

## Precision surgery and genitourinary cancers



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### Abstract

The landscape of the surgical management of urologic malignancies has dramatically changed over the past 20 years. On one side, better diagnostic and prognostic tools allowed better patient selection and more reliable surgical planning. On the other hand, the implementation of minimally invasive techniques and technologies, such as robot-assisted laparoscopy surgery and image-guided surgery, allowed minimizing surgical morbidity. Ultimately, these advances have translated into a more tailored approach to the management of urologic cancer patients. Following the paradigm of “precision medicine”, contemporary urologic surgery has entered a technology-driven era of “precision surgery”, which entails a range of surgical procedures tailored to combine maximal treatment efficacy with minimal impact on patient function and health related quality of life. Aim of this non-systematic review is to provide a critical analysis of the most recent advances in the field of surgical uro-oncology, and to define the current and future role of “precision surgery” in the management of genitourinary cancers. © 2017 Elsevier Ltd, BASO ~ The Association for Cancer Surgery, and the European Society of Surgical Oncology. All rights reserved.

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### Introduction

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allowed better patient selection and more reliable surgical planning. On the other hand, the implementation of minimally invasive techniques and technologies, such as robot-assisted laparoscopy surgery and image-guided surgery, allowed minimizing surgical morbidity. Ultimately, these advances have translated into a more tailored approach to the management of urologic cancer patients. Following the paradigm of “precision medicine”, contemporary urologic surgery has entered a technology-driven era of “precision surgery”, which entails a range of surgical procedures tailored to combine maximal treatment efficacy with minimal impact on patient function and health related quality of life.<sup>1</sup> The aim of this non-systematic review is to

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provide a critical analysis of the most recent advances in the field of surgical uro-oncology, and to define the current and future role of “precision surgery” in the management of genitourinary cancers, with a focus on prostate, bladder and kidney cancer.

## Prostate cancer

Prostate cancer continues to have a high incidence in most industrialized countries, despite decreasing mortality rates.<sup>2</sup> Standardization in multi-parametric MRI techniques allowed better identification of clinically significant cancers,<sup>3</sup> as well as better disease staging.<sup>4</sup> Active surveillance has taken the stage and has been implemented with different protocols worldwide for very low-risk, low-risk, and selected intermediate-risk disease.<sup>5,6</sup> A better understanding of tumor biology and the availability of novel prognostic and diagnostic tools have significantly changed the paradigm in the management of this disease. Several genomic tests – such as Prolaris<sup>®</sup>, Oncotype DX<sup>®</sup>, and Decipher<sup>®</sup> – are already commercially available, and are now being used, in addition to traditional clinical nomograms, although their role is yet to be defined.<sup>7</sup> Recent introduction of 3D printing technology might further facilitate surgical planning (Fig. 1).

After the golden era of laparoscopic prostate surgery, modern prostate cancer surgery has been mainly driven by the rapid adoption of robot-assisted laparoscopy radical prostatectomy (RARP),<sup>8,9</sup> which now represents the gold standard treatment option in most industrialized countries.<sup>10,11</sup> Moreover, the implementation of multi-

parametric MRI imaging to prostate biopsy techniques<sup>12</sup> (Fig. 2) has paved the way to the concept of “focal therapy”.<sup>13</sup> This paragraph will be focused on these two main areas of clinical interest.

## Robotic surgery for prostate cancer

### Refinements in RALP technique

One of main advantages of robotic surgery is certainly represented by the magnification of the surgical field, allowing a better visualization and easier appreciation of fine anatomical details. Overall, a better understanding of surgical anatomy of the prostate has translated into recognition of key anatomical structures, and its possible variations. Thus, the RARP procedure can be regarded as an individualized operation that can be tailored to the specific characteristics of the patient and the cancer.<sup>14</sup> The “trifecta” (cancer control, continence, and potency) has become the standard metrics to assess the outcomes of RARP,<sup>15</sup> as patient reported health related quality of life is regarded as an important parameter to consider in prostate cancer treatment.<sup>16</sup> Therefore, refinements in surgical technique have been mainly directed towards the preservation of patient’s functions, namely urinary continence and sexuality.

Factors contributing to the continence status of men undergoing prostate cancer surgery have been extensively investigated. Besides preoperative parameters (such as age, prostate size, membranous urethral length, and BMI), the impact of surgical dissection, damage to neurovascular bundles, and postoperative fibrosis have been recognized

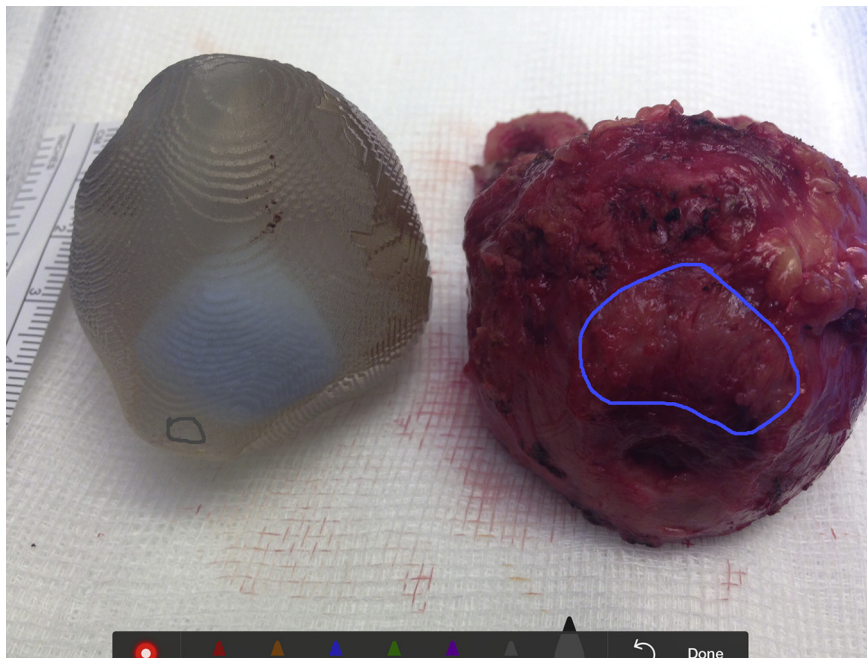


Figure 1. 3D printed prostate showing anterior T3 tumor close to sphincter (courtesy of Prof. Prokar Dasgupta, King’s College London, Guy’s Hospital, London, UK).



Figure 2. MRI-US fusion transperineal prostate biopsy (courtesy of Prof. Francesco Porpiglia, San Luigi Hospital, University of Turin, Orbassano, Italy).

(Fig. 3).<sup>17</sup> Several techniques aiming at restoring the disrupted anatomy secondary to the removal of the prostate gland have been investigated (Table 1).<sup>18–30</sup> These techniques are based on three key concepts: preservation (bladder neck sparing, puboprostatic ligaments, puboprostatic collar, pubovesical complex, urethral length); reconstruction (posterior and/or anterior reconstruction) (Fig. 4); reinforcement (bladder neck plication and/or sling suspension).<sup>31</sup> This

has also resulted in a debate on the use of a standard nomenclature – such as the one proposed by the ESUT – to facilitate outcome comparisons and surgical education.<sup>32</sup>

Sexual dysfunction can represent a common clinical issue in patients undergoing prostate cancer surgery.<sup>33</sup> Several factors contribute to postoperative recovery of erectile function, including patient characteristics (age, baseline erectile function, co-morbidities), surgical technique (non-versus uni- or

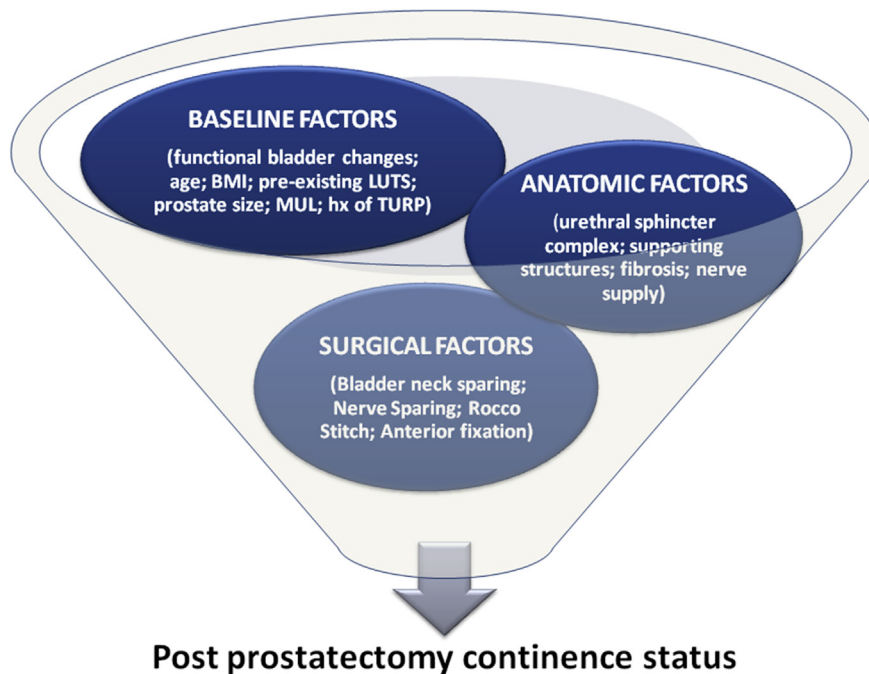


Figure 3. Factors contributing to urinary continence status post radical prostatectomy.<sup>17</sup>

Table 1  
Overview of surgical techniques aiming at improved continence status after RALP.

Anatomical principle	Reference	Technique
Preservation	Friedlander <sup>18</sup>	Bladder neck sparing
	Lim <sup>30</sup>	Retzius sparing
Reinforcement	Lee <sup>24</sup>	Bladder neck plication stitch
	Bahler <sup>22</sup>	Small intestinal submucosa bladder neck sling
	Lei <sup>19</sup>	Selective suture ligation of dorsal venous complex
	Patel <sup>20</sup>	Periurethral suspension stitch
	Nguyen <sup>21</sup>	Urethral sling fashioned from autologous vas deferens
Reconstruction	Dal Moro <sup>27</sup>	Complete Reconstruction of the Posterior Urethral Support (CORPUS)
	Propiglia <sup>23</sup>	Total anatomical reconstruction
	Student <sup>25</sup>	Advanced reconstruction of vesicourethral support (ARVUS)
	Jeong <sup>26</sup>	1-step posterior reconstruction
	Hurtes <sup>28</sup>	Anterior retropubic suspension with posterior reconstruction
	Coelho <sup>29</sup>	Modified posterior reconstruction

bi-lateral nerve sparing; extrafascial versus inter- or intrafascial), and surgeon factors (surgical volume and skills)<sup>34</sup> (Fig. 5). Despite extensive research in the field of prostate anatomy, controversies remain in regard to the location, distribution and function of periprostatic nerve fibers. Certainly, it is not possible to reproduce exactly the same dissection in every patient, and therefore the surgeon has to find for each case the best balance between an oncologic safe margin and the anatomical integrity of the nervous system (Fig. 6). As anatomical knowledge has increased, there has been a shift from the simplistic dichotomy “non-nerve sparing versus nerve sparing” or “intra-inter-extra-fascial” towards the

concept of “incremental nerve sparing” or “incremental safety margin”.<sup>14</sup> In this regard, grading systems have been proposed to define the extent of tissue margin on the prostate.<sup>10,35,36</sup> Tewari et al. proposed four grades of dissection by using the veins on the lateral aspect of the prostate as a vascular landmark.<sup>35</sup> Patel and coworkers proposed an inverse (grade 5 optimal nerve sparing, grade 1 no nerve sparing) five-grade scale by using the arterial periprostatic vasculature as landmark and by identifying a “landmark” artery.<sup>36</sup>

The concept that cautery-free dissection or pinpointed low-energy cauterization should be implemented when aiming at nerve preservation is well established.<sup>33</sup> In addition to this, investigators have explored several other technical refinements that would minimize nerve damage. Some noted that counter-traction on the neurovascular bundle (done by either the assistant or the console surgeon) might translate into neuropraxia and delayed recovery of sexual function.<sup>37</sup> A Retzius-sparing approach pioneered by Boccardi and coworkers in order to perform the entire procedure through the pouch of Douglas might translate into higher potency rates.<sup>38</sup> The Martini Clinic group described a safe and effective way of performing intraoperative neurovascular structure-adjacent frozen section examination (so called “NeuroSAFE”) during RARP.<sup>39</sup> More recently, Patel et al. showed that the placement of dehydrated human amnion/chorion membrane around the neurovascular bundle can translate into earlier return of potency.<sup>40</sup> Other technologies are being investigated to facilitate precise identification of periprostatic nervous structures, such as fluorescence imaging and confocal laser endomicroscopy.<sup>41</sup>

#### RARP: long term oncological data and comparison with open surgery

More than 15 years have passed since RARP was first described,<sup>42</sup> and mature data are now available

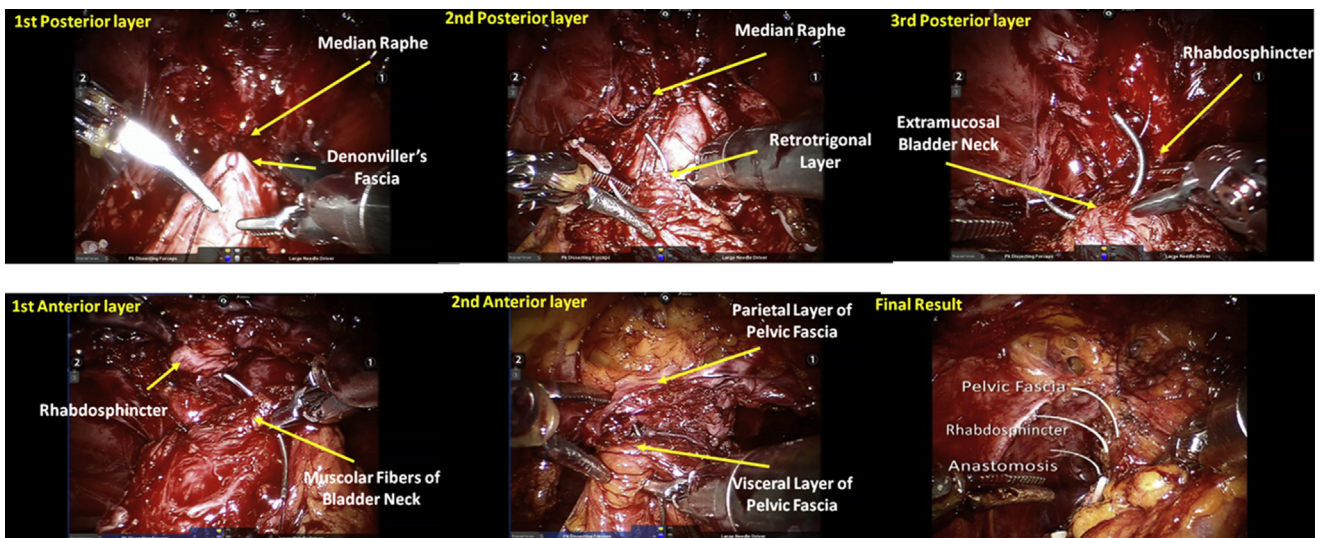


Figure 4. Total (posterior and anterior) anatomical reconstruction during robot-assisted radical prostatectomy (courtesy of Prof. Francesco Propiglia, San Luigi Hospital, University of Turin, Orbassano, Italy).

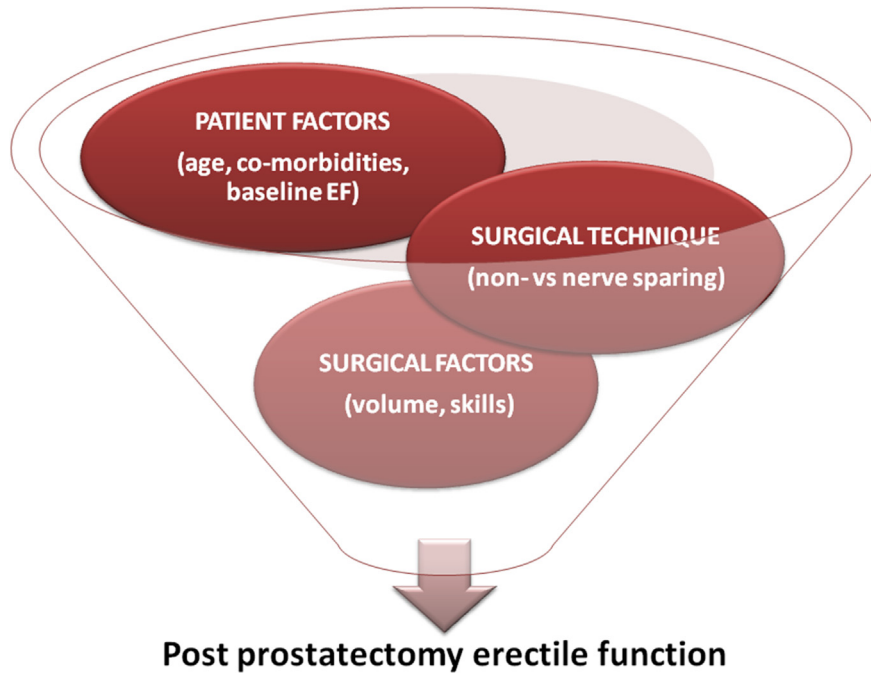


Figure 5. Factors contributing to potency status post radical prostatectomy.<sup>34</sup>

showing that the procedure is effective in long term cancer control, even in patients with high-risk disease (Table 2).<sup>43–49</sup>

Theoretically, robot-assisted surgery should be the ideal model to determine the impact and limitations of “surgical precision” providing better ergonomic for the surgeon, particularly during reconstructive steps, better vision and magnification during dissection of the prostate and surrounding anatomical details. Nevertheless, there is still a debate on “robotic versus open surgery” for prostate cancer

mainly fueled by large population-based data analyses (Table 3).<sup>50–56</sup> Hu et al. reported two large analyses from the SEER Medicare dataset. They found that RARP is associated with lower likelihood of positive surgical margins for intermediate-risk (15.0% versus 21.0%; OR: 0.66) and high-risk (15.1% versus 20.6%; OR: 0.70) disease, as well as less use of additional cancer therapy (at 24 months OR: 0.67).<sup>50</sup> Moreover, they found that RARP is associated with an equivalent risk of all cause (HR 0.85) and cancer specific (HR 0.85) mortality.<sup>55</sup>

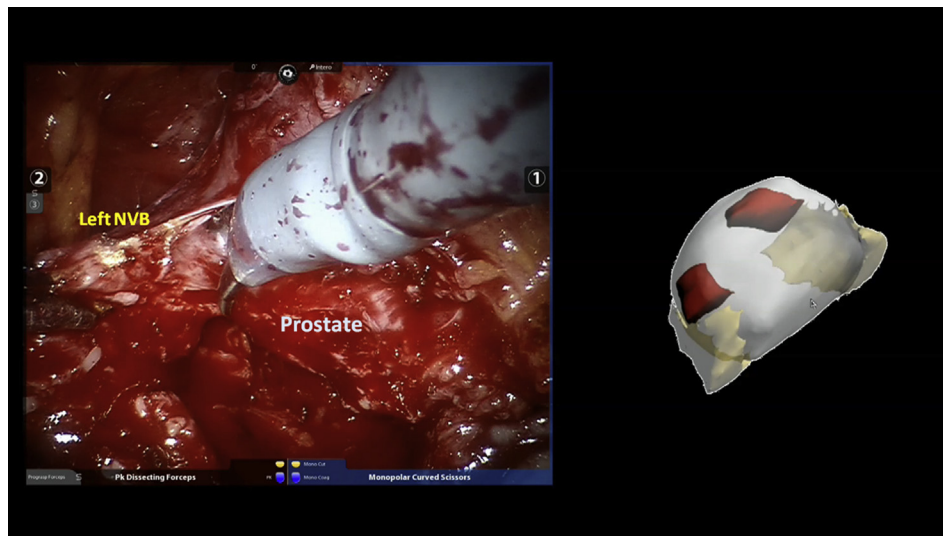


Figure 6. Image-guided nerve sparing robot assisted radical prostatectomy (courtesy of Prof. Francesco Porpiglia, San Luigi Hospital, University of Turin, Orbassano, Italy).

Table 2  
Oncological outcomes of RALP: overview long term data.

Reference	Institution	Pts, n	Time period	Median follow-up, months	BRFS	CRFS	CSS
Sooriakumaran <sup>43</sup>	Karolinska University, Stockholm, Sweden	944	2002–06	75.6	82.6% @ 9 yrs	—	—
Abdollah <sup>44</sup>	Henry Ford Hospital, Detroit, MI, USA; Martini Clinic, Hamburg, Germany; San Raffaele University, Milan, Italy	1100*	2002–13	49	50% @ 10 yrs	87% @ 10 yrs	—
Diaz <sup>45</sup>	Henry Ford Hospital, Detroit, MI, USA	483	2001–03	120	73.1% @ 10 yrs	—	98.8 @ 10 yrs
Abdel Raheem <sup>46</sup>	Yonsei University, Seoul, Korea	800	2005–10	64	76.4 @ 5 yrs	94.6% @ 5 yrs	96.7% @ 5 yrs
Suardi <sup>47</sup>	OLV Robotic Surgery Institute, Aalst, Belgium	184	—	67.5	81% @ 7 yrs	—	—
Billia <sup>48</sup>	Guy's and St. Thomas' Hospitals, London, UK	175	—	—	95.4% @ 5 yrs	—	98.3% @ 5 yrs
Liss <sup>49</sup>	University of California—Irvine, Orange, CA, USA	289	2002–06	—	84.9% @ 5 yrs	—	99% @ 5 yrs

BRFS = Biochemical recurrence free survival; CRFS = Clinical recurrence free survival; MFS \*D'Amico high risk only.

In another large retrospective analysis of administrative data Leow et al. looked at outcomes and costs of over 600,000 radical prostatectomies done in the USA over a 10-year period.<sup>52</sup> First of all, they found utilization of robotic surgery rapidly increased from 1.8% in 2003 to 85% in 2013 ( $p < 0.001$ ). Moreover, RARP patients were less likely to experience complications ([OR 0.68,

$p < 0.001$ ) or to receive blood products (OR 0.33,  $p = 0.002$ ). While 90-day direct hospital costs were higher for RARP, costs were no longer significantly different between open and robotics for the highest-volume surgeons ( $\geq 104$  cases/yr; +\$1990,  $p = 0.40$ ) and hospitals ( $\geq 318$  cases/yr; +\$1225,  $p = 0.39$ ). Haglind et al. reported a large prospective controlled nonrandomized trial involving 14

Table 3  
Robotic versus open radical prostatectomy: high quality comparative studies to date.

Reference	Study design	Country	No. of patients	Study period	Endpoints	Main findings
Hu <sup>50</sup>	Retrospective observational study from SEER database	USA	5556 RALP versus 7878 ORP	2004–09	SM status; use of additional cancer therapy	RALP associated with improved SM status for intermediate- and high-risk disease and less use of post-prostatectomy ADT and RT
Haglind <sup>51</sup>	Prospective, controlled, non randomized multicenter (LAPPRO study)	Sweden	1847 RALP versus 778 ORP	2008–11	UI and EF @ 12 months; SM status	RALP modestly beneficial in preserving EF. No significant difference regarding UI or SM
Leow <sup>52</sup>	Retrospective observational study from Premier Hospital database	USA	311,135 RALP versus 318,458 ORP	2003–13	Outcomes and costs	RALP confers a perioperative morbidity advantage; costs no longer significantly different when highest-volume surgeons and hospitals
Seo <sup>53</sup>	Systematic review and meta-analysis	Korea	61 studies	—	Outcomes	RALP better risk of UI, EF, and complications. SM and BCR rates comparable
Yaxley <sup>54</sup>	RCT	Australia	157 RALP versus 151 ORP	2010–14	UI and EF @ 6 and 12 weeks	Similar UI and EF outcomes
Hu <sup>55</sup>	Retrospective observational study from SEER database	USA	6430 RALP versus 9161 ORP	2003–12	ACM, PCSM and use of additional cancer therapy	RALP with less use of additional postoperative cancer therapies, and equivalent ACM and PCSM
Thompson <sup>56</sup>	Prospective observational single surgeon study	Australia	866 RALP versus 686 ORP	2006–12	Quality of life and SM	After a long learning curve, RALP has superior sexual, early urinary, and pT2 SM outcomes

SEER = surveillance epidemiology and end results; LAPPRO = laparoscopic prostatectomy robot open; RCT = randomized controlled trial; RALP = robot-assisted laparoscopic radical prostatectomy; ORP = open radical prostatectomy; SM = surgical margin; UI = urinary incontinence; EF = erectile function; ADT = androgen deprivation therapy; RT = radiation therapy; BCR = biochemical recurrence; ACM = all cause mortality; PCSM = prostate cancer specific mortality.

Table 4  
Ongoing trials on radical surgical treatment of primary tumor in patients with oligometastatic prostate cancer ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)).

Institution	Name of trial	Study design	Treatment groups	Study sample	Primary endpoint	Expected to be reported
MD Anderson Cancer Center (USA)	–	RCT	BST versus BST + RP or RT	120	PFS	2018
Oxford University (UK)	TRoMbone	RCT	ADT versus ADT + RP	50	Feasibility to randomize @ 6 months	2018
Martini Clinic (Germany)	g-RAMPP	RCT	ADT versus ADT + RP	452	CSS	2025
University of Vienna (Austria)	–	Prospective phase I–II	RP	50	90-day complication rate	2021

RCT = randomized clinical trial; PFS = progression-free survival; CSS = cancer specific survival; BST = best systemic therapy; RP = radical prostatectomy; RT = radiation therapy; ADT = androgen deprivation therapy.

Centers from Sweden and comparing robotic (n = 1847) to open (n = 778) radical prostatectomy.<sup>51</sup> They could only find a modest benefit of robotic surgery for preservation of erectile function, whereas no difference was found in terms of continence and positive margin rates. Seo et al. reported the latest systematic review and meta-analysis of studies comparing open to robotic surgery for prostate cancer.<sup>53</sup> They included 61 studies, and confirmed that RARP carries a lower risk of complications and urinary incontinence, as well as higher potency rate, whereas positive margin rates and recurrence free survival were similar. However, the authors pointed out the low quality of available studies.

Moreover, they did not include the only available randomized controlled trial, which was recently reported by Yaxley et al. from the Royal Brisbane and Women's Hospital (Brisbane, Australia).<sup>54</sup> Primary outcomes were urinary function and sexual function at 6 weeks, 12 weeks, and 24 months and oncological outcome (positive surgical margin status and biochemical and imaging evidence of progression at 24 months). The trial was powered to assess health-related and domain-specific quality of life outcomes over 24 months. In this preliminary report the authors reported the early outcomes at 6 weeks and 12 weeks. Overall, 151 in the radical retropubic prostatectomy group proceeded to surgery and 157 in the RARP group. Urinary function scores did not differ significantly between the radical retropubic prostatectomy group and RARP group at 6 weeks post-surgery (p = 0.09) or 12 weeks post-surgery (p = 0.48). Sexual function scores also did not differ significantly between the groups at 6 weeks (p = 0.45) or 12 weeks (p = 0.18) post-surgery. There was also no difference for proportion of positive surgical margins between the two groups (10% for open and 15% for robotic, p = 0.21), as well as for postoperative complications (9% for open and 4% for robotic, p = 0.052). Obviously, these findings generated different interpretations. As there was no difference between the two techniques one might argue that the application of robotic surgery does not provide any benefit to the patient. On the other hand, by taking a close look, few important points need to be pointed out. The two surgeons involved in the trial had a very different surgical experience as one had

performed about 200 robotic cases (in 2 years) and the other over 1500 open cases (in 15 years) at the start of the trial. Thus, it can be argued that robotic surgery allowed the less experienced surgeon to achieve equal outcomes significantly faster. This concept is also supported by the findings from the study by Thompson et al., who analyzed over 1550 cases to determine whether a well established open surgeon (over 3000 cases) could achieve better outcomes by switching to robotics. They found that, after a learning curve, the surgeon could indeed improve, especially their functional outcomes.<sup>56</sup>

#### *New frontiers of prostate cancer surgery: oligometastatic cancer and nodal recurrent cancer*

Over the past years, oligometastatic cancer – clinically defined as disease with up to five extra-pelvic lesion – has been recognized as separate clinical entity from advanced cancer, mostly thanks to the implementation of functional imaging.<sup>57</sup> A growing body of evidence seems to support the hypothesis that a radical treatment to their primary tumor, alongside “metastasis-directed therapy”, might be beneficial for patients with oligometastatic cancer. These have been suggested by recent large population-based studies, from both USA<sup>58</sup> and Europe.<sup>59</sup> Gandaglia et al. reported on the outcomes of a selected cohort of 11 patients with oligometastatic disease treated with radical prostatectomy and extended pelvic lymph node dissection. Adjuvant androgen deprivation therapy was administered to 10 patients (91%). The 7-yr clinical progression-free and cancer specific survival rates were 45% and 82%, respectively.<sup>60</sup> Ongoing trials whose findings will be available within the next few years, will better define the best approach for oligometastatic prostate cancer (Table 4) ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)).

Salvage lymph node dissection has been recently proposed as possible treatment option in selected prostate cancer patients with disease recurrence limited to regional and/or retroperitoneal nodes.<sup>61</sup> This novel therapeutic approach has become available due to recent advances in the field of nuclear medicine imaging modalities, such as PET/CT and PET/MRI.<sup>62</sup> Several centers have reported initial series with encouraging results (Table 5),<sup>63–67</sup> but further clinical investigation is required.

Table 5  
Reported series on salvage lymph node dissection in recurrent prostate cancer.

Reference	No. of patients	Imaging modality	Surgical technique	Follow-up	Outcomes
Suardi <sup>63</sup>	59	11C-choline PET/CT scan	Open	81.8 mo <sup>ˆ</sup>	BR: 59.3% 8-yr BCR-free survival in patients with BR: 23% 8-yr CR- and CSM-free survival: 38% and 81%
Osmonov <sup>64</sup>	45	11C-choline PET/CT		42.7 mo*	BCR-free survival: 73.3%; CSS: 91.7%; OS: 80.6%
Winter <sup>65</sup>	13	11C-choline PET/CT		72 mo <sup>ˆ</sup>	BR: 91%; Complete biochemical remission: 30%
Montorsi <sup>66</sup>	16	11C-choline or (68)Ga-PSMA PET/CT	Robotic	40 days	BR: 33.3%
de-Castro Abreu <sup>67</sup>	10	Carbon-11 acetate PET/CT imaging		2 mo	In patients with positive nodes, median PSA decreased by 83%

BR = biochemical response; BCR = biochemical recurrence; CR = clinical recurrence; CSM = cancer specific mortality; CSS = cancer specific survival; OS = overall survival; <sup>ˆ</sup> = median; \* = mean.

### Focal therapy for prostate cancer

Focal therapy has been conceived as a minimally invasive tissue-preserving treatment strategy for localized prostate cancer.<sup>68</sup> The rationale supporting this strategy is mainly based on the concept of “index lesion”, and on the increased ability to detect this lesion (and to rule out high-risk lesions) thanks to the standardization of MRI imaging-based biopsy techniques.<sup>69</sup>

In a recent systematic review, Valerio et al. analyzed 37 studies including over 3200 patients in order to summarize the current evidence on different modalities of focal therapy for prostate cancer.<sup>70</sup> Overall, seven different sources of energy have been tested, with some of them (high-intensity focused ultrasound [HIFU], cryotherapy, photodynamic therapy [PDT], brachytherapy) studied on larger samples, some others (laser interstitial thermotherapy [LITT], irreversible electroporation [IRE]) still in a more preliminary stage of assessment (Table 6). Among these, HIFU and cryotherapy are those that have been mostly implemented in clinical practice. However, evidence supporting the use of newer technologies, such as PDT, in low-risk cancer is being reported in large scale phase III studies.<sup>71</sup>

### Bladder cancer

Urothelial bladder cancer represents a complex disease with a high prevalence, and high morbidity and mortality if not optimally treated.<sup>72</sup> Traditionally, its best

surgical treatment depends on the stage of the disease: for non-muscle-invasive cancer, transurethral resection (TURB) followed by induction and maintenance immunotherapy with intravesical BCG or chemotherapy represents the current standard<sup>73</sup>; for muscle-invasive cancer, radical cystectomy with neoadjuvant chemotherapy offers the best chance for cure, whereas in selected patients bladder-sparing modalities, consisting of transurethral resection with chemo-radiation, can be considered.<sup>74</sup>

Over the past decade, two major areas of research in the field of bladder surgery have been investigated, that of new optimal imaging technologies for non-muscle-invasive disease, and that of robotic surgery for the management of muscle-invasive disease.

### Innovations in optical imaging technology

Precision surgery for bladder cancer patients mostly relies on initial diagnostic endoscopic accuracy. The current standard “white light cystoscopy” presents significant shortcomings, including suboptimal detection of flat lesion (*carcinoma in situ*), inaccurate tumor delineation to facilitate complete resection, challenging differential diagnosis with inflammatory lesions, and difficult determination of grade and stage. Therefore, novel technologies have been developed and implemented to aid the surgeon during endoscopic management of bladder cancer.<sup>75</sup> These can be broadly categorized in macroscopic (photodynamic diagnosis [PDD]); narrow band imaging [NBI]; post-processing

Table 6  
Focal therapy for prostate cancer: current evidence.<sup>70</sup>

Technique	No. of studies	No. of patients	Median follow-up, months	Overall survival, %	Disease specific survival, %	Adverse event rate, %	Continence rate, %	Potency rate, %
HIFU	13	346	12	100	100	1.5	100	88.6
Cryotherapy	11	1950	26	100	100	2.5	100	81.5
PDT	3	116	6	100	100	10.6	na	88.4
LITT	4	50	4.5	100	100	0	100	100
Brachytherapy	2	339	61	na	99.9	na	95.2	na
IRE	3	66	6	100	100	0	100	100

HIFU = high-intensity focused ultrasound; PDT = photodynamic therapy; LITT = laser interstitial thermotherapy; IRE = Irreversible electroporation; na = not available.



of the endoscopic image [SPIES]) and microscopic (confocal laser endomicroscopy [CLE]; optical coherence tomography [OCT]) ones.

PDD is also known as “fluorescence” or “blue light” cystoscopy. It requires preoperative intravesical administration of a contrast agent (a protoporphyrin analogue), a blue light (380–480 nm) source, and specialized lens and camera. PDD has been implemented in Europe for the past two decades using 5-aminolevulinic acid (5-ALA). Its derivative hexaminolevulinatate (HAL; Hexvix<sup>®</sup>/Cysview<sup>®</sup>) has become more recently available and it was approved by the FDA in 2010 on the basis of a phase III trial showing a 16% reduction in rate of recurrence at 9 months versus white light cystoscopy.<sup>76</sup> PDD seems to provide a better detection of both papillary and flat appearing CIS lesions. Burger et al. reported a meta-analysis of raw data from prospective studies on 1345 patients, and they found that PDD detected significantly more Ta tumors (14.7%) and CIS lesions (40.8%) than standard cystoscopy. Moreover, about 25% patients with at least one additional Ta/T1 tumor was identified when using PDD, and in 26.7% of patients, CIS was detected only by PDD. Overall, recurrence rates up to 12 months were significantly lower with PDD (34.5% versus 45.4%).<sup>77</sup> However, a prospective randomized multicenter study found no significant difference in tumor recurrence and progression when using PDD.<sup>78</sup> In another pooled analysis of 3 phase III multicenter trials detection rate for CIS was 87% with PDD and 75% for standard cystoscopy.<sup>79</sup> However, no data to date have suggested that use of PDD translates into a reduction in disease progression. False positive can be regarded as a drawback of the technology, as they occur in 10–12% of patients.<sup>76</sup>

NBI is a technology that filters out the red spectrum of white light resulting in blue and green spectra that are preferentially absorbed by hemoglobin, thus enhancing the mucosal and sub-mucosal vasculature without need of any dye. This technology has been incorporated into rigid and flexible scopes, which carry a toggling functionality between white light and NBI, allowing real time assessment of suspicious areas. The first study on NBI was reported by Herr and Donat in 2008, suggesting a better detection rate than white light cystoscopy.<sup>80</sup> Since then, multiple other series have been reported. A recent meta-analysis of 8 studies including 1022 patients showed the sensitivity and specificity of NBI and white light cystoscopy to be 94% versus 85% and 85% versus 87%, respectively.<sup>81</sup> Another recent meta-analysis demonstrated that NBI-TURB can reduce the risk of recurrence at 3 months, 1 year and 2 years.<sup>82</sup> The Clinical Research Office of the Endourological Society (CROES) conducted a prospective randomized single-blind multicentre study comparing NBI and white light in patients with primary non-muscle-invasive bladder cancer. Overall, 965 patients were enrolled in the study (481 underwent –assisted TURB and 484 received NBI-assisted TURB). In patients at low risk for disease recurrence, recurrence rates at 12 months were significantly

lower in the NBI group (5.6% versus 27.3%;  $p = 0.002$ ).<sup>83</sup> Similar results can be obtained by the use of SPIES, as the image quality and definition is similar to NBI.<sup>41</sup>

While PDD, NBI and SPIES have been clinically implemented on a large scale, other technologies such as CLE and OCT are still considered investigational. CLE is a technology that allows *real time* microscopy of the mucosa, and, after being primarily used in gastroenterology, it has been recently approved for clinical use in the urinary tract as micro-endoscopy probes (up to 2.6 mm in diameter) passing through the channel of a standard rigid cystoscope are now available.<sup>84</sup> Fluorescein is used as contrast agent to be administered intravesically or intravenously. Pioneer work by Sonn et al. showed that CLE is feasible and it can differentiate normal urothelium from bladder cancer.<sup>85</sup> Clinical data remain limited and further investigation is awaited. OCT is another *real time* high-resolution imaging technology that provides cross sectional images of biologic tissues by relying on information gathered by reflected energy (similarly to B mode ultrasound). Current technology uses a 2.7 mm diameter probe that can be passed through the cystoscope allowing visualization of the different layers of the bladder wall and to distinguish benign from malignant characteristics. Few studies have assessed the classification of OCT-assisted cystoscopy of bladder lesions as benign or malignant with a sensitivity of 84–100% and a specificity of 65–89%.<sup>86</sup> Moreover, another study found a 90% positive predictive value for tumor invasion into the lamina propria.<sup>87</sup> Also for OCT, clinical studies are going and further results awaited.

#### *Sexual and organ preserving approaches for radical cystectomy (RC)*

Open RC with pelvic lymph node dissection still represents the gold standard treatment for non-metastatic muscle-invasive and selected high-risk non-muscle-invasive bladder cancer.<sup>88</sup> With better understanding of neuro-functional anatomy, sexual-preserving RC techniques have been developed over the years in order to achieve superior functional outcomes, in both male and female patients with bladder cancer<sup>89</sup> (Table 7). Long term data on “prostate sparing” RC have shown that this can be an oncologically safe procedure with excellent functional results in a subset of carefully selected patients.<sup>90</sup> “Seminal vesicle” cystoprostatectomy also resulted in a high probability of preserving potency, without putting patients at unnecessary risk.<sup>91</sup> “Nerve sparing” radical cystoprostatectomy also showed to not compromise cancer control while providing improved postoperative quality of life.<sup>92,93</sup> In female patients, genital sparing cystectomy (with preservation of the uterus, vagina and ovaries) is feasible in selected women, and it can provide good functional outcome, better sexual function, and favorable oncological outcome.<sup>94</sup> A “nerve sparing” technique in female patients has also been obtained by avoiding damage to

Table 7  
Sexual sparing techniques for radical cystectomy: summary of functional and oncological outcomes.<sup>90–95</sup>

Gender	Techniques	No. of studies	No. of cases	Potency rate, %	Sexual activity rate, %	Daytime continence rate, %	Nighttime continence rate, %	Local recurrence rate, %
Male	Prostate sparing	12	1098	80–90	Na	88–100	31–98	10
	Seminal sparing			79				3
	Nerve sparing			29–78				6
Female	Genital organ preserving	14	318	na	86.7	70.3	67.2	0–13
	Nerve sparing							

the proximal urethra and to preserve the autonomic innervation of the rhabdosphincter.<sup>95</sup>

### Robotic surgery for bladder cancer

Since the first description by Menon et al., in 2003,<sup>96</sup> robot-assisted radical cystectomy (RARC) has been adopted in several institutions worldwide.<sup>97</sup> Over the last decade, the debate has been mainly focused on the perioperative outcomes of RARC versus the open gold standard technique. A recent meta-analysis of 19 studies, including a total of 1779 patients (787 patients in the RARC group and 992 patients in the open group) suggested that, despite the longer operative time, patients undergoing RARC might benefit from lower complication rates, more lymph node yields, less estimated blood loss, lower need for transfusions, and shorter postoperative length of stay.<sup>98</sup> However, another meta-analysis including only the four available RCTs comparing open to RARC, with a total of 239 patients, all with extracorporeal urinary diversion, found no significant difference between techniques in terms of perioperative morbidity, length of stay, positive surgical margin, lymph node yield. RARC group had significantly lower estimated blood loss and wound complications, but again required significantly longer operating time.<sup>99</sup> Thus, further studies are needed to determine the benefit of the minimally invasive approach for radical cystectomy, and results from ongoing trials are largely awaited.<sup>100</sup> These trials have to focus on the difficulty of urinary diversion by the robot-assisted intracorporeal approach as well as on the oncologic impact of the laparoscopic technique.

In this setting, one of the key-factor is certainly represented by the urinary diversion, as this is largely recognized as the surgical step most likely to be associated with occurrence of perioperative morbidity. During the early phase of RARC, extracorporeal urinary diversions were mostly preferred. Over the past 5 years, the evolution of robotic surgery has enabled urologic surgeons to perform urinary diversions intracorporeally.<sup>101</sup> Intracorporeal urinary diversion has the potential benefits of a smaller incision, reduced pain, decreased bowel exposure, and reduced risk of fluid imbalance. A study by the International Robotic Cystectomy Consortium found that patients undergoing intracorporeal diversion after RARC were at a lower risk of 90-day postoperative complication.<sup>102</sup>

Since radical cystectomy represents a cancer surgery, oncological outcomes remain a primary concern. Only few series of minimally invasive radical cystectomy with long term oncological follow-up have been reported to date, with encouraging results.<sup>103–105</sup> Concerns regarding the pattern of recurrence after RARC, with one study showing more frequent extra-pelvic lymph node locations and peritoneal carcinomatosis in RARC patients compared to open surgery patients.<sup>106</sup> In this regard, studies on laparoscopic series have advocated a potential risk associated with the use of pneumoperitoneum.<sup>107</sup> Nevertheless, a study on a recent large series of patients who underwent RARC with intracorporeal urinary diversion at nine different institutions did not identify unusual recurrence patterns.<sup>108</sup>

### Kidney cancer

Despite a rising incidence, the mortality of RCC in developed countries has been stable over the last decade.<sup>109</sup> This phenomenon can be explained by the significant advances in the management of the disease, including refinements in renal biopsy techniques,<sup>110</sup> implementation of active surveillance protocols,<sup>111</sup> and adoption of minimally invasive nephron-sparing surgery procedures.<sup>112</sup> This has resulted into a paradigm shift, which is the idea of tailoring the treatment to each specific case with the ultimate aim of achieving the best oncological outcome and the maximal functional preservation. This process has been facilitated by the application of new technologies, allowing a better surgical planning, within the realm of “precision surgery”.

#### *Expanding indications of nephron-sparing surgery and evolving role of robotic partial nephrectomy*

Current clinical practice guidelines recommend partial nephrectomy (PN) as the gold standard treatment for small (clinical T1a) renal masses, given the advantages of nephron-sparing surgery over radical nephrectomy in terms of renal function preservation.<sup>113,114</sup> Emerging data from centers of excellence as well as from national databases and meta-analyses have demonstrated oncological efficacy for larger masses (cT1b, cT2) with benefits in terms of renal functional preservation.<sup>115–117</sup> On the other hand, an overarching survival benefit from PN is

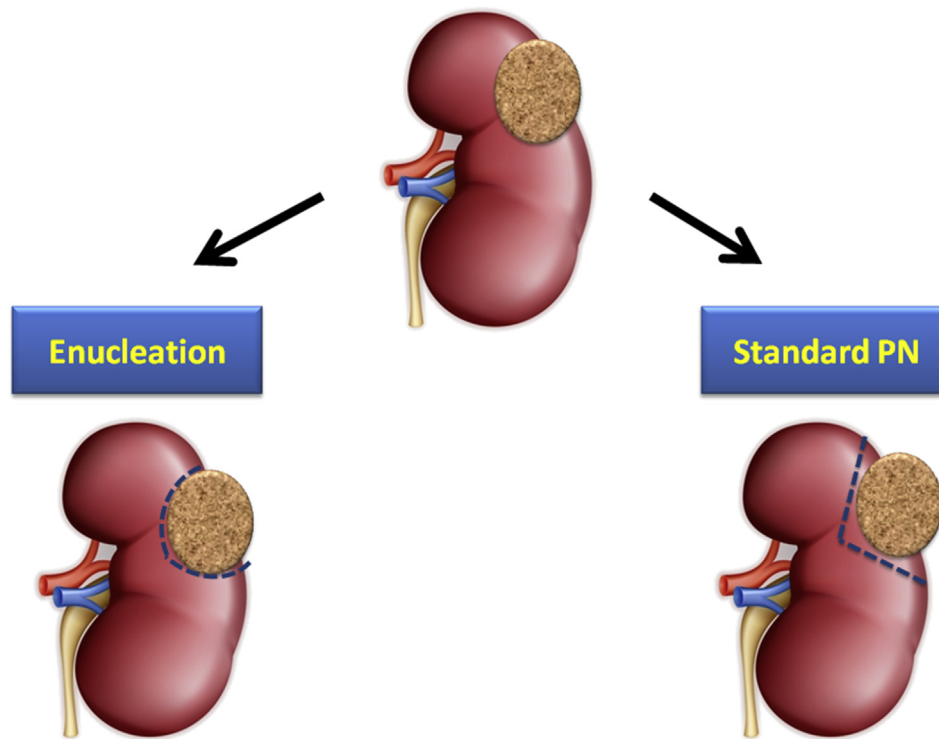


Figure 7. Illustration of enucleation versus standard partial nephrectomy for the resection of renal tumors (dashed line = surgical plan of resection).

more controversial with several retrospective and meta analyses suggesting a survival benefit while the sole randomized clinical (which closed due to poor enrollment and was thus underpowered) trial failing to demonstrate a survival benefit for partial nephrectomy despite improved renal functional outcomes in the partial nephrectomy arm.<sup>118,119</sup>

Despite the oncological equivalence to radical nephrectomy and renal functional benefit, PN has been regarded as a higher risk procedure with increased risk of urinary fistulae and procedure specific complications. This paradigm may be shifting however, with the increasing adoption of the robotic platform. Recent data suggest that robotic technology may enable surgeons across different practice settings to perform nephron-sparing surgery more frequently.<sup>120</sup>

The robotic approach offers the option of a minimally invasive PN recapitulating the safety and effectiveness of the open technique, which can still be regarded as the reference standard. The standardization of each surgical step has allowed for optimization of robotic PN procedure.<sup>121</sup> With increasing surgical experience, indications for robotic PN have significantly expanded to include more demanding clinical scenarios, such as completely intraparenchymal tumors,<sup>122</sup> hilar tumors,<sup>123</sup> and patients with previous ipsilateral nephron-sparing procedure.<sup>124</sup>

Moreover, current evidence suggests that robotic PN can translate into better outcomes than conventional

laparoscopic PN. A recent meta-analysis of 25 studies (including almost 5000 patients) showed that patients treated with robotics presented larger (WMD 0.17 cm,  $p = 0.001$ ) and more complex (WMD 0.59 RENAL score,  $p = 0.002$ ) tumors. Nevertheless, robotic surgery was associated with a decreased likelihood of conversion (RR 0.36,  $p < 0.001$ ), and lower risk of complications (RR 0.84,  $p = 0.007$ ) and positive margins (RR 0.53,  $p < 0.001$ ), and shorter warm ischemia time (WMD 4.3 min,  $p < 0.001$ ).<sup>125</sup> Thus, robotics might replace laparoscopy as the most common minimally invasive approach for PN whenever the necessary technology is available.<sup>126</sup> However, in the hands of expert surgeons and with the aid of last new tools, such as 3D imaging and the ETHOS chair a more ergonomic position for the surgeon can facilitate the pure laparoscopy approach.<sup>127</sup>

From the standpoint of the surgical technique, the recent debate has been primarily focused on the management of the renal hilum. The recognized role of warm ischemia time as a modifiable factor impacting the postoperative renal functional outcome<sup>128</sup> prompted several groups to explore the feasibility and safety of “zero-ischemia” (off clamp) and “minimal ischemia” (selective clamping) techniques.<sup>129</sup> With the increasing awareness regarding the preservation of healthy parenchyma as a major determinant of postoperative renal function,<sup>130</sup> another matter of debate has become the tumor resection technique. While the standard PN procedure implies the resection of a rim of renal

Table 8  
Focal therapy for kidney cancer: overview of available techniques.<sup>132–137</sup>

Technique	Commercial names	Mechanism	Technique	Major complication rate, %	Failure rate, %	FU, months	Oncological outcomes	Current status
CRYO	Endocare <sup>®</sup> (Healthtronics); Visual-ICE <sup>®</sup> (Galil)	Rapid cooling leading to cell necrosis	Perc (CT guided); Lap (US guided)	0–9.5	1.5–13	20–97.9	RFS: 77% DFS: 85–97% CSS: 98.5–100%	Established in clinical practice
RFA	LeVein <sup>®</sup> (Boston); Cool-tip <sup>®</sup> (Covidien); RITA StarBust <sup>®</sup> (Angiodynamics)	Heat conduction inducing cellular death	Perc (CT guided or MRI guided); Lap (US guided)	8	2.5–10	27–65.6	RFS: 88–94.2% DFS: 61.9–90.6% CSS: 96.8–100%	
MWA	Acculis <sup>®</sup> (Angiodynamics); Evident <sup>®</sup> (Medtronic); KY2000 (Kangyou Medical)	Kinetic energy transformed into heat, leading to cell death	Perc (CT guided); Lap (US guided)	2–3	3–4.2%	6–32	RFS: 62–91.3% DFS: 92.3% CSS: 85.7–100%	Investigational
IRE	Naonoknife <sup>®</sup> (Angiodynamics)	Electropulses creating nanoscale defects in cellular membrane	Perc (CT or US guided);	0	10	1–10	RFS: 90	

CRYO = cryotherapy; RFA = radiofrequency ablation; MWA = microwave ablation; IRE = irreversible electroporation; FU = follow-up; RFS = recurrence free survival; DFS = disease free survival; CSS = cancer specific survival.

parenchyma around the tumor, some groups have advocated “enucleation” techniques<sup>131</sup> with the aim of maximizing preservation of nephrons while effectively removing the cancer (Fig. 7).

#### Tumor ablation techniques

With the aim of further minimizing the surgical morbidity, focal kidney ablation can be offered as an effective minimally invasive nephron-sparing treatment option. Several ablative technologies have been investigated to date; cryoablation and radiofrequency ablation (RFA) certainly represents the two modalities that have been most extensively implemented in clinical practice,<sup>132</sup> whereas other ablative procedures (microwave ablation, electroporation) are still investigational<sup>133–136</sup> (Table 8).

Overall, probe-ablative therapy provides an attractive nephron-sparing treatment for small renal masses in older patients with significant medical co-morbidities who are poor candidates for standard extirpative surgery. In well selected patients, kidney ablation can offer several advantages, including improved patient procedural tolerance, faster recovery, preservation of renal function, and reduction in the risk of complications. It is likely that outcomes associated with ablative modalities will improve with further advances in patient selection, technology and application. Emerging data suggest that for both cryoablation and RFA, patients with non-clear cell and lower grade histologies may have improved outcomes.<sup>137</sup> Patient counseling about thermal ablation should include a discussion of the risks of local recurrence, and potential need for re-intervention. Newer energy-ablative modalities have the potential to become additional nephron-sparing options, but further investigation is needed.

#### Conclusions

Over the past two decades, the paradigm of urooncological surgery has moved away from the obsolete principle of exclusively radical “one-size-fits-all” procedures. The current surgical therapy of the most common genitourinary cancers aims to combine the maximal oncological efficacy with the minimal impact on patient’s quality of life and functionality. A better knowledge of anatomy and cancer biology coupled with better diagnostic instruments allowed to improve surgical indications, to optimize surgical planning, and to tailor the surgical procedure to each specific patient. The application of novel technologies (robotic surgery, focal therapy, new imaging systems) have facilitated a minimally invasive approach in most of urologic cancer patients. We entered an era of “precision surgery”; nevertheless, the management of patients with genitourinary cancers remains suboptimal, and further translational research is needed to address many unmet needs in this field.

#### Conflicts of interest

The authors have no conflict of interest.

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