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Sentinel nodes in complex areas: innovating radioguided surgery

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Publication date
2011

[Link to publication](#)

Citation for published version (APA):

Vermeeren, L. (2011). *Sentinel nodes in complex areas: innovating radioguided surgery*. [Thesis, fully internal, Universiteit van Amsterdam].

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Chapter 1

Introduction and outline

INTRODUCTION

In contrast to benign lesions, malignant tumours have the potential to metastasise. The presence of metastatic disease dramatically influences a patient's prognosis. Many cancers have the potential to spread via the lymphatic pathways to regional lymph nodes, while blood-borne dissemination generates distant metastatic deposits. The knowledge whether or not a tumour has disseminated is highly relevant for treatment planning. The TNM-classification system has been developed to obtain worldwide consensus on tumour staging. Most tumours have their own TNM-criteria that can be used to determine prognosis and plan therapy.¹ The TNM-stage takes into account the size and extent of the primary lesion, involvement of regional nodal basins and presence of distant metastasis.² Besides physical examination, several imaging techniques are available to detect lymphatic and distant proliferation. Ultrasonography of regional nodal basins in combination with fine needle aspiration cytology may detect nodal involvement with varying sensitivity rates (5 -82%) depending on the site of the body,³⁻⁶ but small nodal tumour deposits frequently elude detection.⁷⁻⁸

THE SENTINEL LYMPH NODE

The value of lymphatic mapping is based on the notion that lymphatic dissemination occurs before haematogenous spread, which is often true for many tumour types.

Occult lymph node metastases can be detected and removed by regional lymph node dissection, but the risk of post-operative morbidity from this invasive procedure is noteworthy, while the chance of a node-negative resection specimen is considerable. Based on the concept of sequential lymphatic tumour spread, the sentinel node procedure has been proposed as a refinement of staging for detection of microscopic metastatic disease and to prevent an unnecessary node dissection in case of node-negative findings. A sentinel node can be defined as a lymph node on a direct drainage pathway from the primary tumour.^{9,10} This particular node is likely to be the first to harbour metastasis and can be used to represent the tumour-status of the entire nodal basin.

At the end of nineteenth century, Halsted recognised the stepwise progression of breast cancer through the regional lymph nodes and the term 'gland sentinel' was introduced in 1923 by Braithwaite to describe a direct tumour-draining lymph node that he identified after dye injection.^{11,12} In 1960 Gould et al. described a 'sentinel node' at the confluens of the anterior and posterior facial vein as the first node to be involved in parotid cancer.¹³ Later on, Cabañas

described the 'sentinel lymph node' in penile cancer as a node in a specific location in the groin that receives the initial lymphatic drainage.¹⁴ In the following years, lymphoscintigraphy was introduced to guide the way towards the first tumour-draining lymph node and blue dye was suggested to visualise direct tumour-draining channels and nodes intra-operatively.^{9, 15}

In melanoma, the tumour status of the sentinel node has been proven to provide relevant prognostic information and, when compared to watchful waiting, sentinel node biopsy appears to increase the chance of survival in node-positive patients.¹⁶ The procedure is now widely performed for staging and to guide further regional treatment. Lymphatic mapping has evolved into a routine staging method for patients with clinically localized breast cancer.^{17, 18} Although lymph node metastases are an important prognosticator for almost every type of malignancy, exact drainage patterns have not yet been identified for all tumours. Drainage pathways have not yet been well-established in some areas with a complex anatomy or at locations that are difficult to approach surgically, although sentinel node biopsy may spare such patients an unnecessary and/or risky regional lymphadenectomy. This thesis focuses on innovative techniques and procedures to optimize identification of sentinel nodes in such difficult areas.

OUTLINE OF THIS THESIS

In **chapter two** several new technological advances to improve sentinel node detection are introduced and reviewed. The indication for lymphatic mapping in head and neck malignancies is described and the problems that face us with sentinel node identification in this complex area are summarized. In the following chapters, the two main modalities that are evaluated in this thesis are introduced: single photon emission computed tomography with radiographic computed tomography (SPECT/CT) and a portable gamma camera.

SPECT/CT

Figure 1 shows how fusion of SPECT and CT creates an image in which the radioactive signal is placed in its anatomic context. In **chapter three**, the routine procedure of conventional lymphoscintigraphy is described and the use of SPECT/CT is outlined. Specific indications to perform SPECT/CT are reviewed. The added value of SPECT/CT for preoperative sentinel node identification in head and neck melanoma is evaluated in **chapter four**, while **chapter five** focuses on the importance of preoperative SPECT/CT to accurately detect and localise sentinel

nodes in prostate cancer. SPECT/CT also detects and localises nodes in aberrant locations, which is demonstrated in **chapter six**. The case description in the **appendix** demonstrates that SPECT/CT can enlighten specific interpretation difficulties.

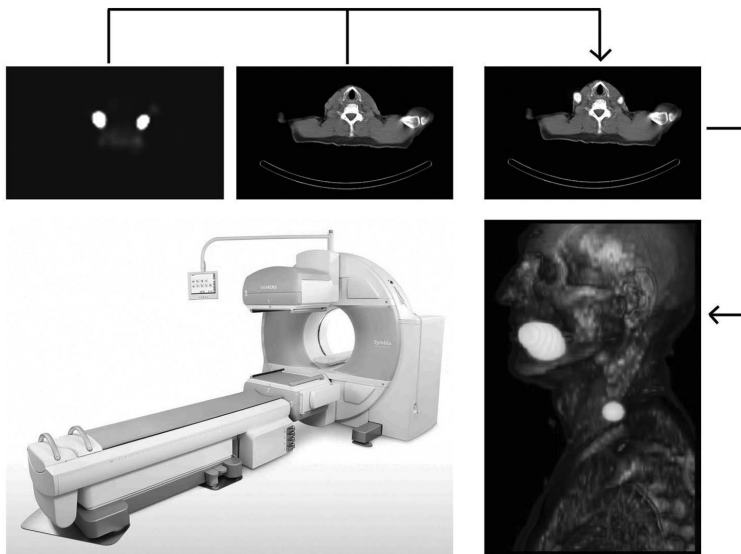


Figure 1 | SPECT/CT. The SPECT/CT system (SymbiaT, Siemens) is shown in the lower left corner of the figure. After SPECT acquisition, a CT is performed in the same session, without moving the patient. The SPECT displays the radioactive signal, while the CT shows the anatomic outline at the same level. After fusion of the two techniques, two dimensional fusion images show the location of the radioactive nodes. Also, a three dimensional overview can be constructed. This whole procedure is explained in more detail in chapters three, four and five.

PORTABLE GAMMA CAMERA

Portable gamma cameras have been designed for radioguided surgery, and a possible application of these devices can be localising lymph nodes intra-operatively. Figure 2 shows such a camera and the intra-operative images that can be displayed on its screen. In **chapter seven**, the intra-operative use of a portable gamma is introduced and the images in our first patients are shown. In the subsequent **chapter eight**, the advantages of real-time imaging using the portable gamma camera are analysed for intra-operative detection of sentinel nodes in the neck. Results and added value in prostate cancer are outlined in **chapter nine**.

Conventional planar lymphoscintigraphy is usually performed preoperatively to visualise lymphatic drainage from breast cancer, but due to limited resources large gamma cameras are not always available. **Chapter ten** describes the potential use of the portable gamma camera for preoperative imaging.

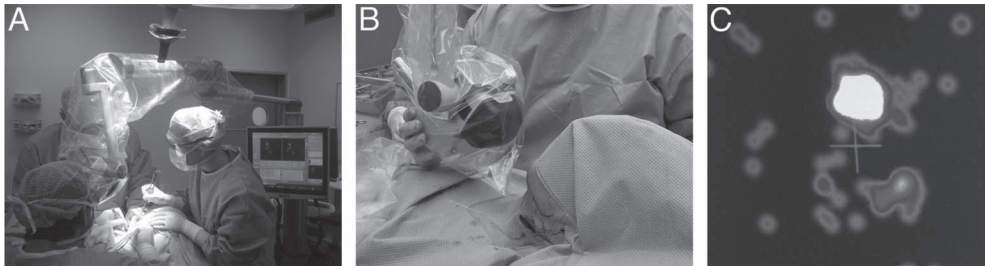


Figure 2 | Portable gamma camera. The intra-operative situation is shown with the portable gamma camera (Sentinella, Oncovision) positioned over the patient's head. The camera and its arm are wrapped in a sterile plastic sheath (A). The detector is positioned above the surgical field (B) in order to display the radioactive sentinel nodes on screen (C).

NEW HORIZONS FOR LYMPHATIC MAPPING

Not only imaging devices might be optimised to improve sentinel node detection, but enhancement of radiotracers might further improve the detection rate of sentinel nodes as well. **Chapter eleven** shows how an adjustment of the radiotracer labelling procedure, by doubling the number of colloid particles, can lead to better sentinel node detection in prostate cancer.

Precise localisation and removal of sentinel nodes is a prerequisite to achieve successful staging, but can be challenging in case of para-aortic sentinel nodes, due to their proximity to vital structures. **Chapter twelve** describes and evaluates our approach to para-aortic sentinel nodes with the use of preoperative SPECT/CT and the portable gamma camera for intra-operative guidance. Since lymphoscintigraphy has not been performed before in patients with kidney tumours, exact lymphatic drainage patterns were not known. In **chapter thirteen**, the feasibility of sentinel node mapping in patients with renal cell carcinoma is demonstrated and lymphatic drainage patterns from the human kidney are described. Previously administered treatment can influence lymphatic flow. **Chapter fourteen** shows lymphatic drainage patterns

and sentinel node yield after lymphoscintigraphy in patients who have undergone radiotherapy for prostate cancer in the past. A lymphatic mapping protocol for the tumour with the largest diameter might be advised in patients with multifocal and multicentric breast carcinoma.^{2,19} We hypothesized that harvesting of all nodes with direct drainage from any cancer can be ensured if tracer injection is performed in or around all lesions. **Chapter fifteen** describes our method and the first results with lymphatic mapping of breast cancer patients with multiple tumours following intralesional injection of the radiopharmaceutical in each tumour.

This thesis ends with general conclusions and future perspectives, followed by summaries in English, Dutch and Spanish.

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