Interventional molecular imaging, a hybrid approach

General introduction

Chapter 1

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Accurate detection of tumor tissue is a key feature in the diagnosis of cancer, and surgery is one of the major pillars in further management of the disease. Using preoperatively obtained images, the area of interest can be linked to the anatomy of the patient, enabling planning of the surgical intervention.

During surgical exploration morbidity may be caused by the unnecessary removal of healthy tissue and/or the unintentional damage to delicate anatomical structures. Furthermore, the inability to completely excise the cancerous tissue increases the need for invasive re-excisions. More accurate surgical visualization of the area's of interest can supplement the surgeons eyes and help improve surgical outcome.

Accurate preoperative identification, surgical planning, and intraoperative visualization can be integrated using hybrid imaging agents that contain both a radio- and fluorescent label. This hybrid interventional molecular imaging concept was initially validated in sentinel lymph node (SLN) biopsies, but can be further expanded by the implementation of imaging agents that specifically visualize tumor cells. In this thesis both the preclinical and clinical introduction of this hybrid concept is described.

Part I of this thesis is focused on combined pre- and intraoperative imaging of the SLN. **Chapter 2** provides an overview of radioactive, fluorescent and size-dependent properties of non-targeted hybrid nanoparticles and their (potential) value in SLN detection.

In **Chapter 3** conventional preoperative lymphoscintigraphy with technetium labeled albumin colloids is quantitatively compared with optical intraoperative guidance using the near-infrared dye indocyanine green (ICG) in a mouse model for metastatic breast cancer. A self-assembled hybrid complex (ICG-^{99m}Tc-nanocolloid) is applied, in order to attain identical dynamics of the radioactive and fluorescent components.

In a spontaneous mouse prostate tumor model (**Chapter 4**), the lymphatic distribution pattern of the hybrid imaging agent ICG-^{99m}Tc-nanocolloid was quantitatively compared to that of the visible dye patent blue, ICG, and dual labeled human serum albumin particles (ICG-^{99m}Tc-Vasculosis).

In a clinical reproducibility study, described in **Chapter 5**, lymphoscintigraphic drainage patterns of ^{99m}Tc-nanocolloid and ICG-^{99m}Tc-nanocolloid are compared, showing that the addition of ICG does not alter the drainage properties of the radiocolloid.

Chapter 6 describes the added value of combined pre- and intraoperative imaging

using ICG-^{99m}Tc-nanocolloid in patients who underwent robot assisted laparoscopic prostatectomy (RALP) with (S)LN dissection for prostate cancer.

An additional feature of ICG-^{99m}Tc-nanocolloid is demonstrated in **Chapter 7,** wherein the location of the ICG-^{99m}Tc-nanocoloid tracer deposit in embedded prostate samples is related to the lymphatic drainage pattern as seen on lymphoscintigraphy.

In **Part II** of this thesis the preclinical evaluation of a number of differently labeled Ac-TZ14011-based CXCR4 targeting imaging agents, including hybrid derivatives, are described.

In **Chapter 8** expression of CXCR4 in preclinical (tumor) models is compared to the clinical situation. Furthermore, peptide structures and receptor affinities of CXCR4 targeting T140 peptide derivatives are evaluated.

The ability to accurately stain the CXCR4 receptor in both cells and tumor tissue using a fluorescently labeled version of Ac-TZ4011 (Ac-TZ14011-FITC) is compared to CXCR4 targeting antibodies in **Chapter 9**.

In a mouse tumor model resembling human ductal carcinoma in situ (DCIS; **Chapter 10),** an indium labeled version of Ac-TZ14011 (^{111}In-Ac-TZ14011) is used to longitudinal monitor lesion development by way of CXCR4 expression levels.

Chapter 11 describes the synthesis and evaluation of hybrid Ac-TZ14011 derivatives that contain both a DTPA chelate and a fluorescent dye. Like the untargeted hybrid agent ICG-^{99m}Tc-nanocolloid, the hybrid version of the targeting peptide (MSAP-Ac-TZ14011) enables integration of pre- and intraoperative imaging.

The effect of multimerization; increasing the amount of targeting peptides per molecule to reduce the negative influence of the hybrid label on the receptor affinity and distribution is studied in **Chapter 12**.

An expansion of the targeted hybrid imaging approach is discussed in **Chapter 13** wherein MSAP-Ac-TZ14011 is used to assess the CXCR4 expression pattern in fresh tumor tissue specimens. This approach enables target validation and accurate staging of the lesions prior to imaging.

In the future perspectives (**Chapter 14**), additional suggestions for expansion of the hybrid surgical guidance concept are given.