

Image-guided cancer surgery : the value of near-infrared fluorescence imaging during oncologic and gastrointestinal procedures Verbeek, F.P.R.

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Chapter 8

Optimization of sentinel lymph node mapping in bladder cancer using near-infrared fluorescence imaging

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ABSTRACT

Background and objectives

Unlike other cancers, the Sentinel Lymph Node (SLN) procedure in bladder cancer requires special attention to the injection technique. The aim of this study was to assess feasibility and to optimize tracer injection technique for SLN mapping in bladder cancer patients using NIR fluorescence imaging.

Methods

Twenty patients with invasive bladder cancer scheduled for radical cystectomy were prospectively enrolled. Indocyanine green (ICG) bound to human serum albumin (complex ICG:HSA; 500 μ M) was injected peritumourally to permit SLN mapping. ICG:HSA was first administrated serosally (*n*=5), and subsequently mucosally by cystoscopic injection (*n*=15). In the last cohort of 12 patients treated with cystoscopic injection, the bladder was kept filled with saline for at least 15 minutes.

Results

Fluorescent lymph nodes were observed only in the patient group with cystoscopic injection of ICG:HSA. Filling of the bladder post-injection was of added value to promote drainage of ICG:HSA to the lymph nodes, and in 11 of these 12 patients (92%) one or more NIR fluorescent lymph nodes were identified.

Conclusions

The current study demonstrates proof-of-principle of using NIR fluorescence imaging for SLN identification in bladder cancer. Cystoscopic injection with distension of the bladder appears optimal for SLN mapping.

INTRODUCTION

Pelvic lymph node dissection is the standard-of-care for surgical management of muscle-invasive bladder cancer. Lymph node dissection is both of therapeutic and prognostic value as patients with tumour involvement in the lymph nodes have a higher risk of developing disease progression^{1,2}. Over the last few decades, the sentinel lymph node (SLN) concept has been introduced to provide as a less invasive technique for nodal staging compared to lymphadenectomy. SLN biopsy has proven to be feasible and safe in breast cancer, penile cancer, and melanoma for selecting patients who would benefit from lymphadenectomy³⁻⁵. Moreover, SLN mapping has also been suggested as a tool to improve nodal staging by selecting lymph nodes for ultrastaging using serial sectioning and additional immunohistochemistry or reverse transcriptase (RT)-PCR⁶. Though, to date little evidence is available concerning the value of SLN mapping in the management of bladder cancer patients.

The feasibility of the SLN procedure in bladder cancer has been assessed in only a few clinical studies⁷⁻¹². The largest study was able to detect the SLN in 65 out of 75 patients (87%), with a false-negative rate of 6 out of 32 patients (19%)⁷. These results are lagging behind results obtained with SLN biopsy in patients with penile cancer or melanoma^{3,4}. In studies exploring SLN mapping in bladder cancer, only conventional SLN tracers were used, such as radioactive colloids, blue dye, or a combination of both. However, radioactive colloids require the involvement of a nuclear physician and blue dye has been found less sensitive in bladder cancer and flows rapidly to 2^{nd} -tier lymph nodes⁷.

More recently, fluorescence guided surgery has been introduced, and is a rapidly emerging intraoperative imaging modality in the field of urology for identification of tumour tissue, vital structures (e.g. ureters), and for SLN mapping¹³⁻¹⁶. The use of near-infrared (NIR) fluorescence imaging has several advantages, such as a relatively high tissue penetration and low autofluorescence, which makes it possible to detect low concentrations of tracer deeper (i.e., millimetres) into tissue¹⁷⁻¹⁹. As NIR light, with a wavelength between 700-900 nanometres, is invisible to the human eye, NIR fluorescence does not alter the surgical field. Using the clinically-available NIR fluorescence tracer Indocyanine green (ICG), this technique has been successfully used in the clinic for several types of cancer²⁰⁻²².

In bladder cancer, NIR fluorescence imaging has been evaluated in large animals in which different tracers and injection techniques were assessed to optimize fluorescence SLN mapping²³. Though, the fluorescent lymphatic tracers used (HSA800 and fluorescent quantum dots) are currently not clinically available, and results overall were not as promising as in other cancers. The aim of current study is to assess the feasibility of NIR fluorescence SLN mapping in bladder cancer patients and to optimize tracer injection by testing various administration techniques in a clinical trial setting.

MATERIALS AND METHODS

This study was approved by the Medical Ethics Committee of the Leiden University Medical Centre and was performed in accordance with the ethical standards of the Helsinki Declaration of 1975. This study is registered in the Dutch Trial Register as NTR3657. All patients with invasive bladder cancer planned for radical cystectomy at the Leiden University Medical Center were eligible for inclusion. Exclusion criteria were pregnancy, lactation, or an allergy to iodine or ICG. The trial was performed between May 2010 and February 2014. All enrolled patients gave informed consent and were anonymized.

Tracer Preparation

ICG (25-mg vials, Pulsion Medical Systems, Munich, Germany) was resuspended in 10 cc of sterile water. ICG was mixed with human serum albumin (HSA) to form the ICG:HSA complex. To obtain a concentration of 500 μ M of ICG, 7.8 mL of the 3.2 mM ICG solution was diluted in 42.8 ml of Cealb (20% HSA, Sanquin, Amsterdam, The Netherlands) to create the preparation ICG:HSA. A dose of 500 μ M was chosen based on previous dose optimization studies in other cancers²⁴.

Surgical Technique

In addition to the planned cystectomy, patients received the NIR fluorescent tracer ICG:HSA to permit NIR SLN mapping. To optimize the technique, different injection methods were assessed in consequetive series. First, ICG was injected around the tumour (500 μ M, 4 deposits of 0.5 ml) directly into the bladder wall (serosa) after laparotomy (n = 5). Subsequently ICG (500 μ M, 4 deposits of 0.5 ml) was injected cystoscopically (n = 15) around the tumour into the bladder wall (mucosa) directly before surgery. In the last twelve cases the bladder was filled using saline for at least 15 minutes after cystoscopic injection of ICG:HSA to provide moderate bladder distension, which could promote lymphatic drainage. The study protocol is presented schematically in Figure 1.

In all but one patient, extended bilateral exploration of the lymphatic regions draining the bladder was performed before cystectomy. The one patient in whom no lymphadenectomy was performed suffered from non-muscular invasive papillary urothelial carcinoma and synchronous prostate cancer with clinically low risk for positive lymph nodes, which was not an indication for lymphadenectomy. Moreover, suspected lymph nodes outside the lymphadenectomy region were also resected and sent for pathology.

Directly before and during lymphadenectomy, SLN mapping was performed using the Mini-Fluorescence-Assisted Resection and Exploration (Mini-FLARE) camera system as described previously²⁴. SLNs were defined as fluorescent lymph nodes draining from the bladder that could be identified using the Mini-FLARE camera system. Fluorescent hotspots identified intraoperatively or after lymphadenectomy in the resection specimen were sent separately to pathology. Excised fluorescent hotspots and lymphadenectomy specimens were analysed by the pathologist using hematoxylin and eosin staining as per the standard of care.



Figure 1 - Clinical Trial Protocol

1. The tracer ICG:HSA is administered either serosally after laparotomy or cystoscopically into the mucosa. In one cohort of patients, the bladder was distended with saline after cystoscopic injection of ICG:HSA. 2. During lymphadenectomy, the Mini-FLARE imaging system was used for in vivo identification of NIR fluorescent lymphatic vessels and lymph nodes. 3. After resection of NIR fluorescent lymph nodes (SLN) and further lymph node dissection (LND), all tissue was assessed ex vivo using Mini-FLARE to identify possible additional NIR fluorescent lymph nodes. 4. Fluorescent nodes and the lymphadenectomy specimen were sent separately for pathological examination.

RESULTS

Patient characteristics

Patient characteristics and surgical results are presented in Table 1. In total 20 patients with invasive bladder carcinoma were included in this study. Fourteen patients were male, median age was 72 years (range, 47 - 77), median body mass index (BMI) was 26 kg/m² (range, 18 - 40). All patients were clinically staged with muscle invasive disease based on preoperative biopsy. Three patients had a history of radiotherapy to the pelvic area because of invasive bladder cancer (N = 2) or cervical cancer (N = 1). Median tumour size was 38 mm (range, 17 - 93) with tumour invasion stages ranging from T2 to T4. In 3 patients, that were staged as a cT2, no residual tumour was found after resection by pathology. In case a bilateral lymphadenectomy was performed an average of 14 ± 9.1 lymph nodes were resected. In 4 patients tumour-positive lymph nodes were detected during pathological examination. According to the Dutch guidelines, patients did not recieive (neo)adjuvant chemotherapy. No adverse reactions associated with the use of ICG:HSA were observed.

Sentinel lymph node mapping

Different injection strategies were consequetevely evaluated in bladder cancer patients to find the most promising technique. ICG:HSA was administered using abdominal serosal injection in cases 1-5. Though, as these procedures were failing, cystoscopic muscosal injection was applied in the latter 6-20 cases. From case 9 till 20, bladder distension using saline was also applied after tracer injection.

Abdominal serosal injection (cases 1-5): In none of the five patients receiving ICG:HSA by subserosal injection after laparotomy a fluorescent node was observed either *in vivo* or in the resection specimen. In one patient, a possible NIR fluorescent lymphatic vessel was observed. No tumour-positive nodes were detected during pathological examination.

Cystoscopic mucosal injection without bladder distension (cases 6-8): In one out of three patients a single fluorescent lymph node was identified and denominated as a SLN. However, in this patient the fluorescent node was tumour-negative whereas other resected lymph nodes were tumour-positive. No fluorescent lymphatic channels were observed.

Cystoscopic mucosal injection with distension of the bladder (cases 9-20): After cystoscopic mucosal injection and filling of the bladder, in 11 out of 12 cases (92%) a fluorescent node could be identified and denominated as a SLN *in vivo* (Figure 2). In these patients a median of 2.5 (range 0 - 6) SLN were identified *in vivo*. Moreover,

fluorescent lymphatic vessels could be followed to the SLN (Figure 3). In two patients, SLNs identified using NIR fluorescence contained a metastasis. No false-negative cases were observed in this group.

					, 1		
Case	Age	Gender	Tumour stage	SLNs in vivo	No. nodes resected	Tumor positive nodes	Remarks
Intra-	abdom	inal subse	rosal ICG injed	ction			
1	74	М	T3N0	0	6	0	
2	77	V	T3N0	0	4	0	
3	69	М	T1N0	0	13	0	
4	52	V	T2N0	0	15	0	
5	67	М	T0N0 (cT2) ^b	° 0	0 ^a	0	Low grade papillary urothelial carcinoma and synchronous prostate cancer
Cystos	copic s	ubmucosa	l ICG injection	n withoi	ut filling of t	the bladde	r
6	61	М	T4N1	0	1	1	SLN procedure failed, intraoperatively identified positive lymph node,
7	58	М	T4N1	1	7	1	False-negative SLN as detected by NIR fluorescence, tumour detected in a different resected node
8	66	V	T2N0	0	0	0	Previous pelvic lymphadenectomy and radiotherapy [‡]
Cystos	copic s	ubmucosa	l ICG injection	n with fi	lling of the	bladder fo	r 15 minutes with saline
9	47	М	T0N0 (cT2) ^b	' 1	25	0	
10	77	V	T2N0	3	32	0	
11	71	М	T2N0	0	9	0	Previous radiotherapy †
12	77	М	T3N0	1	5	0	
13	76	М	T2N0	1	13	0	Previous radiotherapy [†]
14	74	V	T3N1	1	13	1	Tumour positive SLN detected by NIR fluorescence
15	71	V	T2N0	3	16	0	
16	71	М	T4N0	3	7	0	
17	72	М	T2N0	6	25	0	
18	74	М	T2N1	2	9	1	Multifocal disease. Tumour positive SLN detected by NIR fluorescence
19	72	М	T2N0	4	26	0	
20	72	М	T0N0 (cT2) ^b	4	21	0	

Table 1 - Patient characteristics and sentinel lymph node detection

^a No indication for lymphadenectomy

^b Preoperative tumour stage of based on cystoscopy biopsy

Medical history of pelvic radiotherapy for † bladder cancer or for ‡ cervical cancer

ICG, indocyanine green

SLN, sentinel lymph node



Figure 2 – Intraoperative and ex vivo detection of fluorescent lymph nodes Shown are colour video (left), NIR fluorescence (middle), and a pseudo-coloured merge of the two (right). The upper row shows the intraoperative detection of two NIR fluorescent lymph nodes (arrowheads) along the left external iliac vein. In the lower row, the two NIR fluorescent lymph nodes are clearly identified using NIR fluorescence imaging after excision. Excitation fluence rate was 7.7 mW/cm2. Camera exposure times were 10 ms (upper row) and 15 ms (bottom row). Scale bar = 1 cm.



Figure 3 – NIR fluorescent identification of lymphatic vessels Shown are colour video (left), NIR fluorescence (middle), and a pseudo- coloured merge of the two (right). After exploration, the lymphatic vessel (arrow) draining to the SLN (arrowhead) is clearly identified using NIR fluorescence after injection of ICG:HSA. Excitation fluence rate was 7.7 mW/cm2. Camera exposure times were 10 ms.

DISCUSSION

This clinical study assesses different injection techniques and the feasibility of SLN mapping in bladder cancer patients using NIR fluorescence imaging. Several methods of tracer administration were consecutively evaluated. Unlike the results obtained in large animals, NIR fluorescence guided SLN mapping after abdominal serosal injection of ICG:HSA failed in all patients. As a consequence, we tested additional admin-

istration techniques. Cystoscopic injection of ICG:HSA with subsequent distension of the bladder was found to be crucial for providing drainage of the lymphatic tracer to the lymph nodes and permitted detection of the SLN in 11 out of 12 patients in this group. The positive influence of distension of the bladder on lymphatic drainage was also observed in a preclinical study in canines²³. Possible explanations could be the increased interstitial pressure as result of bladder distension, which facilitates lymphatic flow. In the current study the bladder was only filled with a volume providing moderate bladder distension, as a surplus of bladder distension can result in compression of the lymphatic vessels that hamper lymph drainage^{23,25}. During distension of the bladder no quantification of the bladder pressure was obtained. However, clear lymph drainage was visible in most of these patients. Based on these results, future studies should focus on the relationship between intraluminal bladder pressure and lymphatic flow.

Cystoscopic administration of the lymphatic tracer has multiple advantages over subserosal administration after laparotomy. Cystoscopic injection in the urothelium prior to surgery ensures intact lymphatic vessels, which can be disrupted during surgical exploration. Additionally, tracer administration during cystoscopy provides direct visualization of the location of the tumour compared to only palpation when the tracer is injected serosally after laparotomy. Moreover, injection prior to surgery allows the lymphatic tracer more time to accumulate in the SLN. These advantages of cystoscopic injection over serosal tracer injection could also be reasons no SLNs were identified in the group in which the tracer was administrated after laparotomy.

It is known that the lymphatic drainage pattern of the bladder is complex and drainage is heavily influenced by tumor location, type of tumor, and extent of the disease. Previous studies exploring feasibility of SLN mapping in bladder cancer patients used conventional techniques such as radioactive colloids and blue dye7-10. These tracers have several limitations when used for bladder cancer. Preoperative planning using radioactive colloids and lymphoscintigraphy is more difficult to use in patients with bladder cancer, as radioactivity from the primary injection site interferes with SLN visualization. Moreover, the lymphatic pattern in the pelvis is more complex and SPECT in combination with low dose CT would be necessary to transfer the preoperatively identified nodes to corresponding anatomical locations^{7,9}, which additionally increases cost. On the other hand, when blue due is administered cystoscopically prior to surgery, the long period between the injection and the start of nodal exploration allows blue dye to flow to the 2nd-tier nodes⁷. In the present study, ICG provided direct optical support and as ICG is bound to the large serum proteins in the lymphatic channels, prolonged SLN retention is expected²⁶. Moreover, this technique allows visualization of the lymphatic drainage pattern in real-time, and can therefore provide more insight in the actual drainage from pathway of the tumor. In addition, the advantage of depth penetration of NIR light, made it possible to detect lymph nodes several millimetres into the tissue without the need for ionizing radiation. When preoperative imaging (e.g. SPECT/CT) and intraoperative gamma guidance is desirable, ICG can simply be premixed with radioactive nanocolloid²⁷.

Several limitations were observed in the study. In all treatment groups there were patients in which only few lymph nodes were resected. Resection of only few lymph nodes was most likely mainly due to previous radiotherapy. Moreover, in one patient in whom no lymphadenectomy was performed suffered from non-muscular invasive papillary urothelial carcinoma and synchronous prostate cancer with clinically low risk for positive lymph nodes, which was not an indication for lymphadenectomy. In addition, one patient had a previous pelvic lymphadenectomy as part of surgery for cervical cancer; therefore no lymph nodes were found during lymphadenectomy. Though, SLN mapping was still performed to detect redirected lymphatic flow or potentially remaining lymph nodes.

One false-negative case occurred. In this case, one of the tumour-positive lymph nodes was completely filled with tumour, which could explain the impaired uptake of ICG in these nodes²⁸. Moreover, although ICG was administered cystoscopically in this patient, the bladder was not kept filled after tracer injection, which could have resulted in insufficient lymph drainage of the tracer. In previous studies in SLN biopsy in bladder cancer false-negative cases were also observed, with rates as high as 19%⁷. Due to this reported high false-negative rate, SLN biopsy in bladder cancer is not to be advised for avoiding a lymphadenectomy. Nevertheless, SLN mapping could still be a useful tool to select lymph nodes for ultrastaging (for example using RT-PCR) because ultrastaging of lymph nodes can more accurately assess lymph node status²⁹. In addition, controversy exists on the extent of lymphadenectomy and the minimum number of nodes required for adequate lymphadenectomy^{1,2,30}, as single node metastases can be located outside the obturator spaces along the common iliac and presacral areas^{12,31,32}. At this stage, we believe that SLN mapping using NIR fluorescence imaging is not able to replace the role of the lymph node dissection. However, in vivo SLN mapping can be suggested as a tool to improve assessment of lymph node status and for identifying SLNs lying outside the pre-operative planned resection, which potentially can still carry metastases. In addition, NIR fluorescence imaging can also provide a useful tool for the detection of aberrant lymphatic pathways or crossover lymphatic drainage to contralateral lymph nodes³³. Furthermore, as NIR fluorescence imaging facilitates real-time visualization of lymphatic vessels and SLNs it could also be of added value during laparoscopic lymph node assessment in high-risk patients. It is expected that the development of new imaging systems and probes, which will improve depth penetration, image sensitivity and increase retention in the SLN, will further improve NIR fluorescence image-guided surgery^{19,34}.

CONCLUSIONS

The current study demonstrates proof of principle of using ICG:HSA-based NIR fluorescence imaging for SLN identification in bladder cancer, but also identified complex issues regarding the injection technique. Cystoscopic mucosal injection with distension of the bladder appears the optimal injection technique. Using this technique a fluorescent node could be identified and denominated as a SLN *in vivo* in 11 out of 12 cases (92%). A next step in the development of this technique can be the diffuse injection of ICG in the bladder mucosa. It is expected this will result in harvesting more SLNs, and could potentially provide more insights in actual lymphatic drainage pattern and also reduce the number of false negatives cases. This feasibility study allows initiating larger clinical trials to assess sensitivity more precisely and assess which patient groups can benefit from NIR fluorescence based SLN mapping.

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