Innovating image-guided surgery: Introducing multimodal approaches for sentinel node detection

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INTRODUCTION AND OUTLINE OF THE THESIS
Solid malignancies have the potential to metastasize. For most cancers, metastatic spread can arise through two separate pathways; via the lymphatic system to regional lymph nodes, or via the bloodstream. Lymphatic dissemination often occurs first. Because the presence of metastatic disease drastically influences the patient’s prognosis, the knowledge whether or not a tumor has disseminated is highly relevant for treatment planning. For many years, regional lymph node dissection was routinely performed alongside primary tumor surgery, even if the nodes appeared clinically normal. Unfortunately, routine regional lymph node dissection exposes the patients without lymph node metastases to unnecessary potential morbidity without providing any survival benefit. With the introduction of the sentinel node concept, a minimally invasive diagnostic modality emerged for early detection of occult lymph node metastases. Since its introduction, the sentinel node procedure has gone through a major development process. Nevertheless, there is still room for further improvement. This thesis focuses on the clinical introduction of novel multimodal approaches that help optimize SN detection in cancer patients.

The sentinel node in a historical perspective

Lymphatic tumor spread and its implications for treatment have been studied for centuries. At the end of the 19th century, the American surgeon William S. Halsted hypothesized that cancer spreads through the lymphatic system in a stepwise pattern, generally metastasizing to a regional lymph node first. The term ‘gland sentinel’ was introduced in 1923 by Braithwaite to describe a direct tumor-draining lymph node that he identified after dye injection. In the 1950s, investigators observed lymphatic transport of radioactive gold particles after subcutaneous injection and in 1960, Gould et al. described a ‘sentinel node’ as the first node to be involved in parotid cancer. Nearly two decades later, the Paraguayan urologist Ramon Cabañas referred to the ‘sentinel lymph node’ in penile cancer as a node in a specific location in the groin that receives the initial lymphatic drainage. It was not until the late 1980s that the concept of lymphatic mapping to selectively remove lymph nodes on the direct drainage pathway from the primary tumor was proposed by Donald L. Morton et al. This innovative technique has evolved throughout the years to become the sentinel node procedure as we know it today.

Definition of the sentinel node

A sentinel node (SN, first-tier node, first-echelon node) is defined as any lymph node on a direct drainage pathway from the primary tumor. This definition reflects the physiology of lymphatic drainage and the stepwise dissemination of cancer to a regional lymph node basin; it also acknowledges the possibility that more than one lymph node can be directly connected with the tumor and thus be a potential first site to harbor metastasis before further progression to so called higher-tier / higher-echelon nodes (Fig. 1). The SN procedure is a multidisciplinary diagnostic modality based on the combination of preoperative imaging, intraoperative...
detection and refined histopathological analysis to enable detection of subclinical metastases. Finding a tumor-positive SN subsequently allows patients with lymph node metastases to be treated in an early phase, avoiding an unnecessary lymph node dissection in case of node-negative findings. At present, the SN procedure is routinely performed in patients with melanoma and breast cancer,\textsuperscript{10-12} but the application is continuously expanding for staging and to guide further regional treatment in head and neck, urological, and gynaecological malignancies.\textsuperscript{13-16}

**Lymphatic mapping using lymphoscintigraphy**

Lymphoscintigraphy was incorporated into the SN procedure to enable preoperative lymphatic mapping. In patients scheduled for SN biopsy lymphoscintigraphy is traditionally performed after intra/peritumoral injection of radiolabeled colloid particles. In Europe, the most frequently used radiotracer is $^{99m}$Tc-nanocolloid. Following injection, radioactive colloid particles migrate through the lymphatic system and retain in the SNs due to incorporation into the macrophages by phagocytosis. This enables prolonged lymph node retention and an adequate detection window. By acquiring dynamic, early and delayed planar images, lymphoscintigraphy can visualize the SNs in the majority of cases. Correct identification of SNs requires careful interpretation of the dynamic and static images. The main criteria to identify lymph nodes as SNs are the visualization of lymphatic ducts, the time of appearance, the lymph node basin, and the intensity of lymph node uptake. Following these criteria, visualized radioactive lymph nodes on scintigraphy may be classified as\textsuperscript{17}:

1) **Definitely SNs**: this category includes all lymph nodes draining from the site of the primary tumor through an own lymphatic vessel, or a single radioactive lymph node in a lymph node basin.

2) **Highly probable SNs**: this category includes lymph nodes appearing between the injection site and a first draining node, or nodes with increasing uptake appearing in other lymph node stations.

3) **Less probable SNs**: all higher echelon nodes (in trunk and extremities) or lower echelon nodes (head and neck) may be included in this category.
SPECT/CT

Lymphoscintigraphy solely provides two-dimensional information. SPECT/CT is a hybrid modality that combines the functional information of single photon emission computed tomography (SPECT) with the morphological information of computed tomography (CT), adding the third-dimension. The resulting fused SPECT/CT images are able to depict SNs in their anatomical landscape providing a helpful roadmap for surgeons. In recent years, SPECT/CT has proven to be a valuable addition to lymphoscintigraphy for various malignancies with the ability to detect additional SNs and to identify aberrant drainage patterns.\(^{18-21}\) However, dynamic imaging using lymphoscintigraphy remains indispensable in distinguishing SNs from higher echelon nodes. In this thesis, SPECT/CT imaging was a part of the applied protocols and was performed (preceded by lymphoscintigraphy) in all studied patients. The SPECT/CT camera used in this thesis is shown in Fig. 2.

**NOVEL MODALITIES FOR INTRAOPERATIVE SN DETECTION**

**Portable gamma camera**

Intraoperatively, the conventional gamma ray detection probe allows for SN detection based on acoustic tracing. Unfortunately, this technique does not provide visual information nor depth estimation. Moreover, spatial resolution can be a limitation, especially when SNs are located in the vicinity of the injection site. A portable gamma camera allows for visualization of radioactive hotspots in the operating room.\(^{22}\) Another advantage of this device compared to a handheld gamma probe is that it has a larger area of detection. The portable gamma camera used in this thesis is equipped with a 4-mm pinhole collimator and its head can be positioned in different angles towards the patient. The field of view depends on the distance between the camera and the imaging plane. By placing the camera head closer to the patient, the detection sensitivity and resolution are increased compared to the conventional gamma probe. A laser pointer cross corresponds with a red cross in the center of the screen, which enables localization of the hotspots in the field of view. This is valuable in determining the site of incision and for post-excision confirmation that all radioactive lesions of interest have been removed, or that there is remaining activity lodging in an adjacent SN that needs to be removed. In addition, two-dimensional intraoperative navigation to SNs using a portable gamma camera was shown to be feasible by placing a \(^{125}\)I-seed on a (laparoscopic) gamma probe or pointer device and performing dual-isotope gamma-imaging.\(^{23}\) In this thesis, two models of the portable gamma camera (Fig. 3) were used during SN biopsy in more than 250 patients. Both cameras have similar properties.

**Fluorescence imaging**

Since the introduction of the SN procedure, additional intraoperative injection(s) of vital blue dye are used to visualize SNs and their afferent lymphatic ducts in real-time during the surgical act.\(^{8,24}\) Recently, fluorescence agents have been
introduced to facilitate optical SN identification. Near-infrared (NIR) fluorescence imaging differs markedly from the visual detection of the more common vital blue dye. Blue dye visualization is a result of light absorbance, which is maximal in the visual range and minimal in the NIR range, whereas fluorescence is based on light emission by so-called fluorochromes. The process of fluorescence can be divided into three steps: 1) Excitation of the molecule by light of a certain wavelength; 2) Internal conversion; and 3) Emission of fluorescent light. Each fluorochrome has its own particular excitation and emission maximum wavelengths. In practice, this means that one needs both a light source matching the excitation maximum of the fluorochrome and a camera system for the detection of the emission light. For NIR fluorochromes this is especially important since the emission wavelengths lie beyond the visual spectrum of the human eye. In general, emissions are classified in visual emissions with a wavelength of 400-650 nm, far-red emissions (650-700 nm), and the by eye invisible NIR emissions 700-1000 nm. Because light in the NIR field penetrates through tissue better than light in the visual spectrum, the NIR dyes can help visualize tissue-embedded SNs before they can be identified by the naked eye using blue dyes. However, since surrounding tissues also cause signal attenuation via absorbance and/or scattering, the depth at which a fluorescent signal can be detected is still limited to approximately 10 mm. The most widely applied NIR tracer is indocyanine green (ICG). Originally applied for NIR fluorescent angiography, it is now increasingly being used for other indications, including SN visualization. This thesis describes the clinical introduction of a novel hybrid approach in which the beneficial properties of both the standardly used radiocolloid and NIR fluorescence imaging are combined in one tracer (applied for SN biopsy in more than 250 patients). One of the two fluorescence cameras which were used in this thesis is depicted in Fig. 4.

Intraoperative image navigation
Translating the 3D diagnostic information from SPECT/CT into real-time feedback that can guide the surgeon during the operation remains a challenge. A recently developed device (Fig. 5) enabling navigation through optical tracking of a pointer device within a mixed reality virtual view based on preoperatively acquired imaging data may help transfer 3D functional imaging to the operating room. The first clinical experiences with this intraoperative navigation approach are reported in this thesis.

Outline of the thesis
Part 1 of this thesis focuses on the clinical introduction of a hybrid SN tracer. In this compound, the fluorescent indocyanine green (ICG) is combined with the radioactive 99mTc-nanocolloid yielding ICG-99mTc-nanocolloid. A first step in the clinical introduction of this new tracer was to ensure that the lymphatic drainage pattern is not altered compared to the original (gold standard) radiocolloid. To this
end, chapter 2 compares the drainage patterns of both tracers using lymphoscintigraphy and SPECT/CT. In chapter 3, the feasibility of using this hybrid tracer for both preoperative SN identification and combined radio- and fluorescence guided SN biopsy is evaluated in head and neck melanoma patients. Whether or not the addition of fluorescence imaging can assist in the localization of SNs for oral cavity carcinoma is assessed in chapter 4. The objective of chapter 5 was to compare the intraoperative SN visualization rate of the fluorescence component of the hybrid tracer ICG-\textsuperscript{99m}Tc-nanocolloid to that of blue dye in a large group of patients with penile carcinoma. Additionally, this chapter studies the distribution of ICG-\textsuperscript{99m}Tc-nanocolloid within the lymph nodes in ex-vivo specimens. Chapter 6 aims to identify the melanoma indications and draining basins where the hybrid approach is of most added value. Surgery is gradually shifting from the open approach towards less invasive laparoscopic and robot-assisted techniques. Chapter 7 introduces the application of the hybrid approach in a laparoscopic setting during robot-assisted prostatectomy followed by SN biopsy. By postoperatively relating the fluorescence deposits in the embedded prostate tissue specimens to the preoperatively detected SNs, chapter 8 evaluates the influence of the location of intraprostatic tracer placement on the lymphatic drainage pattern.

Part 2 describes how the 3D anatomical information provided by SPECT/CT imaging can help identify aberrant drainage patterns and can act as a roadmap towards intraoperative navigation. The purpose of Chapter 9 was to investigate whether lymphoscintigraphy and SPECT/CT after intralesional injection of radiopharmaceutical into each tumor separately in patients with multiple malignancies in one breast yields additional SNs compared to intralesional injection of the largest tumor only (as is common practice). Chapter 10 evaluates the utility of SPECT/CT and intraoperative portable gamma camera imaging for laparoscopic SN localization in stage I testicular cancer. In chapter 11, a case series is presented where SPECT/CT visualized lymphatic drainage from renal cell carcinoma along the thoracic duct. Chapter 12 provides a proof of concept using phantom studies and one clinical pilot case on how intraoperative navigation based on the already available preoperative 3D SPECT/CT images may help improve the efficacy of the hybrid approach in laparoscopic surgery. Chapter 13 aims to explore the clinical feasibility and accuracy of this SPECT/CT-based 3D navigation approach.

This thesis ends with concluding remarks and future perspectives, followed by summaries in English, Dutch and Spanish (chapter 14).
Figure 2. Symbia T SPECT/CT system, Siemens, Erlangen, Germany.
Figure 3. Portable gamma cameras: Sentinella S1 (left) and S102 (right), Oncovision, Valencia, Spain

Figure 4. Hamamatsu PDE NIR fluorescence camera, Hamamatsu, Japan
Figure 5. DECLIPSE-Spect navigation system, SurgiEye, Munich, Germany
REFERENCES


