Review Article: Surgery: Urological Surgery

Narrative review on applications of fluorescence-guided surgery in adult and paediatric urology

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Abstract: More recently, there has been a substantial increase in the use of fluorophores to guide open and laparoscopic procedures with the ultimate aim to optimize both oncological and functional outcomes and to reduce operative time and blood loss. Fluorescent dyes are currently adopted to allow safer and more accurate dissections during both oncological and reconstructive procedures thanks to their ability of highlighting tumour margins and tissue vascularization. Urology is one of the fields in which fluorescence-guided surgery (FGS) has proved to be most useful. In particular, it has assumed a pivotal role in the surgical treatment of oncological patients affected by kidney, bladder, prostate and penis cancers and in the management of paediatric urological conditions. This review aims to provide an update on the use of FGS in adult and paediatric urology, drawing attention to its most recent and interesting applications in this very innovative field of research. Although FGS has been only recently introduced in the clinical scenario, it can be already considered a powerful tool to improve oncological, anatomical and functional outcomes in both adult and paediatric urology. An increased identification of lymph nodes (LNs), a more accurate visualization of tumour margins and a better definition of blood supply and lymphatic drainage have proved to be greatly beneficial for patients undergoing urological procedures, whether they are adults or children. Longitudinal studies with larger sample sizes are still needed to draw firm conclusions and to confirm its benefits in urology.

Keywords: Fluorescence-guided surgery (FGS); fluorophores; dyes; adult urology; paediatric urology

Received: 30 December 2020; Accepted: 18 October 2021; Published: 25 June 2022.

doi: 10.21037/amj-20-194

View this article at: https://dx.doi.org/10.21037/amj-20-194

Introduction

In the past decades, technological advances such as high-resolution computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) have improved the preoperative work-up of patients undergoing surgery. However, their introduction in the operating room remains limited and, when it occurs, the co-registration of preoperative images within the surgical field may not always match the definitive intraoperative findings.

In this regards, fluorescence-guided surgery (FGS) has shown its capacity to improve surgical outcomes, filling the gap between preoperative imaging and intraoperative findings. As a matter of fact, FGS has been able to provide invaluable anatomical and functional information during invasive procedures, including sentinel lymph node (SLN) mapping, identification of solid tumours, lymphography and angiography (1-4).

FGS requires two components to work properly: a fluorescent probe and an imaging device (5). Among the fluorescent agents, many have become available, but only a few have been clinically approved. They can be used as injectable solutions of the fluorophores alone or in alternative the dyes can be conjugated to targeting molecules, such as monoclonal antibodies. Indocyanine green (ICG) has been one of the most frequently employed in urology, even though other molecules have been adopted, such as 5-aminolevulinic acid (5-ALA), its metabolite, hexaminolevulinate (HAL), and methylene blue (MB). Among the new generation of tracers targeting specific proteins, the IRDye800CW has been the most commonly used in clinical practise (6,7).

The wavelength emitted varies from dye to dye and it can be within the visible or in the near-infrared (NIR) spectrum, as in the case of ICG and MB.

As regards to imaging devices, there have been many adopted in the urological field. The most commonly used and the first-ever approved by the Food and Drug Administration (FDA) has been the SPY system (8). Others are the photodynamic eye system (9), the IC-view system (10) and the fluorescence vascular imaging (FVI) (11).

Although, most of the current applications of FGS are mainly reported with regards to adult surgery, there has recently been a substantial increase in the number of publications in the field of paediatric surgery (12).

This review aims to collect the most recent applications of fluorescence optical imaging in urology, exploring its benefits and highlighting its indications for the surgical treatment of urological disorders in both adults and children. We present the following article in accordance with the Narrative Review reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-20-194/rc).

Methods

A non-systematic literature search of PubMed and EMBASE databases was carried out in August 2021 in order to select relevant papers published between January 1990 and July 2021, which provided data on urological applications of FGS. In order to identify eligible studies, a broad search was conducted using various combinations of keywords such as: “Fluorescence-guided surgery” [All Fields] OR “fluorophores” [All Fields] OR “dyes” [All Fields] OR “indocyanine green” [All Fields] OR “5-aminolevulinic acid” [All Fields] OR “hexamynolevulinate” [All Fields] OR “methylene blue” [All Fields] OR “IRDye800CW” [All Fields] OR “urology” [All Fields] OR “paediatric urology” [All Fields]. The inclusion criteria were studies published in the English language reporting results, indications and outcomes regarding the use of fluorescence-guided technology in urology.

Discussion

FGS is a promising technology that has been recently introduced in cancer surgery and might potentially change the future of reconstructive and oncological procedure and at the same time improving patients’ outcomes. In particular, its applications have shown to be ideal in the urological field where it has been widely used with very interesting results.

Kidneys and ureters

FGS has provided highly satisfactory results for both surgical oncology, transplant and reconstructive surgery.

Several authors have described the use of FGS to allow an easier identification of tumours and to perform partial nephrectomies (PNs) more safely, with the ultimate aim to achieve an adequate degree of oncological radicality preserving at the same time the function of the spared renal parenchyma (13,14).

Tobis *et al.* (13) reported the use of ICG to highlight the renal vasculature and to distinguish 17 renal cortical tumours from normal tissue with the potential to maximize oncologic control and nephron sparing during 16 open PNs. Following the administration of aliquots of 1–5 mL of ICG (2.5 mg/mL solution), the difference in fluorescence between the normal parenchyma and tumour tissue allowed a clear outline of the tumour margins, especially in malignant cases.

Similarly, Mitsui *et al.* (14) concluded that the fluorescence imaging system was very helpful for confirming negative margin status, in even the most complex cases, during 16 ICG-based open PNs for organ-confined small renal tumours.

Moreover, NIR fluorescence imaging proved to play a key role during robot-assisted PNs, as reported by several authors (15-18).

Angell *et al.* (17) in their study devised a dosing strategy and assessed the reliability of NIR fluorescence to localize 79 cortical tumours. Two doses of ICG were injected: the test dose, before surgery, and the calibrated dose,

before resection. The test dose was deliberately low to avoid confusing over-fluorescence while the calibrated dose was defined on the extent of differential fluorescence achieved by the first dose. The authors concluded that, with standardized dosing regimen, NIR fluorescence was highly reliable in achieving differential fluorescence of kidney and renal cell carcinomas.

Mattevi *et al.* (18) described the use of NIR fluorescence imaging to guide selective arterial clamping during 20 consecutive robot-assisted PNs and compared their outcomes with 42 conventional ones. The ICG solution was administered twice: the first dose (5 mg of 2.5 mg/mL solution) after arterial clamping and the second dose (2.5 mg of 2.5 mg/mL solution), after the excision of the tumour mass to check the remaining kidney perfusion. In terms of early functional outcomes, it was seen, not only a lower loss of GFR in the operated renal unit (P=0.046), but also a lower total GFR loss (P=0.007) in patients undergoing the fluorescence-guided robot-assisted PNs. Interestingly, no positive margins were detected in the fluorescent-guided procedures while three were identified in the standard group (7.1%) with a statistically significant difference (P=0.025).

Although a standardized way to administer the fluorescent agents and long-term functional benefits have yet to be established, all authors agreed in considering FGS a safe and reliable option to improve the oncological outcomes and to maximize nephron-sparing during PN in surgical oncology.

To go further, FGS has also been adopted to differentiate benign from malignant lesions. The study carried out by Hoda *et al.* (19) demonstrated the reliability of 5-ALA FGS in predicting the type of lesions affecting 77 patients with kidney cancer, with an accuracy of 94% and a predictive positive value of 98%. In detail, they administrated 15–25 mg/kg of oral 5-ALA 4 hours before the laparoscopic procedure. While, 58/61 (95.1%) renal cell carcinomas showed a positive response when exposed to light, only a single case of angiomyolipoma (6.3%) showed positivity to light, among 16 non-malignant lesions.

Even if Manny *et al.* (20) reported that tumour hypofluorescence couldn't be considered a reliable way to establish the malignancy of the mass (sensitivity: 84%; specificity: 57%), they proved the efficacy of ICG-FGS in decreasing the ischemia time, in the identification of hilar vessels and tumour-specific vessels and in enhancing the contrast between the tumour and, the surrounding healthy parenchyma (15).

Moreover, ICG has been adopted by Vignolini *et al.* (11) to assess graft and ureteral reperfusion during 6 robot-assisted kidney transplants from living donors. The authors concluded that the intensity of the fluorescent signal resulted to be a reliable indicator with which to evaluate the renal parenchyma, the ureter and the vascular anastomoses, even though, larger studies were needed to standardize the technique.

Furthermore, fluorophores have been valuably employed by Verbeek *et al.* (21) to avoid severe urological complications during complex lower abdominal surgeries. In particular, the injection of 10 mg/mL of MB solution (0.25–1 mg/kg) allowed an easier identification of the ureters during 12 open abdominal surgeries.

Conversely, Hanna *et al.* (22) described the use of ICG to perform 5 robotic ureteral reimplantations to repair distal ureteral injuries, secondary to laparoscopic gynaecologic surgeries. The intraoperative vascular assessments using ICG assisted in ensuring a well-vascularized tension-free ureterovesical anastomosis and all the patients had complete resolution with no evidence of anastomotic complications.

Bladder

5-ALA and its metabolite, HAL, have been widely adopted in bladder surgery.

In particular, many authors described the use of 5-ALA/HAL photodynamic diagnostic (PDD) cystoscopy as a meaningful tool to increase the detection of non-muscle-invasive bladder cancers (BC) (23-26).

Hermann *et al.* (23) reported that an endovescical instillation of 50 mL of HAL 60 minutes before the planned PDD cystoscopy allowed the identification of 20 neoplastic lesions (c) otherwise missed by the white light (WL).

The same authors conducted a randomized clinical trial comparing the BC recurrence rate after conventional transurethral resection of the bladder (TURB) in WL and after HAL-guided TURB in Ta/T1 patients (24). Interestingly, in 44 out of 90 patients (49%; 95% CI: 38–60%) the fluorescence-guided cystoscopy after complete WL TURB identified residual tumour tissue: residual Ta tumour in 37, residual T1 tumour in 3, residual carcinoma in situ (CIS) tumour in 4 patients. Noteworthy, a significantly longer recurrence-free period (P=0.02) and a histologically-verified reduction in the recurrences rate (P=0.05) were reported in patients allocated in the HAL-TURB arm.

Gakis *et al.* (25) moved in the same field, describing the

impact of PDD-guided TURB on the survival rate of 89 patients, subsequently undergoing radical cystectomy (RC) and bilateral pelvic lymphadenectomy for BC, compared to a control group of 135 patients undergoing the traditional WL-TURB. Their results revealed that patients in the PDD-guided TURB group (n=66: HAL; n=23: 5-ALA) had not only a lower number of TURB before RC (P<0.001); a lower incidence of re-resections (P=0.015) and a longer time lapse between the first TURB and the RC (P=0.044) but also required less adjuvant chemotherapy (P=0.001) and displayed higher survival rates.

Moreover, Zare *et al.* (26) conducted a multicenter prospective study analyzing the feasibility of integrating HAL-guided TURB in the follow-up of 69 patients affected by non-muscle invasive BC. Despite the additional time required for the instillation of the fluorescent dye, this procedure was associated with an easier detection of early recurrent and more extended lesions.

In spite of all these promising results, more prospective randomized clinical trials are still required to allow a better understanding of the impact of PDD-guided TURB on surgical outcomes and survival of patients affected by BC.

Moreover, some authors have reported the application of fluorescence optical imaging during partial or RC to assess the lymphatic drainage, to identify tumour location or to evaluate ureteral blood flow (27-30).

Manny *et al.* (27) described the feasibility of FGS in 10 robotic RCs using real-time cystoscopic injection of ICG for tumour marking and identification of sentinel lymphatic drainage. Its additional intravenous injection for mesenteric angiography allowed the maximal preservation of bowel vascularity to the conduit and remaining bowel segments.

Schaafsma *et al.* (28) prospectively enrolled 20 patients with invasive BC scheduled for RC. ICG bound to human serum albumin was injected peritumourally to permit SLN mapping: in 5 patients directly into the bladder wall (serosa) after laparotomy and in 15 patients cystoscopically into the bladder wall (mucosa) before surgery. The authors reported that fluorescent lymph nodes (LNs) were observed only in the patient group with cystoscopic injection. Filling of the bladder post-injection with saline for at least 15 min was added in 12 patients to promote drainage of the conjugate to the LNs. Noteworthy, in 11 of these 12 patients (92%) one or more NIR fluorescent LNs were identified.

In their study, Doshi *et al.* (29) described the use of NIR fluorescence imaging with intravenous ICG injection to assess ureteral vascularity prior to ureteroenteric anastomosis during RC. They concluded that it reduced the risk of ureteroenteric anastomotic stricture (UES) and increased the time lapse for its occurrence.

Conversely, Lee *et al.* (31) retrospectively reviewed 8 patients who underwent 10 robotic ureteroenteric reimplantations due to benign UES that developed after RC. The injection of ICG directly into the ureter or in the intra-urinary diversion allowed for precise identification of the strictured ureter and urinary diversion and for the localization the UES margins.

Prostate

Fluorophores has been also adopted to guide SLN biopsy and LN dissection during laparoscopic and robot-assisted radical prostatectomies (32-37).

In 2014, Manny *et al.* (38) described their initial clinical experience in 50 patients undergoing fluorescence-enhanced robotic radical prostatectomy using real-time lymphangiography and tissue marking with ICG. The injection of 0.4 mL of a 2.5 mg/mL ICG solution into each lobe of the prostate resulted in a quick and reliable diffusion of dye throughout the organ without visible fluorescence in the periprostatic structures in all patients. ICG injection was able to identify the potential SLN prostatic drainage in 76% at a mean time of 30 min post-injection with 100% sensitivity, 75.4% specificity, 14.63% positive predictive value, and 100% negative predictive value for the detection of nodal metastasis.

In 2015, Hruby *et al.* (33) injected 2.5 mL of ICG per prostatic lobe under transrectal ultrasound guidance at the start of the laparoscopic radical prostatectomy in 38 patients with clinically localized intermediate and high risk prostate cancer. They added super-extended pelvic lymph node dissection (PLD) as control and proved that fluorescence targeted PLD had superior sensitivity (97.7%) and negative predictive value (99%) to detect LN metastasis.

The same year, Yuen *et al.* (39) injected ICG into the prostate under transrectal ultrasound guidance just before surgery in 66 consecutive patients with clinically localized prostate cancer. Lymphatic vessels were successfully visualized in 65 patients (98%) and SLN in 64 patients (97%). They concluded that this novel method was technically feasible, safe and easy to apply with minimal additional operative time.

In 2016, Nguyen *et al.* (40) performed a lymphatic mapping study and determined the value of fluorescence SLN detection with ICG for the detection of LN metastases in 42 intermediate and high risk patients undergoing radical

prostatectomy and extended PLD. A complex drainage pattern of the prostate was delineated by this study, which showed that lymphatics cross over to the opposite side and that the common iliac regions and the fossa of Marcille should not be overlooked.

In 2018, Miki *et al.* (41) reviewed a prospective cohort of 50 consecutive patients with intermediate to high risk localized prostate cancer undergoing laparoscopic radical prostatectomy and SLN biopsy guided by fluorescence detection using intraoperative imaging with ICG. Noteworthy, over 90% of positive SLN were identified at two predominant sites: one site was the junctional LNs, located at the junction between internal and external iliac vessels; the other was the distal internal iliac LNs, located along the inferior vesical artery. They concluded that particular attention should be paid to analyzing these LNs to reduce the possibility of overlooking metastasis.

Similarly, in 2018, a prospective randomized clinical trial with 120 patients with intermediate or high risk prostate cancer undergoing extended PLD in robot-assisted radical prostatectomy was conducted by Harke *et al.* (42).

Patients were prospectively randomized into two groups: the intervention group receiving the transrectally injection of ICG into the prostate before the docking of the robot and the control group undergoing conventional extended PLD. The authors concluded that even if ICG seemed to be beneficial for a more meticulous diagnostic approach and for a better understanding of the lymphatic drainage, the sensitivity of the procedure was not sufficient to recommend stand-alone ICG-PLD.

More recently, in 2020, Shimbo *et al.* (43) reported their experience with ICG-guided extended PLD during 100 robot-assisted radical prostatectomies. They concluded that although the direct role of fluorescent LN in SLN identification appeared to be limited (34% sensitivity and 64.8% specificity rates), the identification of 5 main lymphatic pathways could contribute to high-quality extended PLD.

Interestingly, Jeschke *et al.* (32) investigated the feasibility of visualizing the prostate lymphatic drainage by injecting 2.5 mL of ICG into each prostatic lobe of 26 consecutive patients with clinically localized prostate cancer and compared these results with the standard ^{99m}Tc-labelled colloid radio-guided SLN dissection. The fluorescent approach allowed the real-time visualization of the lymphatic vessels and the identification of additional 120 LNs compared with the ^{99m}Tc exploration alone.

To go further, van der Poel (34) developed a hybrid multimodal radiocolloid, the ICG-^{99m}Tc-nanocolloid, with the aim to optimize the SLN dissection during 11 robot-assisted laparoscopic prostatectomies associated with an increased risk of LN metastasis. Being it both radioactive and fluorescent, a single administration allowed for pre-operative SLN mapping through SPECT/CT guidance and intra-operative fluorescence detection through NIR fluorescence laparoscopy. While the real-time fluorescence guidance proved particularly valuable in areas, where accurate gamma tracing was hindered by background signals, the fluorescence detection was limited by the severe tissue attenuation of the signal.

To confirm the efficacy of the ICG-^{99m}Tc-nanocolloid for SNL detection, Meershoek *et al.* (36) proved that this hybrid tracer outperformed free ICG in a masked, randomized controlled trial wherein prostate cancer patients received either ICG-^{99m}Tc-nanocolloid (n=15) or ICG-^{99m}Tc-nanocolloid and free ICG (n=10) before robot-assisted SLN biopsy and extended PLD.

To go further, Van den Berg *et al.* (37) presented the first-in-human multispectral fluorescence imaging approach in 10 patients with prostate cancer in which ICG-^{99m}Tc-nanocolloid-based SLN identification was supported by additional lymphangiographic guidance provided by fluorescein. The multispectral imaging allowed the identification of different anatomic features: while the ICG-^{99m}Tc-nanocolloid-based imaging visualized 85.3% of SLNs, the fluorescein imaging identified the lymphatic ducts in 80% of patients. These findings suggested that the lymphangiographic tracer could provide additional information during SLN biopsy and that FGS using differently coloured dyes may improve functional and oncological outcomes in patients affected by prostate cancer.

The use of the ICG-^{99m}Tc hybrid tracer has been widely investigated not only as a SLN marker but also as a tool for the identification of tumour margins during prostate cancer dissections. Unfortunately, only unreliable results have been achieved so far; therefore more sensitive and specific probes have been developed in preclinical studies. In particular, in prostate specific membrane antigen (PSMA)-positive prostate cancers, the conjugation of a NIR light-emitting dye with PSMA-inhibitors have been extensively investigated (44-47). The success of these preclinical studies has high potential for the clinical translation of these fluorescently labelled probes. In the foreseeable future, they could lead to a better visualization of tumour margins and increased oncological outcomes during prostate cancer surgery.

Penis

The role of FGS has been also investigated for the surgical treatment of penile carcinomas and precancerous lesions of the penis (48,49).

Penis laser therapy should be preferred to more radical and mutilating curative surgeries in younger and sexually active patients in order to preserve the organ function and the overall quality of life. However, a significant increase in the local recurrence rate have been reported by several authors (50-52). In this scenario, FGS may be beneficial to improve the detection rate of penile neoplastic lesions and their tumour margins to allow a more complete radical surgery.

In particular, Schlenker *et al.* (49) investigated the long-term recurrence rate of 26 patients affected by premalignant CIS (n=11) and invasive penile carcinoma (n=15) treated by 5-ALA-guided laser coagulation. Noteworthy, no intra- or peri- operative side effects were observed and a significant reduction in the rate of local recurrence was reported compared to the 48% reported in literature for laser therapy. In particular, local recurrence did not occur in Tis patients while it was recorded in 26.7% of patients with invasive penile carcinoma, 3 of whom developed more than 3 years after a first surgical procedure and were more likely "de novo" cases.

The same fluorescent dye has been adopted for achieving maximum tumour resection of penile-scrotal extramammary Paget's disease (48). Despite the small sample size of the study (only 5 patients were included), not only the 5-ALA helped to define the tumour margins, but it also allowed the identification of 31 distant scatter lesions, which in 4 cases proved to be positive after serial biopsies pathology.

The ICG-^{99m}Tc hybrid tracer has been also investigated for the intraoperative optical SLN identification in case of penile cancer (53,54).

In particular, Brouwer *et al.* (53) reported the advantages of the ICG-^{99m}Tc-nanocolloid compared to the gold standard combination of the radiocolloid with blue dye in 65 patients with penile squamous cell carcinoma. Noteworthy, the ICG-base fluorescent imaging enabled the visualisation of 96.8% of SLNs, while only 55.7% was stained by blue dye (P<0.0001).

Similar results were also confirmed by a larger study enrolling 400 patients, as published by Dell'Oglio *et al.* (54). The analysis of the 266 patients who received both the ICG-^{99m}Tc-nanocolloid and blue dye revealed that the fluorescence imaging yielded a 39% higher SLN detection rate than the blue dye (95% CI: 36–43%, P<0.001).

Application in paediatric urogenital surgery

Although the available literature has been mostly focused on FGS in adult surgery, more recently, there has been an increasing interest in its application in paediatric urology.

In the field of paediatric oncology, Abdelhafeez *et al.* (55) described the use of ICG to facilitate accurate, real-time recognition of 12 renal tumours (5 Wilms tumours and an epithelioid angiomyolipoma) at the time of nephron-sparing surgery. The intravenous infusion of ICG the day before surgery (1.5 mg/kg) allowed the successful localization of hypo-fluorescing tumours in all 8 patients.

In 2016, Herz *et al.* (56) described its application in 6 paediatric robot assisted laparoscopic heminephrectomies (HNs) with the ultimate aim to reduce the risk of innocent moiety injury. In particular, ICG-FGS helped to highlight unexpected renal vascular anatomy in 3 children, saving the remaining moiety from possible iatrogenic injuries and avoiding massive intraoperative bleeding.

In one case, a vessel that was believed to be perfusing the lower affected moiety was in fact perfusing the upper innocent moiety. Had selective arterial mapping not been used, that artery would most likely have been ligated, leading to innocent moiety loss. Two of the three other cases showed continued vascularization of the moiety to be excised, despite ligating what was believed to be the perfusing vessels. ICG-FGS showed the remaining vessels and allowed for safe moiety removal.

Esposito *et al.* (57) compared the results of 9 ICG-guided HNs with 52 standard laparoscopic HNs in children. They observed that the fluorescence-guided procedures were associated with lower median operative times (75.5 *vs.* 166.2 min; P<0.001) and with a lower rate of postoperative complications (0% *vs.* 19.2%; P<0.001).

The same authors described the use of ICG in 4 robot-assisted deroofing of simple renal cysts, which resulted in a lower incidence of residual liquid on the bottom of the cyst on long term follow-up, compared to 10 standard minimally invasive approaches (0% *vs.* 61.5%; P<0.001).

Interestingly, the comparative analysis between 3 ICG-guided and 149 standard laparoscopic nephrectomies showed no significant difference between the two techniques regarding the median operative time (52 *vs.* 47 min; P=0.33), the overall success rate (100% *vs.* 100%; P=0.33) and the postoperative complications rate (0% *vs.*

0.9%; P=0.33) (45).

Conversely, ICG optical imaging was reported to allow a safer dissection of the renal hilum in two patients undergoing a retroperitoneal laparoscopic nephrectomy in the series of procedures collected by Fernández-Bautista *et al.* (58).

They also adopted the intravenous injection of ICG to perform an angiography-assisted laparoscopic varicocelectomy in a 13-year-old boy with asymmetric testes and testicular pain. This allowed a safer selection and ligation of all the vascular structures of the spermatic cord without compromising the lymphatic vessels.

On the other hand, Esposito *et al.* (59) preferred the ICG-guided fluorescence lymphography as a highly reliable technique to perform 41 paediatric minimally invasive varicocelectomies. In their series, 2 mL of ICG solution (5 mg/dL) was injected in the left testicle of 25 boys with grade II or III left varicocele. During surgery, the lymphatic vessels were easily isolated and spared. As a consequence, at 18-months' follow-up, no persistence or recurrence of varicocele and no postoperative hydrocele were recorded.

Future perspectives and potential new applications of FGS in urology

Although the past decade has witnessed meaningful advances in the clinical application and technical development of FGS, there is still room for further developments.

To date, biomedical fluorescence imaging has mainly relied on NIR-I (wavelength: 700–900 nm) dyes, which have been preferred over visible light (wavelength: 380–800 nm) due to the less tissue autofluorescence and absorbance. However, the limited tissue penetration (up to 10 mm) and the low tissue contrast of NIR-I dyes have reduced their clinical applications. More recently, studies are investigating NIR-II (wavelength: 1,000–2,000 nm) dyes as promising tools for achieving higher contrast, greater sensitivity and improved penetration depths with interesting surgical applications in adult and paediatric urology (60).

To increase the signal from tumour cells and to minimize background noise, not only NIR-II fluorophores but also tumour-specific targeted probes are currently under investigation. In this regards, Hekman *et al.* (6,7) has published the first human study on the use of ^{111}In-DOTA-girentuximab-IRDye800CW to improve intraoperative visualization of clear cell renal cell carcinoma.

Finally, complementary analytical tools, such as artificial intelligence, can be added to a fluorescence optical imaging system to improve decision-making proficiency of FGS (61).

Conclusions

The available literature has shown that FGS could be considered a powerful tool to improve oncological, anatomical and functional outcomes in both adult and paediatric urology. An increased identification of SLNs, a more accurate visualization of tumour margins and an better definition of blood supply and lymphatic drainage have been described as greatly beneficial for patients undergoing urological procedures. Longitudinal studies with wider sample sizes are still needed to draw firm conclusions and to confirm its benefits in the clinical scenario.

Acknowledgments

Funding: This work was supported by Associazione per il Bambino Nefropatico ABN Onlus, 20122 Milano, Via Commenda.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *AME Medical Journal*, for the series "New Frontiers and Technologies in Urology". The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://amj.amegroups.com/article/view/10.21037/amj-20-194/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://amj.amegroups.com/article/view/10.21037/amj-20-194/coif). The series "New Frontiers and Technologies in Urology" was commissioned by the editorial office without any funding or sponsorship. GM served as the unpaid Guest Editor of the series and serves as an unpaid editorial board member of *AME Medical Journal*. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/amj-20-194
Cite this article as: Paraboschi I, Farneti F, Jannello L, Manzoni G, Berrettini A, Mantica G. Narrative review on applications of fluorescence-guided surgery in adult and paediatric urology. AME Med J 2022;7:15.