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Surgery in Motion

Multispectral Fluorescence Imaging During Robot-assisted Laparoscopic Sentinel Node Biopsy: A First Step Towards a Fluorescence-based Anatomic Roadmap

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Abstract

Background: During (robot-assisted) sentinel node (SN) biopsy procedures, intraoperative fluorescence imaging can be used to enhance radioguided SN excision. For this combined pre- and intraoperative SN identification was realized using the hybrid SN tracer, indocyanine green–^{99m}Tc-nanocolloid. Combining this dedicated SN tracer with a lymphangiographic tracer such as fluorescein may further enhance the accuracy of SN biopsy.
Objective: Clinical evaluation of a multispectral fluorescence guided surgery approach using the dedicated SN tracer ICG^{99m}Tc-nanocolloid, the lymphangiographic tracer fluorescein, and a commercially available fluorescence laparoscope.
Design, setting, and participants: Pilot study in ten patients with prostate cancer. Following ICG^{99m}Tc-nanocolloid administration and preoperative lymphoscintigraphy and single-photon emission computed tomograpy imaging, the number and location of SNs were determined. Fluorescein was injected intraprostatically immediately after the patient was anesthetized. A multispectral fluorescence laparoscope was used intraoperatively to identify both fluorescent signatures.
Surgical procedure: Multispectral fluorescence imaging during robot-assisted radical prostatectomy with extended pelvic lymph node dissection and SN biopsy.
Measurements: (1) Number and location of preoperatively identified SNs. (2) Number and location of SNs intraoperatively identified via ICG^{99m}Tc-nanocolloid imaging. (3) Rate of intraoperative lymphatic duct identification via fluorescein imaging. (4) Tumor status of excised (sentinel) lymph node(s). (5) Postoperative complications and follow-up.
Results and limitations: Near-infrared fluorescence imaging of ICG^{99m}Tc-nanocolloid visualized 85.3% of the SNs. In 8/10 patients, fluorescein imaging allowed bright and accurate identification of lymphatic ducts, although higher background staining and tracer washout were observed. The main limitation is the small patient population.
Conclusion: Our findings indicate that a lymphangiographic tracer can provide additional information during SN biopsy based on ICG^{99m}Tc-nanocolloid. The study suggests that multispectral fluorescence image–guided surgery is clinically feasible.
Patient summary: We evaluated the concept of surgical fluorescence guidance using differently colored dyes that visualize complementary features. In the future this concept may provide better guidance towards diseased tissue while sparing healthy tissue, and could thus improve functional and oncologic outcomes.

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1. Introduction

Fluorescence imaging is rapidly finding its way into the operating theatre. A wide spectrum of fluorescent tracers has already been explored in clinical (first-in-human) studies as either free dye or a dye-functionalized targeting agent [1]. In the field of urology, fluorescence guidance has amongst others been used for sentinel node (SN) biopsy of prostate cancer [2,3]. For this procedure, the near-infrared (NIR) fluorescent dye indocyanine green (ICG), especially in the form of the hybrid tracer ICG–^{99m}Tc-nanocolloid, was shown to enhance the more traditional radioguided ^{99m}Tc-nanocolloid-based SN biopsy procedure [4–6].

During the widely applied radioguided SN biopsy procedure of for example melanoma and breast cancer intraoperatively blue dye is injected to allow the surgeon to optically define the lymphatic flow (lymphangiography) of a tumor; here lymphangiographic tracers such as blue dye help to visualize the lymphatic ducts that run from the injection site to the SN [7,8]. As alternatives to blue dye, the visible fluorescent dye fluorescein and the NIR fluorescent dye ICG in its free form have been used [4,9–11]. While the fluorescent alternatives provide enhanced detection sensitivity compared to blue dye, their detection can be complex in combination with ICG^{99m}Tc-nanocolloid. In this context, the concept of multicolor, or multispectral, fluorescence imaging can provide a solution.

Multispectral imaging involve concurrent use of multiple fluorescent dyes to highlight various molecular, physiological, and/or anatomic features [12,13]. Factors critical in achieving successful multispectral imaging guidance are: (1) the clinical availability of fluorescence tracers that do not spectrally overlap (eg fluorescein and ICG exhibit maximum emission at 515 and 820 nm, respectively); and (2) a fluorescence camera capable of detecting different fluorescence emissions. It should be noted that some of the currently available NIR fluorescence laparoscopes designed for combined use with ICG have evolved from laparoscopes developed for photodynamic diagnostics, which detects fluorescence emitted in the visual range [14].

In this study we investigated if intraoperative lymphangiography with fluorescein can provide additional guidance during ICG^{99m}Tc-nanocolloid-based SN biopsy for prostate cancer. To this end we required intraoperative multispectral imaging. Hence, the secondary aim of the study was to prove the clinical feasibility of intraoperative multispectral fluorescence imaging.

2. Patients and methods

2.1. Preclinical evaluation of fluorescein as an angiographic agent

Initial preclinical experiments using fluorescein are described and discussed in the Supporting material.

2.2. Clinical evaluation of the multispectral fluorescence imaging approach

2.2.1. Patients

Between October 2013 and August 2015, ten patients with intermediate- or high-risk prostate cancer with a > 5% risk of lymph node metastases as estimated using the Briganti nomogram [15] were included in a clinical study approved by the local medical ethics committee (Dutch trial register NTR4451) after they provided written informed consent.

Patients were scheduled for robot-assisted radical prostatectomy (RARP) and SN biopsy followed by extended pelvic lymph node dissection (ePLND). The patient characteristics are shown in Table 1.

2.2.2. Preoperative procedure

A detailed description of ICG^{99m}Tc-nanocolloid preparation, the injection procedure, and preoperative imaging approach is provided in the Supplementary material. In brief, ICG^{99m}Tc-nanocolloid (mean

Table 1 – Patient characteristics, pathology and follow-up

	Age (yr)	Preoperative data				Postoperative data and pathology					Complications [a]	BCR PSA (ng/ml)	Adjuvant therapy	FU (mo)
		PSA (ng/ml)	Prostate size (cm^3)	Stage	Biopsy GS	pTNM, pR	GS	SNs (*n*)	LNs (*n*)	T$^+$ SNs/LNs (*n*)				
1	57	7.4	11	cT3bN0M0	3 + 4	pT3aN0 Mx, pR0	3 + 4	4	10	0/0	–	0.12 (at 4.5 mo)	RTX + HTX	26
2	73	3.4	19	cT3aN0M0	3 + 4	pT2cN0 Mx, pR0	3 + 4	5	13	0/0	–	-	-	24
3	68	12.7	25	cT2cN0M0	3 + 5	pT4aN1M1a, pR0	3 + 5	3	22	3/18	–	4.95 (at 2 mo)	HTX	27
4	69	10.8	37	cT2aN0M0	3 + 4	pT2cN0 Mx, pR0	3 + 4	1	6	0/0	–	-	-	25
5	68	5.2	92	cT3aN0M0	4 + 5	pT2cN0 Mx, pR0	3 + 3	9	11	0/0	–	-	-	20
6	68	15.0	37	cT2bN0M0	4 + 3	pT3aN0 Mx, pR0	3 + 5	4	11	0/0	–	-	-	18
7	70	9.4	52	cT2aN0M0	4 + 3	pT2cN0 Mx, pR0	4 + 3	6	12	0/0	–	-	-	16
8	66	6.3	44	cT1cNxMx	3 + 4	pT2cN1 Mx, pR0	3 + 4	1	19	0/1	I	-	-	14
9	66	9.4	40	cT3aN0M0	3 + 4	pT2aN1M0, pR1	3 + 4	7	17	2/17	II	-	-	14
10	65	6.6	70	cT2cN0M0	3 + 4	pT3aN0 Mx, pR0	3 + 4	12	11	0/0	–	Unknown [b]	Unknown [b]	Unknown [b]
Mean	67	8.6	55.6					5.2	13.2					
Total								52	132	5/36				

PSA = prostate specific antigen; GS = Gleason score; SNs = sentinel nodes; LNs = lymph nodes; T$^+$ = tumor-positive; BCR = biochemical recurrence; RTX = radiotherapy; HTX = hormonal therapy.
[a] Clavien-Dindo grade.
[b] Patient follow-up elsewhere.

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