carcinoma and thyroid cancer are described below.

Technique of sentinel lymph node localization

The day before the operation, lymphoscintigraphy is performed. One or two doses of in total 60 MBq \textsuperscript{99m}Tc nanocolloid (0.2 ml) are injected around the primary tumour for lymphoscintigraphy and intraoperative lymph node detection. Immediately after injection, dynamic images are taken with a gamma camera to visualize lymphatic drainage. After 2 h, static scintigrams are taken (Figure 2).

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure2.png}
\caption{Lymphoscintigraphy of a malignant melanoma of the lower leg. Left: after injection of radioactivity (posterior view of the right calf); middle: dynamic image 3-5 min after the injection, with lymphatic vessel and sentinel lymph node in the inguinal region; right: static scintigram 2 h after injection, inguinal region with highest activity in the sentinel lymph node.}
\end{figure}

The position of the sentinel lymph node is indicated on the skin. The operation is performed within 24 h after lymphoscintigraphy. After inducting anaesthesia, a dose of 1.0-2.0 ml Patent blue-V (Laboratoire Guerbet, Aulnay-Sous-Bois, France) is administered around the primary tumour. Before any incisions are made, the level of radioactivity is measured over the presumed sentinel lymph node site with the aid of a gamma probe (Neoprobe\textsuperscript{®} 1000, Neoprobe Corporation, Dublin, OH) (Figures 3 and 4). A skin incision is made over the most radioactive point. The incision is placed in the axilla in such a way that it can be incorporated in the incision for the subsequent mastectomy or axillary
node dissection. Usually a 2-3 cm incision is enough for localizing blue lymphatics. Lymphatic vessel(s) are carefully followed to the sentinel lymph node, which is identified by blue discouloration (Figure 5). The accumulated radioactivity in the sentinel lymph node is measured with the gamma probe. A combination of blue lymph vessel(s), blue node(s) and a hand-held probe are used for tracing. The sentinel lymph node(s) is (are) excised and the radioactivity is measured ex vivo to confirm the nodal activity. The wound is then explored with the probe for additional areas of high radioactivity, to trace or exclude other first echelon nodes.

Until now, several surgeons have applied the patent blue technique alone or together with the hand-held gamma probe with varying success. In general, the identification of the sentinel lymph node proved to be more successful with the probe than with patent blue dye alone. Overall, most investigators are now using both techniques together to achieve better results.

Sentinel lymph node biopsy can also be performed under local anaesthesia. Histopathological examination after serial sectioning and haematoxylin-eosin and immunohistochemical staining are conducted at most institutes. Then the decision can be made whether the patient requires immediate or later complete lymph node dissection under general anaesthesia.

**Figure 3.**
Gamma detection probe and monitoring equipment.

**Figure 4.**
Level of radioactivity measured over the presumed sentinel lymph node site, with the aid of a hand-held gamma detection probe.

**Figure 5.**
After making a 2-3 cm incision, a lymphatic vessel is carefully followed to the sentinel lymph node, which is identified by blue discouloration.
Sentinel lymph node biopsy for malignant melanoma

In 1992, Morton et al. described 223 clinical stage I patients with primary melanoma. A procedure was developed using vital blue dye that permits intraoperative identification of the sentinel lymph node. The sentinel lymph node was successfully identified in 194 (82%) out of the 237 lymphatic basins. Routine haematoxylin-eosin-staining (12%) or exclusively immunohistochemical staining (9%) detected metastases in 40 specimens (21%). There was a false-negative rate of less than 1%. In more recent studies comprising 150 sentinel lymph node biopsies, Morton stated that there have been no false-negatives and that he had successfully identified the sentinel lymph node in 96% of the patients.

In 1997, Albertini et al. described the addition of intraoperative radiolymphoscintigraphy to vital blue lymphatic mapping. In this technique the localization of the sentinel lymph node became easier and more widely applicable. This study consisted of 106 consecutive patients with a cutaneous melanoma of more than 0.76 mm Breslow thickness. A total of 200 sentinel lymph nodes and 142 neighbouring non-sentinel lymph nodes were harvested from 129 basins in 106 patients. When correlated with blue dye mapping, 70% of the sentinel lymph nodes demonstrated blue dye staining, while 84% of the sentinel lymph nodes were defined as ‘hot’ by radioisotope localization. With the use of both intraoperative mapping techniques, identification of the sentinel lymph node was possible in 96% of the nodal basins. Micrometastases were identified in sentinel lymph nodes in 15% of the patients by routine histology. Two patients had micrometastatic disease in ‘hot’ but no blue-stained nodes.

Karakousis described a series of 55 patients in whom blue dye alone was used. The sentinel lymph node was identified in 93% of the cases and proved to be positive in 24%. Albertini et al. concluded that the two techniques of intraoperative radiolymphoscintigraphy and the use of blue dye are complementary. The scintigraphic images and probe direct the surgeon to the area of greatest activity, which often enables the identification of blue afferent lymphatics that would not otherwise be apparent. By using both mapping procedures, the surgeon is reassured, because a visual test (blue dye) and a quantitative test (gamma probe) ensure that all sentinel lymph nodes are removed.

Sentinel lymph node biopsy in breast cancer

Current standard care for invasive breast cancer is complete removal of the tumour with documented negative margins by either mastectomy or lumpectomy followed by complete axillary lymph node dissection.

In 1994, Giuliano et al. described the technique of lymphatic mapping and sentinel lymph node biopsy in breast cancer. Vital blue dye alone was injected at the cancer site in 174 patients with primary breast cancer. Sentinel lymph nodes were identified in 114 out of the 174 (65.5%) procedures and sentinel lymph node biopsy accurately predicted the axillary lymph node status in 109 out of the 114 (95.6%) cases. There was a definite learning curve, as all false-negative sentinel lymph nodes occurred in the first part of
However, in 17% of cases, the intraoperative diagnosis was falsely negative, because micrometastatic foci were subsequently identified on permanent section. This percentage is high enough to cause concern, and may represent a limiting factor for the sentinel lymph node biopsy procedure. A patient whose sentinel lymph node is negative in frozen section but is positive on histology will require a further operation to clear the axilla, which is likely to increase her distress.

The largest series of patients with breast cancer and sentinel lymph node biopsy has been described by Cox et al. Sentinel lymph node biopsy was performed in 466 consecutive patients with newly diagnosed breast cancer. Vital blue dye and lymphoscintigraphy were used. The sentinel lymph node was successfully identified in 440 (94.4%) patients. There was only one false-negative sentinel lymph node (defined as a pathologically negative sentinel lymph node with pathologically positive lymph nodes at a higher level in the chain). In 105 out of the 440 (23.8%) successful identifications, the sentinel lymph node was positive for metastatic disease. The authors concluded that accurate sentinel lymph node identification can be made when all blue and hot lymph nodes are harvested as sentinel lymph nodes. Therefore, lymphatic mapping and sentinel lymph node biopsy are most effective when a combination of vital blue and radiolabeled sulphur colloid are used. A difficulty in the series of patients of Cox is that in most of their patients an axillary clearance is not performed if the sentinel lymph node biopsy was negative. Therefore, sensitivity in this series of patients could not be given.

In an interesting article Roumen et al. stated that in many papers, data are provided about the sensitivity, specificity, positive and negative predictive value of the sentinel lymph node biopsy procedure. The only interesting item is the sensitivity, which tells us something about the number of false-negative sentinel lymph nodes. Ideally, the sensitivity should be 100%, i.e. no false-negative nodes. A false-negative sentinel lymph node is defined as a pathologically negative sentinel lymph node with pathologically positive lymph node(s) at a higher level in the chain. Mentioning specificity is nonsense, as this number is always 100% by definition, as no-one will ever find a positive sentinel lymph node in a pathologically negative axillary basin. On the other hand, finding a negative node in a completely negative basin does not provide any specific information about the correctness of the sentinel lymph node procedure. The same holds true for the positive predictive value, which by definition is always 100% in such series. This is because the sentinel lymph node and axillary status are dependent variables. The idea is that the number of false-negative biopsies should only be compared with the number of positive axillary basins discovered after an obviously successful sentinel lymph node biopsy procedure. The negative axillary basins should be excluded. This then is the sensitivity of the procedure.

The sensitivities of the three series of patients described by Giuliano et al. and Veronesi et al. are listed in Table 1.
Table 1.  
Sensitivity of sentinel lymph node biopsy (SLN) in breast cancer in three series of patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>SLN identified</th>
<th>Sensitivity (%)</th>
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<tbody>
<tr>
<td>Giuliano (1994)⁷</td>
<td>174</td>
<td>114</td>
<td>88 (37/42)</td>
</tr>
<tr>
<td>Giuliano (1997)⁸</td>
<td>107</td>
<td>100</td>
<td>100 (42/42)</td>
</tr>
<tr>
<td>Veronesi (1997)¹⁸</td>
<td>163</td>
<td>160</td>
<td>95 (81/85)</td>
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A very interesting question after sentinel lymph node biopsy in breast cancer patients is the clinical impact of micrometastases that are detected with immunohistochemistry or with the use of polymerase chain reaction (PCR). What impact should the sentinel lymph node procedure have on adjuvant radiotherapy, hormonal and/or chemotherapy? At a strategy meeting for sentinel lymph node researchers at the National Cancer Institute in the USA in the Autumn of 1997, Giuliano speculated that if women had negative sentinel lymph nodes, a tumour under a certain size, plus negative immunohistochemistry and PCR tests, she might be able not to have systemic treatment, because of an extremely low risk of distant metastases.

**Sentinel lymph node biopsy in penile cancer**

In most cases, the treatment for penile cancer is surgical excision of the primary tumour alone. The indication for elective lymph node dissection depends on the size of the primary tumour.

Kapteyn investigated excisional biopsies of the sentinel lymph node based on individual lymphatic drainage, as an indicator of lymph node dissemination in patients with penile carcinoma.¹⁰ Nineteen patients with primary or recurrent squamous cell carcinoma of the penis underwent lymphatic mapping with ⁹⁹ᵐTc nanocolloid, patent blue dye and a hand-held gamma probe. No sentinel lymph nodes were found intraoperatively in four cases so regional lymph node dissection was not done. Five patients had positive sentinel lymph nodes and underwent regional lymph node dissection. In three patients dissemination was unilateral and in two bilateral. During follow-up (mean 23 months), there was one false-negative sentinel lymph node.

**Sentinel lymph node biopsy in vulvar cancer**

About 90% of vulvar malignancies are squamous cell cancers. Prognosis mainly depends on the inguinofemoral lymph node status. The value of sentinel lymph node biopsy has recently been investigated by de Hullu et al.⁹ In a feasibility study on the identification of the sentinel lymph node, 11 patients underwent lymphoscintigraphy and blue dye injection around the primary tumour. During the operation, a hand-held gamma probe was used to identify the sentinel lymph node. After removal of the sentinel lymph node, complete inguinofemoral lymphadenectomy was performed in all the patients. Ten patients could be evaluated. In eight patients, all the inguinofemoral lymph nodes
were negative for metastases, while in two patients, both the sentinel and non-sentinel lymph nodes showed metastatic disease. De Cicco et al. found comparable results in 15 patients, but he used lymphoscintigraphy alone.4

Sentinel lymph node biopsy in Merkel cell carcinoma
Merkel cell carcinoma is an aggressive cutaneous tumour with a propensity for local recurrence and early regional lymph node metastases. In contrast with malignant melanoma, there are no prognostic factors that predict metastases in patients with Merkel cell carcinoma. Messina et al. treated 12 newly diagnosed patients in a surgical protocol that consisted of preoperative lymphoscintigraphy, without blue dye.14 Two patients had metastatic disease in their sentinel lymph nodes and complete dissection of the nodal basins revealed additional positive nodes. The node-negative patients received no further surgical therapy and had no evidence of recurrent local or regional disease at a maximum of 26 months follow-up (median 10.5 months). The conclusion was that sentinel lymph node biopsy might identify a population of patients who would benefit from further surgical lymph node dissection.

Sentinel lymph node biopsy in thyroid cancer
Lymph node metastases from well-differentiated thyroid cancer are associated with high regional recurrence rates. Surgical options consist of blind nodal sampling, ‘berry picking’ procedures, and modified radical neck dissection. Kelemen et al. recently investigated the feasibility of sentinel lymph node biopsy in thyroid cancer.12 Seventeen patients with a suspicious thyroid nodule that was not accompanied by palpable cervical adenopathy had a sentinel lymph node biopsy. During surgery, the affected thyroid lobe was exposed and isosulfan blue dye was injected directly into the thyroid mass. Within seconds, the blue dye passed along the lymphatics to the sentinel lymph node, which was then excised. Lymphatic mapping and sentinel lymph node biopsy was followed by total thyroidectomy, except in one patient, who underwent lobectomy for benign disease. In 12 patients, the diagnosis of thyroid cancer was confirmed histopathologically. Cervical lymphatic mapping was unsuccessful in two patients, whose lymphatics mapped to the retrosternum. Five (42%) out of the 12 malignant nodules were associated with positive sentinel lymph nodes. Neck dissection was performed in these five patients and in two patients (17%) the sentinel lymph node was the only tumour-bearing lymph node. As an alternative, selective lymph node dissection lessens not only the chance of locoregional relapse, but also the number of complications.

Future trials in breast cancer and melanoma
Recently four new large multicenter studies on breast cancer have been published by McNeil.13 The American College of Surgeons Oncology Group, will use routine histology
to determine which women have positive sentinel lymph nodes, then they will be randomized to have either axillary lymph node dissection or no further dissection. Women whose sentinel lymph nodes are negative will have no further dissection. Groups will be compared for patient outcome, including regional recurrence and survival. This study will also determine the significance of micrometastases that show up only on immunohistochemical tests.

The Bay Area Sentinel Node Study, a community hospital-based study, is randomly assigning patients to receive one of the two methods of locating sentinel lymph nodes: blue dye alone or blue dye with radioactive tracer. All the patients will have both sentinel lymph nodes and standard axillary node dissection. Sentinel lymph node identification rate, accuracy (false negative rate) and community surgeons’ learning curves will be compared. A major objective is to determine which patients are most appropriate for sentinel lymph node biopsy by correlating factors like tumour size and grade with the false-negative rate. It will also examine the role of preoperative lymphoscintigraphy.

In the Moffitt Cancer/Department of Defense Study, patients are being randomized over two groups who have sentinel lymph node biopsies: those whose sentinel lymph nodes are positive (they will receive axillary node dissection) and those whose sentinel lymph nodes are negative (they will have no further dissection). Regional recurrence, and recurrence-free and overall survival will be compared. The study is also comparing two assays for micrometastases-immunohistochemistry and polymerase chain reaction in nodes, blood and bone marrow-to learn how they correlate with each other and with outcome.

A trial at the University of Vermont/National Surgical Adjuvant Breast and Bowel Project will randomly assign patients over two groups, one to have axillary node dissection and one to have sentinel lymph node biopsy. Groups will be compared for recurrence-free and overall survival, lymph oedema and other side effects, and long-term regional control of the disease.

The European Organisation for Research and Treatment of Cancer (EORTC) is also engaged in designing a study on breast cancer in which sentinel lymph node biopsy will play a central role.

At present, experience with sentinel lymph node biopsy is still restricted and the available published data are limited to a handful of nonrandomized series of patients. Therefore, many questions have to be answered by future trials. In the recently published data by McNeil13 some of these questions have been listed for breast cancer, e.g. what is the long-term impact of sentinel lymph node biopsy on recurrence and survival rates? What is the false-negative rate? Which patients should be candidates and what are the cut-off points for tumour size (3, 4 or 5 cm)? Is there always one lymph vessel going to one sentinel lymph node or are there sometimes more lymph vessels and more sentinel lymph nodes? What is the impact of multicentric primary breast cancer? What should we do if internal mammary nodes are demonstrated? What is the clinical impact of occult
micrometastases that are detected with immunohistochemistry or with the use of PCR?
After how many sentinel lymph node biopsies is a surgeon experienced enough? Should
the technique of using blue dye always be compared to a radioactive tracer and should it be injected into the tumour, around the tumour or into the overlying skin? All these
questions have to be answered before sentinel lymph node biopsy can be adopted as a
routine surgical procedure.
In the meantime, one study is in progress on malignant melanoma at the John Wayne
Cancer Center, in which wide local excision alone is being randomized against wide local
excision and sentinel lymph node biopsy. Regional lymph node dissection is carried out if the sentinel lymph node is found to contain tumour cells.

Conclusion
Lymphoscintigraphy and gamma-probe-guided localization of radiolabeled lymph
nodes can direct the surgeon non-invasively to the exact location of the sentinel
lymph node. Once localized with the gamma probe, it is quick and easy to remove the
sentinel lymph node through a small skin incision. The identification of the node from
other tissue is aided by using blue dye which stains the lymph node. A combination of
radioactivity and blue dye may be complementary for locating the sentinel lymph node.
References


the study; sentinel lymph nodes identified in the most recent 87 procedures were 100% predictive. In 16 out of the 42 (38.0%) clinically negative/pathologically positive axillae, the sentinel lymph node was the only lymph node with tumour involvement. In 1997, Giuliano described a second series of 107 patients with sentinel lymph node biopsies in breast cancer. Sentinel lymph nodes were identified in 100 patients: 42 patients had metastases in sentinel lymph nodes. No sentinel lymph node specimen was tumour-negative if the corresponding axillary lymph node specimen for the same patient was tumour-positive.

Veronesi et al. described a consecutive series of 163 sentinel lymph node biopsies in women with operable breast cancer. As radioactive tracer, human serum albumin labelled with Technetium was injected subdermally close to the tumour site on the day before surgery and scintigraphic images of the axilla and breast were taken. A mark was made on the skin over the site of the radioactive node (sentinel lymph node). During breast surgery, a hand-held gamma probe was used to locate the sentinel lymph node and it was possible to remove it separately through a small axillary skin incision. The sentinel lymph node predicted the axillary lymph node status accurately in 156 (97.5%) out of the 160 patients. In 32 (38%) out of the 85 cases with metastatic nodes, the only positive node was the sentinel lymph node. Veronesi et al. stated that one advantage of blue dye injection was that it could be done a few minutes before the operation, whereas lymphoscintigraphy must be carried out at least 2 h before surgery. However, the use of blue dye alone has an important drawback, because axillary tissue must be dissected blindly until blue vessels and the blue node are located. This node can lie at some distance from the incision. The advantage of a small hand-held gamma probe is that it locates the node and indicates exactly where the skin incision should be made (Figure 6). It also guides the surgeon to the sentinel lymph node itself, which makes this procedure quick and consistently successful.

Veronesi also discussed the sentinel lymph node diagnosis on frozen section. Immediate and reliable intraoperative information on the condition of the sentinel lymph node is vital for the technique’s success, since the surgeon must decide whether or not to do a total axillary lymph node dissection. Veronesi described that in 83% of his cases, the intraoperative diagnosis was confirmed by the final histological examination.

Figure 6.
The hand-held probe locates the sentinel lymph node in breast cancer and indicates exactly where the skin incision should be made in the axilla.
‘Sentinel lymph node biopsy as a surgical staging method for solid cancers’

Melanoma
Multiple retrospective studies have validated the accuracy of sentinel lymph node biopsy and its importance as a prognostic tool for melanoma. Sentinel lymph node biopsy has become the standard approach for staging the regional lymph nodes. The accuracy of detecting occult lymph node metastases is the key strength of sentinel lymph node biopsy. Reverse transcriptase polymerase chain reaction (RT-PCR) analyses of the sentinel lymph nodes have been found to be more sensitive than haematoxylin and eosin staining or immunohistochemistry techniques, but lack of specificity makes this technique impractical for routine use.

Three major multicenter, prospective, randomized studies are underway to determine the therapeutic benefit of sentinel lymph node biopsy in melanoma.

In 1994, the Multicenter Selective Lymphadenectomy Trial (MSLT)-I was initiated by Morton to determine the therapeutic benefit of sentinel lymph node biopsy and the accuracy of the technique on a worldwide basis. Preliminary results show a high level of accuracy and low morbidity (10%). In 2005, at the American Society of Clinical Oncology, Morton reported the third interim analysis out of five planned analyses. To date, there is no difference in survival between the wide local excision (WLE) and observation group compared with the WLE and sentinel lymph node biopsy group. However, patients in the sentinel lymph node biopsy group, who were treated with complete lymph node dissection (CLND) for metastases, had a better chance of survival compared with patients of the observation group who underwent delayed dissection for palpable nodes.

In 2005, a second trial, MSLT-II was initiated by the same research group. This trial should provide insights into the clinical significance of lymph nodes evaluated by RT-PCR and the value of completion lymph node dissection for patients found to have tumour-positive sentinel lymph nodes by haematoxylin-eosin, immunohistochemistry, or RT-PCR.

The Sunbelt Melanoma Trial examines the efficacy of sentinel lymph node biopsy as a treatment for tumour-positive regional lymph nodes and the role of adjuvant interferon-alpha. It can be concluded that the therapeutic value of sentinel lymph node biopsy in melanoma is still not confirmed.

Breast cancer
Results are required from multicenter randomized trials (focusing on postoperative morbidity and recurrence-free and overall survival after sentinel lymph node biopsy followed by completion axillary lymph node dissection (ALND) in case of a tumour-positive node), before sentinel lymph node biopsy can be accepted as best practice in
the care of breast cancer patients. To date, the only published randomized trials that focus on postoperative morbidity and recurrence-free and overall survival are a large multicenter study (n = 1031), a small multicenter study (n=298) and a single-institution study (n = 516).\textsuperscript{7-9} These trials were conducted to compare quality-of-life outcomes between patients with clinically node-negative invasive breast cancer who received sentinel lymph node biopsy and patients who received standard ALND. These studies have shown that sentinel lymph node biopsy is a safe and effective alternative to routine axillary dissection for nodal staging in early-stage breast cancer. Compared with standard axillary treatment, sentinel lymph node biopsy is associated with reduced arm morbidity and better quality of life with no increase in anxiety levels.\textsuperscript{10-12} However, there are insufficient data to answer the most important question about sentinel lymph node biopsy; its effect on recurrence rates and survival. The answer to this awaits results from the Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial as well as data from the ongoing National Surgical Adjuvant Bowel and Breast Project (NSABP-32) and the American College of Surgeons Oncology Group (ACOSOG) trials.

There are insufficient data to determine whether micro-metastases (lymph node metastases larger than 0.2 mm, but not larger than 2 mm) represent an adverse prognostic indicator and whether ALND should be carried out in all cases. Likewise, it remains unclear whether the presence of micro-metastases should be a factor in treatment decisions. However, metastasis is found in non-sentinel lymph nodes in 20\% to 35\% of patients, with micro-metastases in the sentinel lymph node. Until results of further studies addressing the clinical relevance of micro-metastases in the sentinel lymph node are published, the guidelines of the American Society of Clinical Oncology (ASCO) recommend routine ALND for patients with micro-metastases found on sentinel lymph node biopsy, regardless of the method of detection.\textsuperscript{13} In patients with sub-micro-metastases (tumour deposits in the marginal sinus ≤0.2 mm) and isolated tumour cells found on sentinel lymph node biopsy, ALND can safely be omitted from treatment.\textsuperscript{14} The ASCO does not recommend sentinel lymph node biopsy for patients with tumours larger than 5 cm. The guidelines do approve sentinel lymph node biopsy for women with more than one primary tumour, since recent studies have shown that the same sentinel lymph node is ‘sentinel’ for the entire breast.\textsuperscript{15-17} There remain variations in the technique of sentinel lymph node biopsy in breast cancer and controversies still exist surrounding a number of issues including the site of tracer injection, the value of extra-axillary nodal staging, the role for intraoperative assessment of the sentinel lymph node, the role of immunohistochemistry and the role of sentinel lymph node biopsy in women treated by neoadjuvant chemotherapy.

**Penile cancer**

Sentinel lymph node biopsy in penile carcinoma is of important diagnostic, prognostic,
and therapeutic value at the cost of only minor morbidity.\textsuperscript{18} The Netherlands Cancer Institute’s recent 10-year results in 123 patients with clinically negative groins, and in a further 17 in whom only one side was clinically negative, demonstrated improved results compared with previous reports. Sentinel lymph node metastases were present in 37 inguinal regions of 31 patients, while it was the only tumour-positive node in 78\% (29 out of 37). Morbidity was minor (8\%). The estimated 5-year disease-specific survival rates for patients with a tumour-negative or -positive sentinel lymph node were 96 and 66\%, respectively (p=0.001). However, false-negative results occurred in 16\% (six out of 37). Most of these occurred early in patients’ treatment and, after interim analysis of the false-negatives, important modifications were made to their treatment protocols. The research group in the Netherlands Cancer Institute now routinely performs preoperative ultrasonography and fine-needle aspiration cytology. Furthermore, exploration of the groin without visualized sentinel lymph nodes and intraoperative palpation of the wound have been introduced. As one case was actually missed on the initial histology, serial sectioning of the node with immunohistochemical analysis was instituted. Apparently, these modifications have resulted in no false-negative cases in the 60 dynamic sentinel lymph node biopsies carried out after 2001.\textsuperscript{19}

As with other areas of research in penile cancer, the field suffers from the disease’s inherent rarity; large prospective studies with long follow-up are both difficult and time consuming. Nonetheless, for sentinel lymph node biopsy to find acceptance, it must be tested within the gold standard of a controlled trial randomizing between sentinel lymph node biopsy and a wait and see policy. This can only happen with close collaboration between specialist cancer centers and may require the formation of national multicenter groups.\textsuperscript{20,21}

\section*{Vulvar cancer}

Vulvar cancer is the most frequently investigated gynaecological cancer with regard to sentinel lymph node detection because of its anatomical location and easily accessible nodal basin.\textsuperscript{22} For patients with vulvar cancer, sentinel lymph node biopsy is a promising staging technique. Based on 169 patients in five studies, the sentinel lymph node procedure with at least the preoperative use of a radioactive tracer, eventually combined with blue dye, is highly accurate in predicting lymph node metastases, with a predictive value of a tumour-negative sentinel lymph node of nearly 100\%.\textsuperscript{23}

Based on the promising results of the accuracy studies, an observational international multicenter study has been coordinated by the UMCG (GROningen INternational Study on Sentinel lymph nodes in Vulvar cancer = GROINSS-V I). Only in case of a positive sentinel lymph node, is complete inguinofemoral lymphadenectomy performed and patients with negative sentinel lymph node(s) are observed every two months. The final results of this study will give an initial insight into the safety of the sentinel lymph node biopsy procedure in patients with vulvar cancer. In GROINSS-V II, a second observational
international, multicenter study, patients receive radiotherapy on their groins instead of inguinofemoral lymphadenectomy when micrometastases are found in the sentinel lymph node(s).\textsuperscript{24} Although there are no randomized controlled trials yet, some data suggest that sentinel lymph node detection in vulvar cancer may alter clinical practice and reduce the number of radical groin lymphadenectomies and thereby reduce morbidity. The clinical implementation of the sentinel lymph node procedure and the role of additional histopathological techniques of the sentinel lymph nodes have to be further investigated. However, carcinoma of the vulva is a rare malignancy and therefore large randomized treatment trials based on sentinel lymph node triage are difficult to perform.

A multicenter phase III study is ongoing in the United States (Gynaecology Oncology Group (GOG)-173) to further determine the accuracy of the sentinel lymph node biopsy procedure in vulvar carcinoma, by performing the sentinel lymph node biopsy procedure with isosulfan blue, followed by standard complete lymphadenectomy. Pre- or intraoperative lymphoscintigraphy is optional (http://www.cancer.gov/clinicaltrials).

**Merkel cell carcinoma**

Sentinel lymph node biopsy detects Merkel cell carcinoma spread in one third of patients whose tumours would have otherwise been clinically and radiologically understaged, and who may not have received treatment to the involved node bed. Sentinel lymph node biopsy seems important for both prognosis and regional therapy and should, according to some authors, be performed routinely for patients with Merkel cell carcinoma.\textsuperscript{25-28}

**High-risk cutaneous squamous cell cancer**

Preliminary studies suggest that sentinel lymph node biopsy is technically feasible with low morbidity in patients with high-risk cutaneous squamous cell carcinoma. Further studies with larger populations and longer follow-up are essential to better delineate the advantages of this technique in the treatment of these patients.\textsuperscript{29,30}

**Thyroid cancer**

Sentinel lymph node biopsy is technically feasible in patients with thyroid cancer. However, the role of this procedure in the clinical decision-making of these patients remains to be defined due to the questionable biological meaning of nodal metastases. Further studies are needed but currently, elective neck dissection in high-risk patients with differentiated thyroid cancer is probably safer than the alternative of sentinel lymph node biopsy and neck dissection when the node is tumour-positive.\textsuperscript{31}

In current literature, the average rate of sentinel lymph node identification is 91\% (range, 66\% to 100\%) in thyroid cancer, and, when identified, the sentinel lymph node accurately
predicts the disease status of the neck in most patients (range, 80% to 100%). Limitations and pitfalls to carrying out sentinel lymph node biopsy on thyroid cancer patients include staining of parathyroid glands, identification of lymph nodes draining into the mediastinum, and the ‘shine-through’ effect. Sentinel lymph node biopsy is technically feasible, but for a disease in which nodal metastases are of debatable prognostic value, and elective neck dissection is not routinely indicated (except in medullary carcinoma), the clinical value of sentinel lymph node biopsy in the management of patients with differentiated thyroid cancer appears less promising.32,33

**Lung cancer**
Sentinel lymph node biopsy in non-small-cell lung cancer is feasible, but the detection rate has to be improved. The technique is not yet sufficiently sensitive to have a role in reducing the extent of nodal dissection in these patients.34,35

**Gastric cancer**
Sentinel lymph node biopsy can be used to detect the sentinel lymph nodes in patients with gastric cancer. However, the lymphatic drainage of the gastrointestinal tract is much more complicated than other sites, skip metastasis being rather frequent. These issues, and the sensitivity of intraoperative pathologic examination, remain to be resolved before wide clinical application of the procedure in this disease can be instituted.36

**Colorectal cancer**
Sentinel lymph node biopsy is feasible and accurate for staging colorectal cancer, based on results of a multicenter trial.37 Patients with nodal disease may then be treated with adjuvant chemotherapy resulting in reduced recurrence. However, the sentinel lymph node biopsy procedure in combination with preoperative short-course radiotherapy and total mesorectal excision is not reliable in patients with rectal carcinoma.38

**Anal cancer**
Carcinoma of the anal canal is a relatively rare disease, comprising 1-2% of the gastrointestinal malignancies. Because of the low incidence of this cancer, sentinel lymph node biopsy has been investigated in only a limited number of patients. Notwithstanding this, sentinel lymph node biopsy has proven to be safe and highly effective in the detection of occult metastases in this disease, although results are still rather preliminary. Further multicenter studies with larger numbers of patients are needed to validate the results from the initial studies and determine the ultimate role of the sentinel lymph node biopsy procedure in guiding individual treatment decisions.39

**Cervical, uterine and ovarian cancer**
Sentinel lymph node detection in cervical, uterine and ovarian cancers is less reliable,
not only because of technical difficulties, but also because there is no discrete lymph node basin in these malignancies. At present given the limited evidence available, sentinel lymph node biopsy will not become part of clinical assessment and will not alter clinical management in these cancers.22

**Prostate, urinary bladder and testicular cancer**

Preliminary results show that sentinel lymph node biopsy is feasible in prostate cancer and suggest that it may enhance the pathologic staging compared to modified pelvic lymphadenectomy, due to the individual variability of the lymphatic drainage of this cancer.40,41 For urinary bladder and testicular cancer preliminary studies on sentinel lymph node biopsy demonstrate that the procedure is likely feasible also for these tumours.42,43 Whether it is possible to replace standard diagnostic methods with this procedure remains to be determined in further studies.

**Oral and oropharyngeal squamous cell carcinoma**

The sentinel lymph node biopsy concept has only been gaining support in head and neck cancer literature during the last few years, and several pilot studies have been published. The procedure has shown high sensitivity rates in pilot studies for oral and oropharyngeal squamous cell cancer across the globe, and is reliable and reproducible.32,44,45 The accuracy of sentinel lymph node biopsy in patients with head and neck squamous cell carcinoma is currently under investigation in a multicenter study sponsored by the American College of Surgeons Oncology Group (ACOSOG) that compares the results of sentinel lymph node biopsy with standard elective neck dissection.46

In summary, the diagnostic usefulness of sentinel lymph node biopsy has been well established in melanoma, breast, penile and vulvar cancer, but its therapeutic value remains unproven, with the exception of breast cancer. 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 staging 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.
References


