Optimization of Near Infrared Fluorescence Tumor Localization during Robotic Partial Nephrectomy

Jordan E. Angell,* Tariq A. Khemees and Ronney Abaza†

From the Robotic Urologic Surgery, Department of Urology, The Ohio State University Wexner Medical Center and James Cancer Hospital, Columbus, Ohio

Abbreviations and Acronyms

ICG = indocyanine green

NIRF = near infrared fluorescence

RCC = renal cell carcinoma

RPN = robotic partial nephrectomy

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* Correspondence: Robotic Urologic Surgery, The Ohio State University Wexner Medical Center, 515 Doan Hall, 410 W. 10th Ave., Columbus, Ohio 43210 (telephone: 614-293-0981; FAX: 614-293-0982; e-mail: jordan.angell@osumc.edu).

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For another article on a related topic see page 1907.

Purpose: Near infrared fluorescence allows the differentiation of tumors and normal parenchyma during robotic partial nephrectomy. This may facilitate tumor excision but requires proper dosing of indocyanine green. Under dosing causes inadequate fluorescence of peritumor parenchyma. Overdosing causes tumors to fluoresce inappropriately. Currently there are no described dosing strategies to our knowledge to optimize near infrared fluorescence and reported doses vary widely. We devised a dosing strategy and assessed the reliability of near infrared fluorescence for differential fluorescence.

Materials and Methods: Robotic partial nephrectomy with near infrared fluorescence was performed for 79 tumors. Dosing strategy involved at minimum 2 indocyanine green doses, including the test dose and the calibrated dose before resection. The test dose was deliberately low to avoid confounding over-fluorescence. The second dose was calibrated depending on the extent of differential fluorescence achieved with the test doses. Intraoperative assessment of tumor fluorescence was recorded before pathological assessment.

Results: Mean tumor size was 3.5 cm (range 1.1 to 9.8) with a mean R.E.N.A.L. score of 8 (range 4 to 12). Median indocyanine green test dose and re-dose before clamping were 1.25 mg (range 0.625 to 2.5) and 1.875 mg (range 0.625 to 5), respectively. Differential fluorescence was achieved in 65 of 79 tumors (82%) that did not fluoresce. After 3 exclusions for the inability to assess fluorescence or indeterminate histology, 60 of 76 tumors were renal cell carcinoma. Of 60 renal cell carcinomas 55 behaved appropriately and did not fluoresce (92%). Overall 65 of 76 tumors behaved appropriately for an 86% agreement between histology and near infrared fluorescence behavior.

Conclusions: With our dosing regimen near infrared fluorescence was highly reliable in achieving differential fluorescence of kidney and renal cell carcinomas. Standardized dosing is needed before deciding whether near infrared fluorescence improves robotic partial nephrectomy outcomes and additional studies may further improve reliability.

Key Words: robotics; nephrectomy; fluorescence; indocyanine green; carcinoma, renal cell

The standard of care for small renal masses is excision with partial nephrectomy,[1] with robotic partial nephrectomy becoming a common and accepted modality for nephron sparing.[2,3] Currently preoperative imaging and intraoperative ultrasonography are used by most surgeons for tumor localization. Recent studies have suggested that NIRF may have

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a role in aiding the differentiation of normal renal parenchyma and cortical tumors during open and robotic partial nephrectomy.[4–6] The consistency of NIRF in providing this differential fluorescence of tissues is unclear and its usefulness in RPN has been challenged.[4,7]

Indocyanine green is a water-soluble dye, approved by the Food and Drug Administration, that allows for tissue fluorescence with NIRF when injected intravenously.[8,9] Due to the presence of the membrane protein bilitranslocase in renal proximal tubule cells, ICG is retained by normal kidney parenchyma but not by tissues lacking bilitranslocase,[10] including renal cell carcinomas.[11] This property theoretically allows for the potential that normal renal parenchyma would fluoresce during partial nephrectomy while the tumor being excised would not, and is the basis for the integrated NIRF system adapted for use with the da Vinci® Surgical System for RPN.

Investigators have reported variable success using NIRF for tumor localization and differentiation from surrounding normal renal tissue, but the reason for this inconsistency in success is unclear. We believe that ICG dosing is integral to the successful application of NIRF in achieving differential tissue fluorescence, but no dosing studies or standardized dosing strategies have been reported to date. Current published studies describe a wide range of ICG doses, administering anywhere from 0.75 to 7.5 mg per patient, with no explanation of how dosing was determined.[4–6,11]

In our experience the under dosing of ICG prevents adequate fluorescence of normal parenchyma surrounding a tumor and makes visual differentiation of tissues difficult, while overdosing causes all tissues to fluoresce (fluorescent washout), including RCCs, when biologically they should not. To achieve adequate fluorescence of the normal kidney while the tumor remains dark on NIRF visualization, a dosing window exists that has not previously been described. We report our experience with NIRF in robotic partial nephrectomy, and are the first to describe a standardized ICG dosing strategy and the resulting reliability in achieving differential tumor fluorescence with this regimen.

MATERIALS AND METHODS

Between May 2011 and November 2012 a prospective database of all patients who underwent RPN with the use of robotic NIRF was reviewed with institutional review board approval. All procedures were performed by a single surgeon (RA) and NIRF was used in all but 1 RPN performed during the study period such that the study cohort represented a nearly consecutive experience of all renal masses treated with RPN by the surgeon.

All RPN procedures were performed transperitoneally with a previously described technique.[12] Intraoperative laparoscopic ultrasonography was performed in all cases initially to identify tumor location, after which the overlying Gerota fascia and perinephric fat were removed to allow visualization of the planned resection plane.

Once the tumor and a portion of surrounding normal kidney tissue were visualized, the standardized NIRF regimen was initiated. This involves a dosing strategy consisting of at minimum 2 ICG doses, including a test dose and a calibrated second dose just before vessel clamping for tumor resection. The test dose is given as soon as the tumor is identified to plan the dose that will be given during tumor resection. If the test dose is unintentionally too high, causing all tissues and the tumor to fluoresce, this allows as much time as possible to pass while preparations are made for tumor resection to allow ICG to be cleared from the kidney and tumor.

Occasionally the fluorescence caused by overdose will persist, and interfere with attempts to create differential fluorescence of kidney and tumor. Therefore, our ICG dosing protocol begins with a test dose that is deliberately low, as low as 0.625 mg depending on the size of the patient. Typically a starting dose of 1.25 mg is chosen except in patients of small stature and/or unusually low body mass index. Sutures and all necessary items for extirpation of the tumor are then readied. When the test dose provides differential fluorescence as desired, this same dose is given just before arterial clamping (fig. 1). If parenchymal fluorescence or differential fluorescence is inadequate, ICG just before arterial clamping will be given at a lower or higher dose. In other words, when the test dose provides inadequate fluorescence of the kidney such that tumor and kidney are dark, a higher dose is used on re-dosing. If the test dose causes uniform fluorescence including tumor and normal kidney, or fluorescent washout as we refer to it, then we lower the re-dose until differential fluorescence is achieved. With experience, overdosing was rarely encountered as we recognized the need to begin with lower doses to avoid this scenario.

After the re-dose for tumor resection, the arterial clamp is placed when ICG can be seen in the venous return in the renal vein. The integrated robotic NIRF system allows instantaneous toggling between white light and NIRF modes during tumor resection to aid in the assessment of tumor margins (fig. 2). Since the arterial supply to the area of resection is clamped, ICG given immediately beforehand persists indefinitely and will not be cleared from the kidney until perfusion is reestablished. The excised specimen will also continue to fluoresce for reassessment of the margins of resection at any time after renorrhaphy or even after specimen extraction (fig. 2).

Intraoperative fluorescence of tumors or lack thereof and dosing of ICG were recorded intraoperatively. Assignment of tumor fluorescence behavior was based on the optimal differential fluorescence or lack thereof achieved after re-dosing based on findings with the initial test dose. Intraoperative findings were compared with histological findings on final pathology using permanent section without frozen sections performed in any patient. A positive margin was defined as 1 or more tumor cells at

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