Current Applications of Near-infrared Fluorescence Imaging in Robotic Urologic Surgery: A Systematic Review and Critical Analysis of the Literature

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Herein, we provide a systematic review and critical analysis of the current evidence on the applications of near-infrared fluorescence in robotic urologic surgery. Article selection proceeded according to Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria. Overall, 14 studies were identified and included. Indocyanine green fluorescence imaging system has been tested for several applications, robotic partial nephrectomy representing the most studied one. Available evidence suggests this technology can be of aid in visually defining the surgical anatomy, thus ultimately facilitating the task of the console surgeon. Whether the added cost is justified by better outcomes remains to be determined. UROLOGY 84: 751−759, 2014.

Robotic surgery has been successfully used to address the breadth of both extirpative and reconstructive procedures within urology.[1] Fluorescence image-guided surgery may engender improved intraoperative identification of anatomic structures, providing surgeons with an enhanced view of the operative field and the potential for improved surgical outcomes.[2]

In this regard, the inclusion of near-infrared fluorescence (NIRF) using indocyanine green dye (ICG) to the robotic platform is being currently tested in different surgical specialties, including general and thoracic surgery[3,4] and gynecology.[5] ICG is a sterile Food and Drug Administration−approved water-soluble dye. Its use has been widely adopted in clinical research because of 4 favorable characteristics[3]: (1) it is confined to the vascular compartments after intravenous administration, (2) plasma life of 3-5 minutes, (3) low toxicity, and (4) can be detected with an NIRF camera.

Since Tobis et al[6] first reported on the use of NIRF with ICG in robotic partial nephrectomy (RPN), other indications have been explored in our specialty.[7] However, the role of this novel tool remains to be defined.

The objective of this study is to provide a systematic review and critical analysis of the current evidence on the applications of NIRF in robotic urologic surgery.

METHODS

A systematic literature review was performed in December 2013 using PubMed and Scopus to identify relevant studies. An update search was performed at the time of resubmission of the manuscript, in April 2014.

Two separate searches were done by applying a free-text protocol with the following search terms: "indocyanine green," "near infrared fluorescence," "robotic surgery."

Article selection proceeded according to the search strategy based on Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria (www.prisma-statement.org; Supplementary Fig. 1). Only studies describing the use of NIRF during urologic robot-assisted laparoscopic procedures were included for further screening. In addition, references from the selected articles retrieved in the search were assessed. Conference abstracts and single case reports were not included. Given the limited amount of data, studies coming from the same institution but addressing different specific issues were included.

RESULTS

Overall, 14 studies, published since 2011, were identified and included in this review. The most studied application

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Table 1. Near-infrared fluorescence in robotic partial nephrectomy: case series (LoE 4*)

Reference (Year)	Number of Cases (Malignant/Benign Histology)	RENAL Score (Range)	ICG Dose, mg	Hypofluorescence, n (%)		Histology/NIRF agreement†, %	WIT, min	PSM, %
				Malignant Histology	Benign Histology			
Tobis et al[6] (2011)	11 (10/1)	7.5 (4-9)	3 (1-5), injections × 5 (0.75-7.5)	8 (80)	NR	NR	19.3 (0-33)	0
Tobis et al[8] (2012)‡	19§ (13/6)	7.7 (4-10)‖	10.6 (5-25)‖	13 (100)	0 (0)	100	21.7 (8-37)‖	5.2
Manny et al[9] (2013)	100 (77/23)	6 (4-11)	5-7.5	74 (96)	23 (100)	74	15 (7-30)	nr
Angell et al[10] (2013)	79 (60/19)	8 (4-12)‖	Test dose 1.25 (0.6-2.5); re-dose 1.87 (0.6-5)	55 (92)	6 (54)	86	12.5 (0-26)‖	0
Bjurlin et al[11] (2013)	52 (39/13)¶	6 (6-8)	5-10	NR	NR	NR	17 (12.8-25)	3.8

ICG, indocyanine green dye; LoE, level of evidence; NIRF, near-infrared fluorescence; Nr, not reported; PSM, positive surgical margin; WIT, warm ischemia time.
Values expressed as median (range) unless otherwise specified.
* LoE according to the Oxford Center for Evidence-based Medicine.
† Defined as having hypofluorescence in case of malignant tumors and isofluorescence or hyperfluorescence in case of benign tumors.[10]
‡ Study done using the SPY Endoscopic Imaging System (see text).
§ Two cases done laparoscopically.
‖ Mean value.
¶ Selective arterial clamping only.

has been RPN, with 5 case series (level of evidence 4; Table 1)[6,8-11] and 3 case-control studies (level of evidence 3b; Table 2).[12-14]

More limited evidence exists for other applications (Table 3), including prostate cancer (radical prostatectomy and pelvic lymphadenectomy),[15-17] ureteral surgery,[11,18] adrenal surgery,[19] and radical cystectomy.[20]

COMMENT

Partial Nephrectomy: Case Series

RPN seems to offer a wider range of indications, better operative outcomes, and lower perioperative morbidity than laparoscopic partial nephrectomy.[21,22] Moreover, robotic technology may enable surgeons to more frequently perform nephron-sparing surgery.[23] Tumor identification represents a key step during RPN to obtain complete tumor removal. Although the clinical significance of margin status has been questioned,[24] the achievement of a negative surgical margin is still recognized as a feature of good surgical quality and oncologic safety.[25] Routine use of intraoperative ultrasonography has been applied to guide the surgeon in tumor identification.[26] However, it can be clumsy to handle and influenced by operator-dependent factors. Thus, other forms of intraoperative real-time imaging could be of further help to the console surgeon during the procedure.

The rationale behind the use of ICG in kidney cancer surgery is based on experimental evidence showing renal cortical tumors demonstrate reduced expression of bilitranslocase, a carrier protein for ICG present in normal proximal tubule cells.[27] This process leads to a reduction in NIRF of these tumors, allowing visual differentiation from the surrounding parenchyma. As the ICG dye is cleared by hepatic metabolism and is not nephrotoxic, it seems to be an ideal agent for partial nephrectomy procedures.

In 2011, Tobis et al[6] were the first to report the application of NIRF in 11 cases of RPN. Renal vasculature was easily identified in all of them, including several with complex branching of the renal arterial supply. Tumors, cysts, and an area of fat necrosis were mostly hypofluorescent and easily distinguished from normal parenchyma. In 3 patients, tumors were comparatively isofluorescent such that ICG did not help in tumor identification. The authors speculated this was because of the normal parenchyma overlying the tumor and suggested that in cases of predominantly endophytic tumors, ICG may be most useful for tumor margin identification only after the overlying normal parenchyma is incised. Limitations of this initial pilot study were the small sample size, the low complexity of most tumors, and the lack of definition of optimal dosing.

The same group evaluated the SPY Endoscopic Imaging System (Novadaq, Inc) and its feasibility for use during minimally invasive partial nephrectomy.[8] The raw imaging output of this system was a gray-scale image, with increasing amounts of fluorescence appearing brighter.