Sentinel node biopsy. Evolving from melanoma to breast cancer
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CHAPTER 5

SENTINEL NODE BIOPSY FOR MELANOMA IN THE HEAD AND NECK REGION

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ABSTRACT

Background: Lymphatic drainage in the head and neck region is known to be particularly complex. The present study explores the value of sentinel node biopsy for melanoma in the head and neck region.

Methods: Thirty consecutive patients with clinically localised cutaneous melanoma in the head and neck region were included. Sentinel node biopsy was performed using blue dye and a gamma probe after preoperative lymphoscintigraphy. Mean follow-up was 23 months (range 1-48).

Results: In 27 of 30 patients, a sentinel node was identified (90%). Only 53% of sentinel nodes were both blue and radioactive. A sentinel node was tumour-positive in eight patients. The sentinel node was false-negative in two cases. Sensitivity of the procedure was 80% (8/10).

Conclusions: Sentinel node biopsy in the head and neck region is a technically demanding procedure. Although it may help determine whether a neck dissection is necessary in certain patients, further investigation is required before this technique can be recommended for the standard management of cutaneous head and neck melanoma.
INTRODUCTION

Melanoma runs an unpredictable course, particularly in the head and neck region, but a known fact is that lymphatic dissemination often precedes distant dissemination\(^1\,^2\). Lymphatic dissemination, including micrometastases, occurs in some 30% of the patients without palpable lymphadenopathy. It is difficult to identify these patients through tumour-related prognostic factors (Breslow thickness, Clark level, ulceration, site) or non-invasive methods\(^3\). Elective lymph node dissection can be performed in high risk groups but leads to overtreatment in the majority of patients. Moreover, elective neck dissection can cause damage to the eleventh nerve and does not convincingly improve survival\(^4\,^5\). Another complicating factor is the intricate lymphatic drainage system of the head and neck region. In 34% to 84% of the patients, drainage is discordant with clinical prediction\(^6\,^8\) and bilateral drainage is seen in approximately 10% of the patients\(^9\). The sentinel node biopsy might be a staging procedure that overcomes these problems.

A sentinel node (first-echelon node) is a lymph node that receives drainage directly from the primary tumour site\(^1\,^0\). According to the hypothesis of step-wise dissemination, this is the first node to become involved when lymphatic spread occurs. The lymphatic drainage pattern can be visualised with lymphoscintigraphy\(^1\,^1\). Intraoperatively, the sentinel node can be identified with the aid of a vital dye injected at the primary lesion site\(^1\,^0\) and/or a gamma detection probe. With a combined approach, the sentinel node can be identified in 98% of the patients with cutaneous melanoma\(^1\,^2\). The majority of patients with lymph node metastases are identified with this approach. False-negative sentinel nodes are found in less than 5% of the cases in our experience\(^1\,^2\).

Most of the previous lymphatic mapping studies have concentrated on melanomas of the trunk and extremities, rather than of the head and neck. Lymphatic mapping in the head and neck presents particular problems\(^7\). It is more difficult to visualise the lymphatic drainage with
lymphoscintigraphy because the sentinel nodes are often close to the highly radioactive site where the tracer is injected. The tracer travels fast: if more than one node is visible within a few minutes after injection, it is difficult to distinguish sentinel nodes from non-sentinel nodes. Additionally, sentinel nodes may be very small and located in sites that are not easily accessible, for example in the parotid gland. In this article, we describe the combined experience of two institutions in lymphatic mapping in the head and neck with preoperative lymphoscintigraphy and intraoperative use of both a vital dye and a gamma ray detector.

MATERIALS AND METHODS

All patients who presented from February 1994 at the Netherlands Cancer Institute or from May 1995 at the Groningen University Hospital through December 1997 were asked to participate in this study if they had clinically localised primary cutaneous melanoma anywhere in the head and neck region. Patients were eligible if the Breslow thickness of the primary lesion was more than 1.0 mm. Patients were excluded if therapeutic wide local excision of the primary lesion had already been performed or if any other procedure had taken place that might have changed the lymphatic drainage pattern. Informed consent was obtained from all patients, and the study protocol was approved by the Ethical Committees of the participating institutions.

A total of 30 patients were entered in this study, 19 men (63%), 11 women (37%). The mean age of patients was 51 years (range 23-79 years). In two patients, the melanoma was still present when scintigraphy was performed. The primary melanoma was located on the face in six cases, on the scalp in eight, on the ear in four and in 12 cases in the neck. Sixteen patients had a nodular melanoma, nine a superficial spreading melanoma, three a lentigo maligna melanoma and in two cases the histological type could not be determined. The median Breslow thickness of the lesions was 3.0 mm (mean 3.8 mm, range 1.2-12.0 mm). Eleven patients (37%) had a
melanoma of over 4.0 mm thickness. The level of invasion was Clark III in six cases, IV in 17 cases, V in six cases and could not be determined in one case. Ulceration was present in nine lesions (30%). Thus, a large proportion of patients had unfavourable prognostic factors.

The same protocol was used at both institutions. Preoperative lymphoscintigraphy was performed with $^{99m}$Tc-labeled human albumen colloid (Nanocoll®, Sorin Biomedica Diagnostics S.p.A., Saluggia, Italy). Sixteen to 26 hours before surgery, 50 MBq of the radioactive tracer in a volume of 0.1 to 0.4 ml was injected intradermally around the primary melanoma or biopsy scar. The tracer was administered at two to eight sites, depending on the length of the wound. Immediately after injection, dynamic images were obtained during 20 minutes, using a gamma camera with low energy, high resolution collimators. Subsequently, static images were made during five minutes in an anterior and a lateral view. If necessary, oblique or posterior images were obtained. Static images were repeated at two hours after injection. The location of the sentinel node(s) was then marked on the skin with ink.

Immediately prior to surgery, 0.5-1.0 ml of patent blue dye (Blue Patente V, Laboratoire Guerbet, France) was injected at the primary tumour site. Measurements were made over the skin marks with a gamma ray detecting probe (Neoprobe® 1000, Neoprobe Corporation, Dublin, Ohio) to confirm the location of the sentinel nodes as seen on scintigraphy. These sites were then explored in search of a blue stained lymphatic vessel. Each blue vessel was carefully dissected up to the site where it drained into a lymph node. The probe was used to confirm that a blue node was indeed radioactive. If no blue stained lymphatic vessels were found, the probe was used to guide the dissection. If the sentinel nodes could not be found with either of the tracers, the search for radioactive lymph nodes was resumed after wide local excision of the primary site. This reduces the background level of radioactivity to almost zero. If a sentinel node was found to be located in the parotid gland, it was removed only if it was likely that this could be done without damaging facial nerve branches.
A lymph node was considered to be a sentinel node if a blue lymphatic vessel was identified, leading from the primary site to this node and/or if the radioactivity measurements were in accordance with the scintigraphy findings. A node was also regarded a sentinel node if it was clearly radioactive and located so close to the injection site or to another radioactive node that it could not be seen separately on scintigraphy.

The sentinel nodes were examined in six permanent histological sections or 12 if the node was larger than one cm, and stained with H&E and immunohistochemistry (S100 and HMB45). Formal lymph node dissection was performed according to the standards of neck dissection classification if (micro)metastases were found in a sentinel node.

No patient was lost to follow-up. Mean follow-up was 23 months (range 1 - 48).

RESULTS

LYMPHOSCINTIGRAPHY

A total of 61 sentinel nodes were visualised with lymphoscintigraphy in 27 of 30 patients (mean 2.3 per patient, range 1-4). Approximately 60% of all sentinel nodes became visible within ten minutes after injection and 86% within thirty minutes. Scintigraphy did not visualise a sentinel node in three cases. In two of these cases, the primary site was located just posterior to the mandibular angle. In the third patient, the skin surrounding the primary site lateral in the neck was contaminated with the radioactive tracer. The "hot spot" at the injection site may have obscured an underlying sentinel node in either of these cases.

The drainage patterns are listed in Table 1. Twenty-five patients showed drainage to lymph nodes on the ipsilateral side of the neck. Two
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patients with a melanoma in the midline on the scalp and in the posterior neck showed bilateral drainage from the primary site. In 10 cases, unexpected drainage was visualised to sentinel nodes in levels that were not adjacent to the skin area where the primary melanoma was located. For example, drainage was seen from a melanoma caudally in the lateral neck to a node in level II/III and from the face to a level III node.

**SURGERY**

In 27 of the 30 patients, a sentinel node was identified during surgical exploration. A total of 70 sentinel nodes were excised (mean 2.6 nodes per patient, range 1-5). The location of the sentinel nodes excised is listed in Table 2. These 70 nodes were removed from a total of 52 basins (mean 1.9 basin per patient, range 1-4). It took 17 minutes on average to identify the first sentinel node (range 3-90 minutes, median 13 minutes). About half of the sentinel nodes excised (37/70 = 53%) were both blue and radioactive.

![Fig. 1. Right lateral view on head and neck of a 23-year old man with a melanoma on the parietal skull, Breslow 3.0 mm. The arrow indicates the location of the injection site. Within two minutes after injection, a lymphatic vessel was visualised draining onto a suboccipital sentinel node. At the same time, another sentinel node was seen in the midjugular region, which was found in level 5 during surgery. Both nodes were easily retrieved. The suboccipital node contained metastases. Modified radical neck dissection was performed and no other metastases were found.](image)
Thirty sentinel nodes (43%) were radioactive but not blue. Only a few sentinel nodes (3/70 = 4%) were coloured blue but not radioactive. No sentinel node was identified in three cases. In two of these cases, no sentinel node was visualised with scintigraphy either. In the third case, the only sentinel node was located in the parotid gland and was left untouched.

In 18 patients (60%), there was a discrepancy between the number of sentinel nodes seen on scintigraphy and the true number as identified during the operation. Nine of the 61 sentinel nodes indicated by lymphoscintigraphy were not retrieved. Four of these nodes were located in the body of the parotid gland and were left untouched. One sentinel node was not explored separately since the frozen section of the sentinel node that was excised first in this patient was tumour positive, and a lymph node dissection followed in the same session. In two cases no radioactive or blue node was identified at the site of exploration and in the remaining two cases radioactive tissue was excised in which no lymph node was found histologically. Eighteen sentinel nodes were recovered during the operation that had not been depicted on lymphoscintigraphy. Sixteen of these nodes were too close to another sentinel node to be seen separately on the scan. Twice, a sentinel node was found that was located too close to the injection site to be visualised.

**Pathology**

The sentinel node was tumour-positive in eight patients. All tumour-positive sentinel nodes were located in levels immediately adjacent to the skin area where the primary melanoma was located and at clinically predicted sites. In six of these patients, formal lymph node dissection followed. An average number of 24 lymph nodes was removed (range 13-34) and none of these lymph nodes was found to be tumour-positive (Figure 1). The remaining two patients with a melanoma on the temple had tumour-positive sentinel nodes in the parotid gland and tumour-negative subdigastric sentinel nodes. Subtotal parotidectomy with
subdigastric biopsy was performed and no additional tumour-positive lymph nodes were found.

FOLLOW-UP

Fifteen of the 19 patients with negative sentinel nodes have remained disease free with an average follow-up of 21 months (range 1-48). Four patients had a recurrence. In two of these four cases the sentinel node biopsy was false-negative. One of these patients had a melanoma on the upper lip and had two tumour-free submandibular sentinel nodes removed. Lymph node dissection was performed after 11 months for palpable lymph node metastasis at the same level. The other patient had a melanoma in the parietal region and three tumour-free sentinel nodes (retroauricular and from level III) were removed. Seventeen months later one palpable tumour-positive suboccipital node was removed in a posterolateral lymph node dissection. This patient developed a lymph node recurrence in level V at 21 months and liver metastases at 29 months. The third patient with a relapse had a recurrence in the neck after five months, confirmed by fine needle aspiration cytology. A modified radical neck dissection was performed but surprisingly, no tumour was found in the 35 lymph nodes or at the primary site. Therefore we don't know whether this was a local recurrence or in transit metastases or a lymph node recurrence. The fourth patient with recurrent disease after removal of a negative sentinel node died of brain metastases at 21 months.

Of the eight patients with a tumour-positive sentinel node, five did not have any sign of recurrent disease since surgery (mean follow-up 23 months, range 6-41 months). One patient had lung metastases resected at 17 months and had a local recurrence at the primary tumour site at 38 months. This patient is still tumour-free at six months after last surgery. Another patient presented with a lymph node recurrence in the neck 17 months after formal lymph node dissection. A third patient had in transit metastases resected at eight months.
The three patients in whom no sentinel node was identified are alive without evidence of disease after a follow-up of 37, 33 and 28 months respectively.

**DISCUSSION**

This study confirms the findings by Morton and O'Brien that early metastatic disease of melanoma in the head and neck can be identified with lymphatic mapping and sentinel node biopsy, but not without a considerable number of technical difficulties. The main drawbacks were that in 10% of patients, no sentinel node could be identified, 15% of the sentinel nodes which were seen on lymphoscintigraphy could not be retrieved, in four out of 10 patients a sentinel node in the parotid gland was left untouched and three patients relapsed in the neck after a negative sentinel node biopsy.

Lymphoscintigraphy did not reveal a sentinel node in three cases. The large amount of radioactivity that remains at the injection site may have obscured an underlying sentinel node in these cases. This problem is more likely to occur in the head and neck region than in other locations because of the proximity of the primary lesion to the draining nodes. Nevertheless, this was found to be a problem only occasionally in previously published series. Scintigraphy failed in only one of the first 110 patients with melanoma at all sites we have studied and in none in other large series, except for the study performed by Krag et al.

On the other hand, there is the problem that in the neck area often a large number of non-sentinel nodes is visualised. These are frequently difficult to distinguish from the sentinel nodes and need not be removed (Figure 2). This problem may be solved by using tracers with a greater particle size, which will accumulate predominantly in the first-echelon node so that less will pass through to depict higher-echelon nodes. A trade-off of a greater particle size is that the flow of the tracer through the
Fig. 2. Right lateral view on head and neck of a 37-year old man with a melanoma behind the right ear, Breslow 4.0 mm. The arrow indicates the lower border of the injection site. Within a few minutes, a chain of several lymph nodes was visualised. Two infra-auricular sentinel nodes were removed of which the one dorsally in the parotid gland was tumour-positive. Modified radical neck dissection and superficial parotidectomy were performed and no other metastases were found.

lymphatics is decreased. This seems acceptable since sentinel nodes in the head and neck are usually visualised within a few minutes after injection of the tracer. It is therefore unlikely that decreased flow affects the quality of the dynamic images.

In our study, a sentinel node was found in 90% of the patients. This is largely comparable to the results in other series. Morton identified a sentinel node in 90% of his patients with the use of only blue dye. Wells, Bostick and Alex reported slightly higher success rates with both blue dye and a radioactive tracer (95%, 93% and 96% respectively).

The finding that in half of our cases the sentinel node was either blue or radioactive indicates that both the blue dye and the radioactive tracer are of value. Wells also reported that a large proportion of sentinel nodes in the head and neck region (33%) was radioactive but not blue. In other parts of the body, this percentage is substantially less. Morton suggested to inject the blue dye repeatedly to solve this problem.
The number of sentinel nodes identified during surgery was different from the number of nodes that was visualised with scintigraphy in 18 of our patients (60%). In four of these cases, we did not explore a sentinel node in the parotid gland because it was unlikely that this could be done without damaging facial nerve branches. Further studies are needed to evaluate the benefit of sentinel node biopsy to justify risking damage to the facial nerve branches. Moreover, the possible benefit of sentinel node biopsy for patients with head and neck melanoma is probably small in those with metastases in the parotid gland, because these patients have the poorest survival among patients with stage III melanoma in head and neck, regardless of cervical node status. If we do not regard these four patients, the scintigraphic image still failed to reveal the correct number of sentinel nodes in almost half of the study population. This is far more often than the 19% discrepancy we experienced with lymphatic mapping in other locations. This was to be expected, since gamma cameras cannot distinguish two radioactive nodes separately if they are within about one cm from one another because of the physical properties of radioactive emission. In the neck, many nodes are found in close proximity of each other, and as stated above, the tracer often spreads to non-sentinel nodes as well. Therefore, for the head and neck region in particular our earlier finding is true: a surgeon needs to be proficient in both using the blue dye technique and the gamma detection probe in order to obtain the best possible result.

Thus far, 10 patients in the study have been diagnosed with lymph node metastases: eight synchronously and two metachronously. Eight patients were identified by sentinel node biopsy: sensitivity of sentinel node biopsy is therefore 80% (8/10) so far. In the patients with a tumour-positive sentinel node, no additional tumour-positive nodes were found in the lymph node dissections that followed. Thus, it can be concluded that in these cases the sentinel node was indeed the first lymph node to be involved. These findings also confirm the findings by Morton and Reintgen that lymphatic dissemination of melanoma proceeds in a step-wise fashion. However, it is still unclear whether lymphatic mapping
improves survival and regional tumour control. Morton et al. have initiated a multicenter trial to investigate this.

There were two false-negative sentinel node biopsies among 10 patients with lymph node metastases. This compares unfavourably to similar studies\(^9,14,15,22\) reporting no false-negative results in series with up to 14 patients with metastases. The sensitivity rate was 100% in three of the aforementioned publications\(^9,14,15\), in the present study it is only 80% (8/10). One must bear in mind that numbers of patients with metastases in these reports are small. Additional false-negative cases may come to light in the future in all series since the mean duration of the follow up is only 23 months in our study and 27\(^9\), 12\(^15\), 46\(^14\) and 30\(^22\) months in the others. It is too early to draw final conclusions since experience is limited, but our results suggest that the sentinel node biopsy is not as successful in the head and neck region as it is in other locations.

An explanation for false-negative sentinel nodes could be that the sentinel node does contain micrometastases but that these are not caught in the examined histological slides. RT-PCR could be useful to diminish this risk, being a more sensitive method to detect metastases. The false-negative sentinel nodes in this study were re-examined histologically, but no tumour was found. It is also conceivable that micrometastases occlude the lymphatic vessel leading to the sentinel node or occlude the sentinel node itself, diverting the lymphatic stream to another node, that will then be incorrectly labelled as sentinel node.

In conclusion, sentinel node biopsy for melanoma in head and neck is a technically demanding procedure. Although sentinel node biopsy may help determine whether a neck dissection is necessary in certain patients, further investigation is required before this technique can be recommended for the standard management of cutaneous head and neck melanoma.
REFERENCES


