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

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The work described in this thesis shows how intraoperative lesion identification can be improved via the introduction of (hybrid) tracers and optimized (hybrid) imaging modalities capable of detecting these tracers. In **part one** of this thesis, the reader is introduced to the concept of fluorescence image-guided surgery and the evolution thereof. Furthermore, the hybrid approach for image-guided surgical guidance is presented. **Part two** of this thesis describes the clinical evaluation of the hybrid approach using the hybrid indocyanine green (ICG)-technetium-99m ( $^{99m}\text{Tc}$ )-nanocolloid. To further refine the hybrid approach for surgical guidance, **part three** of this thesis describes the development and evaluation of different types of (hybrid) imaging modalities.

## **PART ONE**

In chapter 2, the concept of fluorescence image guidance is introduced by describing the various fluorescence tracers and detection modalities used within the field of urology. Although both visible and near-infrared fluorescence tracers are commonly used for e.g. cancer diagnosis (e.g. protoporphyrin IX precursors 5-ALA or HAL), (lymph-)angiography (e.g. fluorescein or ICG), ureter visualization (fluorescein) and sentinel node mapping (ICG- $^{99m}\text{Tc}$ -nanocolloid), the majority of (commercially) available fluorescence cameras can only detect the near-infrared fluorescence signal of ICG.

Chapter 3 provides an overview of the clinically available tracers for sentinel node biopsy, a routine clinical procedure in staging of patients with early stage cancer. Radiotracers (e.g.  $^{99m}\text{Tc}$ -nanocolloid) have proven to be of great value in this setting as they allow for non-invasive preoperative sentinel node mapping, as well as providing intraoperative radioguidance. To allow for intraoperative optical detection of the sentinel node(s), generally blue dye(s) or the near-infrared fluorescence tracer (ICG) are used as a separate entity. With the introduction of hybrid tracers, e.g. ICG- $^{99m}\text{Tc}$ -nanocolloid, integration of the pre- and the intraoperative approach was facilitated allowing direct translation of preoperative imaging information in the operation theatre. Furthermore in this chapter, using the hybrid tracer the hybrid approach for sentinel node biopsy is introduced and put into perspective with respect to the conventional radioguided and blue dye-based approach.

## **PART TWO**

**Part two** of this thesis focuses on the evaluation of the hybrid tracer ICG- $^{99m}\text{Tc}$ -nanocolloid for various indications of sentinel node biopsy as such to determine its clinical value. In chapter 4, the technology was evaluated in 14 patients with oral cavity carcinoma. In this setting the fluorescence signature of the hybrid tracer proved to be of particular value for the identification of near-injection site sentinel nodes. Chapter 5 evaluated the feasibility of the hybrid tracer-based sentinel node biopsy procedure in a large cohort of penile cancer patients (n=65; 119 groins). Here the fluorescent signature of the hybrid tracer allowed optical identification of 96.8% of the sentinel nodes, while using blue dye merely 55.7% of the sentinel nodes could be visualized (p<0.0001). Compared to blue dye,

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fluorescence imaging provided improved tissue penetration resulting in the visualization of sentinel nodes through the intact skin in some patients. Ex vivo evaluation of four tumor-positive sentinel nodes also revealed that the hybrid tracer was mainly present in the unaffected lymphatic tissue of the sentinel node.

In [chapter 6](#), the hybrid tracer approach was evaluated in 104 patients with melanoma (in the head-and-neck, on the trunk or on an extremity), with drainage to, amongst others, the neck, axilla and groin. Here radioguidance alone allowed the identification of 93.8% of the sentinel nodes, while the fluorescent signature of the same tracer gave an intraoperative detection rate of 96.7%. In contrast, with blue dye only 61.7% of the sentinel nodes could be visualized. Fluorescence imaging provided welcome guidance when no blue dye was used or when sentinel nodes failed to take up blue dye (n=12 patients), or in case the SNs could not be detected using gamma tracing (n=5 patients).

From **part two** it can be concluded that there is a definite value in using the hybrid tracer for sentinel node biopsy in comparison to the conventional radio- and blue dye-guidance. Moreover the results from the above-described studies illustrate that this value seems to be biggest when sentinel nodes reside in close proximity to the injection site and/or at a location of complex anatomy (e.g. the parotid gland).

### PART THREE

To accommodate routine clinical embedment of the hybrid tracer, further improvements in the surgical imaging modalities are required. **Part three** of this thesis focuses on refining currently clinical grade imaging hardware, as well as on the introduction of a novel hybrid imaging modality. In [chapter 7](#) a prototype handheld open surgery fluorescence camera that allows fluorescence guidance under ambient light conditions is presented. In seven patients, in a direct comparison to its predecessor, this prototype fluorescence camera identified a higher number of sentinel nodes intraoperatively (100% vs. 81.4%), more transcutaneous sentinel node visualization (40.7% vs. 22.2%) as well as lymphatic duct visualization (7.4% vs. 0%). In an additional 20 patients, the value of the technical improvements made was further underlined; in some patients real-time fluorescence-guided sentinel node excision was possible where previously fluorescence imaging was mainly used to confirm localization of the sentinel node(s) (**part two**). [Chapter 8](#) is aimed at improving laparoscopic fluorescence imaging during sentinel node identification in patients with prostate cancer that were to undergo robot-assisted laparoscopic sentinel node biopsy (n=40). Here, optimization of the hybrid tracer formulation and injection resulted in an improvement of intraoperative sentinel node identification from 63.7% to 85.2%, which further increased to 93.5% after improving the fluorescence imaging laparoscope. Similarly as described in [chapter 7](#), improvements eventually resulted in enabling real-time fluorescence guidance. In [chapter 9](#) this same fluorescence laparoscope was further refined to allow for the intraoperative detection of two complementary fluorescence signatures (ICG-<sup>99m</sup>Tc-nanocolloid and fluorescein) via a so-called multispectral fluorescence imaging approach. In a pilot study in ten patients the hybrid tracer could be

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used for sentinel node visualization, whereas the visible dye fluorescein could be used as a lymphangiographic agent highlighting the ducts running to the hybrid tracer-stained sentinel node(s). Results from this study showed that intraoperative multispectral imaging is clinically feasible.

Alternative to optimization of the fluorescence imaging technologies, optimization of gamma imaging modalities can be explored. In [chapter 10](#) the introduction of a navigation technology for surgical guidance is presented. With this navigation technology, using augmented- and virtual-reality, preoperative imaging information is made directly available to the surgeon in the operation theatre. Using this set-up, an average error of  $8.0 \pm 2.1$  and  $8.5 \pm 5.4$  mm in the coronal and saggital/axial plane was found when navigating the conventional gamma probe in 3D preoperative SPECT/CT images to the sentinel node in the groin (n=5 patients).

Hybrid imaging modalities capable of detecting both signatures may further enhance the clinical application of hybrid tracers. [Chapter 11](#) describes the evaluation of a modality that allows combined radio- and fluorescence tracing. The feasibility of the prototype opto-nuclear probe for combined radio- and fluorescence-guided sentinel node identification was demonstrated ex vivo in clinical (non)sentinel node samples (n=150), and in a pilot study in patients with head-and-neck malignancies or penile cancer (n=9). Of the 20 sentinel nodes that were intraoperatively evaluated, the prototype opto-nuclear probe detected the radio- and fluorescence signal in all nodes. Fluorescence tracing could be performed under ambient light conditions.

The general conclusion from **part three** of this thesis is that the introduction of novel imaging modalities, or the improvement of current existing hardware, required for radio- and/or fluorescence-guided surgery has the potential to further refine currently existing surgical procedures. The above-described studies all present pilot studies though, of which the results will have to be validated in larger, preferably multicenter, studies.

## OUTLOOK

In the **outlook**, [chapter 12](#), we describe how we envision the hybrid approach for sentinel node biopsy of prostate cancer in the near future. Although this chapter is focused on sentinel node biopsy for prostate cancer, the same approach can easily be translated to other malignancies and targets, e.g. nerves. Via the introduction of navigation technologies, in the hybrid guidance concept the preoperative imaging information can be directly linked to the findings in the operation theatre. Additionally, the introduction of (novel) gamma and fluorescence imaging technologies can help to further optimize intraoperative sentinel node identification. When reaching beyond proof-of-principal studies, integrated use of the proposed technologies (**part three**) in combination with (hybrid) tracers (**part one and two**) can result in new surgical treatment paradigms.