In search of the sentinel node: validation and sophistication of lymphatic mapping and sentinel node biopsy in breast cancer and melanoma
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CHAPTER 2
Sentinel lymph nodes

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General anatomy and physiology of the lymphatic system

Lymphatic capillaries are 10 to 50 µm in diameter, consist of a single endothelial layer with a discontinuous membrane and are supported by collagen filaments. They are filled with lymph fluid originating from the interstitial space due to an osmotic pressure gradient and fluctuating intraluminal pressures. These intraluminal pressures are caused by lymphatic flow that is generated by lymph formation, contractions of the vessel wall and external pressure. Lymph fluid absorbed by lymphatic capillaries drains into larger collecting lymphatic vessels. Such lymphatic vessels drain into marginal and medullar sinuses located between germinal centres within a lymph node. These centres contain large numbers of phagocytic cells that accumulate protein colloids. Then, a plexus within the lymph node drains to the efferent lymphatic vessel that joins the artery and vein in the hilum. Direct drainage of the marginal sinus into the efferent vessel also exists (figure 1).

Figure 1. The different relations between lymphatic vessels and lymph nodes. Afferent lymphatic ducts on the left discharge their contents into the marginal sinus. One lymphatic duct runs through the node on the right and another over its surface, bypassing the germinal centres. (Illustration made by P.J. Tanis)

The sentinel node

The sentinel node is the lymph node upon which the primary tumour drains directly. Lymph fluid moves subsequently to second-tier and third-tier nodes. Lymph from the primary tumour region does not necessarily travel to the nearest node. Two lymphatic
channels originating in the primary tumour can run to two different sentinel lymph
nodes (figure 2).

The sentinel node hypothesis implies orderly progression of metastases from a primary
lesion through the lymphatic system. The concept is only relevant in tumours with
pre-dominant lymphatic dissemination, such as melanoma and cancer of the breast,
penis or colon. If the first node contains a metastasis, there is a chance of tumour
spreading downstream. In case of a tumour-negative sentinel node, second-tier and
third-tier nodes are generally without metastases.

Figure 2. A sentinel lymph node is the lymph node upon which the primary tumour drains directly.
Two lymphatic channels originating in the primary tumour can run to two different sentinel lymph
nodes. Lymph fluid moves subsequently to second-tier (*) and third-tier nodes. The sentinel node is
not always the node nearest to the primary tumour.

Lymphatic mapping

The lymphatic drainage pattern can be visualized by lymphoscintigraphy after
injection of a radio-labelled tracer in or near the site of the tumour. The radio-labelled
tracer is cleared from the lymphatic channels and accumulated by the phagocytic
cells in the lymph node. Lymphoscintigraphic images depict the lymph channels and
the lymph node or nodes that contain the injected tracer. Dynamic scintigraphy and
intraoperative blue dye mapping give insight in the lymphatic drainage pattern, which
enables the surgeon to find the sentinel node(s).
The earliest sentinel lymph node identification techniques involved the injection of a
vital blue dye, usually isosulfan blue. It was a key point in the general acceptance of
sentinel node biopsy. The blue dye was injected intradermally at the primary tumour site in melanoma patients. An incision was made over the expected lymph node region and the lymphatic channel was visually identified. This channel was dissected and followed to the first draining lymph node.

Subsequent reports described the use of radio-labelled tracers, such as technetium-99m-bound colloids. Colloids with a small particle size can rapidly pass the openings of interendothelial junctions and allow visualization of the lymphatic channels leading directly to the sentinel node. A disadvantage of small sized particles is that some of the tracer moves on to nodes further downstream because phagocytic cells in the first node cannot trap them all. Larger colloid particles enter lymphatic channels more slowly. The tracer almost never moves on to subsequent nodes, but the channels are visualized less often.

Nowadays, the lymphatic mapping technique mostly used involves administration of a radio-labelled tracer into or near the primary lesion in combination with blue dye. During surgery, the sentinel node is found with the assistance of both blue dye and a gamma-ray detection probe. Preoperative lymphoscintigraphy is added for better specification of the location and number of sentinel nodes.

**Sentinel node biopsy**

A sentinel node biopsy is a minimally invasive technique that was initially developed as an alternative to complete lymph node dissection in patients with a melanoma.\(^7,8\)

The majority of patients are spared a more complex surgical procedure with a higher morbidity rate while the same staging information is obtained.

All nodes of a complete node dissection used to be bisected and evaluated by haematoxylin-eosin staining. This way, metastases larger than two millimetres were usually identified. With the selective sentinel node biopsy, the pathologist can focus on the one or few nodes that are most likely to contain metastatic disease. The sentinel nodes are evaluated by both haematoxylin-eosin and immunohistochemistry staining, which occasionally distinguish metastases with a size of one tumour cell.

The combined procedure of lymphatic mapping and sentinel node biopsy provides prognostic information, identifies patients who may benefit from early regional therapy and, depending on the situation, from adjuvant systemic treatment. This way optimal survival rates may be realized.
Breast Cancer

The predominant lymphatic drainage pathway from the breast is towards the axilla. Metastases initially remain localized in the lower axilla and then may travel higher up the chain to the subclavicular and the supraclavicular basins (figure 3). Axillary lymph node dissection used to be performed in almost every breast cancer patient. This operation has several side effects, such as lymph oedema, pain and decreased mobility of the arm, and often no metastases were found. With the introduction of sentinel node biopsy, axillary lymph node dissection is only indicated if this node is involved. As a result, many patients are spared an unnecessary operation. Whether the omission of routine axillary node dissection jeopardises regional tumour control and survival is still subject of research. Large observational studies revealed excellent results in patients who did not receive axillary node dissection because of a tumour-negative sentinel node. A 2005 review showed that the recurrence rate in such patients was 0.4%, but the median duration of follow up was 32 months, not enough to gain a definitive impression.

Figure 3. A tumour (black area) with lymphatic channels to nodes in the axilla (A) and to lymph nodes below (B) and above (C) the clavicle. A metastasis may be found along this lymphatic pathway.
Melanoma

There is consensus on the way lymphatic mapping should be carried out in melanoma patients. Preoperative lymphoscintigraphy and intraoperative use of blue dye and a gamma-ray detection probe are standard. The first large studies on sentinel node biopsy in melanoma showed a 95% sensitivity. Recent studies show false-negative rates of around 10%. False-negative means that the sentinel node is disease-free, while there are metastases in the lymph node basin. Patients with an involved sentinel node have a five-year survival rate of around 65% and in patients with a tumour-negative sentinel node this is 90%. A large randomized study showed that early regional node dissection based on a positive sentinel node improves survival in patients with an intermediate-thickness melanoma.

Concluding remarks

The development of the sentinel node concept is a milestone in the understanding of dissemination of solid malignancies. The introduction of lymphatic mapping in 1989 initiated the widespread use and general acceptance of this approach. Many patients are spared unnecessary surgery without compromising regional control and the accuracy of staging. Lymphatic mapping with sentinel lymph node biopsy has become a standard component in the management of patients with breast cancer or melanoma. This suggests potential in other tumours that spread primarily through lymphatic channels.

Further study needs to focus on more peripheral issues such as the prognostic significance of micrometastases and techniques such as molecular assays or markers. These may provide more information to optimize the staging of tumour dissemination and will enable the fine-tuning of therapy.
References