Usefulness of the Indocyanine Green (ICG) immunofluorescence in laparoscopic and robotic partial nephrectomy

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CIRUGÍA GUIADA POR LA IMAGEN Y OTROS AVANCES EN LA AYUDA AL DIAGNÓSTICO Y TRATAMIENTO QUIRÚRGICO UROLÓGICO
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USEFULNESS OF THE INDOCYANINE GREEN (ICG) IMMUNOFLUORESCENCE IN LAPAROSCOPIC AND ROBOTIC PARTIAL NEPHRECTOMY

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Summary.- *The trend towards the organ sparing and robotic assisted surgeries is clear and is going to expand in the future. Hence, the tools surgeons need to facilitate such minimallly invasive approaches are going to be even more important. The Indocyanine green (ICG) is a water-soluble, relatively hydrophobic dye which bounds to plasma protein and can be used intraoperatively as real time contrast agent. Near infrared fluorescence (NIRF) helps in differentiating the renal planes, and the most common reagent used for the NIRF is ICG. The combination is used frequently during nephron sparing surgery in urology to ensure the ischemia of the kidney after clamping the renal artery, moreover it can help to identify the arterial blood supply to the tumor allowing selective clamping and thus minimizing the ischemia time. Several studies assessed the role of ICG in nephron-sparing surgery and provided evidence that its use allows to improve perioperative and oncological outcomes. This review provides an overview of the articles published regarding the use of ICG during partial nephrectomy, about the oncological outcomes and safety.*

Keywords: *Robotics. Organ-sparing surgery. Partial nephrectomy. ICG.*

Resumen.- *La tendencia hacia la cirugía conservadora y robótica es clara hoy en día y va a aumentar en el futuro. Por lo tanto, las herramientas que los cirujanos necesitan para facilitar dichos abordajes de cirugía mínimamante invasiva van a ser incluso más importantes. El verde de indocianina (ICG) es un tinte soluble en agua, relativamente hidrofóbico que se une a proteinas plasmáticas y puede usarse intraoperatoriamente como agente de contraste en tiempo real. La fluorescencia cercana al infrarrojo ayuda a diferenciar los planos renales, y el reactivo más utilizado es ICG. La combinación es utilizada frecuentemente en Urología durante la cirugía renal conservadora para asegurar la isquemia del riñón después del clampaje de la arteria renal; además, puede ayudar a identificar el riego arterial del tumor,*

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permitiendo un clampaje selectivo y minimizando así el tiempo de isquemia. Varios estudios evalúan el papel de ICG en la cirugía renal conservadora y ofrecieron evidencias de que su utilización permite mejorar los resultados perioperatorios y oncológicos. Este artículo de revisión ofrece una visión general de los artículos publicados sobre el uso de ICG durante la nefrectomía parcial, sobre los resultados oncológicos y la seguridad.

Palabras clave: *Robótica. Cirugía conservadora. Nefrectomía parcial. ICG.*

INTRODUCTION

The historical development in surgery shows a clear trend towards the minimal-invasive approach. The open surgery although not completely replaced, but overshadowed through the laparoscopic surgery and the laparoscopic surgery is in turn now seriously challenged and slowly but surely being replaced through the robotic assisted surgery. The robotic assisted surgery provides better movement, excellent magnification, better ergonomics and moreover the results are comparable to the laparoscopic surgery (1), and hence the logical trend is to develop constant refinements to improve the results. Now in the United states more than 80% of the radical prostatectomies are performed robotically, the renal surgeries including nephrectomies, pyeloplasties, nephroureterectomies, organ sparing surgeries and even renal transplantations are being performed increasingly robotically assisted.

Mentioning the organ sparing surgery in the urology almost automatically let one think about the partial nephrectomy! If in the past the partial nephrectomy was reserved only in case of a tumor in a solitary kidney or small tumors less than 4 cm, the procedure is now performed in most renal tumors (2) and according to the current EAU Guidelines, the partial nephrectomies should be offered to the patients with T1 tumors. The minimal invasive approaches such as laparoscopic and robotic assisted surgery has enhanced and facilitated this trend. The advantages compared to the open approach are lower blood loss, lesser transfusion rates, lower postoperative pain, faster recovery time and better cosmetic results. Number of parameters such as RENAL score, exophytic/endophytic properties of the tumor, centrality index are used for the preoperative planning (3). An important issue during the partial nephrectomy is the ischemia during the resection of the tumour, which however can have a negative impact on the renal function, which in turn lead to the development of off-clamp techniques. A meta-analysis showed a positive impact on the short and long term renal function (4). Other ischemic techniques are superselective transarterial embolization, selective clamping, zero-ischemia partial nephrectomy with controlled hypotension and parenchymal clamping (3). With the use of selective clamping, a complete ischemia of the kidney is off course avoided and for the better visualization near-infrared fluorescence with the administration of indocyanine green confirms the devascularized area and helps determining the resection area (5).

The ICG and the near infrared flouresecnce

Indocyanine green is a water-soluble, tricarbocyanine dye, but relatively hydrophobic, with a molecular weight of 775 daltons. It was developed for near infra-red (NIR) photography by the Kodak research laboratories in 1955 and approved for clinical use in 1959 by the FDA (6) for determining cardiac output, hepatic function and blood flow, and ophthalmic angiography (7).

Following intravenous injection, ICG is rapidly bound to plasma proteins, especially such as bili-translocase. This bili-translocase, is expressed in the renal parenchyma excluding glomeruli (8) with minimal leakage into the interstitium, quickly spreads throughout the vascular system, and can be visualized through a NIR fluorescence camera system. It is extracted by the liver and nearly exclusively excreted by the liver appearing unconjugated in the bile. The usual dose for standard clinical use (0.1–0.5 mg/ml/kg) is well below the toxicity level (9).

The ICG can be visualized under near-infrared fluorescence (NIRF) with a specialized camera and can be used intraoperatively as a real-time contrast agent. It does penetrate the living tissue and has a good safety profile (6). The use of intraoperative dye is although not new in the surgery, as George Moore described fluorescein to identify intracranial neoplastic tissue (10,11). As far as the urology is concerned, the ICG is used during radical prostatectomy to guide sentinel lymph node dissection (12), during partial adrenalectomy (13) ureteral reconstructions (7) and renal surgeries.

The use of the ICG in partial nephrectomy

The near infrared fluorescence (NIRF) is a tool to assess the real time renal vascularity and help in differentiating the renal planes and the most common reagent used for the NIRF is the ICG. The combination of the NIRF with ICG is useful after clamping the main renal artery to ensure the complete ischemia of the

kidney. If there is a fluorescence, then most probably an accessory vessel proximal to the clamp is missed. After giving the dose of ICG immediately after arterial clamping, the kidney remains dark on NIRF in case of no other arterial inflow (14). Secondly, the ICG helps to identify the arterial blood supply to the tumor, allowing selective clamping and minimization of warm ischemia time (15). Thirdly, the hypofluorescence of the renal tumors allows the differentiation of their margins (16) and can confirm adequate ischemia during selective clamping of the renal artery and subsequently reduce the proportion of renal parenchyma that is subjected to ischemia (17). Furthermore, ICG can differentiate the tumor from normal kidney parenchyma: after an intravenous injection of ICG, the renal cell carcinoma appear hypofluorescent compared with normal kidney parenchyma (18). Last but not least, it might help to assess the integrity of the vascularization and in consequence the amount of spared vital renal parenchyma at the end of the renorraphy.

Several studies assessed the role of ICG in partial nephrectomy setting and provided evidence that the use of ICG in partial nephrectomy is feasible, safe and allow to improve perioperative and oncological outcomes. Here are some notable works.

Tobis et al. described the use of ICG, during 16 open partial nephrectomies, and no positive surgical margins were found in this study (19). The same group used the technique in 11 patients during robotic assisted laparoscopic nephrectomies, however in two patients a conversion to robotic nephrectomy because of renal vein thrombus and extensive adhesions was necessary. The warm ischemia time was 19.3 minutes, estimated blood loss around 100 ml. The group used a total of 0.75 to 7.5 mg per injection and repeated the injections as necessary to achieve optimal visualization taking care to remain below the recommended daily maximum dose of 2 mg/kg. Fluorescence was seen in the renal vasculature between 5 and 60 s after injection in all patients and renal parenchyma was seen to fluoresce in 1 min from injection. The tumors demonstrated decreased or no fluorescence compared to the surrounding parenchyma in 8 patients and equivalent fluorescence in 3 patients. All surgical margins were negative (20).

In a large series of 94 consecutive patients Krane et al. compared 47 patients with and 47 without ICG-usage during robotic partial nephrectomy. If possible, the a selective clamping of the renal artery was applied. All patients were hydrated intraoperatively and received 12.5 mg mannitol 15 minutes before and after vascular clamping. The ICG was administered at a dose of 5-7.5 mg of freshly prepared drug. The ICG was then diluted to 2.5 mg/mL and reconstituted in distilled water. The maximum dosage was 2 mg/kg, and was given within 6 hours of reconstitution. The intravenous injection was given immediately before clamping the renal artery, when the surgeon was ready to initiate warm ischemia. The initial pass of the dye into the kidney could be seen as fluorescence of the artery and then the renal vein under NIRF. The main renal artery or selective vessel to the renal tumour was clamped once it was identified with the pass of the dye. Subsequently, the renal tissue immediately turned fluorescent uniformly and remained so until the renal artery was later declamped, resulting in quick wash out of the dye. Tumor excision was started along the prescored area on the kidney surface and deepened down into the parenchymal tissue. The basic tenet is differentiation between ICG uptake by tumor and normal renal parenchyma is present. The dissimilar appearance of fluorescence of the renal mass from the normal parenchyma was readily apparent as the incision approached near the tumor capsule. No intraoperative reports indicated a positive tumor margin (16). The warm ischemia time was decreased in the ICG group (15 Vs. 17 minutes) and more patients in the ICG group underwent the tumour excision without hilar clamping (30% Vs. 10%).

Angell et al. reported 79 patients following a different strategy to determine the optimal ICG dose (21). This comprised of giving a minimum of two ICG doses including a test dose prior to complete kidney exposure and a calibrated second dose done just before the tumour excision. The test dose was according to the patient weight and stature and was a median of 1.25 mg (range 0.625 to 2.5 mg). Based on tumor visualization of the test dose, the group calibrated the second dose and reported a median dose of 1.875 mg (range 0.625 to 5 mg). Following this strategy 92% accuracy of successful tumor differentiation was achieved.

In a recent retrospective analysis Yamasaki et al. compared 83 patients who underwent laparoscopic partial nephrectomy using ICG with 74 patients who did not. Tumor margins were identified in 82% of cases in the ICG group and the warm ischemia time was significantly shorter but the volume of blood loss was higher in the ICG group. The rate of positive surgical margins was comparable between the groups (22). Similarly, Bjurlin et al. reported the successful differentiation of the tumor from normal kidney parenchyma between 73% to 100% using ICG (17).

As mentioned earlier, the selective clamping of the artery, feeding the area where the tumor is located, leads to proper preservation of renal parenchyma which in turn could lead to better renal

function postoperatively. McClintock et al compared outcomes of 42 zero-ischemia robotic partial nephrectomies using NIRF and selective arterial clamping to a matched cohort of cases with main artery clamping and found significant preservation of short-term postoperative renal function (1.9% vs 16.8% change in estimated glomerular filtration rate) (15). Lanchon et al. prospectively collected datas of 30 patients undergoing super-selective robot-assisted partial nephrectomy for a solitary tumor. The tumor devascularization was assessed using indocyanine green near-infrared fluorescence and a matched-pair analysis with a retrospective cohort undergoing early-unclamping was conducted, adjusting on tumor complexity and preoperative eGFR. Super-selective RAPN was successful in 23/30 patients (76.7%). Super-selective clamping was associated with an improved eGFR variation at discharge (p=0.002), 1-month (p=0.01) and 6-month post-op (-2%vs-16% p=0.001). It also led to a better relative function on scintigraphy (46%vs 40% p=0.04) and homolateral eGFR (p=0.04), and fewer upstaging to CKD stage ≥3 (p=0.03) (23) (Table I).

Although the innovative technique to use the ICG can differentiate between normal renal and malignant tissue, there are limitations as well. Manny et al. (26) questioned the reliability to differentiate the malignant from benign tissue (positive predictive value 84% and the negative predictive value 57%) in 100 consecutive patients and furthermore questioned the usefulness of additional information provided by the ICG as compared to the preoperative imaging. Moreover, the demarcation of endophytic tumors can be difficult too using ICG (20). Similarly, Krane et al. found no advantage of ICG dye in patients who had completely endophytic tumors or in patients undergoing RPN without hilar clamping (16). However, Simone et al. reported 10 patients using a novel technique for marking preoperatively endophytic renal tumors with transarterial superselective intrarenal mass delivery of indocyanine green (ICG)-lipiodol mixture, in order to enhance surgical margins control during purely off-clamp (OC) RAPN. Median tumor size was 3 cm, median operative time was 75min (65-85) No conversion to on-clamp partial nephrectomy or radical nephrectomy was needed. Surgical margins were negative in all cases (27).

According to Klaassen et al. (28) the lack of uptake in peripelvic/intrarenal fat and the collecting system may prevent the ICG delineation of the most medial/central extent of the tumor. Furthermore they see an increased risk of iatrogenic injury because of the dark surrounding intracorporeal field in relation to the ICG illuminated kidney especially when toggling between white light and near infrared fluorescence imaging.

As far as the safety is concerned, the ICG is generally considered to be safe but there are reports of severe complications too which should be taken in account. ICG has generally been considered safe and accepted as having a low incidence of morbidity. Hope-Ross et al prospectively evaluated complications from intravenous ICG use for video angiography in 1226 patients, incidence of mild, moderate, and severe complications were 0.15%, 0.2%, and 0.05% respectively (29). Chu et al. reported a case of a life-threatening anaphylaxis following IV ICG during a robotic urologic surgery (30).

CONCLUSION

Indocyanine green is a tricarbocyanine dye which rapidly binds bound to plasma proteins and

Table I. Published institutional studies reporting outcomes of robotic partial nephrectomy.

Study	Year	Patients (n)	Median Age (years)	Median Size (cm)	Median WIT	% Malignant
Tobis et al. (20)	2011	9	69	3.8	19	91
Borofsky et al. (24)	2012	27	60*	2.8*	0	81
Krane et al. (16)	2012	47	60*	2.7	15	79
Harke et al. (5)	2013	22	63*	3.8*	12	50
Bjurlin et al. (25)	2013	48	54	2.6	17	75
Angell et al. (21)	2013	79	55*	3.5*	13	79
Manny et al. (26)	2013	100	60	3	15	84

can be visualized under near-infrared fluorescence (NIRF) with a specialized camera. The combination of the NIRF with ICG is useful to ensure the complete ischemia of the kidney, identifying the arterial blood supply to the tumor, allowing for selective clamping; Furthermore, the hypofluorescence of the renal tumors in comparison to normal renal parenchyma after ICG usage, might allow for better differentiation of margins and more precise dissection of the tumor.

Its use is safe while performing the robotic and laparoscopic partial nephrectomy especially in exophytic renal tumors. It can also facilitate selective clamping, and lead towards better kidney function postoperatively. The visualization of endophytic tumors with ICG is challenging.

Anyway NIRF using ICG is an additional tool during laparoscopic and robotic partial nephrectomy, however, further prospective studies however are needed to prove if ICG can reduce surgical collateral damages and improve oncological outcomes.

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