Use of Indocyanine Green (ICG) During Robotic Surgery for Renal Cancer

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11.1 Introduction

Robotic technology enables the performance of complex urologic surgeries with greater precision, miniaturization of instruments, and smaller incisions than traditional laparoscopic or open approaches. An evolution is image-guided surgery: the principle that optical enhancements can improve visualization of internal anatomical structures or pathological features and can facilitate surgery. Real-time intraoperative identification of malignant versus benign tissue can help surgical outcomes by simultaneously decreasing positive surgical margin and local recurrence rate while preventing over-aggressive resection of vital structures. A particular enhancement in image-guided surgery that has been utilized significantly for both oncologic and non-oncologic surgeries is the Fire-Fly technology using indocyanine green (ICG) for near-infrared fluorescence imaging (NIRF). In contrast to white light, NIRF, with the addition of fluorophores, permits deeper photon penetration, superb optical contrast, less scatter, and a high signal-to-background ratio [7], van den [21]. Optical enhancement using ICG-NIRF has been shown to facilitate surgical performance in both the oncologic and non-oncologic settings. ICG received initial FDA approval in 1959 (NDA 011525). Based on the most

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recent labeling package insert submitted in 2015, the current FDA-approved indications for ICG include determination of cardiac output, hepatic function, and liver blood flow, as well as, ophthalmic angiography.

ICG has been used off-label for urologic surgery since 2006 [19, 20]. Initially described for open partial nephrectomy in the urologic literature, intravenous injection of ICG was utilized to clearly demarcate the vasculature and fluorescence patterns of the tumor in 15 patients [19, 20]. The technology was later developed in a laparoscopic and robotic cohort utilizing the Endoscopic SPY Imaging System [19, 20]. The da Vinci® surgical platform (Intuitive Surgical, Sunnyvale, CA) equipped with Firefly technology (Novadaq Technologies, Mississauga, ON) allows surgeon-controlled utilization of NIRF. The robotic application was first studied in patients with suspected renal cell carcinoma [10]. Subsequently, other urologic organs have been extensively studied including prostate, bladder, and adrenal glands. The urologic oncologic and non-oncologic applications of ICG-NIRF are vast [2, 3, 14]. For oncologic surgery, molecular-guided surgery can facilitate upper, combined upper and lower, and lower tract pathologies as well as lymph node dissection within the retroperitoneum and pelvis. For non-oncologic surgery, specifically reconstructive surgery, ICG-NIRF allows for deeper tissue penetration and real-time perfusion status that can aid in ureteral stricture repair, anastomotic viability, and identification of critical vasculature. Despite its vast applications in urology, dedicated recommendations for the use of ICG are not available in urological guidelines.

11.2 Pharmacodynamics

ICG, a tricarbocyanine, is a water-soluble molecule with a peak spectral absorption at 806 nm and with peak emission fluorescence at 830 nm. ICG is only visualized with near-infrared fluorescence (found on the da Vinci Surgical Systems equipped with Firefly® technology). After intravenous administration, ICG becomes rapidly bound to albumin (95%) and can be near-instantaneously visualized within the vasculature and target organs through a NIR fluorescence camera system. The novel Firefly® system incorporates a NIR fluorescence camera system, namely the SPY Imaging System (Novadaq Inc., Missisaugua, ON, Canada), directly into the da Vinci Si® and Xi® and allows the surgeon to switch between visible light and fluorescence-enhanced views in real time [11].

ICG should be handled in with generalized sterile techniques as with an intravenously administered agent. Common drug interactions that can reduce the peak absorption of ICG include sodium bisulfate found in many heparin products (NDA 011525 Food and Drug Administration Suppl-27 Labeling-Packaging Insert 2021). ICG is classified as a pregnancy category C compound and thus further research in this area is warranted prior to administering ICG in pregnant females (NDA 011525 Food and Drug Administration Suppl-27 Labeling-Packaging Insert 2021). According to the FDA, the usual dose for ICG varies with age with adults receiving a maximum total dose of 5.0 mg and children and infants receiving a maximum

Fig. 11.1 On the da Vinci Xi the Fire-Fly modus can be adjusted selecting "sensitive" modus

total dose of 2.5 mg and 1.25 mg, respectively. The total dose should anyway be <2 mg/kg, and specific dosages are recommended according to the target organ [15]. ICG is removed from circulation exclusively by the liver to bile juice, and, depending on liver performance, is eliminated from the body with a half-life of about 3–4 min.

11.3 Firefly Technology

The technique of fluorescence imaging, the so-called Firefly System®, is integrated into the robotic console, and allows the surgeon to switch to fluorescence mode on using the fingerswitch on the surgical handles after ICG injection. As a result, the surgical field is illuminated with a special infrared light source that is able to see the glowing areas infused with the dye. On the da Vinci® Xi system he Fire-Fly modus can be adjusted selecting "sensitive" modus (Fig. 11.1). This can be done by the surgeon at the console or by anybody at the vision screen cart.

11.4 Side Effects

ICG should not be used in patients with concomitant allergy to iodides and it is considered contraindicated for these patients. Anaphylactic deaths have occurred after administration of ICG during cardiac procedures [4], however, no studies have found any impact of ICG on carcinogenesis, mutagenesis, and impairment of fertility. ICG can be used in patients with chronic kidney disease, since it is not nephrotoxic and is cleaned by hepatic metabolism [16].

11.5 Indications for ICG During Robotic Surgery for Renal Cancer

11.5.1 Vasculature Identification

Renal vascular anatomy can have a lot of variations, and one of the most popular uses of ICG technology, especially during surgery for renal cancer, is vasculature identification [5, 6]. This application may include intra-operative identification of vessels for selective clamping during partial nephrectomy, or the assessment of arterial and/or venous clamping.

11.5.1.1 Identification of the Vessels

The identification of vessels in the renal hilum may be challenging, especially for less experienced surgeons. In these cases, the use of ICG technology might be of help, allowing for a precise description and identification of renal vessels, and providing a helpful guide for surgical dissection.

11.5.1.2 Selective Clamping

ICG may support selective clamping and thereby minimize ischemia time of healthy and non-tumor-bearing renal parenchyma, by improving identification of the renal vascular anatomy and the arterial blood supply to the tumor [9]. Indeed, when a selective clamping is planned or if an incomplete clamp is suspected, due to the possible presence of non-diagnosed ancillary renal arteries, the exclusion of blood supply from the target resection area can be confirmed with ICG.

In addition, ICG technology can be used to check selective blood supply to specific parts of the kidney. From a technical standpoint, after all renal vessels are clamped, the bulldogs are removed one by one to observe which part of the parenchyma is perfused, with the goal to preserve kidney perfusion, especially in patients with solitary kidney or reduced kidney function.

11.5.1.3 Check Adequate Clamping During On-Clamp Partial Nephrectomy

In case of difficult hilar anatomy, and in absence of 3-D reconstruction, the surgeon might be in doubt whether all arteries are identified or isolated, or whether the target area of the kidney will be still perfused after clamping (e.g. lower pole for lower pole tumor). In this situation, ICG can be used to assess whether the area that has to be dissected is still receiving blood supply or not.

11.5.2 Dissection of Tumor Margins

The use of ICG may facilitate the identification of the tumor which appears hypo-fluorescent as opposed to the highly vascularized healthy renal tissue, hence allowing a more accurate dissection and proper preservation of renal parenchyma [1, 12, 17, 19, 20]. This is because renal cell carcinomas lack bilitranslocase, a

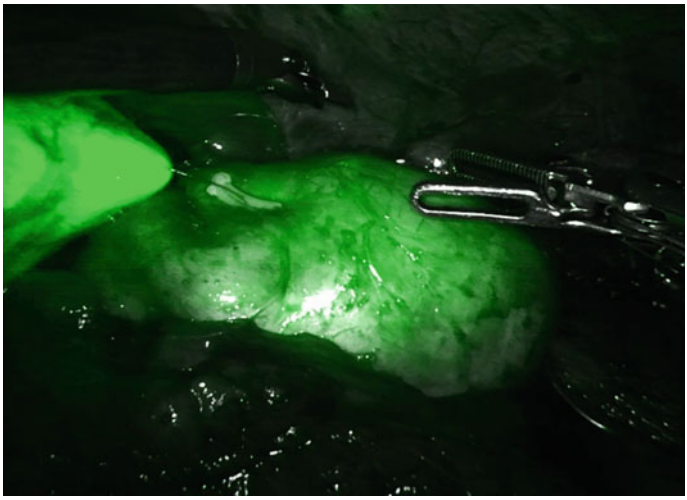

Fig. 11.2 Complete parenchyma reperfusion after renorrhaphy with ICG fluorescence imaging

carrier protein of ICG present in normal proximal tubule cells [8], allowing for clear discrimination between cancer and normal kidney tissues. By contrast, oncocytomas and chromophobe RCC are both known to express bilitranslocase and as such, may appear iso-fluorescent after ICG infusion.

An extension of this application is that, after tumor resection, the surgeon can evaluate the surgical margins and inspect whether there might be macroscopic residuals (R2 resection). Although this use is not validated, ICG technology might be of added value to assess the completeness of resection.

11.5.3 Check Tissue Viability After Renorrhaphy

ICG may also be used to assess the amount of remnant vital renal parenchyma by exploring the integrity of vascularization, which might have been compromised during renorrhaphy. Once the bulldog clamp is removed, and the kidney is re-vascularized, ICG fluorescence can be used to check for tissue perfusion (Fig. 11.2). If there is no ICG uptake on the resection margin, the surgeon can untighten the renorrhaphy in order to restore adequate perfusion.

11.5.4 Other Indications for ICG in Robotic Renal Surgery and New Applications

Other applications of ICG technology in partial and/or radical nephrectomy may include sentinel lymph node dissection during partial and/or radical nephrectomy, or super-selective infusion of ICG during partial nephrectomy for the identification of endophytic tumors. This new technique has been developed recently,

and includes a super-selective catheterization of tertiary and quaternary arterial branches supplying the renal tumors [18]. Via a femoral approach, interventional uro-radiologist selectively delivers ICG mark into the tertiary-order arteries feeding the tumor, in order to mark the tumor and minimize any ischemic injury to the surrounding parenchyma. In case of avascular renal masses, the mixture can be delivered in close proximity to the lesion in order to obtain a peripheral ICG-marked rim of healthy parenchyma.

11.6 Conclusions

ICG technology has now emerged as a safe and feasible tool for an enhanced surgical experience. Its introduction in robotic surgery for renal cancer has changed practice, facilitating surgical performance mainly with respect to vascular identification. Given the versatility of ICG technology, other applications are possible but have to be further validated. Although the applications of ICG in renal surgery are promising, the actual clinical benefit for the patient remains to be determined and as such, further investigations are needed to improve the understanding on the impact of ICG.

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