Sentinel node procedure in prostate and bladder cancer utilizing Differential Magnetometry: A first patient trial

L. Molenaar[a*], M.M. van de Loosdrecht[a], J. van Baarlen[b], I.A.M.J. Broeders[c,d], B. ten Haken[a] and H. Roelink[e]

[a] *Magnetic Detection & Imaging group, Faculty of Sience and Technology, University of Twente, Enschede, The Netherlands*
[b] *Department of Pathology, LabPON Hengelo, Hengelo, The Netherlands*
[c] *Department of Surgery, Meander Medical Centre, Amersfoort, The Netherlands*
[d] *Robotics and Mechatronics, Faculty Electrical Engineering, Mathematics and Computer Science, University of Twente, Enschede, The Netherlands*
[e] *Department of Urology, ZGT Almelo, Almelo, The Netherlands*
[*] *Corresponding author, email: l.molenaar@utwente.nl*

Most patients diagnosed with a primary tumor receive local radical tumor and lymph node resection. An alternative treatment is the sentinel node biopsy (SNB), which has the potential to map otherwise missed lymph nodes and decrease over-treatment. A first clinical test will be performed on patients diagnosed with a primary prostate or bladder tumor. The primary goal of this trial is to create an improved lymph node mapping by using a CE-approved magnetic tracer. The secondary goal is to compare an existing magnetic detector with a newly developed magnetic handheld detector.

I. Introduction

I.I. Medical background

Patients diagnosed with a primary prostate or bladder tumor, but without visible metastases on PET-CT, can still have occult metastases in local lymph nodes. To discover and possibly counter this, a pelvic lymph node dissection is currently performed in The Netherlands in patients with increased risk of metastases [1]. The same pelvic lymph nodes are resected for both prostate and bladder tumor patients. The radical pelvic lymph node resection consist of the following areas: fibro fatty tissue along the external iliac vein up to the deep circumflex vein and the femoral canal (distal limit), up to and including the bifurcation of the common iliac artery (proximal limit), the pelvic sidewall and medial dissection limit is defined by perivesical fat (lateral limit) and lymph nodes along the internal iliac artery [1]. Known disadvantages of this radical lymph node resection are missed lymph nodes during resection, over-treatment (60-96% [2, 3]), and missed metastases during histopathological analysis.

A sentinel node biopsy (SNB) procedure can potentially overcome these drawbacks. In the current SNB procedure for patients with primary breast cancer, a radioactive tracer is used. However, the use of this tracer is associated with strict rules and regulations, hampering availability for hospitals.

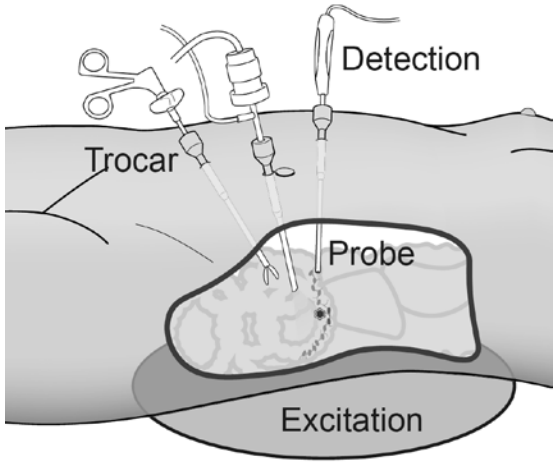

Figure 1: *Novel laparoscopic probe for magnetic sentinel node biopsy. Excitation and detection part of the system are separated to improve depth sensitivity.*

Recently a radiation-free alternative, Magtrace® (Endomagnetics Ltd, UK), a superparamagnetic iron oxide nanoparticle (SPION) tracer, was developed in combination with the SentiMAG® (Endomagnetics Ltd, UK) detector for human use [4]. When the SPIONs are injected before the operation, it is possible to map the draining lymph nodes with an MRI-scan. The SentiMAG® can be used during surgery to assist with finding the seen lymph nodes on the scan. However, this device has two crucial downsides: First, it is impossible to use the device in combination with metal surgical instruments. Second, it is not only sensitive to

SPIONs but also to the diamagnetic human tissue which limits the sensitivity and requires time-consuming balancing [5]. Differential Magnetometry (DiffMag), a new magnetic measurement technique was developed by our group to overcome these drawbacks, by detecting at the specific magnetic signature of SPIONs.

I.II. Technical background

This DiffMag technique utilizes nonlinear properties of SPIONs, similar to Magnetic Particle Imaging (MPI) and Magnetic Particle Spectroscopy (MPS). The main differences are that we use a smaller AC amplitude (± 1 mT) and measure in the time domain instead of harmonic spectra. Our technique negates the magnetic field of the human body and stationary metal (surgical) instruments, making it a selective measurement for SPIONs. In contradiction to the SentiMAG® detector, stationary surgical steel can be used in close proximity to the detection probe, making DiffMag easier to use in clinical practice. A handheld probe based on our DiffMag principle was developed that contains both excitation and detection coils for use in open surgery [6].

In the Netherlands, most prostate/bladder surgeries are performed laparoscopically. However, in laparoscopic surgery, the diameter of the probe is restricted by the use of standard trocars. The depth sensitivity of a coil is determined by the diameter of the coil, according to Biot-Savart law. As a result, making the handheld probe smaller would result in inadequate depth sensitivity, making it impossible to find sentinel nodes in laparoscopic surgery. This problem is solved by separating the excitation and detection part of the DiffMag handheld system. The excitation coils will be large and placed underneath the patient, as shown in Fig. 1. The detection coils can be small enough to fit through standard laparoscopic trocars (12 mm). A first laparoscopic prototype has been developed on this principle. However, it is still too early to use in a first clinical trial. For this reason, a first clinical test will be executed with the Diffmag handheld probe for open surgery. Both probes are based on the same physical principle, ensuring the usability of the results for this trial for the further development of the laparoscopic probe.

I.III. Objectives

The primary goal of this trial is to map normally missed high risk lymph nodes during standard laparoscopic pelvic lymph node dissection. The draining lymph nodes will be visualized through the use of Magtrace® and a preoperative MRI-scan. In the ideal situation the physician would have the means to detect the Magtrace® absorbed lymph nodes during the operation. However, as explained no laparoscopic magnetic detector is yet available. For this reason the secondary goal of this study is to compare *ex vivo* our DiffMag detector with the SentiMAG®. It is our hypothesis that the new DiffMag detector is at least as accurate as the SentiMAG® when identifying lymph nodes.

II. Material and Methods

II.I. Study design

This is a prospective, interventional, single center pilot trial. Twenty patients with a primary prostate or bladder tumor will be included. One day before surgery, Magtrace® will be injected around the tumor under ultrasound guidance, followed by an MRI-scan to pre-operatively localize the draining SNs. After resection of the tumor and lymph nodes, first the DiffMag probe will be used for *ex vivo* detection of the SN, followed by the SentiMAG®. The results of both devices will be compared, in order to validate the new DiffMag technique. This research aims to increase the detection rate of tumor draining lymph nodes and prove the efficacy of the DiffMag technique.

III. Results

Before the proposed study can start, permission of the Dutch Medical Ethical Committee is obligatory. All the necessary documents are finished and submitted, approval is expected soon. This study is planned to start in April 2019.

IV. Conclusions

This clinical patient trial will give the physician a more complete map of the draining lymph nodes. It would be ideal for the physician to measure SPIONs in the lymph nodes real-time, not just beforehand based on a MRI-scan. To further our laparoscopic DiffMag prototype, we use the secondary goal of this research as input for the further development. Since most prostate/bladder operations are performed laparoscopically, a magnetic detector fit for a trocar is mandatory. The DiffMag technique will enable us to decrease the diameter of the probe while maintaining an acceptable detection depth.

ACKNOWLEDGEMENTS

Financial support from the Netherlands Organization for Scientific Research (NWO), under the research program Magnetic Sensing for Laparoscopy (MagLap) with project number 14322 is gratefully acknowledged.

REFERENCES

1. Briganti, A., et al., *Updated nomogram predicting lymph node invasion in patients with prostate cancer undergoing extended pelvic lymph node dissection: the essential importance of percentage of positive cores.* Eur Urol, 2012. **61**(3): p. 480-7.
2. Cagiannos, I., et al., *A preoperative nomogram identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer.* J Urol, 2003. **170**(5): p. 1798-803.
3. Brouwer, O., et al., *De schildwachtklierprocedure bij prostaatkanker.* Tijdschrift voor Urologie, 2012. **2**(4): p. 84-91.
4. Winter, A., J. Woenkhaus, and F. Wawroschek, *A Novel Method for Intraoperative Sentinel Lymph Node Detection in Prostate Cancer Patients Using Superparamagnetic Iron Oxide Nanoparticles and a Handheld Magnetometer: The Initial Clinical Experience.* Annals of Surgical Oncology, 2014. **21**(13): p. 4390-4396.
5. Pouw, J.J., et al., *Phantom study quantifying the depth performance of a handheld magnetometer for sentinel lymph node biopsy.* Physica medica, 2016. **32**(7): p. 926-931.
6. Waanders, S., et al., *A handheld SPIO-based sentinel lymph node mapping device using differential magnetometry.* Physics in Medicine and Biology, 2016. **61**(22): p. 8120.