Sentinel node biopsy. Evolving from melanoma to breast cancer
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One of the major recent developments in the management of melanoma has been the revival of the concept of sequential lymphatic dissemination by Morton, Cochran and co-workers from Santa Monica. They proposed lymphatic mapping and selective lymphadenectomy based on the hypothesis that the primary skin tumour drains initially to a particular lymph node in a regional lymphatic field, and then on to other nodes in that field.

Tumour cells travelling in lymphatics will first lodge in the lymph node on the direct drainage pathway: the "sentinel" node or "first-echelon" node. Other nodes will not become involved until a later phase. The status of the sentinel node can be taken to reflect the status of the entire lymphatic field, and to indicate whether or not complete regional lymph node dissection should be performed. The impact of this novel approach on regional tumour control and survival is currently being investigated in a prospective randomised study. Patient accrual for this study will be completed in the spring of 1998. Elective (prophylactic) lymph node dissection for melanoma is likely to become a thing of the past if the concept is validated.

Many surgeons are now beginning to perform sentinel node biopsies. Descriptions of this surgical technique using blue dye have been published before. The addition of lymphoscintigraphy and intraoperative gamma ray detection has since increased the sensitivity of the technique substantially.

The purpose of this paper is to share the pertinent aspects of lymphatic mapping and sentinel node biopsy as they were taught to us by others and as they were developed by ourselves in the course of a four
year period in which we have performed over 200 such procedures. Our false-negative rate with this approach is 1.3%.

PATIENT SELECTION

It is impossible to describe sound indications for lymphatic mapping because evidence of the value of this approach is not yet available. The potential survival benefit can be calculated to be small at best. What one can say is that the procedure is not worthwhile in patients with a thin melanoma, since the risk of dissemination from such a lesion is small.

Lymphatic mapping and sentinel node biopsy can help select patients who may benefit from adjuvant systemic treatment. There are clues to suggest that in particular patients with early stage lymph node involvement benefit from such treatment\(^5\).

LYMPHOSCINTIGRAPHY

Lymphatic mapping and selective lymphadenectomy require a concerted effort from nuclear medicine physician, surgeon and pathologist. First, lymphoscintigraphy is performed in the Department of Nuclear Medicine. A radioactive tracer is injected intradermally all around the tumour or biopsy wound. A small particle colloid labelled with Technetium-99m (half-life 6 hours) is suitable for this purpose. The tracer is taken up by the lymphatic system and flows to the regional lymphatic field. In a first-echelon node, it is accumulated in the macrophages through phagocytosis and retained.

Thus, the tracer is a lymph node seeking agent, not a tumour-seeking agent. Dynamic lymphoscintigraphy elegantly visualises the flow of the tracer and can help distinguish first-tier nodes from second-tier nodes\(^6\). The draining lymphatic field(s) are outlined and the number and position
of the sentinel nodes are depicted. The site of these nodes can be marked on the overlying skin by the nuclear medicine physician, providing valuable information for the surgeon. Scintigraphy should preferably be done within 36 hours preceding the operation, so that the surgeon can benefit from the radioactivity that is retained in a sentinel node. In depth descriptions of the technique and results of lymphoscintigraphy can be found elsewhere.

**Surgical Technique**

Drainage from the wound edges after a wide excision is not necessarily to the same lymph node as drainage from the original lesion. Since this risk is probably smaller after diagnostic excision with a narrow margin, one should perform the sentinel node biopsy preferably preceding therapeutic wide excision, although the latter can conveniently be done in the same session.

A single day admission is adequate. Depending on the circumstances, the operation can be done with general, regional or local anaesthesia. Immediately prior to commencement of the operation, approximately 1 ml of vital dye (isosulfan blue, patent blue) is injected intradermally at the tumour site. The needle should be firmly connected to the syringe, for the resistance encountered during injection into the skin may cause disconnection of the needle with unwanted distribution of the tracer. Spilled dye can be removed with water.

It is wise to outline the margin for the wide local re-excision with a marking pen before the injection, since a small biopsy scar tends to be obscured by the blue dye. Because the skin area involved may not have an identical drainage pattern everywhere, the dye should be administered all around the biopsy scar. Similar to the radioactive tracer, it should be injected adjacent to the scar, as close as possible to the original melanoma site.
The dye is immediately taken up by the lymphatic system and stains the lymphatic channel within a few minutes. There is no need to elevate the injection site. The site and the direction of the incision over the regional lymphatic field are chosen with the aid of the skin mark placed by the nuclear medicine physician, keeping in mind that formal regional node dissection possibly needs to follow.

An incision length of a few centimetres is sufficient. The subcutaneous tissue is explored in search of the blue stained lymphatic channel underneath Scarpa's fascia. One should try to find the lymphatic channel at a stretch where one is certain that it hasn't passed the first node yet. Massaging the injection site and the skin in between the biopsy scar and the nodal basin may stimulate the lymph flow when a lymphatic duct is not immediately apparent. The lymphatic duct is dissected and followed until it enters a blue-stained first-echelon node. This can be done by either sharp or blunt dissection. Lymphatic channels are fragile, a subtle surgical technique is mandatory. Damaging the lymphatic duct will deprive the remaining stretch of its supply of blue dye. It will then quickly loose its colour and cannot be traced any further. Finding a blue node without afferent blue lymphatic vessel requires considerable luck. The operative field should be kept absolutely dry, since even a minute quantity of blood tends to obscure the view.

Once the sentinel node is identified, it is excised from the surrounding fat. Sentinel nodes can be just 2 mm in size, but we have also seen elongated nodes of over 5 cm in length. Afferent and efferent lymphatic channels are ligated and the subcutaneous cavity is obliterated to prevent postoperative lymph fistula and seroma. A drain is not necessary.

There is a definite learning curve for this procedure. But once the technique has been mastered, the operation is usually simple to carry out. The sentinel node can be found in over 95% of the cases and usually within 10 minutes\textsuperscript{11}. When the node cannot be found within 45 minutes or when multiple lymphatic fields need to be explored, a repeat injection of blue dye may be helpful.
An alternative surgical technique exploits the radioactivity that remains inside the sentinel node after the preceding lymphoscintigraphy. Before the operation, the location of the sentinel node can be determined through the intact skin using a gamma ray detection probe. A gamma ray detector with a fixed sound pitch produces its sound when the number of registered counts per second exceeds a certain background level that can be chosen. Going over the lymphatic field one can thus outline a more or less circular region of increased radioactivity around the sentinel node. By increasing the background level at which the detector produces its sound, the skin area overlying the node can be decreased in size. The location of the node can be determined precisely by repeating this process a few times: "shrinking circle technique".

Preoperative knowledge of the node's exact location helps to minimise the extent of the dissection. Since the radioactivity content of a sentinel node exceeds that of the subcutaneous fat by a factor of 600 on average, a sterilised gamma detection probe enables one to easily find the sentinel node in an open wound in 99% of the cases. The radioactive content of the node can be confirmed outside the wound. The wound can then be scanned for additional radioactive sentinel nodes. An amount of less than 100 MBq Technetium-99m is sufficient for both scintigraphy and gamma ray probe detection. The ensuing radiation dose to the patient and to the operation room personnel is amply within the acceptable range.

**Which one of the two detection techniques is to be preferred?**

The technique using the probe is easier to learn and has a higher success rate: up to 99%. The technique using a vital dye is quicker to perform once it is mastered. When lymphoscintigraphy leaves no doubt as to the number of sentinel nodes, either technique is appropriate. However, sometimes some of the radioactive tracer passes through the sentinel node and is accumulated in a higher-echelon node. When multiple nodes light up on the scintigraphy images, one cannot always clearly

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distinguish first-tier nodes from second-tier nodes even with dynamic imaging.

In a review of 150 patients, we found that scintigraphy did not indicate the correct number of sentinel nodes in 17%\textsuperscript{12}. With the aid of the blue dye, the lymphatic channel can be visualised to actually prove whether a node is a first-echelon node, receiving drainage directly from the site of the primary lesion, or a second-echelon node, receiving drainage from a first-echelon node. This cannot be accomplished with the probe, since the probe does not identify lymphatic channels. The notion that the node with the highest level of radioactivity, by definition, is the sentinel node is wrong. A large second-echelon node may accumulate more of the radiopharmaceutical than a small first-echelon node. On the other hand, one can usually find a blue node using the gamma detection probe when one has failed to identify the blue lymphatic channel. Also, sometimes a sentinel node is blue but not radioactive. Sometimes, it is the other way around. Therefore, we recommend that surgeons embarking upon lymphatic mapping should acquire proficiency in both techniques in order to obtain the best results.

A third approach entails administration of a radioactive tracer on the operating table\textsuperscript{13}. With the probe, one can track the progression of the tracer through a lymphatic channel. Although a smaller tracer dose is sufficient, this technique has its drawbacks. The radioactivity content of a sentinel node is not as high, because the accumulation in the node is still in an early phase and, at the same time, the radioactivity level of the background is relatively high. This results in a less favourable sentinel node-to-background ratio of radioactivity. Tracking multiple lymphatic channels simultaneously may also present a problem. Finally, this approach requires the administration of the radiopharmaceutical in the operating room. The handling of radioactivity outside the Department of Nuclear Medicine is in many hospitals prohibited by local regulations.
A few words of advice when purchasing a gamma detection probe. A number of devices is commercially available. Prices typically range from $25,000 to $30,000. A device that produces a variable sound pitch depending on the number of registered counts per second allows the surgeon to take in its information without taking his eyes off the operative field. A small diameter probe is more convenient to handle in a wound than a larger diameter probe but is less sensitive in registering counts. A straight probe makes it easier to determine the direction of a high radioactivity level. In a deep axilla, it is easier to look beyond the probe when it has an angle.

A probe that can be outfitted with a collimator has an advantage. A collimator is a shield that reduces the radioactive rays that reach the probe from the side. Use of the collimator improves the sense of direction but at the cost of a lower number of counts that is registered.

PITFALLS

A melanoma on the arm usually drains upon a single node in the axilla and a melanoma on the leg usually drains upon two sentinel nodes in the inguinal region, but this is by no means a rule. We have seen up to five sentinel nodes in one lymphatic field.

Surgical exploration of a "hot spot" on a scintigram sometimes reveals retention of the tracer in what appears to be a plexus in a lymphatic channel instead of a lymph node. Actual sentinel nodes are encountered outside the recognised lymphatic fields in up to 21% of the patients\textsuperscript{14}. We have repeatedly found sentinel nodes just lateral from the areola and in the flank. Drainage to nodes in the triangular intermuscular space frequently
occurs in patients with melanoma on the back. Without performing lymphoscintigraphy these "extra-anatomic" nodes will go unnoticed.

The bulk of the radioactivity remains at the injection site. The high number of counts from this area may overwhelm the smaller number of counts from a lymph node that is close by. Pointing the gamma detection probe in the direction of the primary melanoma site is to be avoided. Using a collimated probe reduces the confusing number of counts from the primary tumour and facilitates finding the sentinel node. The problem of a low sentinel node-to-background radioactivity ratio because of a nearby injection site can also be overcome by performing the wide local re-excision before exploring the nodal field.

In the inguinal region, lymphoscintigraphy sometimes suggests the presence of two sentinel nodes, when in fact there is drainage to opposite ends of a single elongated node. When it is unclear whether one of two radioactive nodes on the images is a second-echelon node, it is wise to start by exploring the node furthest away from the primary melanoma site. This way, the risk of damaging the blue dye inflow of the other node is limited.

POSTOPERATIVE COMPLICATIONS

Postoperative complications are seen in less than 10% of the patients and are usually minor and transient: wound infection, hematoma, seroma, wound dehiscence, neuropraxia. We have occasionally noticed a limited amount of edema. In a rare patient with a melanoma at the upper back, a faint blue discoloration remains visible for over a year.
PATHOLOGY

Frozen section microscopy and immediate formal regional node dissection in case of a tumour-positive outcome appear attractive, since the patient is spared a possible second operation. However, frozen section microscopy has not shown to be reliable in a series of 101 patients: false-negative results were encountered in eight of seventeen patients with dissemination to the sentinel node\textsuperscript{16}. Making sentinel node biopsy and formal node dissection a two-stage procedure has the advantage that it eliminates the need to reserve theatre time that one uses in only one of five patients.

The pathologist should be encouraged to devote extra attention to the definitive examination of a sentinel node, cutting multiple sections and using special immunohistochemical staining techniques, since this is the node in which tumour cells are most likely to be encountered.

CONCLUDING REMARKS

In conclusion, lymphatic mapping and sentinel node biopsy is a multidisciplinary undertaking, requiring a team effort from nuclear medicine physician, surgeon, and pathologist. Although the procedure is usually remarkably simple, it can be challenging at times. The introduction of lymphoscintigraphy and intraoperative gamma ray detection has increased the ability to identify a sentinel node to virtually 100%. The best results can be obtained with the use of both a vital dye and intraoperative tracing of a lymph node seeking radiopharmaceutical.
REFERENCES


