

## Review

**History of sentinel node and validation of the technique**

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**Abstract**

Sentinel node biopsy is a minimally invasive technique to select patients with occult lymph node metastases who may benefit from further regional or systemic therapy. The sentinel node is the first lymph node reached by metastasising cells from a primary tumour. Attempts to remove this node with a procedure based on standard anatomical patterns did not become popular. The development of the dynamic technique of intraoperative lymphatic mapping in the 1990s resulted in general acceptance of the sentinel node concept. This hypothesis of sequential tumour dissemination seems to be valid according to numerous studies of sentinel node biopsy with confirmatory regional lymph node dissection. This report describes the history and the validation of the technique, with particular reference to breast cancer.

**Keywords:** history, lymphatic dissemination, review, sentinel node**Introduction**

Lymphatic tumour spread and its implications for treatment and survival have been studied for centuries. Different theories regarding the dissemination of solid tumours have been introduced, based on experimental data and observations during follow-up of cancer patients. These resulted in discussion about the place of regional lymph node dissection in the treatment of diseases that were thought either to be systemic from the beginning or to spread initially to lymph nodes. Elective regional lymph node dissections became controversial because of overtreatment of the many patients without lymph node metastases. These patients suffer from associated morbidity without survival benefit. With the introduction of the sentinel node concept, a minimally invasive procedure became available for detection of occult lymph node metastases. This report describes the history and the validation of the technique, with particular reference to breast cancer.

**Dissemination theories**

Bartholin was the first to notice the existence of a 'lymphatic' in 1653. Numerous subsequent investigations elu-

cidated the intricate lymphatic system. Virchow, in the nineteenth century, formulated the theory that lymph nodes filter particulate matter from lymph. This important assumption led to the awareness that cancer could be cured at an early stage with adequate surgery, in contradiction to the Greek philosophy implying that cancer is the local manifestation of a systemic disease. The next logical step in the evolution of Virchow's theory was the introduction of the radical mastectomy by Halsted at the end of the nineteenth century [1].

To determine the barrier function of lymph nodes, several investigators injected inanimate particles or tumour cells into certain afferent lymphatics in animal models. Studying mesenteries of dogs and rabbits, Gilchrist saw no passage of carbon suspensions through any node after injections with varying pressures [2]. Zeidman and Buss injected stained  $V_2$  carcinoma cells into the afferent lymphatics of popliteal nodes in rabbits [3]. They found that tumour cell emboli are immediately trapped in the subcapsular sinus and do not spread to the next node for at least 3 weeks.

The Halstedian model with *en bloc* dissection as the guiding principle of cancer surgery lost ground when the systemic hypothesis was reintroduced in the 1960s. Nodal involvement was suggested not to be an orderly contiguous extension, but rather a marker of distant disease [4]. Fisher and Fisher found that less than 40% of  $^{51}\text{Cr}$ -labelled  $\text{V}_2$  carcinoma cells were retained in a rabbit's popliteal node [5]. This finding was explained by the presence of lymphaticovenous pathways in lymph nodes, although the existence of free communication between the venous and lymphatic system is controversial. The ineffectiveness of the lymph node barrier is not in line with the better prognosis of cancer patients without nodal involvement. Alternative theories were considered. Tumour cells that traverse lymph nodes could be destroyed more readily or are less apt to develop distant metastases. Tumour cells that remain in lymph nodes could be those forming secondary tumours [5].

The spectrum hypothesis may be the most consistent with clinical observations. Hellman noted that breast cancer is best thought of as a spectrum of disease with increasing inclination towards metastasising as a function of tumour growth and progression [4]. A lymph node metastasis may either be the only site of dissemination, especially in small tumours, or can be a marker of distant disease. The observation that many cancer patients are cured after adequate locoregional treatment illustrates why the spectrum theory is attractive. The introduction of the sentinel node concept was a logical attempt to clarify the controversy caused by the described hypotheses.

### First descriptions of a sentinel node

A normal-appearing node at the junction of the anterior and posterior facial vein was sent for frozen section investigation during a total parotidectomy in 1951. In the description of Gould, the pathology report was 'lymph node with metastatic tumour' [6]. Intraoperative examination of this lymph node in its typical anatomical location guided the decision to perform a radical neck dissection during the following parotidectomies.

Two decades later, Cabañas observed the existence of a sentinel node in the lymphatic drainage of the penis [7]. Lymphangiographic studies elucidated the precise location of such sentinel nodes. Direct drainage from the penis to the lymph nodes associated with the superficial epigastric vein was observed. After making an incision parallel to the inguinal ligament, the sentinel lymph node was identified by inserting the finger under the upper flap toward the pubic tubercle.

Studying lymphatic drainage of testicular cancer also revealed the existence of a sentinel node. Chiappa *et al* postulated primary testicular lymph centres using lymphangiographic studies [8]. More knowledge about the

primary metastatic sites of testicular cancer was later obtained through surgical and histopathological exploration of the retroperitoneum. Weissbach and Boedefeld examined the feasibility of a limited retroperitoneal lymph node dissection, based on their observations of areas in which solitary metastases occur. Lymph nodes in these areas were called sentinels [9]. Weissbach and Boedefeld stated that 'a more limited approach strictly for the purpose of pathological staging, which aims at the prevention of long-term damage without compromising diagnostic accuracy, must be based on the knowledge of the pathways of lymphatic dissemination and, particularly, on the first sites of nodal involvement'.

Kett *et al* administered contrast medium in breast lymphatics that were visualised with the aid of areolar blue dye injection [10]. They observed flow to an isolated lymph node, called the 'Sorgius' node, and subsequent drainage through many lymphatic vessels and lymph nodes to the collecting system around the axillary vein. Using breast lymphoscintigraphy in 1980, Christensen *et al* observed 'primary draining nodes' [11]. Haagensen studied the route of metastases through the axillary lymph node filter and stated that the nodes of the central group are not only most often involved, but also most often exclusively involved [12]. An interesting finding is that he used the term sentinel node for specific lymph nodes of the inferior deep cervical group because of their close relationship to the jugular-subclavian venous confluence.

### The concept of lymphatic mapping with sentinel node biopsy

It is remarkable in light of the previous descriptions that the concept of lymphatic mapping was not introduced until the end of the twentieth century. Morton *et al* have used cutaneous lymphoscintigraphy with colloidal gold since 1977 to identify the lymphatic drainage pattern of melanomas located at ambiguous sites [13]. In addition to this preoperative procedure, they also developed a technique for intraoperative mapping to selectively remove lymph nodes on the direct drainage pathway from the primary melanoma. This sentinel node was considered to be the first site of metastatic disease. The work of the group at the John Wayne Cancer Institute initiated one of the most interesting recent developments in surgical oncology.

The concept of sentinel node biopsy is based on two basic principles: the existence of an orderly and predictable pattern of lymphatic drainage to a regional lymph node basin, and the functioning of a first lymph node as an effective filter for tumour cells. With the widespread use of sentinel node biopsy, sufficient data was provided to prove that sequential lymphatic dissemination and entrapment of tumour cells in first draining lymph nodes occur [14,15]. The sentinel node concept is actually based on the Halsted theory that stressed the importance of locoregional cancer

treatment because of the step-wise spread. The spectrum and systemic hypotheses, however, suggest that lymph node involvement can be an indicator of distant disease and therefore sentinel node biopsy is also a staging tool to select patients for adjuvant systemic treatment.

### Evolution of the technique of lymphatic mapping

The static approaches for sentinel node biopsy applied from halfway through the twentieth century did not produce any enthusiasm for the concept. The reason for this might be that these techniques, only based on the typical anatomical patterns, were not reproducible and did not take into account the interindividual variability of lymphatic drainage. The introduction of the blue dye mapping by Morton and coworkers was the key point in the general acceptance of sentinel node biopsy. After a feasibility study in a feline model, they injected patent blue or isosulfan blue intradermally at the primary tumour site in melanoma patients. An incision was subsequently made over the site of expected lymphatic drainage, and the lymphatic channel was visually identified. This channel was followed to the first draining lymph node by meticulous dissection. This technique of intraoperative lymphatic mapping was presented at the World Health Organisation's Second International Conference on Melanoma in 1989 [16]. Morton *et al*'s original report followed 3 years later [13].

Visualisation of lymphatic drainage is not new. Haagensen *et al* describe the old anatomical studies using injections of various tracer fluids in *The Lymphatics in Cancer* [17]. Sappey tried to clarify the intricate lymphatic system of the breast using mercury injections at the end of the eighteenth century. Surgeons and nuclear medicine physicians later visualised the lymphatic system with vital dyes and radioactive isotopes. Finally, it was a multidisciplinary team at the John Wayne Cancer Institute in Santa Monica which combined the visualisation of lymphatic drainage with the sentinel node concept in melanoma patients.

The development of sentinel node biopsy in breast cancer also started at the John Wayne Cancer Institute in 1991. The first article of blue dye mapping in breast cancer by Giuliano *et al* was published in 1994 [18]. Injection of radiolabelled colloids with intraoperative detection of the sentinel node using a gamma-ray detection probe was introduced a little later [19]. Preoperative lymphoscintigraphy was added for better specification of the location and number of sentinel nodes. Different methodologies based on these two lymphatic mapping techniques are nowadays applied all over the world.

### Validation of the sentinel node concept

In initial sentinel node procedures in 34 breast cancer patients, Giuliano reported that tumour was found in 39 of 63 sentinel nodes (62%) compared with 93 of 688

non-sentinel nodes (14%). He stated that 'this suggests that a primary breast carcinoma spreads to the axilla along a specific pathway of lymph nodes that cannot be identified by random axillary sampling' [20]. But the main question is whether absence of tumour cells in the sentinel node is indicative of the absence of tumour cells in the other lymph nodes of the regional basin. An important parameter in studies concerning this question is the false negative rate. The false negative rate is the number of false negative procedures divided by the sum of the true positive and false negative procedures ( $1 - \text{sensitivity}$ ), although some investigators calculate it in their own way.

Morton *et al* found, in the first 194 lymphadenectomy specimens that had an identifiable sentinel node, that non-sentinel nodes were the sole site of melanoma metastasis in only two patients [13]. The sentinel node was involved with tumour in 38 patients, resulting in a false negative rate of 5% (2/40). This result showed a high degree of accuracy in identifying early-stage melanoma patients with clinically occult lymph node metastases and suggests that the concept is valid. With extensive pathological examination of sentinel nodes and non-sentinel nodes in breast cancer, Turner *et al* described that, if the sentinel node is tumour free, the probability of involvement of a non-sentinel node is 1 in 1087 [21]. Numerous studies in melanoma and breast cancer patients have confirmed that the sentinel node is the first node reached by metastasising cells as they enter the regional lymphatic basin in the vast majority of patients. A review of sentinel node biopsy in breast cancer reported an accuracy of more than 95% in all studies [22]. A wide range of false negative rates among different centres does, however, exist. Unacceptable failure rates can occur because of technique, physician and patient related factors. The first observational study of sentinel node biopsy not followed by routine axillary lymph node dissection in 133 breast cancer patients showed no axillary recurrences after a median follow-up of 39 months [23].

### Conclusion

The development of the sentinel node concept is a recent milestone in the understanding of dissemination of solid malignancies. The concept is based on Halsted's theory and the experimental work of Gilchrist, Zeidman and others, which supported the hypothesis of sequential dissemination through the lymphatic system. After incidental reports of non-guided sentinel node procedures, it was the introduction of the technique of intraoperative lymphatic mapping in 1989 that initiated the widespread use and general acceptance of this approach. Now that the technique has been validated, many breast cancer patients are spared a regional lymph node dissection without compromising local control and the accuracy of staging.

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