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

Brouwer, O.R.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
SUMMARY
Founded on Halsted’s hypothesis of sequential tumor spread, selective biopsy of the tumor draining lymph nodes enables early detection of clinically occult nodal metastases while sparing patients the morbidity of an unnecessary lymph node dissection. Originally introduced for melanoma and breast cancer, the sentinel node (SN) biopsy is a multidisciplinary diagnostic procedure based on the injection of a radiocolloid followed by lymphatic mapping using lymphoscintigraphy and SPECT/CT to identify the SNs. Intraoperatively, SNs are traditionally localized using a gamma ray detection probe and a separate injection of blue dye to visualize the SNs. Over the last decade, the procedure has expanded to malignancies with lymphatic drainage to areas of more complex anatomy or located deeply in the abdomen. SN biopsy in these patients may be challenging and may benefit from additional intraoperative tools. This thesis focuses on the clinical introduction of novel multimodal approaches in order to help optimize the SN procedure.

PART I: HYBRID RADIO- AND FLUORESCENCE GUIDED SENTINEL NODE BIOPSY

The first part of this thesis unveils the clinical introduction of a hybrid radioactive and fluorescent tracer (ICG-\textsuperscript{99m}Tc-nanocolloid) allowing for both preoperative SN mapping and combined radio- and fluorescence guided SN biopsies. Chapter 2 describes a validation study comparing the lymphatic drainage pattern of ICG-\textsuperscript{99m}Tc-nanocolloid with the drainage pattern of \textsuperscript{99m}Tc-nanocolloid as the gold standard in 25 patients with various malignancies. This study showed that the lymphatic drainage patterns of ICG–\textsuperscript{99m}Tc-nanocolloid and \textsuperscript{99m}Tc-nanocolloid are identical, indicating that the addition of the fluorescent moieties does not alter the biological properties of the parental radiocolloid and warranting further clinical evaluation of hybrid ICG–\textsuperscript{99m}Tc-nanocolloid. Chapter 3 examines the feasibility of combining lymphoscintigraphy and intraoperative radio- and fluorescence guided SN identification in patients with head and neck melanoma using ICG–\textsuperscript{99m}Tc-nanocolloid. Lymphatic drainage was observed in all 11 patients. All preoperatively identified SNs could be intraoperatively localized using combined radio- and fluorescence guidance. In the 7 patients in whom blue dye was used, 43% of the SNs stained blue, whereas all were fluorescent. In chapter 4, the added value of intraoperative fluorescence imaging to the conventional radioguided procedure using ICG–\textsuperscript{99m}Tc-nanocolloid was evaluated for oral cavity malignancies. At least one SN was preoperatively identified using the radioactive signature of ICG–\textsuperscript{99m}Tc-nanocolloid in all 14 patients. The addition of intraoperative fluorescence imaging was shown to be of particular value when SNs were located in close proximity to the primary tumor, since in 4 patients a SN located close to the primary injection site could only be localized using fluorescence imaging. Chapter 5 demonstrates how fluorescence imaging enabled by ICG–\textsuperscript{99m}Tc-nanocolloid significantly improves optical SN detection compared to blue dye in 65 patients with penile carcinoma. All patients were injected with both hybrid ICG–\textsuperscript{99m}Tc-nanocolloid and blue dye (the latter shortly before surgery). Preoperative
imaging enabled SN identification in all patients (total 183 SNs dispersed over 119 groins). Intraoperatively, all SNs identified by preoperative mapping were localized using combined radio-, fluorescence and blue dye guidance. 96.8% of SNs could be visualized using fluorescence imaging, while merely 55.7% was stained by blue dye ($p<0.001$). Furthermore, fluorescence imaging offered an improved tissue penetration compared to blue dye, allowing earlier visualization of the SNs, which was exemplified by cases where superficially located SNs were visible through the skin. Additional ex vivo examination of 4 tumor-positive SNs revealed that the fluorescent signal was mainly present in the unaffected lymphatic tissue of the SN. Chapter 6 aimed to evaluate the value of ICG-$^{99m}$Tc-nanocolloid for SN biopsy in a large population of patients with melanoma with drainage to the neck, axilla and groin. 104 patients were prospectively included. A total of 246 SNs were preoperatively identified. No adverse reactions to ICG-$^{99m}$Tc-nanocolloid were observed. Intraoperatively 98% of the SNs could be intraoperatively visualized using the fluorescence camera, whereas the 69 patients in whom blue dye was used, only 63% of the SNs had stained blue at the time of excision ($p<0.05$). Fluorescence imaging was particularly valuable for intraoperative SN detection in 17 patients (16%). In these cases SNs were localized close to the injection site or located in a complex anatomical area. Chapter 7 shows that ICG-$^{99m}$Tc-nanocolloid is also applicable during minimally invasive procedures. Eleven patients undergoing robot-assisted prostatectomy followed by SN biopsy were included. Intraoperatively, SNs were identified in real-time using a combination of a laparoscopic gamma probe and a NIR- optimized fluorescence laparoscope. Although fluorescence imaging facilitated SN localization in areas with a high radioactive backgrounds signal such as the injection site, fluorescence detection was limited by the severe tissue attenuation of the signal. Therefore, radio guidance to the areas of interest is still indispensable. Ex vivo gamma and fluorescence imaging of the dissected nodes showed a high signal intensity correlation for all individual patient samples, underlining that all radioactive nodes were indeed fluorescent and radioactive. In Chapter 8, additional ex vivo fluorescence imaging revealed a large variation in the locations of intraprostatic tracer deposits in embedded prostate samples of 19 patients. Tracer deposits in the peripheral zone correlated with a higher number of visualized LNs than deposits in the central zone (on average, 4.7 vs. 2.4 LNs per patient). Furthermore, tracer deposits in the mid gland correlated with a higher number of visualized LNs than deposits near the base or apex of the prostate (on average, 6 vs. 3.5 LNs per patient). As such, ICG-$^{99m}$Tc- nanocolloid also provides a unique tool to postoperatively investigate the influence of the location of tracer deposits on lymphatic drainage patterns, long after the radioactive signal has decayed. The results from this study suggest that the location of intraprostatic tracer deposition may be of influence on the lymphatic drainage pattern, and as such, the SN procedure as a whole.
PART II: SPECT/CT AS A 3D ROADMAP FOR INTRAOPERATIVE NAVIGATION

The second part of this thesis is focused on the value of SPECT/CT and describes the first steps in translating SPECT/CT to the operating room using mixed reality models for intraoperative navigation in 3D. Chapter 9 underlines that the breast should not necessarily be regarded as one single entity with regard to its lymphatic drainage. In a 4-center effort, 50 patients with multiple tumors in one breast were prospectively included to investigate whether lymphoscintigraphy and SPECT/CT after intralesional injection of radiopharmaceutical into each tumor separately yields additional SNs compared to intralesional injection of the largest tumor only. Additional lymphatic drainage was depicted after the second and/or third injection in 32 patients (64%), suggesting that separate tumor-related tracer injections may be a more accurate approach to mapping and sampling of SNs in patients with multicentric or multifocal breast cancer. In chapter 10, ten patients with clinical stage I testicular cancer were studied to evaluate the utility of SPECT/CT and real-time intraoperative imaging with a portable gamma camera for laparoscopic SN localization. SPECT/CT was shown to enable accurate anatomic localization of retroperitoneal SNs in all patients. In 3 patients aberrant drainage was observed to SNs adjacent to the testicular vessels. The portable gamma camera enabled real-time intraoperative SN visualization in all 9 patients in whom the device was used. Histopathologic examination revealed metastases in 1 excised SN alongside the testicular vessels. Chapter 11 shows another example of how SPECT/CT is able to accurately identify aberrant drainage patterns in patients with renal cell carcinoma (RCC). Of 42 patients included in an ongoing trial, 4 showed early lymphatic drainage following the course of the thoracic duct. In one patient, this was observed without any retroperitoneal lymph node interposition. This drainage pattern may be associated with the lung frequently being the primary metastatic site. Ideally, the detailed 3D information provided by SPECT/CT would be available in a form of real-time feedback that can guide the surgeon during the operation. Chapter 12 provides a proof of concept and technical overview in a phantom study demonstrating how the navigation of an optically tracked fluorescence endoscope by means of mixed reality can potentially help translate the preoperatively acquired SPECT/CT images to the operating room in the form of 3D navigation. The aim of chapter 13 was to explore the clinical feasibility and accuracy of this approach using a navigated gamma probe in 10 patients with penile carcinoma undergoing SN biopsy. The average error in the coronal and saggital planes were 5.0 and 5.3 mm, respectively. In 3 patients, 3D SPECT/CT navigation pointed to the exact same location on the skin as the conventional probe. Taken together, surgical navigation based on a mixed reality protocol using preoperatively acquired SPECT/CT images was shown to be feasible. Although real-time confirmation of the navigation accuracy through gamma tracing and/or fluorescence imaging remains indispensable, the application of 3D navigation based on preoperatively acquired functional nuclear imaging data opens a whole new perspective in (hybrid) image guided surgery, as
PET/CT and PET/MRI may be incorporated in the nearby future.