Advancing surgical guidance: from (hybrid) molecule to man and beyond

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CHAPTER 1

GENERAL INTRODUCTION, OUTLINE OF THIS THESIS

GENERAL INTRODUCTION

Radiotracers, in combination with positron emission tomography imaging (PET), or single photon emission computed tomography (SPECT) imaging, provide a very sensitive technique for the localization of cancer [1, 2]. Combined with anatomical imaging techniques (such as computed tomography (CT) or magnetic resonance imaging (MRI)), nuclear medicine has become important for the non-invasive identification of various cancers and detection of metastasis. More and more the combined technique of SPECT/CT, PET/CT, and PET/MRI is also used to guide interventions, for example treatment response measurements and surgical procedures [3, 4].

Surgery, often combined with (neo-adjuvant) chemo-, hormonal- or radiotherapy, can be considered the main pillar in the management of cancer. However, when approaching the tumor or lymph nodes that possibly contain metastases, during the surgical procedure it is not always clear what has to be removed. Here interventional molecular imaging technologies may provide outcome. Using radio- or fluorescence-guidance, or a combination of both, may direct the surgeon more accurately to the lesion(s) of interest.

Ideally, a combination of a radiotracer and a fluorescence tracer is used in order to allow accurate pre- and intraoperative lesion identification [5, 6]. In this thesis, a hybrid approach for surgical guidance, based on the clinical use of the hybrid tracer indocyanine green (ICG)-technetium-99m (^{99m}Tc)-nanocolloid, is presented. Next to the clinical validation of the technique, extensions towards the use of multispectral imaging, hybrid modalities and navigation technologies have been exploited.

OUTLINE OF THIS THESIS

Part one of this thesis introduces the reader into the concept of image-guided surgery and the evolution from fluorescence-based surgical guidance into the hybrid approach for surgical guidance. Chapter 2 provides the reader with the basics of fluorescence imaging, after which clinically available tracers for fluorescence imaging in the field of urology as well as fluorescence imaging hardware requirements are discussed. In chapter 3 the clinically available radiotracers, blue dyes, fluorescence tracers and hybrid tracers for sentinel node biopsy are presented.

Part two of this thesis focuses on the clinical evaluation of the hybrid tracer ICG-^{99m}Tc-nanocolloid for sentinel node biopsy of different malignancies. In chapter 4, in patients that were to undergo sentinel node biopsy for oral cavity carcinoma (n=14), the value of the fluorescent component of the hybrid tracer was evaluated and compared to the conventional radioguided approach. In chapter 5 the hybrid tracer was evaluated in a large cohort of 65 patients with penile cancer. Here optical sentinel node identification via blue dye was compared to optical sentinel node identification via the fluorescent signature of the hybrid tracer. In chapter 6, in 104 patients with melanoma (head-and-neck, trunk or on an extremity) with drainage to amongst others the neck, axilla and groin, we evaluated

the value of the hybrid tracer for sentinel node identification. In all cases findings were compared to the conventional radioguided- and blue dye-based approach.

While the clinical value of the hybrid tracer is evaluated in part two of this thesis, in **part three** the main aim was to study if the hybrid approach for surgical guidance could be further extended via technical improvements made on the hardware side. As a first step herein, chapter 7 describes the use of a prototype fluorescence camera for open surgery procedures, (head-and-neck) melanoma oral cavity, and penile carcinoma; n=27) that, in contrast to many other cameras, works under ambient light conditions and thereby allows for real-time fluorescence imaging-assisted surgical guidance. In chapter 8, in 40 patients with prostate cancer that were to undergo robot-assisted laparoscopic sentinel node biopsy optimization of the hybrid tracer formulation and improvements on the fluorescence laparoscopic camera were studied. In doing so, the surgical guidance process was further refined. In chapter 9, we extended the functionalities of the fluorescence laparoscope in order to allow for the intraoperative detection of multiple fluorescence signatures (ICG-^{99m}Tc-nanocolloid and fluorescein), so-called multispectral imaging.

Next to refining individual modalities, their integration was also explored. In chapter 10 the feasibility and accuracy of 3D navigation of conventional surgical tools to the lesion(s) of interest is presented in patients with melanoma or Merkel cell carcinoma (n=5). Alternatively hybrid surgical imaging modalities were explored. In chapter 11 we describe the evaluation of the first prototype opto-nuclear probe, an imaging modality that allows for conventional gamma tracing as well as fluorescence tracing (head-and-neck malignancies and penile caranoma; n=9).

In chapter 12, the **outlook** of this thesis, steps are described that can extend the hybrid surgical guidance concept on both the tracer and hardware side.

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