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

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CONCLUSIONS AND FUTURE PERSPECTIVES
Accurate staging with SN biopsy can only be achieved if all nodes on a direct pathway from the tumor are identified and harvested. At present, the SN procedure is routinely performed for staging patients with breast cancer and melanoma yielding good results using the standard procedure with lymphoscintigraphy followed by intraoperative SN detection with a gamma probe and blue dye. However, the last decade, the procedure has evolved with expansion to other malignancies with lymphatic drainage to areas of more intricate anatomy like e.g. the head and neck, or deep lymphatic drainage to the pelvis like e.g. for prostate cancer. For these malignancies SN biopsy may be challenged by e.g. unexpected lymphatic drainage patterns, by SNs that lie in close vicinity to the injection site, or by SNs that do not stain blue. It is in these circumstances that novel technologies such as the ones presented in this thesis can be of particular benefit.

**PART I**

This thesis shows that one injection of the novel hybrid radio- and fluorescent compound ICG-\(^{99m}\)Tc-nanocolloid preserves preoperative SN identification using lymphoscintigraphy and SPECT/CT, without alteration of the lymphatic drainage pattern of the original radiocolloid. The fluorescent component of this versatile SN tracer adds real-time intraoperative fluorescence-based SN identification to the traditional radioguided procedure. No adverse reactions were observed in over 250 studied patients.

As evidenced in this thesis one of the main advantages of the hybrid approach is that surgical identification of SNs preoperatively identified on SPECT/CT can be aided by the use of a fluorescence camera. The results of the studies where blue dye was also injected are consistent in demonstrating that intraoperative fluorescence imaging using hybrid ICG-\(^{99m}\)Tc-nanocolloid improves SN detection in comparison to blue dye in terms of tissue penetration (illustrated by the cases where SNs where visible through the skin) and SN visualization rates. One possible explanation for the observed difference in SN visualization rates is the fact that blue dye is injected separately and may already have passed through the SN at the time of excision due to its fast migration through the lymphatic system. Due to a functional tracer uptake mechanism the hybrid approach using ICG-\(^{99m}\)Tc-nanocolloid thereby addresses the migrational limitations of optical dyes such as blue dye or ICG alone. As there is no need for additional injections during surgery, using ICG-\(^{99m}\)Tc-nanocolloid may provide a logistical improvement. The detection window with this tracer is effective up to at least 30 hours. As evaluated by Vermeeren et al. a few years ago, the incorporation of a pin-hole portable gamma camera in addition to the conventional gamma probe increases the effectiveness of the intraoperative SN detection in the head and neck. In the present thesis, the SN procedure for oral cavity cancer and melanoma was further refined using high-resolution fluorescence imaging. This was shown to be especially valuable in an area like the neck with a high lymph node density and where SNs are often located in
close proximity to the injection site. Following the shift of surgery towards less minimally invasive approaches the feasibility of using ICG-\(^{99m}\)Tc-nanocolloid as a SN tracer was also demonstrated during SN biopsy next to robot-assisted laparoscopic prostatectomy. Besides the potential to improve surgical guidance during (robot-assisted) SN biopsy, hybrid ICG-\(^{99m}\)Tc-nanocolloid provides a unique tool to postoperatively monitor the location of tracer deposits in e.g. the lymph nodes, but also the injected organ/tumor. More investigations using this feature may help us to gain more knowledge on organ specific lymphatic drainage patterns in the future. In turn, this may help further improve the SN injection procedure. It should however be noted that despite the added value of fluorescence imaging, the radioactive component remains indispensable for reliable pre- and intraoperative SN identification (the tissue penetration of fluorescence imaging is still limited to approximately 10mm). The successful clinical introduction of this hybrid approach encourages broader implementation of the hybrid surgical guidance concept and opens doors for new hybrid imaging applications like e.g. the current preclinical development of tumor-targeted hybrid tracers. Yet the implementation of the hybrid surgical guidance concept is not limited to the field of oncology alone. Current preclinical efforts are also focused on the potential application of this approach to visualize vital structures during surgery (like e.g. nerves), in order to facilitate to minimize iatrogenic damage. The introduction of hybrid tracers also poses new technologic challenges for manufacturers of imaging systems. At present, separate devices for radioguided and optical sentinel detection are used. In the future, the development of hybrid devices combining the 2 techniques may further improve the logistics in daily clinical practice. Taken together, the combination of the beneficial properties of both the radioguidance and fluorescence imaging in ICG-\(^{99m}\)Tc-nanocolloid may help further optimize pre- intra and postoperative SN identification and contribute to lowering false-negative rates for SN biopsies in areas of complex lymphatic drainage. Larger prospective follow-up studies are necessary to definitively establish the additional clinical value of these new technologies.
PART 2

Conventional lymphoscintigraphy is not always able to define the exact anatomical location of a SN. The lymphatic drainage pattern may be unusual or may not be shown at all. We found that SPECT/CT helps overcome these difficulties. Previous literature reports demonstrated that SPECT/CT is able to reveal additional SNs which were not visible at lymphoscintigraphy. This observation was confirmed in several chapters of this thesis. SPECT/CT enabled identification of aberrant drainage patterns in patients with testicular cancer and for the first time SNs adjacent to the testicular vessels were visualized. As these aberrantly draining nodes are potentially the first site to harbor metastases, it is important to identify and harvest them together with the other SNs within the standard field of dissection. The clinical relevance of this observation was underlined by the finding of metastases in one of the SNs along the testicular vessels. SPECT/CT also identified aberrant drainage through the thoracic duct in kidney cancer patients. Although renal lymphatic tributaries directly joining the thoracic duct without traversing any lymph nodes have been described in cadaver studies, this is the first time this has been visualized in vivo. This drainage pattern may yield fundamental insights into metastatic spread from renal cancer as it may be associated with the lung often being the primary metastatic site. In addition, it may partially explain why randomized trials of lymph node dissection in renal cell carcinoma have not demonstrated an impact on survival.

In patients with multiple malignant tumors within one breast, SPECT/CT demonstrated that separate tracer injections of each tumor might yield additional SNs in more than half of the patients. This suggests that if only the largest tumor is injected, which is common practice, a (tumor-positive) SN might be missed. A larger prospective trial is currently in preparation to substantiate this assumption.

Another important point is the necessity to correlate findings of fused SPECT/CT with those of CT. In many cases, radioactive SNs correspond with single lymph nodes. However, in some cases, a radioactive hotspot on SPECT/CT may correspond with multiple lymph nodes on CT. The observation of these clusters of SNs on the low dose CT component of the SPECT/CT provides important preoperative information that can predict the presence of multiple radioactive SNs at the excision site. Such information may facilitate the surgical procedure. It is important to note that SPECT/CT does not replace lymphoscintigraphy. Sequential lymphoscintigraphy remains essential to distinguish SNs from higher-tier nodes. Therefore, SPECT/CT should be considered as a complementary modality.
In the coming years, SPECT/CT may increasingly be performed routinely in patients where the planar images are difficult to interpret. In melanoma, the universal application of SPECT/CT has been associated with a significant higher 4-year disease-free interval when compared with patients where no SPECT/CT was used. SPECT/CT was performed in more than 300 patients in the studies presented in this thesis. In all patients, SPECT/CT provided useful anatomical landmarks to plan the surgical procedure. However, transferring this preoperative information to the surgical act remains a challenge. Ideally, the 3D diagnostic information from SPECT/CT can be converted into real-time feedback, which can guide the surgeon during the operation. Navigation using mixed reality protocols can potentially help translate the preoperatively acquired SPECT/CT images to the operating room in the form of 3D navigation. Using optical tracking of a reference target placed on the patient (during SPECT/CT acquisition and intraoperatively) and on the gamma probe, we were able to navigate towards inguinal SNs visualized on SPECT/CT with an error lower than 1 cm. This error however, still renders an additional real-time intraoperative tool to confirm the exact SN location essential. In this sense, this navigation approach fits perfectly in the hybrid surgical guidance concept presented in part I, as the radioactive component enables preoperative functional imaging and errors below 1 cm can be compensated by fluorescence imaging of the ICG component.

Because the accuracy of navigation is greatly influenced by the precision and consistency with which the reference target can be repositioned on the patient, this form of navigation is currently more appropriate for the more rigid areas of the body. In order to improve the accuracy of this navigation approach in laparoscopic procedures in the future, adjustments in patient tracking methodology are required. The application of 3D navigation based on preoperatively acquired functional nuclear imaging is a step towards further development with the potential to open a whole new perspective in (hybrid) image-guided surgery, as PET/CT and PET/MRI may be incorporated in the nearby future.
REFERENCES


