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MINI-REVIEW

Robot-assisted partial nephrectomy: How to minimise renal ischaemia

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ABBREVIATIONS

AKI, acute kidney injury;
AO, artery only;
CKD, chronic kidney disease;
NSS, nephron-sparing surgery

Abstract Renal ischaemia research has shown an increase in renal damage proportional to ischaemic time. Therefore, we assessed the importance of renal ischaemic times for warm and cold ischaemia approaches, and explored the different surgical techniques that can help to minimise renal ischaemia in robot-assisted partial nephrectomy (RAPN). Minimising renal ischaemia during nephron-sparing surgery (NSS) is a key factor in preserving postoperative renal function. Current data support a safe warm ischaemia time (WIT) of ≤25 min and cold ischaemic time of ≤35 min, resulting in no significant deterioration in renal function. In general, patients undergoing NSS have increased comorbidities, including chronic kidney disease, and in these patients it is difficult to predict their postoperative renal function recovery. With RAPN, efforts should be made to keep the WIT to < 25 min, as minimising the ischaemic time is vital for preservation of overall renal function and remains a modifiable risk factor. Parenchymal or segmental artery clamping, early unclamping or off-clamp techniques can be adopted when ischaemic times are likely to be > 25 min, but may not lead to superior functional outcome. Careful preoperative planning, tumour factors, and meticulous surgical technique are critical for optimum patient outcome.

Introduction

The 'gold standard' for treatment of T1a renal lesions is partial nephrectomy (PN) where technically feasible [1]. With advances in techniques, larger lesions including T1b renal masses are also being treated with PN. Minimally invasive techniques including laparoscopic PN (LPN) and robotic-assisted laparoscopic PN (RAPN)

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have become established procedures for PN over the traditional open PN (OPN). Cancer control, whilst preserving renal function, is the basis of successful surgery, with a complex interaction between three elements: preoperative parenchymal quality, postoperative parenchymal quantity preserved, and the recovery of the preserved nephrons to the ischaemic insult [2].

The technical difficulty of LPN and morbidity associated with OPN has led to a rapid rise in the utilisation of RAPN due to several advantages. Zhang et al. [3] in a recent meta-analysis showed that although parameters such as operative time, estimated blood loss, and hospital stay were similar for LPN and RAPN, the later had significantly shorter ischaemic times. Along with the known advantages of RAPN such as a three-dimensional view, reduction in tremor, and precise fine EndoWrist movements using the robotic platform, the key advantage with performing RAPN is the shorter learning curve to achieve ischaemic times of < 20 min [4].

Pathophysiology of renal-reperfusion injury

Renal-reperfusion injury is caused by a sudden temporary impairment of blood flow to the kidney. This leads to an inflammatory response and oxidative stress to the kidney from the reduction in oxygen to the tissues, which ultimately leads to an alteration in organ function. The complete pathophysiology of renal-reperfusion injury is not fully understood, with several important mechanisms thought to be involved that can result in subsequent renal failure.

Activation of an inflammatory cascade leading to chemokine release, including pro-inflammatory cytokines such as interleukin 6 and TNFα, play a major role in renal dysfunction that causes renal damage [5].

During renal-reperfusion injury, the damaged tissue produces excessive amount of reactive oxygen species causing oxidative stress, which changes mitochondrial oxidative phosphorylation, ATP depletion, increases intracellular calcium and active membrane proteases, causing cell injury [6].

Types of ischaemia

Animal studies on dogs that were conducted to test the safe limit of renal ischaemia concluded that 30 min is a safe limit, as it allowed full recovery of renal function [7]. Laven et al. [8] demonstrated in a porcine model with a solitary kidney that this warm ischaemia time (WIT) can be extended with full recovery of renal function up to 90 min, although it was noted that decreased renal function occurred in the initial 72 h.

Studies have shown that cold ischaemia can provide superior postoperative renal function recovery when used concordantly with warm ischaemia [9]. When performing OPN the most common method of achieving cold ischaemia is by making an ice slush to go around the kidney. Using this method of initial cooling for 10 min, cold ischaemic times of up to 35 min have been shown to be safe for renal preservation [10].

A study of 660 patients who underwent OPN with half having warm ischaemia and the other half having cold ischaemia, showed that the group with cold ischaemia, despite longer ischaemic times, had no significant difference in postoperative renal function. The authors concluded from their study that although postoperative renal function is primarily achieved by the quality and quantity of parenchymal preservation, the type and duration of ischaemia were the most important modifiable factors [11].

Postoperative renal function in the presence of a normal contralateral kidney can sometimes be masked based on measurement of postoperative serum creatinine or estimated GFR (eGFR) values. One study incorporated technetium 99 m mercaptoacetyltriglycine (^{99m}Tc-MAG3) renal scintigraphy to assess renal function in patients undergoing LPN in the presence of a normal contralateral kidney. The findings showed that split renal function can be altered significantly from 48% down to 36.9% at 5 days and only recover to 42.8% after 1 year. The study concluded that parenchymal preservation and having a WIT of > 32 min were most significant for predicting renal outcome [12].

Patient and tumour factors

Preoperative optimisation

Optimising patients' preoperatively is important for maximising renal function after PN. Minimising renal ischaemia is important, as up to 24% of patients with T1 tumours have a GFR < 60 mL/min/1.73 m^2 (Stage 2 chronic kidney disease [CKD]). Those patients with a GFR < 45 mL/min/1.73 m^2 (Stage 3 CKD) undergoing PN were associated with a higher risk of a 50% reduction in GFR. Another interesting finding is that patients with a normal GFR (Stage 1 CKD) or moderately reduced (Stage 3 CKD) did not get any benefit in renal function despite undergoing nephron-sparing surgery (NSS) compared to the patients with Stage 2 CKD [13].

Furthermore, there is a high incidence of comorbid disease in patients with RCC including diabetes mellitus (9–30%), hypertension (40–69%), smoking history (40–70%), obesity (40%), as well as advanced age [14].

Malcolm et al. [15] compared groups with diabetes, hypertension, high body mass index (BMI) > 30 kg/m^2, age > 60 years, and smoking, as risk factors in patients undergoing radical nephrectomy (RN) or PN against patients with none of these comorbidities and found that all these factors were associated with an increase in postoperative creatinine, decrease in eGFR, and metabolic acidosis.

Whilst reducing WIT is beneficial to any patient undergoing PN, it is of increased importance in patients with significant comorbidities. Comorbidities that may have a detrimental effect on renal function include diabetes, hypertension etc. Such patients are more susceptible to the effects of warm ischaemia to the remaining kidney than patients without these comorbidities.

Even a small elevation in blood pressure is an independent risk factor for developing end-stage renal disease, and the risk is increased as the volume of preserved renal parenchyma is reduced [16].

Therefore, preoperative optimisation of patients' modifiable comorbidities and risk factors, such as diabetes, BMI and hypertension to the normal range, as well as smoking cessation will help reduce potential renal damage caused from surgical ischaemia.

Tumour factors

Tumour size, complexity and location will have an effect on postoperative renal function after PN. Some clinical studies suggest that tumour size may be a good predictor of postoperative renal function [17–20], with others not reaching the same conclusion [9]. Renal scoring systems to attempt to grade tumour complexity, such as the R.E.N.A.L. (Radius; Exophytic/Endophytic; Nearness; Anterior/Posterior; Location) and PADUA (Preoperative Aspects and Dimensions Used for an Anatomical) nephrometry score systems, are used to help predict postoperative renal function but these have not been conclusive [21–23].

For RAPN, the preoperative R.E.N.A.L. nephrometry score was a clear determinate of the amount of non-neoplastic parenchymal tissue removed, with the tumour radius and tumour location in relation to the polar lanes being associated with a larger amount of tissue removed [24].

Increasing R.E.N.A.L. and PADUA nephrometry scores are correlated with longer WITs. However, these could only differentiate between low complexity vs moderate/high complexity and not between moderate and high complexity, suggesting a two-tier system would be more accurate [25].

Medical factors

The main pathophysiological processes leading to renal function impairment that occur during renal ischaemia are: obstructive, vascular/endothelial, and reperfusion injury [26].

Pharmacological agents

One agent that has been commonly used as a renal protective agent for patients at high risk of developing renal failure is mannitol [26]. Retrospective studies suggest that mannitol has no renal protective effect on postoperative renal function [27,28]. A recent randomised controlled trial using fenoldopam (short acting dopamine-1 receptor agonist) showed no improvement in postoperative renal function compared to placebo in the setting of a clamped PN [29].

Preoperative targeted therapeutic agents have been proposed to reduce tumour size and therefore optimise renal parenchymal preservation in localised disease. Pazopanib (a vascular endothelial growth factor [VEGF] receptor inhibitor) has been used in the neoadjuvant setting in a prospective trial. Six out of 13 patients that were initially unable to undergo PN were offered PN after neoadjuvant treatment, resulting in increased renal parenchymal preservation [30]. This approach is not currently widely adopted in clinical practice. These medical interventions have no bearing on minimising WIT intraoperatively, but may have a beneficial effect in optimising postoperative renal function.

Surgical factors

Surgical techniques used will be the main influence for reducing renal ischaemia in RAPN.

Surgical approach

A systematic review comparing RAPN and LPN found a shorter WIT in the RAPN group [31], with studies indicating a trend for a lesser reduction in postoperative eGFR [32,33]. However, no differences were found in the overall global percentage eGFR preservation between LPN and RAPN [34].

Comparing RAPN to OPN, a multicentre study showed a shorter WIT for OPN (15.4 vs 19.2 min; $P < 0.001$) but similar postoperative eGFR values [35].

Regarding the surgical approach for RAPN, various studies have considered the transperitoneal and retroperitoneal approaches, and the WIT appears to be similar. Haber et al. [36], describing the transperitoneal approach, reported an operative time of 200 min and WIT of 18.2 min compared to a large multicentre study by Hu et al. [37], describing the retroperitoneal approach, with an operative time of 165 min and WIT of 19 min. From these studies, the surgical approach does not seem to have a clear advantage of one over the other. However, the overall WIT, renal preservation and outcome was shown to depend on tumour location and individual surgeon expertise and experience.

The increased number of RAPNs performed by a surgeon correlates with a lower WIT and hence improvement in the patient outcome. Studies have shown the learning curve to achieve an ideal WIT of <25 min ranges from 44 to 60 cases [38,39].

Intraoperatively

The incidence of acute kidney injury (AKI) in patients who undergo NSS remains controversial. Studies have shown that overall incidence of AKI, measured either as an increase in serum creatinine or fall in urine output, is 5.5–6.5% across RAPN cases [40,41]. The suggested preventative non-surgical strategies include aggressive fluid hydration to produce a diuresis of >200 mL/h [42] and to keep the pneumoperitoneum pressures at ≤ 15 mmHg [43].

Surgical clamping strategies

There are four main types of strategies that have been introduced to minimise renal ischaemia during RAPN: global renal ischaemia, selective renal ischaemia, off-clamp (zero) ischaemia, and cold ischaemia.

Global renal ischaemia (renal artery and vein)

The traditional ischaemia technique involves clamping of both the renal artery and renal vein (*en bloc*). The impact on renal function with respect to clamping just the renal artery or both renal artery and renal vein remains unclear. A meta-analysis by Zhou et al. [44] showed no difference in these two groups for operative time and length of stay or transfusion rates.

Current practice in RAPN would be clamping the artery only (AO), which could allow low-level tissue oxygenation via venous backflow, although it would carry a higher bleeding risk. One study comparing *en bloc* with AO clamping showed that although WIT was higher in AO group, the overall decline in renal function was the same in both groups [45].

Early unclamping is a technique that has been shown to significantly reduce WIT by up to 50%. Unclamping is often done after internal renorrhaphy has been performed, with further renorrhaphy performed on the revascularised kidney. Even though this leads to a significantly higher blood loss, overall risk of haemorrhagic complications or transfusion rates showed no statistical difference [46].

Selective renal ischaemia

This technique involves the clamping and devascularisation of only the tissue being excised, whilst maintaining perfusion to the rest of the kidney.

In selected patients with favourable tumour locations, such as polar location or exophytic, parenchymal clamping can provide a safe alternative to warm ischaemia. First described in LPN, this has also been used in RAPN successfully, with no positive margin and no decrease in postoperative renal function at 6 months of follow-up [47,48].

With the development of RAPN, the ability to clamp a segmental arterial branch is becoming more feasible. In a study describing LPN in 75 patients, segmental clamping was performed leading to significantly better postoperative renal function, although this group did have higher blood loss and WIT [49]. Segmental ischaemia has also been used successfully in cT1b tumours [50].

To reduce WIT and bleeding, techniques to microdissect the tertiary or quaternary feeding vessels to the tumour combined with pharmacologically induced hypotension can be effectively utilised [51].

Off-clamp (zero) ischaemia

The ultimate method to completely minimise renal ischaemia in RAPN is to excise the tumour with no clamping of the vessels. This technique is possible with careful patient selection with favourable tumour size and location, e.g. small and exophytic with no deep parenchymal invasion [52,53]. In this group of patients with small tumours performing off-clamp PN may reduce the risk of AKI and CKD [54]. In a study comparing clamped RAPN to off-clamp RAPN, off-clamp RAPN was found to lead to better preservation of postoperative renal function and shorter operative time, but higher blood loss [55].

In a comparative study of RAPN performed with different clamping techniques, off-clamp and selective clamping techniques resulted in improved postoperative renal function compared to patients undergoing clamping of the main renal artery. However, as long as the WIT was 20–30 min, there was no significant difference in functional outcomes at 6-months of follow-up [56].

Cold ischaemia

A case series of seven patients described the technique of cold ischaemia in RAPN with promising results. A GelPOINT® access port (Applied Medical Resources Corporation, Rancho Santa Margarita, CA, USA) was used for the camera and assistant ports. After hilar clamping, ice slush was introduced through the GelPOINT via syringes and applied over the kidney surface. This provided the cold ischaemia needed to perform the PN and is useful for more complex tumours that require longer excision time [57].

Excision techniques

Traditional PN has been described as excision of the tumour with a rim of healthy non-neoplastic parenchymal tissue. This will include the most common excision technique of wedge resection, as well as polar resections (tumours in either upper or lower pole), heminephrectomy (for larger tumours confined to either upper or lower pole), and mid-segmental PN (for large interpolar tumours) [58].

Simple enucleation involves the utilisation of blunt dissection along a plane formed by the tumour pseudo-capsule [59]. The renal parenchyma is incised a few millimetres from the edge of the tumour until the natural plane is encountered, followed by blunt separation of renal parenchyma from the tumour [60]. This technique allows for maximal parenchymal preservation by reducing the WIT. A relatively avascular pseudo-capsular plane enables a less complex renorrhaphy, as well as providing a useful guide for excision of the tumour leading to fewer positive surgical margins [61].

Reconstructive techniques

Further studies are required to elucidate the best technique for reconstruction after a PN. Cortical renorrhaphy and tumour-base ablation are known to adversely affect renal volume and lead to a decrease in renal function [62,63]. Bahler et al. [64] compared a RAPN non-cortical renorrhaphy group to a renorrhaphy group; the non-cortical renorrhaphy group had a shorter WIT (12 vs 20 min) with no differences in complications.

A further review by the same group analysed four retrospective controlled studies comparing cortical renorrhaphy to omission of cortical renorrhaphy. They found that three out of the four studies had a reduction in kidney volume or functional loss of 3.8–11.5% vs 15.6–20.4%, respectively. They concluded that cortical renorrhaphy is associated with renal volume and functional loss [65].

Postoperative complications

Minimising ischaemic time is only one part of the complex interaction that can occur during NSS that has an effect on renal function. Postoperative complications such as urinary leaks, infections or bleeding requiring embolisation, will put increased stress on the preserved renal parenchyma leading to a decrease in global renal function.

A study by Verhoest et al. [66] showed that a postoperative complication, baseline renal function, and BMI, were the only independent factors predicting postoperative Stage 5 CKD.

Based on available evidence, the use of a single threshold value for ischaemia time, as a determinant of postoperative renal function, in PN is flawed. Current evidence shows that ischaemia times of up to 30 min in patients with bilateral kidneys can be tolerated without a clinically significant decline in renal function [67].

Conclusion

PN is considered the 'gold standard' for the treatment of small renal tumours. RAPN is the evolution of the surgical technique from the open and laparoscopic approaches. Minimising the ischaemic time is vital for preservation of overall renal function and remains a modifiable risk factor. It has been suggested that a WIT of <25 min is a good measure for positive outcomes, although the duration of ischaemia can be considerably increased with cold ischaemia. Although techniques including: parenchymal and segmental artery clamping, early and off-clamp, have been described to minimise renal ischaemia they do not necessarily lead to superior functional outcome.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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Further reading

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