Surgical Treatment of Localised Renal Cancer

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Abstract
The management of localised renal cancer has been revolutionised with the introduction of laparoscopy and minimally invasive techniques, achieving comparable oncologic results and reduced morbidity. With the detection rate of small renal lesions increasing, the diagnostic approach and surgical treatment shift to nephron-sparing surgery and less invasive techniques.

Today, open partial nephrectomy (OPN), laparoscopic partial nephrectomy (LPN), radiofrequency ablation, and cryotherapy are treatment options. Comparing OPN and LPN, multicentre studies have shown equivalent cancer-specific survival rates. Robot-assisted partial nephrectomy seems to have an advantage with regard to decreased ischemia time compared to conventional laparoscopy.

OPN and LPN are now preferred treatment options for the surgical treatment of smaller renal lesions (<7 cm). With increasing experience in minimally invasive techniques, the laparoscopic and robotic approaches are becoming the preferred techniques in specialised centres. Promising novel augmented reality tracking systems may further improve the surgical and oncologic outcome of laparoscopic and robotic procedures.

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1. Introduction
Renal cancer is the third most common urologic cancer [1]. Most of these renal masses remain asymptomatic, and clinical symptoms such as gross haematuria, flank pain, and palpable tumour, are rare. In most cases, renal cancer is detected on abdominal imaging. Commonly used imaging methods include abdominal ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). The risk of renal cancer increases with age, reaching its peak in the seventh decade of life. Metastatic disease is found in one-fourth to one-third of patients, bilateral tumours occurring in approximately 2% of patients. There has been an overall increase in the incidence of renal cancer, especially for small renal masses (SRMs; 2–4 cm) [1–3]. Widespread use of imaging methods (ultrasound and CT) may be the reason for this increase.

Standard treatment of renal cancer has been radical nephrectomy (RN). Any other treatment options have to be compared to RN in terms of oncologic outcome. However, during the past decade, the management of localised renal cancer has been revolutionised with the introduction of laparoscopy and minimally invasive surgical techniques that show comparable oncologic results and less morbidity for patients [4].

2. Imaging of localised renal cancer
Today, approximately 50% of all renal masses are diagnosed coincidentally because of a higher availability of a variety of imaging techniques [5]. However, histopathologic findings initially revealed benign lesions in up to 20–30% of renal masses <4 cm suspected of being malignant [6]. Therefore,
it is important to have more accurate preoperative diagnostic tools not only for the differentiation between benign and malignant lesions but also for exact imaging and staging of SRMs.

2.1. Abdominal ultrasound

Ultrasound is a widely available diagnostic tool for primary diagnosis of renal masses and is often the first imaging technique used to assess patients suspected of renal cancer. Frequent use causes incidental findings in early stages. Contrast-enhanced ultrasound (CEUS) is a promising safe and easy-to-perform technique that does not require radiation and has no risk of nephrotoxicity. Conventional ultrasound is limited by the capabilities of conventional colour and spectral Doppler imaging, but CEUS offers a combination of Doppler ultrasonography with a contrast agent in the form of gas-encapsulated microbubbles <10 μm in diameter [7]. Limitations are the rapid enhancement and de-enhancement of the kidney, which results in different interpretation of renal masses depending on the examiner’s experience. CEUS has been shown to be useful in the detection of pseudocapsules in renal cell carcinoma (RCC) and allows for differentiation between benign and malignant hyperechoic lesions in cases with diffuse lesion enhancement [8–10].

2.2. Computed tomography

CT remains the most appropriate imaging modality for determining primary tumour extension and differentiating benign from malignant lesions [11]. The presence of enhancement on CT is the most important criterion for identification of malignant disease. A promising tool seems to be the ball versus bean strategy, which describes the growth characteristics of the tumour and therefore the differentiation between benign and malignant lesions [2]. “Ball-type” masses can deform the renal contour and therefore appear as a hump or bulge. “Bean-type” masses do not show any contour deformation and are characterised by infiltrative growth. As such, ball-type lesions indicate benign growth, and bean-type lesions indicate malignant growth. In the case of cystic lesions, the Bosniak classification is recommended for further determination of significance [12].

2.3. Magnetic resonance imaging

In cases with inconclusive CT scans, MRI can provide further information regarding the suspected malignancy, local extension, and in particular vena cava thrombus invasion [13]. In contrast, Hallscheidt et al. showed in a prospective study that CT and MRI achieve similar overall accuracy (0.89 vs 0.84) in tumour staging of RCC [14]. In cases of renal function impairment with an estimated glomerular filtration rate (eGFR) <30 ml/min, gadolinium-enhanced MRI should be avoided because of nephrogenic systemic fibroses and nephropathy [15].

3. Surgical treatment of localised renal masses

The treatment modalities for renal cancer depend on different tumour characteristics, including tumour size, expansion, and location. Furthermore, patient characteristics as well as comorbidities and performance status should be taken under consideration.

Surgical resection remains the standard of care for localised renal cancer [16]. Widespread use of ultrasound and further imaging options (CT, MRI) have increased the detection rate of renal masses, especially those <4 cm [2]. RN has been the gold standard treatment in renal cancer for the past three decades [17].

Today, the main goals of renal cancer surgery are complete tumour excision and preservation of renal function. In a recently published prospective randomised trial, van Poppel et al. reported on the oncologic outcome of 541 patients with SRMs (<5 cm) treated with RN and partial nephrectomy (PN) [18]. The authors found no significant difference in oncologic outcome or overall cancer-specific survival (CSS) after a median follow-up of 9.3 yr. However, overall mortality and cardiovascular events were worse for RN versus PN [19–21]. Huang et al. demonstrated better renal function measured by eGFR for patients after PN [22]. Therefore, nephron-sparing surgery (NSS) is becoming the preferred treatment option. Open PN (OPN) has been shown to have excellent outcomes similar to RN and is recommended generally for T1 tumours [16,23]. Tumour seeding when performing NSS is rare and has been reported in only a few laparoscopic PN (LPN) cases [24].

Minimally invasive treatment options such as LPN, robot-assisted PN, and ablative therapies (radiofrequency [RF] ablation and cryoablation) must be compared in terms of oncologic and functional outcome with OPN. At present, there is no evidence for routine adrenalectomy during NSS [25,26]. Concomitant adrenalectomy is only indicated if a suspicious adrenal gland lesion is identified on preoperative imaging or invasion of the adrenal gland is suspected intraoperatively. The laparoscopic removal of adrenal glands should be performed only in centres by surgeons performing >10 laparoscopic adrenalectomies per year, as it has been shown that, because of the complexity of the minimally invasive procedure, perioperative and postoperative morbidity were strongly influenced by the experience of the performing surgeon [27].

At present, the data do not show any survival advantage for patients undergoing a complete lymph node dissection (LND) in conjunction with RN [28]. In cases of palpable nodes or enlarged lymph nodes detected on preoperative imaging, complete resection should be performed, as in these patients, lymph node metastases can be found in 12.1% [28]. The dissection of lymph nodes remains controversial, as no survival benefit for patients has been shown. For staging purposes, LND can be limited to the hilar region [16].

3.1. Indication for nephron-sparing surgery

An absolute indication for NSS is anatomic or functional solitary kidney and patients with bilateral renal tumours.
Relative indications for NSS are kidney tumours in patients with comorbidities compromising present or future renal function (eg, systemic diseases such as diabetes mellitus or hypertension, stone diseases, chronic pyelonephritis, renal artery stenosis) [21]. Elective indication is defined as a small tumour (≤4 cm) in the presence of a healthy contralateral kidney [16].

3.2. Open partial nephrectomy

When performing NSS, OPN remains the standard treatment option for localised renal cancer [16]. In patients with T1 disease, NSS has proven to be associated with better overall survival (OS) and preservation of renal function compared to RN [19,22]. Therefore, OPN should be offered to all patients with renal masses in solitary kidneys, bilateral renal tumours, and reduced renal function as well as masses <4 cm [29]. With growing experience in OPN, tumours up to 7 cm in diameter and even larger benign renal masses are treated by NSS [29]. Experienced centres report on 98% and 85% 5-yr recurrence-free survival (RFS) and OS rates, respectively [30]. The overall complication rate has been reported as 22% (3% intraoperative, 19% postoperative) [30]. The median tumour size was 2.9 cm (range: 2.3–3.5), the median operative time was 150 min (range: 127–185), and the median cold ischemia time was 31 min (range: 24–45) [30] (Table 1).

3.3. Laparoscopic partial nephrectomy versus open partial nephrectomy

Whereas laparoscopic RN for the treatment of renal cancer has become a standard recommended surgical procedure in the European Association of Urology (EAU) guidelines, LPN is recommended as an alternative treatment option in specialised centres with advanced laparoscopic experience for selected patients with small tumours [4,16]. It has been shown that laparoscopic or a purely retroperitoneoscopic approach for NSS is safe and reproducible, with comparable outcomes [4].

In an earlier series of LPN, high conversion rates and long operating times were reported. Gill et al. reported average operating times of 201 min (range: 25–610)—0.78 times that for OPN (266 min; range: 118–600)—less blood loss (0.80 times OPN), and low conversion rates of 2.1% [4]. However, long-term renal function depends on the duration of warm ischemia time (WIT). WIT for patients who underwent LPN was 1.69 times longer (mean: 30.7 min; range: 4.0–68.0) than for patients treated with OPN (mean: 20.1 min; range: 4.0–52.0) [4]. Recently published data suggest that a WIT >20–25 min may cause clinically relevant renal functional impairment [31,32] and should therefore be avoided. That said, Godoy et al. reported on 101 patients who underwent LPN and found no significant decrease in renal function for up to 40 min of WIT [33]. LPN with clamping of the renal parenchyma only (instead of the vessels) was reported in smaller series and may reduce renal function impairment [34].

LPN is a technically demanding surgical technique [4]. When performing reconstructive surgery, minimally invasive approaches have their limitations. Major complications such as haemorrhage and urinary leakage were reported in early laparoscopic series [35]. However, with increasing experience, better outcomes and even less blood loss compared to OPN have been reported [4]. Whether improvements in haemostatic agents are the reason for less bleeding complications remains questionable. Wille et al. proved the feasibility and safety of Floseal haemostatic matrix (Baxter Healthcare, Deerfield, IL, USA) application in 102 consecutive patients undergoing LPN with a median tumour size of 2.6 cm (range: 0.5–8.5) [36]. Tumour resection was performed with scissors and a harmonic scalpel, with a mean surgical time of 201 min (range: 60–355) and WIT of 25.8 min (range: 6–75); no intraoperative complications occurred.

A prospective, randomised, multicentre study evaluated the haemostatic efficacy and safety of TachoSil (Takeda Pharmaceutical, Osaka, Japan) versus standard suturing in OPN [37]. The primary end point was the intraoperative time to haemostasis. Median time to haemostasis was 5.3 min (3.0; range: <3 to 17) for TachoSil and 9.5 min (8.0; range: <3 to 27) for standard treatment (p < 0.0001). The authors concluded that TachoSil was superior to standard treatment in obtaining intraoperative control of haemorrhage related to NSS of the kidney, with a significantly shorter time to haemostasis.

These kinds of agents are frequently used in LPN and may improve haemostasis as well as urinary leakage [38]. It has been discussed by Breda et al. that not only surgical skills but also patient selection might improve outcome. Further measurement of tumour depth may help to identify patients who could profit from the application of haemostatic agents and glue. Recent published data for LPN are summarised in Table 2.

Table 1 – Open partial nephrectomy

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Mean tumour size, cm (range)</th>
<th>Mean operative time, min (range)</th>
<th>WIT, min (range)</th>
<th>EBL, ml (range)</th>
<th>Survival, %</th>
<th>Complication rate, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marzalek et al. [30]</td>
<td>100</td>
<td>2.9 (2.3–3.5)</td>
<td>150 (127–185)</td>
<td>31 (24–45) CIT</td>
<td>–</td>
<td>98 (5-yr RFS)</td>
<td>22 (22)</td>
</tr>
<tr>
<td>Thompson et al. [19]</td>
<td>358</td>
<td>2.5 (0.2–4.0)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>93 (10-yr OS)</td>
<td>–</td>
</tr>
<tr>
<td>Gill et al. [4]</td>
<td>1628</td>
<td>3.5 (0.6–7.0)</td>
<td>266 (118–600)</td>
<td>20.1 (4–52)</td>
<td>3376 (10–3300)</td>
<td>98.5 (3-yr RFS)</td>
<td>192 (24.9)</td>
</tr>
</tbody>
</table>

WIT = warm ischemia time; EBL = estimated blood loss; CIT = cold ischemia time; RFS = recurrence-free survival; OS = overall survival.
3.4. Robot-assisted partial nephrectomy

Robot-assisted PN is a new minimally invasive technique and an alternative to OPN and LPN [40]. Benway et al. reported functional and oncologic outcome after robot-assisted PN in 183 patients [41]. The mean tumour size was 2.87 cm (range: 1.0–7.9) and operative time was 210 min (range: 86–370), with an average WIT of 23.9 min (range: 10–51). Positive surgical margins were found in 2.7% of cases, and the estimated blood loss was 131.5 ml (range: 10–900). After a median follow-up of 16 mo, no significant decrease in eGFR was detected. Robot-assisted PN provides all the advantages of the minimally invasive aspects of laparoscopy but also offers significant technical help in challenging NSS [40,42,43]. Perioperative and postoperative short-term analyses demonstrated comparable results to LPN [42]. The small patient groups and short follow-up have to be taken into consideration, and a larger patient load could increase the evidence of advantages for RPN. Recent published series are summarised in Table 3.

3.5. Alternative minimally invasive techniques

Ablative, nonsurgical techniques for the treatment of small renal lesions (e.g., RF ablation, cryoablation) seem to have an advantage in morbidity, especially in high-risk surgical patients. Indications for ablative treatment are small renal tumours in elderly patients, bilateral tumours, renal lesions in solitary kidneys, and genetic predisposition for developing multiple tumours [16]. Preoperative biopsy should be performed to verify the dignity of the renal mass. Overall, 5-yr RFS and CSS rates of 90% and 99%, respectively, for biopsy-proven renal cancer with a mean follow-up of 27 mo (range: 1.5–90) was reported recently in 160 patients treated with RF ablation [48]. The mean tumour size was 2.4 cm (range: 1–5.4). Centres experienced in minimally invasive techniques demonstrated data from 51 patients with a 3-yr CSS rate of 98% after cryoablation in sporadic renal tumours [49]. Preoperative measured mean tumour size was 2.3 cm (range: 1–5).

Laguna et al. prospectively assessed the perioperative negative outcomes (17%) and complications (15.5%) in 144 patients undergoing laparoscopic renal cryoablation with multiple ultrathin needles and a median tumour size of 2.6 cm (range: 1.0–5.6) [50]. Most of the complications (78.5%) were declared Clavien grade 1 and 2. The authors concluded that a cut-off tumour size of 3.4 cm predicts the occurrence of perioperative negative outcome. These promising short- and intermediate-term data of ablative techniques do not yet justify these techniques as standard treatment for small renal lesions. Furthermore, long-term oncologic efficacy of ablative techniques remains to be demonstrated [51]. At present, cryoablation seems to result in significantly lower rates of local tumour progression compared to RF ablation (5.2% vs 12.9%; p < 0.001) [51]. Recent published data concerning the oncologic outcome of ablative techniques are summarised in Table 4.

Limitations of RF ablation and similar treatment modalities are the inability to generate tumour-specific heating and therefore effective tumour treatment as well as damaging healthy tissue [54]. The authors demonstrated that multiwalled carbon nanotubes are effective thermal ablation agents that result in long-term survival of tumour-bearing mice [54].

3.6. Future techniques

Exact imaging of the kidney with its vessels as well as the size and location of the tumour are essential for a safe oncologic operation. Visualisation of preoperative CT

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**Table 2 – Laparoscopic partial nephrectomy**

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Mean tumour size, cm (range)</th>
<th>Mean operative time, min (range)</th>
<th>WIT, min (range)</th>
<th>EBL, ml (range)</th>
<th>Complication rate, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thompson et al.</td>
<td>319</td>
<td>2.5</td>
<td>174 (70–105)</td>
<td>28.4</td>
<td>196</td>
<td>12 (10.2)</td>
</tr>
<tr>
<td>Marzalek et al.</td>
<td>100</td>
<td>2.8 (2–3.2)</td>
<td>85 (201–250)</td>
<td>23 (19–27)</td>
<td>24</td>
<td>24 (24)</td>
</tr>
<tr>
<td>Gill et al.</td>
<td>771</td>
<td>2.7 (0.5–7.0)</td>
<td>201 (25–610)</td>
<td>30.7 (4.0–68.0)</td>
<td>300 (25–6000)</td>
<td>192 (24.9)</td>
</tr>
<tr>
<td>Permpingkosal et al.</td>
<td>85</td>
<td>2.4 (0.5–5.3)</td>
<td>225 (103–543)</td>
<td>29.5</td>
<td>436.9 (50–2400)</td>
<td>6 (7.06)</td>
</tr>
</tbody>
</table>

WIT = warm ischemia time; EBL = estimated blood loss.

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**Table 3 – Robot-assisted partial nephrectomy**

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Mean tumour size, cm (range)</th>
<th>Mean operative time, min (range)</th>
<th>WIT, min (range)</th>
<th>EBL, ml (range)</th>
<th>Complication rate, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benway et al.</td>
<td>183</td>
<td>2.87 (1.0–7.9)</td>
<td>210 (86–370)</td>
<td>23.9 (10–51)</td>
<td>131.5 (10–900)</td>
<td>18 (9.8)</td>
</tr>
<tr>
<td>Goo et al.</td>
<td>29</td>
<td>3 (2–4)</td>
<td>197 (172–259)</td>
<td>25 (16–43)</td>
<td>220 (100–370)</td>
<td>–</td>
</tr>
<tr>
<td>Mottrie et al.</td>
<td>62</td>
<td>2.8 (1–7)</td>
<td>90 (63–116)</td>
<td>18.5 (14–25)</td>
<td>95 (50–150)</td>
<td>10 (16.1)</td>
</tr>
<tr>
<td>Scoll et al.</td>
<td>98</td>
<td>2.8 (1–8)</td>
<td>206 (85–369)</td>
<td>25.5 (10–53)</td>
<td>127 (50–800)</td>
<td>13 (13.0)</td>
</tr>
<tr>
<td>White et al.</td>
<td>67</td>
<td>3.7 (1.2–11.0)</td>
<td>180 (150–180)</td>
<td>19 (15–26)</td>
<td>200 (100–375)</td>
<td>15 (22.4)</td>
</tr>
</tbody>
</table>

WIT = warm ischemia time; EBL = estimated blood loss.
imaging as an augmented reality during laparoscopic or robot-assisted renal surgery is one promising new technical modification in NSS [55,56]. Preliminary data for real-time tracking of the kidney seem encouraging [55,56]. Teber et al. reported on a novel augmented reality system using fully automated tracking [57]. In vivo developments have been transferred successfully to the first clinical application.

The primary goal of further on-going studies is the improvement of imaging accuracy according to organ movement. In robotic surgery, which already allows three-dimensional vision of the surgical field, augmented reality could further increase surgical precision and therefore improve outcome.

4. Conclusion

Surgical treatment of small renal tumours (<4 cm) is of growing importance as the detection rate of these tumours increases as a result of the widespread use of imaging. OPN remains the gold-standard treatment of renal tumours qualified for NSS, with long-term results equal to RN with respect to oncologic outcome and better renal functional outcome. Tumours ≤7 cm should be treated by NSS, if possible.

Minimally invasive treatment options such as LPN and RPN are technically demanding, but specialised centres report on comparable outcome. Ablative techniques (cryotherapy, RF ablation) show promising intermediate-term results but cannot so far be considered standard treatment options. The development of augmented reality is promising and could further improve outcomes of NSS in the near future.

Conflicts of interest

The authors have nothing to disclose.

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None.

References


[19] Thompson RH, Boorjian SA, Lohse CM, et al. Radical nephrectomy for T1a renal masses may be associated with decreased overall


