available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Francesco Montorsi and Giorgio Gandaglia on pp. 999–1000 of this issue

Optimisation of Fluorescence Guidance During Robot-assisted Laparoscopic Sentinel Node Biopsy for Prostate Cancer

Gijs H. KleinJan [a,b,†], Nynke S. van den Berg [a,c,†], Oscar R. Brouwer [a,d], Jeroen de Jong [e], Cenk Acar [f], Esther M. Wit [c], Erik Vegt [b], Vincent van der Noort [g], Renato A. Valdés Olmos [a,b], Fijs W.B. van Leeuwen [a,c], Henk G. van der Poel [c,]*

[a] *Interventional Molecular Imaging Laboratory, Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands;* [b] *Department of Nuclear Medicine, The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands;* [c] *Department of Urology, The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands;* [d] *Department of Urology, Leiden University Medical Center, Leiden, The Netherlands;* [e] *Department of Pathology, The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands;* [f] *Acibadem University School of Medicine, Department of Urology, Istanbul, Turkey;* [g] *Department of Biometrics, The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands*

Article info

Article history:
Accepted July 14, 2014

Keywords:
Fluorescence-guided surgery
Radio-guided surgery
Image-guided surgery
Sentinel (lymph) node
Prostate cancer
Hybrid tracer
Hybrid approach

Abstract

Background: The hybrid tracer was introduced to complement intraoperative radiotracing towards the sentinel nodes (SNs) with fluorescence guidance.
Objective: Improve in vivo fluorescence-based SN identification for prostate cancer by optimising hybrid tracer preparation, injection technique, and fluorescence imaging hardware.
Design, setting, and participants: Forty patients with a Briganti nomogram–based risk >10% of lymph node (LN) metastases were included. After intraprostatic tracer injection, SN mapping was performed (lymphoscintigraphy and single-photon emission computed tomography with computed tomography (SPECT-CT)). In groups 1 and 2, SNs were pursued intraoperatively using a laparoscopic gamma probe followed by fluorescence imaging (FI). In group 3, SNs were initially located via FI. Compared with group 1, in groups 2 and 3, a new tracer formulation was introduced that had a reduced total injected volume (2.0 ml vs 3.2 ml) but increased particle concentration. For groups 1 and 2, the Tricam SLII with D-Light C laparoscopic FI (LFI) system was used. In group 3, the LFI system was upgraded to an Image 1 HUB HD with D-Light P system.
Intervention: Hybrid tracer-based SN biopsy, extended pelvic lymph node dissection, and robot-assisted radical prostatectomy.
Outcome measurements and statistical analysis: Number and location of the preoperatively identified SNs, in vivo fluorescence-based SN identification rate, tumour status of SNs and LNs, postoperative complications, and biochemical recurrence (BCR).
Results and limitations: Mean fluorescence-based SN identification improved from 63.7% (group 1) to 85.2% and 93.5% for groups 2 and 3, respectively ($p = 0.012$). No differences in postoperative complications were found. BCR occurred in three pN0 patients.
Conclusions: Stepwise optimisation of the hybrid tracer formulation and the LFI system led to a significant improvement in fluorescence-assisted SN identification. Preoperative SPECT-CT remained essential for guiding intraoperative SN localisation.
Patient summary: Intraoperative fluorescence-based SN visualisation can be improved by enhancing the hybrid tracer formulation and laparoscopic fluorescence imaging system.

† Gijs H. KleinJan and Nynke S. van den Berg contributed equally to the study and share first authorship.
* Corresponding author. Department of Urology, The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX, Amsterdam, The Netherlands. Tel. +31 (0) 20 512 2553; Fax: +31 (0) 20 512 2550.
E-mail address: h.vd.poel@nki.nl (H.G. van der Poel).

http://dx.doi.org/10.1016/j.eururo.2014.07.014
0302-2838/

1. Introduction

Sentinel node (SN) biopsy using a radioactive tracer was introduced for prostate cancer (PCa) to minimise the extent of the pelvic lymph node (LN) dissection (PLND) while retaining diagnostic accuracy [1]. The concept behind SN biopsy is to identify the LNs that are most likely to contain metastatic cells in case migration from the primary prostate tumour has occurred, the so-called SNs. Visualisation of this direct drainage pathway transcends the anatomic location of the SN. Therefore, this technique also enables the identification of potential tumour-bearing LNs outside the extended PLND (ePLND) template [2,3] that would otherwise have been missed. When performing SN biopsy in combination with an ePLND, improved lymphatic staging can be achieved; pathologists can evaluate the SNs more extensively, decreasing the possibility of sampling errors, which can result in improved diagnostic accuracy [4,5].

Since its introduction, the procedure has been subject to various refinements. In the past 15 yr, the surgical technique has shifted from a mainly open procedure to a laparoscopic and later a robot-assisted procedure. For preoperative SN mapping, following the injection of a radioactive tracer, lymphoscintigrams are taken. The introduction of single photon emission computed tomography with computed tomography (SPECT-CT) resulted in improved anatomic SN localisation, allowing better planning of the operation and reducing operative time [6].

To date, intraoperative SN identification is based primarily on the use of a (laparoscopic) gamma probe (LGP; radio-guided approach). The recent introduction of fluorescence imaging (FI) during surgery was shown to aid the surgeon in optical, fluorescence-based, visualisation of the SNs [7,8]. Yet, the limited penetration depth of the near-infrared fluorescent dye indocyanine green (ICG; < 1.0 cm) prohibits preoperative SN mapping, meaning that during surgery meticulous scanning of, and beyond, the entire ePLND template is required [2,6]. This exploration is extensive and time-consuming and may potentially miss SNs. Hence, the use of ICG is often combined with radiocolloid-based preoperative SN mapping methods [8]. To facilitate the integrated use of preoperative imaging with fluorescence guidance, we introduced the hybrid tracer ICG-^{99m}Tc-nanocolloid [6]. Being both radioactive and fluorescent, a single ICG-^{99m}Tc-nanocolloid administration allows for preoperative SN mapping as well as intraoperative fluorescence guidance to these exact hotspots. In our previous studies, the hybrid nature of this tracer was shown to complement the radio-guided approach and outperformed blue dye [9,10].

Following our initial feasibility study in PCa [11], 40 additional PCa patients were included. In these patients, we systematically evaluated whether optimisation of the tracer formulation and FI hardware improvements could help increase in vivo fluorescence-based SN identification during robot-assisted laparoscopic procedures.

2. Methods

2.1. Patients

Between December 2010 and July 2013, 40 patients with localised PCa and a Briganti nomogram–estimated risk >10% of LN metastases were included after informed consent was obtained. Patients were scheduled for robot-assisted radical prostatectomy (RARP) and SN biopsy followed by an ePLND. The first nine patients were included under registration of the feasibility study (N09IGF), and the patient population was completed through off-label use of the hybrid tracer.

Three groups were formed for statistical analysis. In group 1 ($n = 11$; December 2010–April 2011), the previously described hybrid tracer preparation [11] and the Tricam SLII with D-Light C laparoscopic fluorescence imaging (LFI) system (KARL STORZ GmbH & Co. KG, Tuttlingen, Germany) was used. In group 2 ($n = 13$; April 2011–November 2012), the particle concentration was increased, and the injected volume decreased. In group 3 ($n = 16$; December 2012–July 2013), the tracer formulation was identical to that used in group 2, but an upgraded LFI system (Image 1 HUB HD with D-Light P system KARL STORZ GmbH & Co. KG) was introduced.

2.2. Tracer preparation

Two different tracer formulations were used. In group 1, we prepared the hybrid tracer as previously described (0.4 ml in the syringe; referred to as the *previously described tracer formulation*) [11]. In groups 2 and 3, we used the new tracer formulation.

The new tracer formulation was prepared as follows: ^{99m}Tc-nanocolloid was made by adding 2.0 ml pertechnetate (approximately 300 MBq) to a vial of nanocolloid (GE Healthcare, Eindhoven, The Netherlands). ICG-^{99m}Tc-nanocolloid was then formed by adding 0.05 ml (0.25 mg) of ICG solution (5.0 mg/ml; PULSION Medical, Feldkirchen, Germany) to the vial. After in situ formation of ICG-^{99m}Tc-nanocolloid, the tracer was subtracted from the vial and diluted with saline to a total volume of 2.0 ml in the syringe.

Procedures were performed in accordance with the Dutch guidelines for good manufacturing practice and with approval of the local pharmacist.

2.3. Tracer injection

The hybrid tracer was injected transrectally into the peripheral zone of each quadrant of the prostate under ultrasound guidance [11]. In group 1, four deposits of 0.1 ml ICG-^{99m}Tc-nanocolloid were given. After each injection, the needle was flushed with 0.7 ml saline (total injected volume: 3.2 ml). In groups 2 and 3, patients received four deposits of 0.5 ml ICG-^{99m}Tc-nanocolloid (total injected volume: 2.0 ml).

2.4. Preoperative sentinel node mapping

Static planar lymphoscintigraphy was performed 15 min and 2 h after injection, followed by a SPECT and low-dose CT scan (Symbia T; Siemens Healthcare, Erlangen, Germany). SPECT and low-dose CT images were fused, and a three-dimensional (3D) SPECT-CT–based volume-rendering reconstruction was created using OsiriX medical imaging software (Pixmeo, Geneva, Switzerland). Images were analysed by an experienced nuclear medicine physician according to previously described criteria [12].

2.5. Surgical procedure

Operations were performed by HGvdP using the da Vinci S Surgical system (Intuitive Surgical Inc., Sunnyvale, CA, USA). Patients first underwent SN biopsy, followed by ePLND and RARP.