Image guided surgery: clinical validation of lesion identification technologies and exploration of nerve sparing approaches

KleinJan, G.H.

SUMMARY

The studies described in this thesis illustrate the value of surgical guidance techniques and their further refinement.
In **part one** the focus is placed on intraoperative identification of lesions (in this case sentinel nodes) that need to be resected. Here the benefits of the hybrid surgical guidance concept, which combines radio- and fluorescence-guidance, are illustrated.
The review presented in **chapter 2** discusses the most common radioguided surgery approaches. The possibilities of different, clinically used radioactive tracers and their potential hybrid (radioactive and fluorescent) derivatives are reported on. Furthermore, the various imaging devices designed for radioactivity-based detection are briefly reviewed in the context of generating hybrid-imaging modalities.

In **chapter 3** the results of the clinical use of the hybrid tracer ICG-^{99}mTc-nancolloid in 501 procedures performed for different malignancies (skin malignancies (n= 191), vulva cancer (n= 21), penile cancer (n=192), oral cavity (n=51) and prostate cancer (n=40)) are discussed on. In this population 1643 SNs were identified based on the combination of gamma tracing (>98%) and fluorescence (>95%) optical detection. Intraoperative SN detection rates using fluorescence guidance proved to be superior to those of blue dye detection (22-78%). Follow-up revealed that use of the hybrid tracer did not negatively influence the false negative rates and outcome values. This study proved that with the use of ICG-^{99}mTc-nanocolloid the radio- and optical guidance during SN biopsy procedure has become universal for different malignancies and anatomical locations.

In **chapter 4** is demonstrated how an increase in sensitivity and the introduction of anatomical context helped to improve the fluorescence detection of a clinically applied fluorescence laparoscope. This concept was studied in three patient groups of prostate cancer patients scheduled for sentinel biopsy using ICG-^{99}mTc-nanocolloid. In the first group of prostate cancer patients (n=11) scheduled for SN biopsy the standard used concentration of ICG-^{99}mTc-nanocolloid was used in combination with a standard used fluorescence laparoscope. In the second group (n=13) the concentration and volume of ICG-99mTc-nanocolloid were optimized and in the third group (n=16) an improved fluorescence laparoscope was introduced. Mean fluorescence-based SN identification improved from 63.7% (group 1) to 85.2% and 93.5% for groups 2 and 3, respectively (p=0.012).

Chapter 5 describes a study in 55 prostate cancer patients (Briganti nomogram-based risk >5 % on LN metastases) wherein the robot-integrated Firefly fluorescence laparoscope was used to provide guidance during robot-assisted radical prostatectomy, SN biopsy and extended pelvic lymph node dissection. Intraoperative fluorescence imaging using standard fluorescence settings visualized 80.4% (148/184SNs; 50 patients; *ex vivo* 97.8%); SPECT/CT images provided guidance towards the residual SNs. By integrating the fluorescence laparoscope directly into the robotic surgical system a direct link between the preoperative nuclear SPECT imaging information and intraoperative fluorescence detection of SNs was realized.

Chapter 6 evaluated what the relation is between the amount of hybrid tracer (ICG-^{99}mTc-nanocolloid) that had collected in sentinel nodes and their intraoperative identification rates using fluorescence guidance. Intraoperative fluorescence detection findings were derived from a retrospective analysis of 20 head-and-neck melanoma patients, 40 penile and 20 prostate cancer patients scheduled for SN biopsy using ICG-^{99}mTc-nanocolloid. The % of migrated hybrid tracer could be correlated directly to the amount of ICG (range: 0.003–10.8 nmol) and the concentration of ICG (range: 0.006–64.6 μM) in a SN. The study indicates that intraoperative fluorescence detection with ICG is possible when higher than a 0.006 μM concentration.

Part two describes the use of surgical modalities that are used in the hybrid surgical concept. In **chapter 7** the value of a hybrid detection modalities that intergrade radio- and fluorescence imaging functions were assessed in a total of eleven penile cancer patients scheduled for SN biopsy. Two different hybrid detection modalities were created by combining a gamma –ray detection probe (GP) or a gamma camera (GC) with a fluorescence exoscope that allows fluorescence imaging in an open surgery setting. Both combined modalities were evaluated in respectively five and six penile cancer patients during SN biopsy procedures using ICG-^{99}mTc-nanocolloid. To assess the sensitivity of the individual modalities in this set-up, intraoperatively, radio- and fluorescence guided SN detection rates were scored at working distances of 0, 10, 20, and 30 cm. These comparisons indicated that the detection modalities work synergistically; overall the GC was most valuable for rough localization (10-30 cm range) of the SNs, the GP for providing convenient real-time acoustic feedback, while fluorescence guidance allowed detailed real-time SN visualization.

Chapter 8 describes the feasibility, in five penile cancer patients injected with ICG-^{99}mTc-nanocolloid, of a nuclear medicine–based navigation concept that allowed intraoperative positioning of a fluorescence camera based on preoperative SPECT/CT images. The navigation device was used to provide a real-time augmented reality overlay of the SPECT/CT images and video output of the fluorescence camera. Navigation was successful for all 12 intraoperatively evaluated SNs (average error, 8.8 mm; range, 0–20 mm). These results are promising for future surgical application, where localization of lesions could be rather complicated, e.g. of SNs located in the pelvic area.

In **chapter 9**, in eight patients with melanoma located in the head and neck area, SNs were located based on freehandSPECT navigation. Using this approach 87% of SNs could be navigated to based on the freehandSPECT generated 3D image and could be resected under fluorescence guidance. Fluorescence imaging allowed for the identification of the SNs, which could not be identified using navigation. In addition fluorescence imaging provided optical confirmation of the navigation accuracy in all patients. The use of gamma camera based freehandSPECT helped to enhance intraoperative imaging and therewith strengthens the hybrid surgical guidance concept.

In part three the influence of nerve preservation on postoperative functional outcome is assessed and preoperative and intraoperative imaging techniques for nerve visualization are evaluated. An intraoperative score quantifying the nerve preservation during robot-assisted prostatectomy (the fascia preservation (FP) score) was used to improve and predict the postoperative erectile function in patients with prostate cancer. To improve the visualization of peripheral nerves before and during surgery, two possibele techniques were evaluated, D-Prep MRI (preoperative) and fluorescence imaging (intraoperative), respectively

In **chapter 10** anatomy based nerve containing fascia preservation during robot-assisted radical prostatectomy is evaluated in 1241 prostate cancer patients and related to an international index of erectile function (IIEF) score. Based on age, preoperative IIEF score, Charlson comorbidity score index (CCSI), use of clips and the degree of nerve sparing, it was possible to predict the postoperative erectile function after RARP using a dedicated prediction model.

In an attempt to generate a personalized anatomical roadmap that depicts the location of delicate nerves, a D-Prep MRI sequence was applied in the head an neck area (6 volunteers; **Chapter 11**). The technology clearly detected anatomical variations and allowed for the visualization of peripheral nerves > 0.7 mm in diameter. Uniquely, this MRI sequence also provided enhanced insight in the lymphatic anatomy, such as the number of lymph nodes in the surgical field (23.2±4), the sizes of these lymph nodes (range 21-372 mm^3) and distances of lymph nodes to delicate anatomies.

Reasoning that fluorescence imaging could prevent damage to nerve structures by allowing intraoperative identification; in chapter 12 the *in vivo* nerve staining capabilities of locally administered fluorescent lectin-based tracers is described. To allow for fluorescence imaging, WGA, PNA, PHA-L and LEL were functionalized with Cy5. Transfer of these imaging tracers along the sciatic nerve was evaluated in transgenic Thy1-YFP mice (n = 12; in this model the nerves are YFP-fluorescent for reference). On average, this approach allowed for identification of nerves up to 1 cm from the administration site. Although the technique is promising, this technology is far from generating an impact in the clinical setting.
In conclusion, the techniques described in the above mentioned chapters could help to improve the clinical outcome after surgery for patients treated with different malignancies. These techniques could create an optimal balance in tumour or lymph node resection and the sparing of delicate structures in the surrounding anatomical area. Although the techniques are already feasible, their value in the clinical routine have to be proven in additional clinical studies evaluating the postoperative outcome.

OUTLOOK AND FUTURE PERSPECTIVES

The surgical guidance techniques reported in this thesis were used in the first place to improve the pre- and intraoperative detection of the targeted lesion. However, it has been proposed that true optimization of surgical guidance requires that a balance is struck between complete resection of (potentially) malignant tissues and sparing of surrounding structures such as nerves. Fluorescence guidance during surgery could help to improve the intraoperative visual detection of the targeted lesions but could also allow navigation around structures that need to be spared. Such an approach could, for example, help to improve the erectile function and as such result in an improved quality of life in prostate cancer patients. A combination of acoustic, optical and directional guidance could be implied for all surgical fields to improve the surgical precision during operations. A logical extension of these techniques can be found in means to enhance the ability to provide feedback on different features. For example, in the near future multicolor fluorescence could be used to identify the targeted lesions and at the same time distinguish structures that need to be spared. To initiate this concept, in a preclinical (pigs) pilot study we evaluated whether it was technically feasible to intraoperatively distinguish sentinel nodes related to the prostate to those lymph nodes draining from the hind legs. Here two different dyes with complementary excitation and emission spectra were used, allowing for simultaneous visualization of the two independent features (prostate vs. leg, Figure 1).

Although intraoperative information based on (multicolor) fluorescence helped illuminate important details during the surgical resection, this technique is not able to integrate non-invasive preoperative planning information as is available from modalities like CT, MRI and or fuse modalities like SPECT/CT and PET/MRI. Such integration may be realized using navigation technologies. Ideally, the in depth three dimensional imaging information is presented as augmented reality overlay on the patient during the surgical procedure. This provides a roadmap in which surgical tools and modalities can be accurately positioned. Combined we envision that the above techniques could facilitate further improvements in the accuracy of surgery.

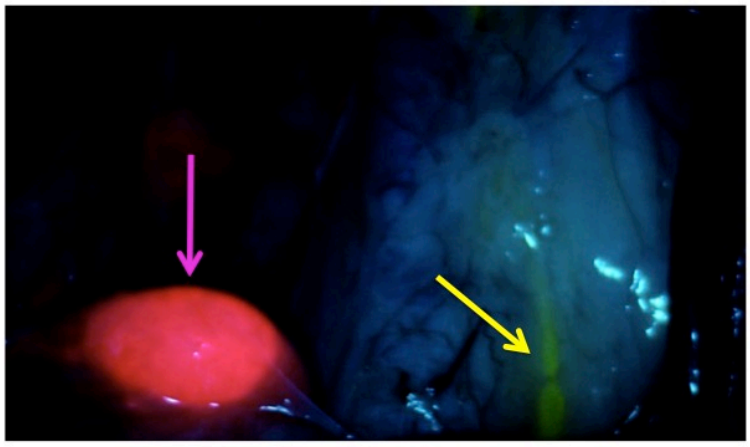

Figure 1. Multicolor lymph node identification

In pink an ICG positive SN directly related to the prostate. In yellow a lymph duct running form the leg.