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Review

New imaging technologies for robotic kidney cancer surgery

Stefano Puliatti [a,b,*,1], Ahmed Eissa [c,1], Enrico Checcucci [d], Pietro Piazza [e], Marco Amato [a], Stefania Ferretti [a], Simone Scarcella [f], Juan Gomez Rivas [g,h], Mark Taratkin [g,i], Josè Marenco [g,j], Ines Belenchon Rivero [k], Karl-Friedrich Kowalewski [l], Giovanni Cacciamani [m], Ahmed El-Sherbiny [c], Ahmed Zoeir [c], Abdelhamid M. El-Bahnasy [c], Ruben De Groote [b,n], Alexandre Mottrie [b,n], Salvatore Micali [a]

[a] *Urology Department, University of Modena & Reggio Emilia, Modena, Italy*
[b] *ORSI Academy, Melle, Belgium*
[c] *Urology Department, Faculty of Medicine, Tanta University, Tanta, Egypt*
[d] *Department of Surgery, Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Turin, Italy*
[e] *Division of Urology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy*
[f] *Department of Urology, Polytechnic University of Marche Region, Umberto I Hospital "Ospedali Riuniti", Ancona, Italy*
[g] *Uro-technology and SoMe Working Group of the Young Academic Urologists Working Party, European Association of Urology, Arnhem, the Netherlands*
[h] *Department of Urology, Hospital Clinico San Carlos, Madrid, Spain*
[i] *Institute for Urology and Reproductive Health, Sechenov University, Moscow, Russia*
[j] *Department of Urology, Fundación Instituto Valenciano de Oncología, Valencia, Spain*
[k] *Urology and Nephrology Department, Virgen del Rocío University Hospital, Manuel Siurot Sin Numero, Seville, Spain*
[l] *Department of Urology and Urological Surgery, University Medical Centre Mannheim, Mannheim, Germany*
[m] *USC Institute of Urology, University of Southern California, Los Angeles, CA, USA*
[n] *Department of Urology, Onze-Lieve-Vrouwziekenhuis, Aalst, Belgium*

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* Corresponding author. Urology Department, University of Modena & Reggio Emilia, Modena, Italy.
E-mail address: Stefano.puliatti@unimore.it (S. Puliatti).
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[1] The authors contribute equally to the article.

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Abstract *Objective:* Kidney cancers account for approximately 2% of all newly diagnosed cancer in 2020. Among the primary treatment options for kidney cancer, urologist may choose between radical or partial nephrectomy, or ablative therapies. Nowadays, robotic-assisted partial nephrectomy (RAPN) for the management of renal cancers has gained popularity, up to being considered the gold standard. However, RAPN is a challenging procedure with a steep learning curve.

Methods: In this narrative review, different imaging technologies used to guide and aid RAPN are discussed.

Results: Three-dimensional visualization technology has been extensively discussed in RAPN, showing its value in enhancing robotic-surgery training, patient counseling, surgical planning, and intraoperative guidance. Intraoperative imaging technologies such as intracorporeal ultrasound, near-infrared fluorescent imaging, and intraoperative pathological examination can also be used to improve the outcomes following RAPN. Finally, artificial intelligence may play a role in the field of RAPN soon.

Conclusion: RAPN is a complex surgery; however, many imaging technologies may play an important role in facilitating it.

1. Introduction

In 2020, renal cancers (RCs) were the 16th most commonly diagnosed cancers worldwide accounting for approximately 2.2% of all cancer diagnoses [1]. Furthermore, RCs were responsible for 1.8% of all cancer-related mortality rendering it among the deadliest urological tumors with a 5-year survival rate of 12% [1,2]. Over the past decade, a slightly increasing trend can be observed for both RC diagnosis and mortality [3]. Renal cell carcinoma (RCC) represents more than 90% of all RCs [3]. Currently, surgical intervention is considered the treatment of choice for most RCCs [4]. The first elective nephrectomy and partial nephrectomy (PN) were performed in the second half of the 19th century. Since then, radical nephrectomy and PN have become the cornerstone of surgical treatment for renal tumors [5]. The first milestone of minimally invasive surgery was settled when Clayman et al. [6] reported the first case of laparoscopic nephrectomy for a renal tumor in an 85-year-old patient. Two years later, the first laparoscopic PN was reported [5]. The second milestone of minimally invasive renal surgery was reported in the early 2000s, when the robotic platform was used for the first time in the management of RCs [7]. The technological advancements and the improvements in the surgical techniques resulted in an increasing interest and expansion of indications for PN [8,9]. Thus, PN became the standard of care for cT1 renal tumors and for selected cT2 ones, due to the advantage of ideal tumor control with the maximal preservation of the renal function [10]. In these settings, the use of PN in the USA has increased from 40.2% in 2004 to 71.3% in 2015, while radical nephrectomy's use has decreased from 59.8% to 28.7% during the same time span [11]. Similarly, the utilization of PN for the management of localized renal tumors has increased by 4.5 folds in Europe over the period from 1987 to 2007 [12]. Furthermore, the rate of robotic-assisted PN (RAPN) has drastically increased, while laparoscopic and open approaches have shown a constant decrease, in the USA, over the same period of time [13].

Noteworthy, RAPN is considered a challenging procedure with a steep learning curve as it carries a substantial risk of intraoperative bleeding especially among less experienced surgeons. Furthermore, the value of warm ischemia time (WIT) remains controversial [14]; however, longer WIT may have injurious effect on the postoperative kidney function [15]. Finally, the reproducibility of each case is limited, due to the inherent differences of each tumor regarding its location, depth, number of vessels, and its relations with surrounding structures [16]. Renal imaging is of paramount importance as it allows the surgeon to create a surgical roadmap and provides a comprehensive understanding of the patient-specific anatomy; however, this roadmap is based on bi-dimensional conventional imaging that may result in suboptimal evaluation of the patient's anatomy. In this setting, several technological advancements have been proposed to enhance these techniques and improve the surgical outcomes [10]. In the current review, innovative imaging technologies that may aid robotic RC surgery will be discussed.

2. Three-dimensional (3D) reconstruction

2.1. Training

Training is the essence of robotic surgery. Historically, training was based on the Halstedian model of "see one, do one, teach one"; however, this has changed overtime to proficiency-based training [17–19]. Moreover, the utilization of several training modalities such as mentored operative practice and procedural simulation using cadaveric and animal models, is limited by the associated high cost, ethical considerations, and the lack of specific pathology [20]. Herein, the value of 3D-printing for surgical training lies in this, which allows the creation of application-specific models [16,19]. Noteworthy, models' validity (the ability of these models to assess the competencies for which they are developed) is an important issue to consider in the field of training. Generally, there are different types of validity including face validity (assessment of the realism of the model), content validity (the ability of the model to assess what it was designed to measure), construct validity (the ability of the model to differentiate between different levels of experience), and criterion validity (the ability of the model to predict the performance of the trainee) [18].

RAPN is a demanding surgery with a steep learning curve ranging from 20 cases for console time optimization, 30 cases for WIT to reach a plateau, and can reach up to 150 cases to achieve competence in some studies [20,21]. Monda et al. [21] developed silicone renal tumor models for the purpose of RAPN training; in the study, 24 participants with different surgical experience (ranging from medical students to fellows and attending urologists) were involved in this study; overall the silicone model demonstrated a high face, content, and construct validity [21]. Similarly, Ghazi et al. [20] created a highly realistic 3D-printed renal model, where they increased the realism of the model by filling the tumor with a mixture of polyvinyl alcohol, iodinated contrast, and fluorescent dye to provide a realistic radiological appearance of the tissue and allow the detection of positive surgical margins. Furthermore, the hollow structures, such as the renal vasculature and pelvicalyceal system, were injected with artificial blood and urine to allow the simulation of intraoperative bleeding and urine leakage in the model. The authors demonstrated construct and criterion validity of the model with excellent ability of operative steps simulation. Some authors demonstrated that this 3D-printed-based simulators may enhance the actual surgical performance, shorten the learning curve, and improve the peri-operative outcomes in terms of clamping precision, operative time, estimated blood loss, and WIT [16,19,22—24].

2.2. Patients' education and counseling

Conventional preoperative renal imaging is essential during patient counseling to aid the shared decision-making process. However, patients and their families might experience difficulties in interpreting and conceptualizing the bi-dimensional imaging [25]. In this setting, 3D-printed models may enhance the patients' understanding of the nature of their tumors and all the available treatment options. Silberstein et al. [26] and Wake et al. [25] reported that patients showed more comprehensive understanding of their tumor anatomy and the surgical procedure when they were shown 3D-printed models. These findings were further confirmed by several authors [27,28], demonstrating the value of these models especially among elderly patients [27].

2.3. Predicting surgical complexity (renal nephrometry scores)

Generally, the tumor factors (*i.e.*, size and complexity) influence the outcomes of RAPN [29]. In this setting, different nephrometry scores have been developed to predict the perioperative outcomes in patients undergoing RAPN; however, most of these scores are based on conventional bi-dimensional imaging, which may provide suboptimal information about renal anatomy. Therefore, the use of 3D virtual models has been proposed to enhance the predictive performance of these models [30,31], due to their ability of providing better insight on tumor's depth and its relation with the surrounding structure, when compared to bi-dimensional images [31,32]. When evaluated via 3D virtual models, nephrometry scores were downgraded in 14%—67% of patients. Furthermore, scores calculated using the 3D virtual models, have shown higher accuracy in predicting complications [30—33]. Interestingly, Huang et al. [34] developed a 3D-based nephrometry score (ROADS score) to guide the surgical plan of hilar tumors. Similarly, Bianchi et al. [35] reported that the complication rate was significantly higher in patients with involvement of the urinary collecting system, endophytic masses, and tumors supplied by primary or secondary segmental arteries on the 3D virtual model, while longer WIT occurred more frequently in patients with higher tumor contact surface area with the kidney and higher endophytic rate on the 3D virtual models.

2.4. Surgical planning

Traditionally surgical planning is based on the conventional bi-dimensional images, which requires complex cognitive processing to conceptualize a 3D reconstructed image from these bi-dimensional images and translate this information to different surgical situations [4]. In this setting, several authors studied the impact of 3D surgical planning on RAPN outcomes [4,23,24,28,36—43]. A 3D surgical planning refers to the development of a patient-specific virtual or physical models that can be used to guide the decision-making process, creating a surgical roadmap, and increasing the surgeons' confidence in treating complex renal tumors [44,45].

The 3D-models-based surgical planning is associated with significantly lower operative time, clamping time, and estimated blood loss [24,39]. These findings have been further confirmed in a randomized controlled trial [36], where 44 and 48 patients were randomized to the 3D virtual model group and the control group, respectively. The authors reported that patients in the control group (no 3D virtual model planning) were significantly more likely to have longer hospitalization time (odds ratio [OR] 2.86, 95% confidence interval [CI], 1.59—5.14), and higher estimated blood loss (OR 1.98, 95% CI, 1.04—3.78), when compared with the study group [36].

Interestingly, the indication for PN was only 47.2% when the computed tomography (CT) images of 20 complex renal masses were shown to urologists, while it increased to 74.5% when the 3D virtual models of the same patients were provided [40]. Similarly, McDonald and Shirk [4] showed that 3D virtual models resulted in changes in the operative plans in 40.0% of the patients. Furthermore, surgical planning using 3D virtual models was associated with significantly higher rates of selective and super-selective clamping compared to the conventional bi-dimensional imaging studies (34.5% and 1.7% *vs.* 17.2% and 0.0%, respectively; $p=0.02$) [30]. Finally, currently published literature has shown a tendency towards increased rate of selective, super-selective, and zero ischemia RAPN when the surgical planning was performed using 3D virtual models [38,41,43].

2.5. 3D-volumetry

Recently, renal volumetric assessment using CT has gained popularity as alternative to mercapto-acetyl triglycine scan for the assessment of split renal function in radical nephrectomy. The renal cortex volume is, indeed, considered a strong predictor of postoperative renal function as it may reflect the available nephron mass [46,47]. In this setting, Mitsui et al. [46] used the 3D-volumetric assessment of the renal cortex together with the measurement of the tumor margins from the resected specimen to accurately predict postoperative renal function after RAPN. Interestingly, the 3D-volumetric assessment of adherent perinephric fat has been proven to accurately predict the console time in patients undergoing RAPN, which in turn may reflect the complexity of the procedure [48].

2.6. Hologram

Holographic reconstruction is a novel technology that creates a fully immersive, interactive, and versatile experience based on 3D-visualization technology, which allows surgeons to better appreciate patient-specific anatomy. This technology is still in its early phases, with only two studies published on its use in the urological field [49,50]. The first study showed that holographic reconstruction was associated with higher interobserver agreement for all the anatomical details compared to conventional CT imaging [50]. Starting from this evidence, Zeng et al. [49] assessed the value of this technology on the perioperative outcomes of RAPN showing that hologram use was associated with shorter operative time and lower perioperative complication rates.

2.7. Intraoperative navigation

Another possible application of 3D-visualization technology is its use for intraoperative navigation. Initially, 3D virtual models were observed in the robotic console below the standard endoscopic view and oriented (usually by an assistant) according to the kidney orientation [51—55]. A propensity score matched analysis of patients undergoing RAPN with and without 3D virtual model guidance (157 patients in each group) showed that 3D-guided RAPN was associated with significantly lower major complication rates (3.8% *vs.* 9.5%, $p=0.04$), lower estimated glomerular filtration rate (eGFR) loss (-5.6% *vs.* -10.5%, $p=0.002$), and significantly higher trifecta rate (55.7% *vs.* 45.2%, $p=0.005$) compared to the control group [55]. Furthermore, this technology can be used to guide selective arterial clamping [51], and reduce the risk of complications in patients with hilar tumors [53].

Interestingly, some surgeons have gone further and superimposed the 3D-reconstructed virtual models over the *in vivo* anatomy on the endoscopic view of the robotic console to create an augmented reality environment during RAPN [56—58]. Porpiglia et al. [57] compared the augmented reality-guided RAPN (AR-RAPN) and intraoperative ultrasonography (US)-guided RAPN demonstrating lower rates of global ischemia, higher rates of tumor enucleation, and lower complication rates in patients undergoing AR-RAPN [57]. Furthermore, patients undergoing AR-RAPN showed significantly higher renal parenchymal preservation [59], higher rates of selective clamping [60], and lower loss of renal function [58]. Interestingly, 87% of urologists appreciated the role of augmented reality navigation for operative guidance and training in urologic robotic surgery [61,62].

Noteworthy, image-guided surgery (intraoperative navigation using preoperative imaging studies) requires accurate alignment of the 3D virtual model with the *in vivo* anatomy (a process known as registration). Registration can be performed using specific intrinsic anatomical landmarks (points) or special markers inserted prior to imaging to act as a landmark for alignment (fiducials). Kidney registration is particularly challenging due to the lack of specific landmarks [63]. In this setting, some authors proposed a touch-based registration and re-registration system during RAPN [64,65]. Touch-based registration depends on the intraoperative tracking of the robotic instrument tip over a surface anatomy creating a 3D surface point set that has been previously registered to the preoperatively segmented patient images [64].

3. Intraoperative imagine

3.1. Morphological intraoperative imaging

Accurate tumor identification is among the fundamental steps of RAPN to ensure optimal cancer control; however, tissue distortion and endophytic tumors can represent a major challenge. To date, intracorporeal visualization of the tumor using US has been considered the simplest approach to assist tumor identification [10]. Intraoperative US during RAPN can be performed using laparoscopic US probe to identify completely endophytic tumors [66], or to facilitate hilar dissection and renal arterial clamping using laparoscopic Doppler US probe [67]. Furthermore, contrast enhanced US for intraoperative mapping of renal and tumor vasculature may expand the indications for selective arterial clamping [68]. However, one of the main limitations of the laparoscopic US probe is that it may interrupt the surgeon as it is controlled by the assistant. Preferably, a drop-in robotic US probe controlled by the console surgeon can be used [69]. Interestingly, a transesophageal echocardiography has been applied safely to identify the proximal extent of an inferior vena cava thrombus in a patient undergoing robotic-assisted radical nephrectomy with inferior vena cava thrombectomy [70].

3.2. Fluorescence intraoperative imaging

The 3D-visualization technology can provide comprehensive understanding of renal vasculature and guide selective arterial clamping; however, it does not allow "real-time" confirmation of ischemia. Intraoperative fluorescent imaging has been proposed to overcome this limitation during radical nephrectomy and PN [71]. Intraoperative fluorescent imaging is based on the concept that near infrared (NIR) wavelength light energy (700–1000 nm) can be detected using high-resolution NIR camera (such as the Firefly® mode in the da Vinci robotic platform) and coded by a pseudocoloring software into green colored outcome [72]. The most commonly used fluorescent dye in the urological practice is indocyanine green (ICG) [73].

During PN, the optimal ischemia time remains a matter of debate in the literature. It is generally believed that a WIT cutoff value of 20–25 min is warranted to preserve the postoperative renal function. However, there are some evidences that a WIT of >30 min in patients with bilateral normal functioning kidneys may not impact the long-term renal function after on-clamp PN [14,74,75]. However, a prolonged WIT is believed to have an injurious effect on the renal function [76]. On the contrary, the off-clamp approach can reduce the postoperative loss of renal function; however, it is a challenging approach that may be associated with an increased risk of intraoperative bleeding disturbing the endoscopic vision and subsequently increasing the rate of positive surgical margins [77]. Considering the functional outcomes, Krane et al. [78] showed that there is no significant difference between different clamping techniques (arterial and venous clamping, arterial clamping, and clampless) as regards the eGFR drop ($p=0.79$). Similarly, the CLamp versus Off Clamp the Kidney (CLOCK) study comparing between on-clamp (<20 min) and off-clamp PN reported no significant difference between both groups as regards the absolute variation in eGFR and ipsilateral split renal function. Noteworthy, this study was carried out in patients with bilateral normal functioning kidneys and cT1 tumor (R.E.N.A.L nephrometry score ≤10) [79]. Interestingly, Ferriero et al. [80] demonstrated that RAPN's learning curve (in surgeons who have completed the required training in minimally invasive surgery) does not affect both functional and oncological outcomes in patients undergoing clampless approach. Over the last decade, urologists have shown increasing interest in selective and super-selective clamping in order to provide the optimal balance between renal functional preservation and renal ischemia [77,81]. ICG can be used to obtain intraoperative imaging of arterial perfusion of the kidney to identify the different branches of the main renal artery, which may reduce the WIT [82] and/or aid selective arterial clamping [83]. A large multi-institutional study including 318 patients confirmed the value of ICG-guidance in expanding the indications for RAPN and increasing the rate of selective arterial clamping [83]. Likewise, several authors demonstrated the feasibility of selective and super-selective clamping under ICG-guidance, which resulted in a superior postoperative renal function preservation [84–89]. A pooled analysis of six comparative studies demonstrated that NIR- or ICG-guided RAPN was associated with shorter WIT; however, there was no significant difference regarding operative time, estimated blood loss, and postoperative complications. Furthermore, this meta-analysis confirmed significantly higher eGFR preservation for ICG-guided RAPN at short-term follow-up (1–3 months) [71].

Moreover, ICG can be used for the differentiation between benign and malignant renal tissues as ICG binds to a transmembrane protein known as bilitranslocase that allows ICG to perfuse intracellularly and accumulate in the proximal convoluted tubules without accumulation in the malignant renal tissues (as cancerous renal cells do not express bilitranslocase). Thus, normal renal parenchyma appears fluorescent under NIR light, while tumorous tissue is hypofluorescent or afluorescent [72]. Sentell et al. [90] demonstrated that differential fluorescence was exhibited in 89.9% of RCCs, 71.9% of oncocytomas, 100.0% of cystic benign tumors, and 16.7% of angiomyolipomas, with an overall success rate of 87.3%. Similarly, Angell et al. [91] achieved differential fluorescence in 82.0% of the patients. Generally, successful tumor differentiation ranges between 73% and 100% of the cases [92]. Importantly, a retrospective study correlating the histopathological findings with the fluorescence patterns at an ICG dose of 5.0–7.5 mg (2–3 mL) reported a limited specificity (57%) and low negative predictive value (52%) for differentiation between benign and malignant masses [93]. These variations were probably related to the lack of ICG dosing standardization, which is essential for achieving differential fluorescence as under-dosing may be associated with hypofluorescence of normal parenchyma and overdosing may lead to tumor fluorescence or hypofluorescence. Over- and under-dosing will generally result in ambiguity in the differentiation between benign and malignant renal tissues. A dose of 0.25–0.50 mL may allow higher rates of differential fluorescence [90].

Simone et al. [94] proposed a novel technique named "ride the green light" to identify completely intrarenal tumors during completely off-clamp RAPN through super-selective trans-arterial delivery of a mixture of ICG-lipiodol (which was added to delay ICG washout from the kidney). Furthermore, intraoperative ICG has been proposed for the evaluation of blood flow to the remaining parenchymal tissue after renorrhaphy especially in patients with chronic kidney disease [83,95]. Tumor-targeted fluorescent imaging is a promising advancement that has already been applied in different malignancies; however, in RCs it is still in its early days. In this technology, a fluorescent dye is conjugated to cancer-specific molecule to allow precise intraoperative imaging of the tumor [96]. Folate receptors are highly expressed in normal renal tissues but scarcely expressed in renal malignancies, which potentially allow fluorescence of the normal parenchyma without fluorescence of the renal tumor [97]. In this setting, OTL38 (On Target Laboratories LLC., West Lafayette, IN, USA), a fluorescent dye that targets folate receptors, was proposed for intraoperative imaging during PN [98]. Shum et al. [97] evaluated the value of OTL38-guided RAPN in three patients, with concordant findings among the population. These results were further confirmed in ten patients undergoing OTL38-guided RAPN [98]. Carbonic anhydrase IX is another target highly expressed in >95% of clear cell RCC but not in normal renal tissues. Girentuximab is a monoclonal antibody that can be used for targeting carbonic anhydrase IX; however, this has not yet been evaluated in clinical studies [96]. Finally, an *ex-vivo* study proposed a dual-modality tumor-targeted imaging to combine the advantage of high penetration of gamma radiations and the advantage of better tumor delineation by the fluorescent imaging by using indium^{111}-girentuximab-

IRDye800CW. This study demonstrated that dual-modality tumor-targeted imaging can accurately identify clear cell RCC [99]. However, there are still scarce data in the literature to support the value of intraoperative tumor-targeted imaging in patients undergoing RAPN.

3.3. Pathological intraoperative imaging

In the era of precise medicine, surgical intervention should be tailored according to patient-specific condition in order to achieve complete cancer control without compromising the negative surgical margins [100—102]. In this setting, urologists have shown increasing interest in the field of intraoperative pathological imaging. To date, intraoperative frozen section is considered the gold standard for pathological examination of surgical margins; however, in patients undergoing PN, where "time is parenchyma", this technique carries several drawbacks due to its time consuming nature and its high rate of false negative, when compared with conventional pathology [103]. Several technologies have been proposed to overcome the limitations including *ex-vivo* fluorescence confocal microscopy [103,104], confocal endomicroscopy [105], and optical coherence tomography [96].

Fluorescence confocal microscopy (VivaScope® 2500M-G4, MAVIG GmbH, Munich, Germany; Caliber I.D., Rochester, NY, USA) is an innovative technology that uses two different wavelengths of laser (785 nm and 488 nm) to provide quickly available images of fresh unprepared specimens similar to the hematoxylin and eosin staining. Initially, this technology was applied to prostatic tissue showing its ability to differentiate between malignant from benign prostatic tissues [106,107]. Later on, fluorescence confocal microscopy was applied in the field of renal biopsy showing high accuracy in the diagnosis of chronic renal lesions such as tubular atrophy, fibrosis, and glomerulosclerosis [104]. Furthermore, it has shown high accuracy (91%), sensitivity (98%), specificity (81%), and area under the curve (0.94) in the detection of benign and cancerous renal tissues [103].

Similarly, confocal laser endomicroscopy is an optical technology that can provide an *in-vivo* real-time images of tissues at microscopic level after injection of a fluorescent dye to augment cellular and tissue architecture. This technology has successfully been used for differentiation between benign and malignant small renal masses [105].

On the same hand, optical coherence tomography uses light reflected from tissue to identify tissue's microstructure. *Ex-vivo* studies of optical coherence tomography has shown its ability to differentiate between benign and malignant renal tissue [96].

Generally, all these technologies have not yet been applied in the clinical practice of RAPN; however, they may have the potential to guide the treatment of small renal masses and improve cancer control in RAPN.

4. Artificial intelligence (AI)

AI refers to the computer science that aims to provide machines with intelligence potentials mimicking human intellect, thus allowing them to perform complex tasks such as visual perception, speech recognition, and language processing [108]. So far, AI has been mainly applied in robotic-assisted urological surgery for skills assessment [109]. Few studies in the literature discussed the value of AI in RAPN [110—112]. The first article developed an AI model that was capable of predicting intraoperative events based on patient demographics and preoperative data, and postoperative events based on intraoperative data [110]. The second article used AI for the recognition of RAPN surgical workflow [111]. Finally, AI was used for computational analysis of the endoscopic view to provide further information that might be camouflaged to naked eyes. In this setting, AI was used to guide hilar dissection during RAPN to detect faint motion of connective tissue surfaces resulting from the pulsation of hidden blood vessels [112].

5. Conclusion

Robotic-assisted surgery for kidney cancers is a complex surgery with a steep learning curve. Several imaging technologies have been applied to aid tumor identification and vascular dissection such as 3D-visualization technology for purpose of training and to create a surgical road map, intraoperative imaging to aid tumor localization, and AI to facilitate complex renal surgeries.

Author contributions

Study concept and design: Stefano Puliatti, Ahmed Eissa, Salvatore Micali, Alexandere Mottrie.
Data acquisition: Ahmed Eissa, Stefano Puliatti, Ahmed El-Sherbiny, Marco Amato, Ahmed Zoeir.
Data analysis: Marco Amato, Pietro Piazza, Enrico Checcucci, Stefano Puliatti, Ahmed Eissa.
Drafting of manuscript: Simone Scarcella, Ahmed Eissa, Stefano Puliatti, Juan Gomez Rivas, Mark Taratkin, Josè Marenco, Ines Belenchon Rivero, Karl-Friedrich Kowalewski, Ruben De Groote.
Critical revision of the manuscript: Stefania Ferretti, Giovanni Cacciamani, Abdelhamid M. El-Bahnasy, Alexandre Mottrie, Salvatore Micali.

Conflicts of interest

The authors declare no conflict of interest.

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