Review

ClinicalPractice

Partial nephrectomy: the benefits of advancing technology

Katharina Maria Bretterbauer[1], Stephan Hruby[1], Lukas Lusuardi[1], Daniela Colleselli[1], Thomas Kunit[1], Günter Janetschek[1] & Michael Mitterberger*,[1]

[1]Department of Urology, Paracelsus Medical University Salzburg, Müllner Hauptstraße 48, 5020 Salzburg, Austria

*Author for correspondence:
Tel.: +43 662 4482 58378
Fax: +43 662 4482 2944
m.mitterberger@salk.at

Practice Points

- Open nephron-sparing surgery is the standard treatment of T1 renal cell cancer. In experienced centers the laparoscopic or robotic approach is a viable alternative.
- Operative approaches: open, laparoscopy (standard or robot-assisted) and laparoscopic single-site surgery. Many studies compared standard laparoscopic technique with robot-assisted partial nephrectomy with controversial results. It is likely that the two methods have similar outcomes. The method used may be dependent on the surgeon's preference, experience and availability. Further randomized controlled trials with long-term oncological data should be conducted to evaluate the superiority of each procedure.
- Imaging: preoperative dual source computed tomography angiography, image-guided surgery and augmented reality view.
- Every minute of renal ischemia contributes to the development of chronic kidney disease. Therefore, all effort is made to shorten warm ischemia time. The novel techniques of zero-ischemia time and segmental arterial clamping were consequently introduced.
- Improvements in hemostasis (sealant agents, high-intensity focused ultrasound clamp) are also promising.
- Sliding clips and barbed suture methods have been introduced to shorten renorrhaphy time.
- The concept of trifecta is that the following three key outcomes should be reached at once: a negative cancer margin, no or minimal decrease in renal function, and no surgical complications.

Open, laparoscopic and robot-assisted approaches are all feasible in partial nephrectomy and every procedure has its own pros and cons. Nowadays, open nephron-sparing surgery is the gold standard treatment of T1 renal cell cancer. In experienced centers, the laparoscopic or robot-assisted approach is a viable alternative. Advances in surgery and imaging techniques provide plenty of potential. With these new technical developments, it is possible to achieve zero ischemia of the kidney in a high percentage of cases, which has a positive effect on long-term renal function outcome. The purpose of this review is to discuss these new developments, which provide improvements to the partial nephrectomy procedure.

Keywords: advancing • future • laparoscopy • novel techniques • partial nephrectomy • robotics • zero-ischemia

The widespread use of imaging procedures has led to an increase in the number of asymptomatic small renal masses found [1]. At the same time, upcoming surgical techniques have allowed urologists to extirpate tumors with less collateral damage and nephron loss when compared with radical nephrectomy. Partial nephrectomy (PN) produces similar oncological outcomes [2]; better overall survival [3], and improved long-term

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renal and cardiovascular functions [4,5]. According to the EAU guidelines [6], open nephron-sparing surgery is the standard operation for treatment of T1 renal cell cancer (RCC) [7–9]. In the last decade, less invasive approaches, such as laparoscopic and robot-assisted procedures, have increased [10]. Ischemia time and volume of remaining kidney parenchyma were established as important influencing factors of residual function of the treated kidney, which led to further development. The objective of this review is to give an overview of the recent technological advances in PN, some of which are established and others that show future potential.

Operative approach

Numerous studies have compared open PN (OPN), laparoscopic PN (LPN) and robot-assisted PN (RALPN). These studies were often limited by selection bias, such as age, medical comorbidities and tumor size, which likely influence the choice of surgical approach. However, even more important prospective randomized trials investigating OPN versus LPN and RALPN, and perioperative morbidity, functional outcome and oncological outcome are still needed [11].

OPN versus RALPN/LPN

In 2014, Schiffmann *et al.* observed that open radical nephrectomy was still the most commonly used treatment for T1 RCC [7]. PN increased over time, but an open approach remained the established standard therapy for T1 renal tumors in centers without advanced laparoscopic expertise. In complex scenarios, such as centrally located tumors, multifocal lesions or tumors in a solitary kidney, open surgery may also be preferable [12]. The disadvantages of OPN are the advantages of LPN/RALPN: OPN involves traumatic access through the muscular plane; a long hospital stay and postoperative regeneration; higher risks of postoperative, chronic pain and herniation; and worse cosmetic outcomes [10]. The identified advantages of OPN over LPN are a shorter warm ischemia time (WIT) [13] and a lower complication rate [10]. However, these differences are, to some extent, due to the learning curve of laparoscopy.

RALPN versus LPN

The LPN became a feasible alternative to OPN because of the advances in laparoscopic techniques, equipment and operator skills [14–17]. The diffusion of LPN is limited by its challenging technique, operation skills, steep learning curve and the need for high patient volumes, which are only achievable in certain centers [18,19]. By contrast, the current robotic systems provide 3D imaging and a great range of fully articulated wrist motion (e.g. EndoWrist, Intuitive Surgical, Sunnyvale, CA, USA) [14,15]. This helps to reduce technical challenges and allows translation of open surgical skills into laparoscopy [14–15,17]. The main problem of RALPN is the lack of availability due to its high purchasing price and maintenance costs [10]. Future studies will determine if improvements in clinical outcome can justify the high costs [20].

A systematic review (including seven studies) was conducted from 2000 to 2012, comparing RALPN (n = 313) to LPN (n = 404) [21]. There were no differences between the two groups in operative time, estimated blood loss, conversion rates, length of hospital stay, complications or positive margins. The only difference between the groups was the significantly less WIT in the RALPN group (mean difference: -2.74; 95% CI: -4.35 to -1.14; 22.6 vs 24.2 min). This parameter was of great importance because, according to Thompson *et al.* [22], the return of the postoperative renal function depended on the duration of ischemic time. A systematic review by Froghi *et al.* of 256 patients compared the two approaches, but could not find any significant differences in estimated blood loss (EBL), WIT, length of stay (LOS) or complication rates [23]. The authors observed that the risk of positive margins may be higher in LPN and RALPN when compared with the open technique. Moreover, they claimed that there is a tendency to resect more healthy renal parenchyma compared with OPN, but failed to give clear data on this. The results were limited by the lack of randomized controlled trials and long-term oncological data.

The majority of minimally invasive PNs are performed via a transperitoneal approach [24]. In a prospective randomized study, no significant difference in regard to morbidity has been shown between the transperitoneal and retroperitoneal approach [25]. The retroperitoneal approach is ideal for patients with prior abdominal surgeries to avoid injuries or complications due to potential adhesions, and it has been successfully used for posterior and lateral renal masses. The retroperitoneal approach permits excellent visualization, operation time is shorter, there is no need for bowel mobilization and LOS is shorter. Other parameters such as postoperative renal function, analgesic requirements and complications do not differ significantly between the transperitoneal and retroperitoneal approach. Other studies also found shorter ischemia times [26] or decreased blood loss [27,28].

In the literature, port-site metastasis (PSM; 0.09%) or peritoneal spread (0.03%) are mentioned as a rare phenomenon after laparoscopic surgery for urological malignancies [29]. Song *et al.* performed a MedLine search for published studies on RCC PSM [30,31]. They found 16 cases from which they tried to determine further contributing factors for PSM. Of the 16 cases, 12 were radical nephrectomy and four were PN. No identifiable technical reason for PSM was found in nine of the cases. The authors proposed multifactorial etiologic factors for PMS: biological aggressiveness (histology, high Fuhrman grade), patient immunosuppression, local wound factors, and technique-related factors such as specimen morcellation, absence of entrapment or tumor rupture. Moreover, PMS is rare – it showed poor prognosis with 31.8% overall 1-year survival rate.

Mini-Incision (MI)–OPN versus LPN & OPN

A contemporary approach of mini-incision (MI)–OPN via a supra-12th rib mini-flank incision was first described by Di Blasio *et al.* [32] and adapted by Wang *et al.* [33]. They used a supra-11th rib mini flank approach in 194 patients and compared if MI–OPN can be an alternative to LPN and OPN. The LPN group showed the longest operation and WIT; LPN and MI–OPN were similar in LOS; and OPN had the highest EBL and lowest incidence of renal artery clamping. Moreover, no difference in glomerular filtration rate could be found at the follow-up (1–3 years).

Laparoendoscopic single-site surgery

Successful cases have been reported using laparoendoscopic single-site surgery (LESS) to reduce the surgical trauma associated with conventional laparoscopy; although, the technique is still in its infancy for PN. LESS is technically more demanding, showing better cosmetic results, but does not yield in better renal function or oncological outcome [34–36]. The high costs also limit its widespread acceptance, although Schwentner *et al.* [37] described a completely reusable LESS-platform (X-Cone, Karl-Storz) that was more cost effective than standard laparoscopy. A new technique in LESS–PN is single incision transumbilical surgery that hopes to combine the best of both worlds: conventional principles of laparoscopy (straight instruments and enables triangulation) with the minimal invasiveness of LESS (excellent cosmetic result and fast recovery of patients) [38]. In initial studies, single incision transumbilical surgery PN is, in experienced hands, a feasible technique for selected exophytic tumors. However, long-term oncological outcome and controlled trials are still needed [39]. The future of LESS may be the introduction of a robotic platform, which can overcome most of the described problems above [40].

To date, there are insufficient randomized data to determine the perfect technique for minimally invasive PN. The chosen approach depends on the characteristics of tumor and patient, as well as the surgeon's choice, skills and experience. The term 'feasible' is subjective. To gain more objective guidelines, descriptive systems are needed to classify which tumor is feasible for nephron sparing and minimally invasive approaches. Renal scoring systems such as PADUA (Preoperative Aspects and Dimensions Used for Anatomic classification) [41] and RENAL (Radius, Exo/endophytic, Nearness, Anterior/posterior, Location) [42] may be helpful in this respect. Both are useful and reproducible tools to predict conversion to nephrectomy, PN-associated perioperative outcomes, EBL, operation and ischemia time [43].

WIT & cold ischemia time

Some research suggests that WIT of less than 20 min is safe and does not result in permanent renal damage [44]. Whereas another study pointed out that postoperative renal function is not so dependent on WIT, but was mainly driven by remnant kidney volume [45]. There is the concept that every minute of ischemia may contribute to the development of chronic kidney disease [22]. It must also be taken into consideration whether damage of the renal parenchyma was present prior to surgery due to diseases such as hypertension or diabetes. Hence, there is a rationale to develop techniques to minimalize renal ischemia times [46].

A few studies have focused on achieving regional hypothermia [47,48]. The strategy of renal cooling is traditionally used during PN and is based on the beneficial effects observed during kidney transplantation [45]. Most surgeons clamp the renal artery and vein, apply the ice slush and maintain renal ischemia for 10–15 min [45]. It has long since been used in OPN and now is applied in LPN. Becker *et al.* assessed the impact of ischemia time during PN with a literature search and suggested that if ischemia is required, the tumor should be removed within 20 min of WIT and 35 min of cold ischemia time (CIT) [49]. However, no controlled studies exist that can define the safety limits for WIT and CIT [50]. Lane *et al.* revealed in a study comparing WIT with CIT in OPN in 660 solitary kidneys that 3 months postoperatively there was no difference in median glomerular filtration rate reduction between WIT and CIT, although CIT was significantly longer than WIT (45 vs 22 min, $p < 0.001$) [45]. The authors supposed that the longer CIT was due to the 10–15 min waiting period to achieve low temperatures. Moreover, they concluded that preserved quantity and quality of renal parenchyma determined long-term renal function. A recent study by Eggener *et al.* confirmed these findings [51].

Gill *et al.* replicated the standard open ice slush renal hypothermia in LPN. The renal vessels were clamped and an endoscopic bag was filled with 600 ml of ice. Although the renal temperature could be decreased, this technique has not been widely applied [52]. Another way to cause renal hypothermia is retrograde endoscopic cold saline perfusion of the kidney. The demonstrated temperatures, however, were not adequate to prevent serious renal damage [53]. A further concept to achieve renal hypothermia consists of perfusing renal parenchyma with a 4°C saline solution by an angiocatheter placed peripherally of the clamp occlusion. In this approach, the optimal renal hypothermia temperature of <15°C also could not be reached [54]. Huang *et al.* scrutinized the auspicious concept of remote ischemic preconditioning to assess the effect on renal protection in LPN [55].

Remote ischemic preconditioning consisted of three cycles of 5 min right lower-limb ischemia and 5 min of reperfusion. It may reduce renal impairment in the short term, but failed in the long term.

Other studies developed an early unclamping technique, which halved the WIT. The technique was developed further so there was 'no vascular clamping'. Although the operation time was shorter, EBL was higher and operative outcome was the same [56]. Further investigations were then carried out for segmental arterial clamping, a new technique that eliminated global renal ischemia during PN [57], and for vascular microdissection techniques [46,58] to achieve a zero ischemia. Only tumor-specific arterial branches were occluded with neurosurgical micro-bulldogs, whereas the main renal artery and vein remain unclamped [46]. Tumor specific parameters (size, depth, lateral location) predicted the number of segmental arteries clamped [59]. The number of clamped branches correlated with reduced postoperative renal function [59]. There are a few drawbacks for the segmental arterial clamping technique: it takes more time and there is a greater risk during infrahilar dissection [59]. In the study of Shao *et al.*, this novel technique slightly increased WIT, which was only segmental [57]. Therefore, the postoperative renal function was better than with the conventional technique. Gill suggested a functional superiority of the zero-ischemia technique over clamped techniques [60].

Imaging & image-guided surgery

The identification of the tumor specific arteries involves preoperative imaging with a novel technique called dual source computed tomography angiography (DSCTA) [59]. The advantages of DSCTA over single-source CT angiography are higher resolution, better image quality and multi-angle reconstruction [61]. The precision of DSCTA to predict the target arteries was 93.6% [59]. It is suggested that the best way to find the specific artery to clamp in real time was to use laparoscopic real-time color Doppler ultrasound or intravenous indigo cyanine green under near-infrared fluorescence imaging [46,62–63]. Near-infrared fluorescence imaging offers the advantage of visual confirmation of tumor devascularization and kidney perfusion in a single view. Moreover, it is not skill-intensive or operator dependent. Other techniques such as visual inspection are inadequate and bear the risk of over-clamping or insufficient regional ischemia [62].

Image-guided surgery is currently being investigated to improve navigation [64]. In the era of augmented reality, it correlates pre- or intra-operative images in real time. Marker-based endoscopic tracking during laparoscopic PN, using a medical overlay of 3D-segmented virtual anatomy, can be helpful during the planning of trocar placement and dissection of the renal hilum. Preoperative multi-slice CT with 3D segmentation of data is required. *Ex vivo* a navigation aid can be placed around the target area, but *in vivo* the virtual image has to be synchronized manually with the endoscopic image according to the anatomical landmark structures (Figure 1). This was not feasible in obese patients because of the amount of perirenal fat [65]. This navigation technique is a helpful tool when dissecting a tumor and isolating renal vessels, whereas, it is unfavorable for laparoscopic re-section of a tumor because the navigation aid may interfere with the resection line.

Pharmacologic renoprotective strategies

Several studies indicated that intravenous application of Mannitol did not influence renal function recovery within 6 months after OPN [66] or LPN [67]. Vasodilatory substances such as angiotensin converting enzyme inhibitors [68], calcium channel blockers, dopamine and its analogs [69], might prevent vasospasm and increase renal blood flow, but there was no evidence from available randomized controlled trials that these agents were beneficial [70]. An elementary step can be adequate pre- and intra-operative hydration [68] and a normal intraoperative blood pressure to guarantee good perfusion of the kidney [71].

Closure of the collecting system & hemostasis

Suturing is the most effective way to achieve hemostasis and prevent urinary leakage, however, it is challenging and time consuming [72,73]. To shorten time for renorrhaphy, several methods were developed to make suturing more practical. The first step was to replace surgical knots by Hem-o-lock clips (Teleflex, Research Triangle Park, NC, USA) [74]. Benway *et al.* described the sliding-clip technique, which is mainly used for RALPN [75]. The surgeon slides the clips to tighten the tension of the renorrhaphy. Another study by Sammon *et al.* introduced barbed sutures (Wuill

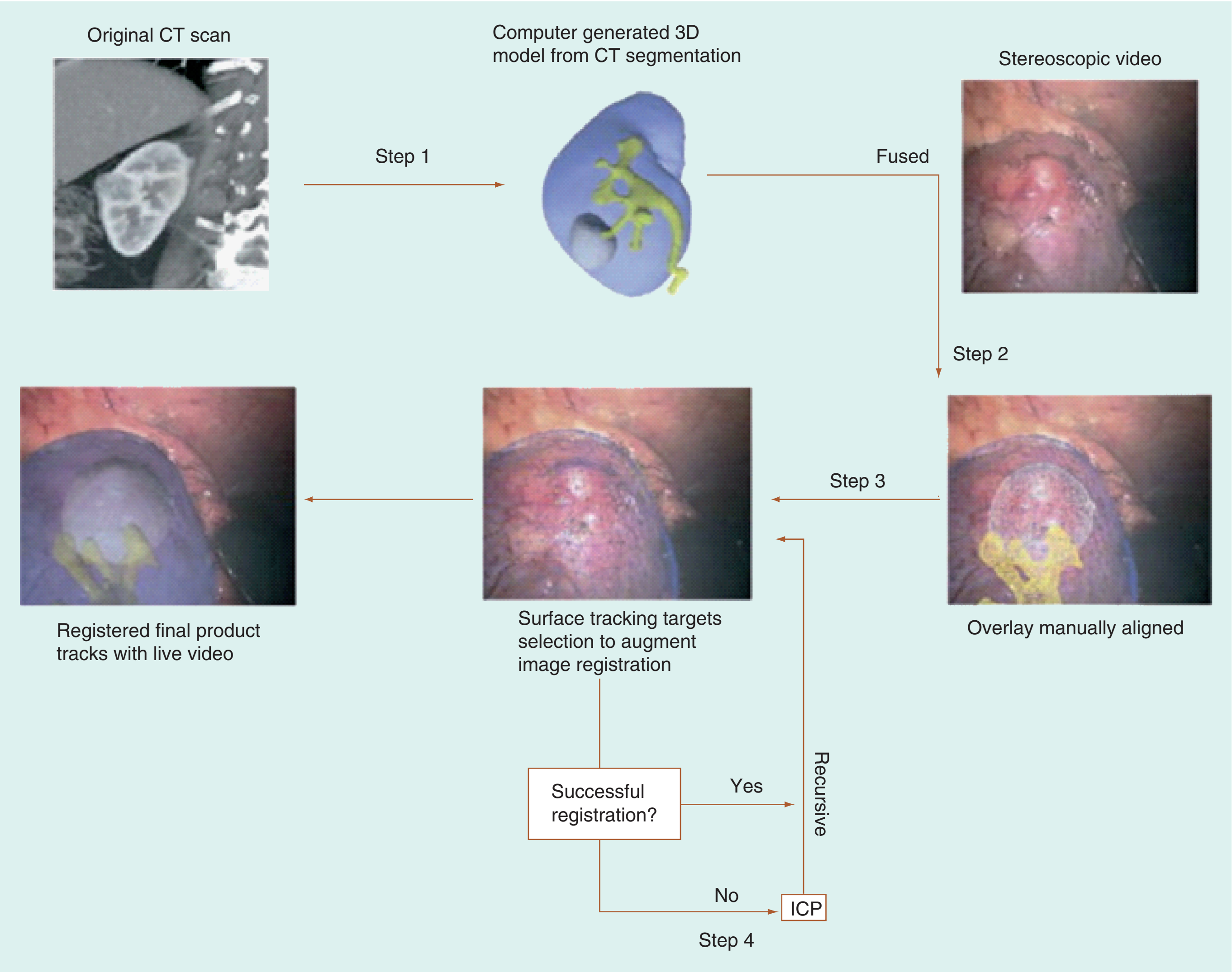

Figure 1. Flowchart displaying intermediary steps needed to achieve successful three-dimensional registration of preoperative computed tomography image to live stereoscopic video.
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or V-Loc), which have unidirectional etching to resist slippage through the tissue and reduce the need for constant tension [72].

Widespread application of LPN has been limited by the lack of reliable means of achieving hemostasis. Several hemostatic agents were studied in an animal model. However, it is difficult to compare hemostatic agents because of the lack of standardization in controls and a combination of hemostatic agents is often used. Sealant products, such as sealant powder [76] or fibrin glue [77], allow rapid clot formation when applied to a bloodless area. FloSeal (human thrombin and bovine gelatin) and oxidized cellulose reduce hemorrhagic events and tend to swell after application, which has the additional benefit of mechanical compression [78,79]. An experimental study in a small cohort (n = 6) showed that successful hemostasis could be achieved with gelatin matrix hemostatic sealants and no suturing was required [80]. However, patient selection is crucial.

Initial high-intensity focused ultrasound reports showed suboptimal results for the treatment of renal tumors [81]; however, a newly introduced high-intensity focused ultrasound clamp may facilitate the excision of renal tumors. This clamp induced hemostasis and created an ablation plane in the kidney in a preliminary porcine model. The future use of this technology may obviate the need for renal hilar clamping [82]. Although these studies are very experimental, they describe promising results that may lead to clinical application in controlling mild parenchymal bleeding.

Costs

In a cost analysis by Mir *et al.*, LPN was the most cost-effective approach at a mean direct costs of US$10,311, with a cost advantage of US$1116 and US$1652 over OPN (US$11,427) and RALPN (US$11,962). LPN was attributed as the most cost effective, due to a shorter LOS compared with OPN and less instrumentation costs versus RALPN [83]. In another cost analysis by Pini *et al.* minimal invasive PN (LPN and reusable LESS-PN) for the treatment of cT1 renal masses was compared with OPN [84]. Unsurprisingly, minimal invasive PN showed longer operative times, shorter LOS and higher total costs (LPN: €4390 vs reusable LESS-PN: €3450, OPN: €2217).

To reduce costs, Tarin *et al.* aimed to shorten the LOS by implementing a common clinical pathway in 1790 patients [85]. After implementation they succeeded in reducing the LOS: 40% (from 5 to 3 days) in open surgery and 33% (from 3 to 2 days) in minimal invasive surgery. While the 30-day major complication rate for PN stayed stable, the 30-days readmission rate slightly increased.

Costs are constantly playing a more important role in medicine. New developed high-end medical systems are, in comparison to established standard procedures, more cost intensive and, therefore, restricted to wealthy areas and so-called 'elite surgeons and patients'. Innovation that is durable and truly makes a difference is one thing, creating pseudo-innovation for advertising pitches that do not really make durable difference is quite another. Therefore, further studies are needed to prove superiority and to justify higher costs.

Conclusion

Different technical developments and innovations will revolutionize the PN procedure to improve postoperative outcome. A routine goal during PN should be the concept of trifecta, in which three key outcome criteria should be reached at once: a negative cancer margin, no or a minimal decrease in renal function and no surgical complications.

Hung *et al.* examined the benefits of advanced technology over a period of 12 years and the influence of trifecta on feasibility [86]. Data for 534 patients were divided into four chronologic eras from 1999 to 2011: the discovery era, conventional hilar clamping era, early unclamping era and anatomical zero ischemia era. Although the tumors tended to be of larger size and more complex, the estimated percent of kidneys preserved was similar and the urological complications tended to be lower in recent eras. Over the years, WIT decreased serially and zero ischemia was reached. It was unsurprising that renal function outcomes were superior in recent eras. The rate of positive cancer margins stayed low at <1% over the years and trifecta was more common in recent eras [86].

Technological advances in PN have led to improved renal functional and oncologic outcomes. However, there is still room for improvement and further efforts are necessary to achieve the ultimate trifecta.

Future perspective

Today the concept of trifecta is state-of-the-art in PN [86]. Looking ahead, new advanced operative techniques, novel precise imaging methods and augmented views will be combined to result in new concepts, such as omnifecta.

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- **The three most important outcomes (no urological complications, negative cancer margins and a minimal decrease in renal functional) are retrospectively reviewed.**