

Surgical and minimally invasive therapies for the management of the small renal mass

Authors: John Withington, Joana B Neves, Ravi Barod

Affiliation: Specialist Centre for Kidney Cancer, Royal Free London NHS Foundation Trust

Corresponding author:

Mr Ravi Barod, BSc (Hons) MBBS PhD FRCS (Urol)

Specialist Centre for Kidney Cancer

Royal Free Hospital

Pond Street, London, NW3 2QG

Phone number: 020 7794 0500 ext 34352

Email address: r.barod@nhs.net

Word Count: 4270

Abbreviations

CEUS: contrast enhanced ultrasound

eGFR: estimated glomerular filtration rate

EUC: early unclamping

HIFU: high intensity focused ultrasound

LPN: laparoscopic partial nephrectomy

LESS: laparoscopic single-site

NSS: nephron-sparing surgery

OPN: open partial nephrectomy

PN: partial nephrectomy

RAPN: robotic assisted partial nephrectomy

RFA: radiofrequency ablation

RN: radical nephrectomy

RTB: renal tumour biopsy

SRM: small renal masses

WIT: warm ischaemia time

Abstract

Purpose of Review

This article aims to summarise recent developments in surgical and minimally invasive therapies in the management of small renal masses (SRM).

Recent Findings

The incidence of the small renal mass is increasing. Standard management of the SRM is partial nephrectomy. More recently, use of ablative techniques to manage the SRM has been increasing and an exciting array of technical advances are currently being made in the field.

Nephron-sparing surgery looks set to become more financially viable with the advent of newer robotic platforms and, potentially even less invasive with the evaluation of single-port access. Real-time imaging promises to improve tumour definition, nephron preservation and vascular management intraoperatively.

Summary

Advances in surgical and minimally invasive therapies for the management of the SRM have the potential to improve cancer clearance and long-term renal function preservation. Patients will experience safer, more reliable and less invasive treatments for their small renal tumours. We describe the current advances underlying these changes.

Keywords

Small renal mass, kidney cancer, minimally invasive surgery, ablation

1. Introduction

This article aims to summarise recent developments in surgical and minimally invasive therapies in the management of SRM (Box 1).

Widespread use of cross sectional imaging has led to an increase in the detection of the SRM[1]. Similarly, against the background of an ageing population, more than half of patients diagnosed with a SRM are elderly[2]. As a result, partial nephrectomy (PN) and minimally invasive ablative techniques have taken a central role in the management of SRM.

In this article, we will first discuss surgical management, including open, laparoscopic, and robot-assisted techniques, approaches to clamping and ischaemia, intraoperative imaging, single site surgery and new robotic platforms. We will then consider the most recent evidence concerning minimally invasive ablative techniques, discuss the role of renal tumour biopsy (RTB) in the context of ablation, the different energy sources used, and the performance of ablation compared to surgery.

2. Surgery for small renal masses

After first being described by Robson[3], radical nephrectomy (RN) was the standard operative procedure performed for all renal tumours. However, the concept of nephron sparing surgery for renal cancer predates the widespread adoption of partial nephrectomy[4]. Initially reported in 1887 as an accidental procedure, partial nephrectomy was later rejected in favour of radical nephrectomy, then accepted as an option in the presence of imperative indications, before finally being recognised in the 'elective' setting[4, 5].

More recently, the "trifecta" of negative cancer margins, no complications, and low ischaemia time was defined with regard to minimally invasive PN and has been widely adopted in the literature[6].

The first and only randomised controlled trial to assess the impact of nephron-sparing surgery (NSS) compared with RN – European Organization for Research and Treatment of Cancer trial 30904 (EORTC 30904), randomly allocated participants with a solitary tumour under 5cm and a normal contralateral kidney to elective PN or RN and reported intermediate to long-term data about oncologic

outcomes and overall survival, with median follow-up of 9.3 years[7]. Unexpectedly, PN was not associated with improved overall survival[7] possibly due to heterogeneity of recruiting centres and slow accrual as potential sources of unmeasured confounding[8].

EORTC 30904 remains the only randomised trial comparing survival between PN and RN and its conclusion that survival is equivalent between the two contrasts with most other reports to date[9-11]. Notably, a systematic review and meta-analysis including EORTC 30904 concluded that overall survival was improved with NSS[12].

In a subsequently published analysis of EORTC 30904 trial data, NSS was shown to reduce the incidence of moderate renal impairment, but not end stage renal failure (median follow-up 6.7 years) or mortality (median follow-up 9.3 years), compared with RN[13]. The increased incidence of moderate renal impairment after RN was consistent with the existing literature[14, 9]. However, the equivalence in mortality reported clearly challenges the better overall survival attributed to NSS by preservation of kidney function[15]. The authors attributed this to 'surgical chronic kidney disease' being potentially less deleterious to survival than 'medical chronic kidney disease'[13]. It is also important to note that among the randomised population, over 90% had normal renal function[13]. However, this may not be representative of the full range of patients undergoing nephron-sparing surgery in most clinical settings.

Also notable from EORTC 30904 was its lack of quality of life related outcomes[7, 13, 16]. Over a shorter follow-up and with a demonstrated increase in moderate renal impairment, such outcomes would have been of significant interest.

The complexity of decision making in this field will be further influenced by aging populations. A recent US study utilising the National Cancer Database from 2002-2011, revealed that for localised (T1) renal tumours, among patients over 70, only 12.6% opted for expectant management[17]. This compared with RN (59.0%), PN (20.0%) and ablation (8.4%). Over the study period, the use of PN nearly doubled with a drop by a third of RN in these patients. The authors of this study conclude that fully informed shared decision-making is needed in these and all patients[17].

An observational study using data from the National Inpatient Sample (NIS) provides insight into changing practice patterns and comparative outcomes, in respect of different approaches to PN: open, laparoscopic and robotic-assisted[18]. Robotic PN (RAPN) is now performed more commonly than laparoscopic PN (LPN) in the US[18], but not in the UK[19]. When both RAPN and LPN were compared against open surgery, using binary logistic regression models adjusted for patient and hospital covariates, odds ratios for blood transfusion, complications and prolonged length of stay were lower with robotic surgery[18].

a. Approaches to Nephron-Sparing Surgery: Open, Laparoscopic and Robotic-Assisted

i. Laparoscopic versus Open Partial Nephrectomy

PN was well-established as an open procedure when LPN was first described[20]. Despite non-randomised comparisons providing evidence of its safety and suggesting equivalent outcomes in terms of renal function and completeness of resection, concerns have always persisted regarding the learning curve of LPN[21, 22]. The generalisability of outcomes from LPN reported by international centres of excellence, remains uncertain[23].

ii. Robotic-assisted versus Open Partial Nephrectomy

The first description of RAPN suggested that this approach led to more accurate lesion resection and easier reconstruction of the renal defect[24].

Although no randomised comparisons between RAPN and the gold standard, open PN (OPN), have been reported, a robust multicentre matched pair analysis of 200 patients has been published[25]. This reported equivalent perioperative, early oncological and functional outcomes between RAPN and OPN[25].

A systematic review and meta-analysis reported lower perioperative complications, less blood loss and shorter lengths of stay, with similar ischaemic times, changes in estimated glomerular filtration rate (eGFR) and early oncological outcomes, between OPN and RAPN[26].

RAPN has recently been reported to convey a clear benefit over open surgery, in terms of perioperative outcomes, in obese patients with cT1 tumours, in a

retrospective study from a single, high volume US centre[27]. This reflects a more generally perceived benefit of robotic surgery as being especially important as the population prevalence of obesity increases[28].

iii. Robotic-Assisted versus Laparoscopic Partial Nephrectomy

Evidence from US administrative data cited earlier in this review, suggested favourable safety-related outcomes in RAPN versus LPN[18]. A recent meta-analysis, comparing these two approaches incorporated 4919 patients (2,681 had RAPN, and 2,238 had LPN) from 25 studies, demonstrated no significant differences between RAPN and LPN in terms of age, gender, laterality and final malignant pathology[29]. Both approaches involved similar operative times, estimated blood loss and postoperative change in estimated glomerular filtration rate. Patients treated with RAPN had larger and more complex tumours, and were associated with a decreased likelihood of conversion to open surgery compared with LPN. RAPN was also associated with a reduced likelihood of complications and shorter warm ischaemia time[29].

This meta-analysis is limited by its inclusion of retrospective, non-randomised studies. Furthermore, it does not report on overall survival, cancer-specific survival, long-term renal function changes or quality of life. Despite these limitations, this is the strongest evidence currently available for comparing laparoscopic and open PN.

b. Clamping strategy

Traditionally, PN relies upon clamping of the main renal arterial supply, with warm ischaemia time (WIT) being understood to correlate with subsequent return of renal function.

The concept of a safe threshold in WIT originated in canine studies[30]. Arguably the strongest clinical evidence for a WIT threshold comes from a combined effort from the Cleveland and Mayo clinics, reporting on 537 patients undergoing OPN in solitary kidneys between 1970 and 2003 and using eGFR to measure renal function. Measuring WIT as a continuous variable, every minute was found to be important and 25 minutes was identified as a safe threshold[31].

A recent collaborative review of evidence concerning ischaemia in PN concluded that the data suggest a benefit of keeping WIT under 25 minutes[32]. However, it is equally unclear whether any additional benefit arose from significantly

shorter WIT. Cold ischaemia allows safer prolonged ischaemia and should be considered when this is expected, especially in presence of imperative indications for PN[33, 32].

A more recent systematic review specifically addressed the question of WIT thresholds[34]. This review concluded that there is currently no evidence to support the concept that WIT less than 25 minutes has any higher risk of causing renal function impairment than zero ischaemia. However, several recent studies were identified, suggesting that prolonged warm ischaemia (>25-30 minutes) could cause functional impairment[34].

Elsewhere, it has been suggested that surgical techniques that minimise or avoid global ischaemia may be associated with improved RF outcomes. A review of 'anatomy based novel surgical approaches', including early unclamping, segmental clamping, tumour-specific clamping and unclamped or 'zero ischaemia' PN, concluded that these approaches may reduce ischaemic time, without sacrificing cancer cure[35]. Factors influencing post-PN renal function were defined as kidney quality, remnant quantity and ischaemia type and duration.

i. Early Unclamping

Early unclamping (EUC) was introduced as a concept during the LPN era, amid concerns about increased WIT compared with OPN. EUC refers to the removal of clamps after one or two running sutures to the tumour bed, but before closure of the renal capsule[36]. A notable single centre series examining the impact of EUC on WIT in RAPN reported a significant reduction in WIT with no additional morbidity, despite slightly higher blood loss[37]. Although the difference in WIT was not as significant in this study as in those reported in the context of LPN, this partly reflects shorter baseline WIT in RAPN with conventional clamping strategies[36, 37].

ii. Selective (Tumour-Specific) Clamping

Originally proposed in the context of solitary kidney PN, selective, tumour-specific, or non-hilar clamping aims to eliminate the need for global renal ischaemia and, in turn optimise the preservation of renal function[38]. A single centre comparative study, in which the mean WIT for the clamped cohort was 25 minutes, reported equivalent oncological outcomes, but improved late renal function[38].

iii. Zero Ischaemia

In an initial series of 15 consecutive LPN (12) and RAPN (3), a technique of zero ischaemia PN was described, incorporating special attention to vascular anatomy on preoperative imaging, controlled intraoperative hypotension, laparoscopic ultrasound to score the proposed resection margin and meticulous microdissection and clip ligation of any specific tertiary or quaternary renal arterial branches supplying tumour[39]. In this series, no patients had transfusion, or complications, zero ischaemia resection was achieved in all patients and all had negative margins[39].

Efforts to technically refine the 'zero ischaemia' concept have subsequently been reported[40, 41]. The sequential preplaced renorrhaphy technique aims to minimise bleeding, while limiting or eliminating WIT, innovatively using simultaneous excision and suturing with promising early results[41].

The technique of robotic unclamped "minimal-margin" PN utilises an enhanced understanding of the pathological and anatomical features of renal and tumour blood supply to enable the complete elimination of all vascular clamping and tumour excision with a minimal margin adjacent to the tumour capsular edge[40].

A retrospective analysis of 534 patients treated in a single centre has charted the evolution of PN, from the origins of the operation, via conventional hilar clamping and early unclamping eras to the contemporary 'zero ischaemia' era, comparing rates of renal function decrease between eras[6]. Renal functional decrease was defined as a greater than 10% reduction in the actual versus volume-predicted postoperative estimated glomerular filtration rate. In this study, increasingly complex tumours, often 4 cm or greater ($p = 0.03$), centrally located ($p < 0.009$) or hilar ($p < 0.0001$) were treated over time, but WIT decreased serially and renal functional outcomes were superior in recent eras. Positive cancer margins were uniformly low at less than 1% and urological complications were lower in recent eras ($p = 0.01$).

Contrary to prevailing opinion, a recent systematic review concluded that general assumptions about safe thresholds in WIT came from a fundamental misunderstanding of renal ischaemia and that WIT greater than 30 minutes could be considered safe in patients with two kidneys[42]. Interestingly, the authors also argue that newer strategies, based on selective, or non-clamping techniques render a complex operation even more challenging and may serve to limit its widespread application[42]. Certainly, just as the techniques outlined in this section have evolved

with increased collective experience, it is logical that more refined techniques will tend to be adopted by surgeons as they progress through their individual learning curves. Surgeons' experience, tumour complexity and baseline renal function will help determine the relative feasibility and importance of incorporating newer techniques, on an individual case basis[43].

c. Intraoperative imaging

In pursuit of the trifecta of optimal outcomes in RAPN, intraoperative imaging conveys technical assistance at least and, potentially improved outcomes. In addition to assisting in the definition of the extent and morphology of tumour, intraoperative imaging holds particular promise in helping to define vascular anatomy.

i. Ultrasound

Intraoperative ultrasound in RAPN can improve visualisation of tumour margins and blood supply, thereby assisting with complete and precise resection and potentially facilitating selective clamping or zero ischaemia[44]. Control of the ultrasound probe by a robotic arm represented a significant step forward, by providing greater surgeon autonomy compared to a laparoscopic ultrasound probe[44].

ii. Near Infrared Imaging with Fluorophores

Near infrared (NIR) imaging with intraoperative administration of indocyanine green offers potential advantages in the definition of renal arterial anatomy and, thereby adequacy of ischaemia.

A recent study assessing the intraoperative use of NIR with indocyanine green reported benefit, in terms of short-term renal function, when NIR imaging was utilised to enable selective renal arterial clamping, although this benefit was attenuated at later follow-up[45]. However, a separate study from the same group found that NIR with indocyanine green was unreliable in identifying malignancy, as correlated with final histology[46].

iii. Contrast-Enhanced Ultrasound

A recent review of the role of intraoperative contrast-enhanced ultrasound (CEUS) in RAPN suggests an area for future investigation in this field[47]. CEUS

incorporates microbubble technology with complementary two-dimensional 'B-mode' ultrasound imaging. The authors suggest a variety of benefits of CEUS, compared with previous intraoperative imaging modalities. Compared with 'drop in' power Doppler, the effect of movement artefact is eliminated, meaning that smaller vessels can be more reliably assessed. Compared with NIR imaging with indocyanine green, CEUS allows imaging with a deeper penetration, obviating the need for dissection of perinephric fat often required with the former.

Most recently, the use of real-time intraoperative ultrasound overlay in RAPN has been described[48]. This represents a progression in technology from the split screen 'Tile Pro' display available using standard da Vinci software[49]. In its first clinical application, a system offering live ultrasound imaging superimposed (with variable transparency) on the robotic console endoscopic display was utilised to assist in defining tumour anatomy. The system also promises an ability to display colour Doppler within the overlay, with the potential to facilitate the process of defining vascular anatomy intraoperatively.

d. Single site surgery

The benefits of minimally invasive surgery, in terms of pain and recovery have engendered interest in even less invasive approaches, including laparoscopic single-site (LESS) surgery.

Data from a non-randomised single centre study, comparing conventional and LESS-RAPN suggest that despite a significantly longer WIT (26.5 vs. 19.8 minutes) and total operative time (83.4 vs. 76.1 minutes), the functional outcomes of LESS-RAPN were comparable to those of conventional RAPN for tumours of similar mean sizes and complexities[50]. No detriment in oncological outcomes or increased complications was demonstrated. Furthermore, patients who underwent LESS-RAPN also reported lower pain levels at the point of discharge from hospital.

More recently, the specific feasibility of a purpose-built single-port surgical system, the da Vinci SP1098 surgical system, has been proposed[51]. Outcomes from cadaveric RN (n=1) and bilateral PN (n=4) were reported. Access was obtained cm anterior and inferior to the tip of the 12th rib using a novel 2.5-cm robotic single-port system that accommodates three double-jointed articulating robotic instruments, an articulating camera, and an assistant port.

Notably, an absence of complications or need to convert must be interpreted

with caution in a cadaveric study. Furthermore, the mean operative time of 91.8 minutes is actually longer than that reported previously in the clinical setting, using an existing robotic platform[50]. If LESS-RAPN were to become widely adopted, robust clinical evaluation of any benefit of replacing existing robotic surgical platforms would be important, not least in view of the likely cost implications.

e. New robotic systems

Robotic surgery is expensive, and has been notable for its dominance by one provider since its inception[52]. Newer robotic surgical platforms offer the introduction of competition into the market, at least, and potentially beneficial technological innovations, as well.

The REVO-I robotic platform has been described in the context of PN, in porcine models[53]. The authors simply reported their experience of completing the operation in porcine models and describe very few technical limitations, compared with the da Vinci system. Validation in the clinical setting is planned.

The ALF-X robotic platform, currently in clinical use in gynaecology, was also tested in porcine models with regard to PN[54]. The authors comment on specific benefits of this platform, comparing it with the da Vinci system, including a more open feeling ‘cockpit’, slightly smaller port size, and enhanced haptic feedback. They note, conversely, that unlike the da Vinci system, in the ALF-X, only one instrument (the needle holder) is ‘wristed’. Notably, however, all instruments in this system are fully reusable, in contrast with the da Vinci platform, and implying potentially major cost savings.

3. Ablation for Small Renal Masses

Traditionally, surgery was the single first line treatment option for SRM. The epidemiology of renal cancer has inevitably encouraged the scientific community to rethink this philosophy: half of patients diagnosed with renal cancer are over 75 years old[55], thus many may have multiple comorbidities, reduced life expectancy (<5 years), and may be considered unfit for major surgery. More conservative approaches have then arisen, such as active surveillance and thermal ablation of renal lesions, and along with them, the re-conceptualisation of the use of renal tumour biopsy (RTB) to inform clinical management.

a. Renal tumour biopsy and ablation

The current state-of-the-art establishes that thermal ablation of SRM should only be considered if whole lesion treatment is considered technically feasible and should be preceded by biopsy[56], done either as a staged procedure or at the same time of treatment. Pathological diagnosis is important not only to plan ablation but, most importantly, to assist in defining post-treatment follow up.

Performing biopsy and treatment together is seen as more efficient but is associated with the inability of repeating biopsy if the first was non-diagnostic[57]. Histological characterisation of the lesion prior to treatment decision may be more advantageous as it allows risk stratification, potentially reducing overtreatment of benign or indolent lesions and incentivising less conservative approaches for aggressive lesions[57]. Additionally, according to a recent retrospective analysis, this can be done without significant added risks[57].

b. Energy sources

Tumour ablation is a wide concept that encompasses the use of image-guided energy delivery to achieve tumour cellular necrosis. Roughly, energy sources can be divided in thermal and non-thermal. Thermal ablation includes the use of heating techniques, such as electrical current in radiofrequency ablation and convergence of acoustic waves in high intensity focused ultrasound (HIFU), and of freezing techniques, like using argon probes to induce repeated freeze-thaw cycles in cryotherapy[58]. An example of non-thermal ablation is irreversible electroporation, whereby pulses of electric current create permanent cell membrane pores that lead to cell death[59].

Ablation is usually done as a day case or overnight stay procedure under general anaesthetic and can be achieved using a variety of energy sources (Table 1). Since its inception, major technical advances have contributed to a progressive improvement in clinical outcomes. In the UK, NICE guidelines support the use of both cryotherapy and radiofrequency ablation (RFA) in renal masses[60-62]. Meta-research comparisons between the two energy sources have shown similar clinical outcomes[63] but a recent observational study at a highly-experienced centre suggests that cryotherapy may be superior to RFA in terms of metastasis-free survival[64]. Cryotherapy can be delivered using laparoscopic or percutaneous

techniques, but the latter seems to be preferred due to increased safety profile[65] and the ability to monitor ice ball formation in real time using CT imaging.

Other energy sources are actively being sought out, such as irreversible electroporation, and HIFU, but are still considered experimental. A recent study on the use of irreversible electroporation in 42 SRM indicated that at 3-year oncological outcomes may be unfavourable compared to other techniques[66]. Similarly, the treatment efficacy of both percutaneous and laparoscopic HIFU and the safety of the former in the treatment renal lesions have been questioned[67, 68]. Overall, evidence is scarce and of low quality for newer energy sources. Technical refinements are still required, and further animal and clinical trials may be needed before introduction to clinical practice.

c. Ablation versus surgery

To date, no randomised controlled trials have compared surgery to thermal ablation. All studies covering ablation outcomes are observational, and thus poorly controlled for confounding factors such as comorbidities and life expectancy. Likewise, reports comparing treatment options for SRM often analyse a combination of different ablation modalities over a long period of time and do not address selection bias. This obviously impacts the applicability of study conclusions to current clinical practice.

According to recent guidelines, PN remains the gold standard treatment for SRM[56, 69]. European guidelines state that ablation of SRM should be considered in patients unfit for surgery, genetically predisposed to multifocal malignant tumours, or who have bilateral tumours or a tumour on a single kidney and a high risk of requiring renal replacement therapy after surgery[69]. However, as evidence accumulates on oncological control and safety, these indications may be widened.

A recent meta-analysis of 60 studies comparing treatment modalities in renal tumours with less than 7cm showed that cancer-specific and metastasis-free survival at 5 years were similar between PN and thermal ablation[70]. While local recurrence-free survival was worse for a single session of thermal ablation (HR 0.37, 95% CI 0.15-0.89), having repeat ablations levelled out the difference between this treatment modality and PN[70]. This is an important point to consider, as it reassures that retreatment with ablation or surgery is still a viable cancer control option after

ablation-associated recurrence. Studies with longer follow up periods are required to see if this 5-year survival equivalence is durable.

Similarly, a SEER analysis of 17,716 SRM diagnosed from 2005 to 2010 not included is the previously cited meta-analysis reported that overall survival for lesions less than 2cm was similar between PN and ablation but lower for RN[71]. Comparison of the three treatment modalities showed that in all lesions under 3cm thermal ablation supplanted RN in terms of overall survival (HR 1.56, 95% CI 1.31-1.85) and cardiovascular survival rates (HR 1.63, 95% CI 1.10-2.43), while cancer specific survival was similar between the two[71]. These results likely reflect the low renal function burden of ablation compared to RN. Overall survival for lesions between 2 and 3cm (HR 1.67, 95% CI 1.34-2.07), and for patients between 50 and 59 and over 70 years old (HR 2.95, 95% CI 1.84-4.74 and HR 1.52, 95% CI 1.21-1.91, respectively) seemed to favour PN[71]. The conclusions of this observational study may have been tainted by selection bias of fitter and younger patients towards PN, and by evolution of ablation techniques over the long period of study, supporting again the pressing need for prospective well-designed studies to aid clinical decision making in SRM.

To summarise, thermal ablation may offer additional important advantages over surgery: it is less invasive, is associated with less perioperative complications[70] and with less renal function loss[72]. Additionally, it seems to be more cost effective than PN[73].

PN can be technically challenging and, considering both the safety and efficacy data available today, thermal ablation doesn't appear to be oncologically inferior to surgery for SRM, especially if under 2cm. Shared decision making is imperative and patients should be informed of the potential advantages and disadvantages of each treatment modality. Randomised controlled trials comparing ablation and PN for SRM are needed. Until high quality evidence is available, prospective registries, including the European REnal CryoAblation Registry (EuRECA)[74], will be of great value to ascertain outcomes and complication profiles of ablation.

4. Conclusion

The treatment of kidney cancer has been dogmatic for a large number of years: RTB was not advised due to fear of seeding, and radical surgery was the only curative option. In the last couple of decades, these philosophies have been shattered for SRM, first with the introduction of nephron-sparing surgery, then with minimally invasive techniques in the form of laparoscopy and robot-assisted surgery, and finally with the adoption of active surveillance, and ablation therapy. Management is also becoming increasingly guided by co-axial RTB, now known to be a safe and accurate technique[75].

While high quality evidence is still lacking to aid decision making, observational studies point towards tailored and shared decision making. Patient characteristics, life expectancy, tumour size, location, and histology, and surgical expertise should inform the adequate first line management of a SRM.

5. References

1. Kane CJ, Mallin K, Ritchey J, Cooperberg MR, Carroll PR. Renal cell cancer stage migration: analysis of the National Cancer Data Base. *Cancer*. 2008;113(1):78-83. doi:10.1002/cncr.23518.
2. Ejeckam G, Tolnai G, Sarkar K, McCaughey WT. Renal oncocytoma. Study of eight cases. *Urology*. 1979;14(2):186-9.
3. Robson CJ, Churchill BM, Anderson W. The results of radical nephrectomy for renal cell carcinoma. *J Urol*. 1969;101(3):297-301.
4. Herr HW. A history of partial nephrectomy for renal tumors. *J Urol*. 2005;173(3):705-8. doi:10.1097/01.ju.0000146270.65101.1d.
5. Herczel E. Uber Nierenextirpation. *Bieter Klinisch Chirurg*. 1890;6:485.
6. Hung AJ, Cai J, Simmons MN, Gill IS. "Trifecta" in partial nephrectomy. *J Urol*. 2013;189(1):36-42. doi:10.1016/j.juro.2012.09.042.
7. Van Poppel H, Da Pozzo L, Albrecht W, Matveev V, Bono A, Borkowski A et al. A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. *Eur Urol*. 2011;59(4):543-52. doi:10.1016/j.eururo.2010.12.013.
8. Sun M, Abdollah F, Bianchi M, Trinh QD, Jeldres C, Thuret R et al. Treatment management of small renal masses in the 21st century: a paradigm shift. *Ann Surg Oncol*. 2012;19(7):2380-7. doi:10.1245/s10434-012-2247-0.
9. Thompson RH, Boorjian SA, Lohse CM, Leibovich BC, Kwon ED, Cheville JC et al. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. *J Urol*. 2008;179(2):468-71; discussion 72-3. doi:10.1016/j.juro.2007.09.077.

10. Huang WC, Elkin EB, Levey AS, Jang TL, Russo P. Partial nephrectomy versus radical nephrectomy in patients with small renal tumors--is there a difference in mortality and cardiovascular outcomes? *J Urol*. 2009;181(1):55-61; discussion -2. doi:10.1016/j.juro.2008.09.017.
11. Weight CJ, Larson BT, Gao T, Campbell SC, Lane BR, Kaouk JH et al. Elective partial nephrectomy in patients with clinical T1b renal tumors is associated with improved overall survival. *Urology*. 2010;76(3):631-7. doi:10.1016/j.urology.2009.11.087.
12. Kim SP, Thompson RH, Boorjian SA, Weight CJ, Han LC, Murad MH et al. Comparative effectiveness for survival and renal function of partial and radical nephrectomy for localized renal tumors: a systematic review and meta-analysis. *J Urol*. 2012;188(1):51-7. doi:10.1016/j.juro.2012.03.006.
13. Scosyrev E, Messing EM, Sylvester R, Campbell S, Van Poppel H. Renal function after nephron-sparing surgery versus radical nephrectomy: results from EORTC randomized trial 30904. *Eur Urol*. 2014;65(2):372-7. doi:10.1016/j.eururo.2013.06.044.
14. Sun M, Bianchi M, Hansen J, Trinh QD, Abdollah F, Tian Z et al. Chronic kidney disease after nephrectomy in patients with small renal masses: a retrospective observational analysis. *Eur Urol*. 2012;62(4):696-703. doi:10.1016/j.eururo.2012.03.051.
15. Laguna MP. Re: Renal function after nephron-sparing surgery versus radical nephrectomy: results from EORTC randomized trial 30904. *J Urol*. 2014;192(2):369-70. doi:10.1016/j.juro.2014.05.064.

16. Thompson RH. Partial versus radical nephrectomy: the debate regarding renal function ends while the survival controversy continues. *Eur Urol.* 2014;65(2):378-9; discussion 9-80. doi:10.1016/j.eururo.2013.07.036.
17. Kim SP, Gross CP, Meropol N, Kutikov A, Smaldone MC, Shah ND et al. National treatment trends among older patients with T1-localized renal cell carcinoma. *Urol Oncol.* 2017;35(3):113.e15-.e21. doi:10.1016/j.urolonc.2016.10.008.
18. Ghani KR, Sukumar S, Sammon JD, Rogers CG, Trinh QD, Menon M. Practice patterns and outcomes of open and minimally invasive partial nephrectomy since the introduction of robotic partial nephrectomy: results from the nationwide inpatient sample. *J Urol.* 2014;191(4):907-12. doi:10.1016/j.juro.2013.10.099.
19. Hadjipavlou M, Khan F, Fowler S, Joyce A, Keeley FX, Sriprasad S. Partial vs radical nephrectomy for T1 renal tumours: an analysis from the British Association of Urological Surgeons Nephrectomy Audit. *BJU Int.* 2016;117(1):62-71. doi:10.1111/bju.13114.
20. McDougall EM, Clayman RV, Anderson K. Laparoscopic Wedge Resection of a Renal Tumor: Initial Experience. *Journal of Laparoendoscopic Surgery.* 1993;3(6):577-81. doi:10.1089/lps.1993.3.577.
21. Marszalek M, Meixl H, Polajnar M, Rauchenwald M, Jeschke K, Madersbacher S. Laparoscopic and open partial nephrectomy: a matched-pair comparison of 200 patients. *Eur Urol.* 2009;55(5):1171-8. doi:10.1016/j.eururo.2009.01.042.
22. Springer C, Hoda MR, Fajkovic H, Pini G, Mohammed N, Fornara P et al. Laparoscopic vs open partial nephrectomy for T1 renal tumours: evaluation of long-term oncological and functional outcomes in 340 patients. *BJU Int.* 2013;111(2):281-8. doi:10.1111/j.1464-410X.2012.11280.x.

23. Ramasamy R. Laparoscopic vs open partial nephrectomy for T1 renal tumours: evaluation of long-term oncological and functional outcomes in 340 patients. *BJU Int.* 2013;111(2):189. doi:10.1111/j.1464-410X.2012.11284.x.
24. Stifelman MD, Caruso RP, Nieder AM, Taneja SS. Robot-assisted Laparoscopic Partial Nephrectomy. *JSLs : Journal of the Society of Laparoendoscopic Surgeons.* 2005;9(1):83-6.
25. Ficarra V, Minervini A, Antonelli A, Bhayani S, Guazzoni G, Longo N et al. A multicentre matched-pair analysis comparing robot-assisted versus open partial nephrectomy. *BJU Int.* 2014;113(6):936-41. doi:10.1111/bju.12570.
26. Wu Z, Li M, Liu B, Cai C, Ye H, Lv C et al. Robotic versus Open Partial Nephrectomy: A Systematic Review and Meta-Analysis. *PLOS ONE.* 2014;9(4):e94878. doi:10.1371/journal.pone.0094878.
27. Malkoc E, Maurice MJ, Kara O, Ramirez D, Nelson RJ, Caputo PA et al. Robot-assisted approach improves surgical outcomes in obese patients undergoing partial nephrectomy. *BJU Int.* 2017;119(2):283-8. doi:10.1111/bju.13675.
28. Sturm R, Hattori A. Morbid obesity rates continue to rise rapidly in the United States. *Int J Obes (Lond).* 2013;37(6):889-91. doi:10.1038/ijo.2012.159.
29. Leow JJ, Heah NH, Chang SL, Chong YL, Png KS. Outcomes of Robotic versus Laparoscopic Partial Nephrectomy: an Updated Meta-Analysis of 4,919 Patients. *J Urol.* 2016;196(5):1371-7. doi:10.1016/j.juro.2016.06.011.
30. Novick AC. Renal hypothermia: in vivo and ex vivo. *Urol Clin North Am.* 1983;10(4):637-44.
31. Thompson RH, Lane BR, Lohse CM, Leibovich BC, Fergany A, Frank I et al. Every minute counts when the renal hilum is clamped during partial nephrectomy. *Eur Urol.* 2010;58(3):340-5. doi:10.1016/j.eururo.2010.05.047.

32. Volpe A, Blute ML, Ficarra V, Gill IS, Kutikov A, Porpiglia F et al. Renal Ischemia and Function After Partial Nephrectomy: A Collaborative Review of the Literature. *Eur Urol.* 2015;68(1):61-74. doi:10.1016/j.eururo.2015.01.025.
33. Ramirez D, Caputo PA, Krishnan J, Zargar H, Kaouk JH. Robot-assisted partial nephrectomy with intracorporeal renal hypothermia using ice slush: step-by-step technique and matched comparison with warm ischaemia. *BJU Int.* 2016;117(3):531-6. doi:10.1111/bju.13346.
34. Rod X, Peyronnet B, Seisen T, Pradere B, Gomez FD, Verhoest G et al. Impact of ischaemia time on renal function after partial nephrectomy: a systematic review. *BJU Int.* 2016;118(5):692-705. doi:10.1111/bju.13580.
35. Klatte T, Ficarra V, Gratzke C, Kaouk J, Kutikov A, Macchi V et al. A Literature Review of Renal Surgical Anatomy and Surgical Strategies for Partial Nephrectomy. *Eur Urol.* 2015;68(6):980-92. doi:10.1016/j.eururo.2015.04.010.
36. Baumert H, Ballaro A, Shah N, Mansouri D, Zafar N, Molinie V et al. Reducing warm ischaemia time during laparoscopic partial nephrectomy: a prospective comparison of two renal closure techniques. *Eur Urol.* 2007;52(4):1164-9. doi:10.1016/j.eururo.2007.03.060.
37. Peyronnet B, Baumert H, Mathieu R, Masson-Lecomte A, Grassano Y, Roumiguie M et al. Early unclamping technique during robot-assisted laparoscopic partial nephrectomy can minimise warm ischaemia without increasing morbidity. *BJU Int.* 2014;114(5):741-7. doi:10.1111/bju.12766.
38. Wszolek MF, Kenney PA, Lee Y, Libertino JA. Comparison of hilar clamping and non-hilar clamping partial nephrectomy for tumours involving a solitary kidney. *BJU Int.* 2011;107(12):1886-92. doi:10.1111/j.1464-410X.2010.09713.x.

39. Gill IS, Eisenberg MS, Aron M, Berger A, Ukimura O, Patil MB et al. "Zero ischemia" partial nephrectomy: novel laparoscopic and robotic technique. *Eur Urol*. 2011;59(1):128-34. doi:10.1016/j.eururo.2010.10.002.
40. Satkunasivam R, Tsai S, Syan S, Bernhard JC, de Castro Abreu AL, Chopra S et al. Robotic unclamped "minimal-margin" partial nephrectomy: ongoing refinement of the anatomic zero-ischemia concept. *Eur Urol*. 2015;68(4):705-12. doi:10.1016/j.eururo.2015.04.044.
41. Rizkala ER, Khalifeh A, Autorino R, Samarasekera D, Laydner H, Kaouk JH. Zero ischemia robotic partial nephrectomy: sequential preplaced suture renorrhaphy technique. *Urology*. 2013;82(1):100-4. doi:10.1016/j.urology.2013.03.042.
42. Mir MC, Pavan N, Parekh DJ. Current Paradigm for Ischemia in Kidney Surgery. *J Urol*. 2016;195(6):1655-63. doi:10.1016/j.juro.2015.09.099.
43. Simone G, Gill IS, Mottrie A, Kutikov A, Patard JJ, Alcaraz A et al. Indications, techniques, outcomes, and limitations for minimally ischemic and off-clamp partial nephrectomy: a systematic review of the literature. *Eur Urol*. 2015;68(4):632-40. doi:10.1016/j.eururo.2015.04.020.
44. Kaczmarek BF, Sukumar S, Petros F, Trinh QD, Mander N, Chen R et al. Robotic ultrasound probe for tumor identification in robotic partial nephrectomy: Initial series and outcomes. *Int J Urol*. 2013;20(2):172-6. doi:10.1111/j.1442-2042.2012.03127.x.
45. McClintock TR, Bjurlin MA, Wysock JS, Borofsky MS, Marien TP, Okoro C et al. Can selective arterial clamping with fluorescence imaging preserve kidney function during robotic partial nephrectomy? *Urology*. 2014;84(2):327-32. doi:10.1016/j.urology.2014.02.044.

46. Bjurlin MA, McClintock TR, Stifelman MD. Near-infrared fluorescence imaging with intraoperative administration of indocyanine green for robotic partial nephrectomy. *Curr Urol Rep.* 2015;16(4):20. doi:10.1007/s11934-015-0495-9.
47. Alenezi AN, Karim O. Role of intra-operative contrast-enhanced ultrasound (CEUS) in robotic-assisted nephron-sparing surgery. *J Robot Surg.* 2015;9(1):1-10. doi:10.1007/s11701-015-0496-1.
48. Hughes-Hallett A, Pratt P, Mayer E, Di Marco A, Yang GZ, Vale J et al. Intraoperative ultrasound overlay in robot-assisted partial nephrectomy: first clinical experience. *Eur Urol.* 2014;65(3):671-2. doi:10.1016/j.eururo.2013.11.001.
49. Hughes-Hallett A, Pratt P, Mayer E, Martin S, Darzi A, Vale J. Image guidance for all--TilePro display of 3-dimensionally reconstructed images in robotic partial nephrectomy. *Urology.* 2014;84(1):237-42. doi:10.1016/j.urology.2014.02.051.
50. Shin TY, Lim SK, Komninos C, Kim DW, Han WK, Hong SJ et al. Laparoendoscopic single-site (LESS) robot-assisted partial nephrectomy (RAPN) reduces postoperative wound pain without a rise in complication rates. *BJU Int.* 2014;114(4):555-61. doi:10.1111/bju.12783.
51. Maurice MJ, Ramirez D, Kaouk JH. Robotic Laparoendoscopic Single-site Retroperitoneal Renal Surgery: Initial Investigation of a Purpose-built Single-port Surgical System. *Eur Urol.* 2017;71(4):643-7. doi:10.1016/j.eururo.2016.06.005.
52. Trehan A, Dunn TJ. The robotic surgery monopoly is a poor deal. *Bmj.* 2013;347:f7470. doi:10.1136/bmj.f7470.
53. Kim DK, Park DW, Rha KH. Robot-assisted Partial Nephrectomy with the REVO-I Robot Platform in Porcine Models. *Eur Urol.* 2016;69(3):541-2. doi:10.1016/j.eururo.2015.11.024.

54. Bozzini G, Gidaro S, Taverna G. Robot-Assisted Laparoscopic Partial Nephrectomy with the ALF-X Robot on Pig Models. *Eur Urol.* 2016;69(2):376-7. doi:10.1016/j.eururo.2015.08.031.
55. Znaor A, Lortet-Tieulent J, Laversanne M, Jemal A, Bray F. International variations and trends in renal cell carcinoma incidence and mortality. *Eur Urol.* 2015;67(3):519-30. doi:10.1016/j.eururo.2014.10.002.
56. Finelli A, Ismaila N, Bro B, Durack J, Eggener S, Evans A et al. Management of Small Renal Masses: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2017;35(6):668-80. doi:10.1200/jco.2016.69.9645.
57. Wells SA, Wong VK, Wittmann TA, Lubner MG, Best SL, Ziemlewicz TJ et al. Renal mass biopsy and thermal ablation: should biopsy be performed before or during the ablation procedure? *Abdom Radiol (NY).* 2017. doi:10.1007/s00261-016-1037-8.
58. Brace C. Thermal Tumor Ablation in Clinical Use. *IEEE pulse.* 2011;2(5):28-38. doi:10.1109/MPUL.2011.942603.
59. Silk M, Tahour D, Srimathveeravalli G, Solomon SB, Thornton RH. The State of Irreversible Electroporation in Interventional Oncology. *Seminars in Interventional Radiology.* 2014;31(2):111-7. doi:10.1055/s-0034-1373785.
60. NICE Guidance IPG405 - Laparoscopic cryotherapy for renal cancer. <https://www.nice.org.uk/guidance/IPG405/chapter/1-guidance>. Accessed March 2017.
61. NICE Guidance IPG402 - Percutaneous cryotherapy for renal cancer. In <https://www.nice.org.uk/guidance/IPG402/chapter/1-guidance>. Accessed March 2017.
62. NICE Guidance IPG353 - Percutaneous radiofrequency ablation for renal cancer. <https://www.nice.org.uk/guidance/ipg353/chapter/1-guidance>. Accessed March 2017.

63. El Dib R, Touma NJ, Kapoor A. Cryoablation vs radiofrequency ablation for the treatment of renal cell carcinoma: a meta-analysis of case series studies. *BJU Int.* 2012;110(4):510-6. doi:10.1111/j.1464-410X.2011.10885.x.
64. Thompson RH, Atwell T, Schmit G, Lohse CM, Kurup AN, Weisbrod A et al. Comparison of partial nephrectomy and percutaneous ablation for cT1 renal masses. *Eur Urol.* 2015;67(2):252-9. doi:10.1016/j.eururo.2014.07.021.
65. Hui GC, Tuncali K, Tatli S, Morrison PR, Silverman SG. Comparison of percutaneous and surgical approaches to renal tumor ablation: metaanalysis of effectiveness and complication rates. *J Vasc Interv Radiol.* 2008;19(9):1311-20. doi:10.1016/j.jvir.2008.05.014.
66. Canvasser NE, Sorokin I, Lay AH, Morgan MS, Ozayar A, Trimmer C et al. Irreversible electroporation of small renal masses: suboptimal oncologic efficacy in an early series. *World J Urol.* 2017. doi:10.1007/s00345-017-2025-5.
67. Ritchie RW, Leslie T, Phillips R, Wu F, Illing R, ter Haar G et al. Extracorporeal high intensity focused ultrasound for renal tumours: a 3-year follow-up. *BJU Int.* 2010;106(7):1004-9. doi:10.1111/j.1464-410X.2010.09289.x.
68. Ritchie RW, Leslie TA, Turner GD, Roberts IS, D'Urso L, Collura D et al. Laparoscopic high-intensity focused ultrasound for renal tumours: a proof of concept study. *BJU Int.* 2011;107(8):1290-6. doi:10.1111/j.1464-410X.2010.09620.x.
69. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M et al. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol.* 2015;67(5):913-24. doi:10.1016/j.eururo.2015.01.005.
70. Pierorazio PM, Johnson MH, Patel HD, Sozio SM, Sharma R, Iyoha E et al. Management of Renal Masses and Localized Renal Cancer: Systematic Review and Meta-Analysis. *J Urol.* 2016;196(4):989-99. doi:10.1016/j.juro.2016.04.081.

71. Moskowitz D, Chang J, Ziogas A, Anton-Culver H, Clayman RV. Treatment for T1a Renal Cancer Substratified by Size: "Less is More". *J Urol*. 2016;196(4):1000-7. doi:10.1016/j.juro.2016.04.063.
72. Yang Q, Meng F, Li K, Wang T, Nie Q, Che Z et al. Safety and Efficacy of Thermal Ablation for Small Renal Masses in Solitary Kidney: Evidence from Meta-Analysis of Comparative Studies. *PLOS ONE*. 2015;10(6):e0131290. doi:10.1371/journal.pone.0131290.
73. Wang Y, Chen YW, Leow JJ, Levy AC, Chang SL, Gelpi FH. Cost-effectiveness of Management Options for Small Renal Mass: A Systematic Review. *Am J Clin Oncol*. 2016;39(5):484-90. doi:10.1097/coc.0000000000000307.
74. European REnal CryoAblation Registry (EuRECA). <https://www.eureca-registry.com/>. Accessed March 2017.
75. Richard PO, Jewett MA, Bhatt JR, Kachura JR, Evans AJ, Zlotta AR et al. Renal Tumor Biopsy for Small Renal Masses: A Single-center 13-year Experience. *Eur Urol*. 2015;68(6):1007-13. doi:10.1016/j.eururo.2015.04.004.

6. Tables

Box 1 – Definition of small renal mass

Small renal mass	Contrast enhancing renal lesion detected, usually incidentally, by imaging, that measures ≤ 4 cm of largest diameter axis
------------------	--

Table 1 – Ablative techniques in kidney cancer

Route	Laparoscopic, percutaneous, (open)
Source of energy	Cryotherapy, radiofrequency, irreversible electroporation, high-intensity focused ultrasound, laser
Advantages	Day surgery procedure, less perioperative complications, reduced loss of renal function, cost-effectiveness
Limitations	Lesion size, lesion location (proximity to hilum, proximity to ureter and ureteropelvic junction, proximity or need to transverse surrounding structures such as bowel or liver)

7. Important References

Hung AJ, Cai J, Simmons MN, Gill IS. "Trifecta" in partial nephrectomy. J Urol.

2013;189(1):36-42. doi:10.1016/j.juro.2012.09.042. **

This paper established the concept of the trifecta in partial nephrectomy, an essential standard against which outcomes are now measured in the operation.

Scosyrev E, Messing EM, Sylvester R, Campbell S, Van Poppel H. Renal function after nephron-sparing surgery versus radical nephrectomy: results from EORTC randomized trial 30904. Eur Urol. 2014;65(2):372-7.

doi:10.1016/j.eururo.2013.06.044. **

This essential paper challenged assumptions about renal function post partial nephrectomy and has stimulated further investigations into the refinement of the management of small renal masses.

Thompson RH, Atwell T, Schmit G, Lohse CM, Kurup AN, Weisbrod A et al.
Comparison of partial nephrectomy and percutaneous ablation for cT1 renal masses.
Eur Urol. 2015;67(2):252-9. doi:10.1016/j.eururo.2014.07.021. *

This paper reports a robust observational comparison of outcomes between surgery and ablation (both cryo- and radiofrequency) for small renal masses. Although overall survival was superior after partial nephrectomy in this single centre cohort, oncological outcomes were equivalent after cryoablation.