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Treatment of Localised Renal Cell Carcinoma

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Abstract

Context: The increasing incidence of localised renal cell carcinoma (RCC) over the last 3 decades and controversy over mortality rates have prompted reassessment of current treatment.

Objective: To critically review the recent data on the management of localised RCC to arrive at a general consensus.

Evidence acquisition: A Medline search was performed from January 1, 2004, to May 3, 2011, using *renal cell carcinoma*, *nephrectomy* (Medical Subject Heading [MeSH] major topic), *surgical procedures*, *minimally invasive* (MeSH major topic), *nephron-sparing surgery*, *cryoablation*, *radiofrequency ablation*, *surveillance*, and *watchful waiting*.

Evidence synthesis: Initial active surveillance (AS) should be a first treatment option for small renal masses (SRMs) <4 cm in unfit patients or those with limited life expectancy. SRMs that show fast growth or reach 4 cm in diameter while on AS should be considered for treatment. Partial nephrectomy (PN) is the established treatment for T1a tumours (<4 cm) and an emerging standard treatment for T1b tumours (4–7 cm) provided that the operation is technically feasible and the tumour can be completely removed. Radical nephrectomy (RN) should be limited to those cases where the tumour is not amenable to nephron-sparing surgery (NSS). Laparoscopic radical nephrectomy (LRN) has benefits over open RN in terms of morbidity and should be the standard of care for T1 and T2 tumours, provided that it is performed in an advanced laparoscopic centre and NSS is not applicable. Open PN, not LRN, should be performed if minimally invasive expertise is not available. At this time, there is insufficient long-term data available to adequately compare ablative techniques with surgical options. **Therefore ablative therapies should be reserved for carefully selected high surgical risk patients with SRMs <4 cm.**

Conclusions: The choice of treatment for the patient with localised RCC needs to be individualised. Preservation of renal function without compromising the oncologic outcome should be the most important goal in the decision-making process.

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1. Introduction

In the last three decades the number of incidentally discovered renal masses has increased, leading to an

increased incidence of asymptomatic organ-confined small renal masses (SRMs) [1]. SRMs account for 48–66% of newly diagnosed renal cell carcinoma (RCC) [2]. This has resulted in an increased incidence of RCC over the last 30 yr.

Although there is controversy on the mortality rate of RCC, cancer statistics show that mortality rates are decreasing (38% in 1997 vs 25% in 2007) [3,4]. Nowadays we have more new techniques and concepts about how to treat RCC. Current treatment should therefore be reassessed [1]. The current standard of care for clinically localised RCC is surgical, preferably with nephron-sparing surgery (NSS) because of the reported excellent oncologic outcome and overall survival (OS). Active surveillance (AS) and minimally invasive ablative technologies have emerged as potential alternatives to surgery in selected patients. In this report, we critically assess the recent data on the management of localised RCC with the objective of arriving at a general consensus.

2. Evidence acquisition

A comprehensive review of the Medline literature for the treatment of localised RCC from January 1, 2004, to May 3, 2011, was conducted. The combination of the following words was used: *renal cell carcinoma*, *nephrectomy* (Medical Subject Heading [MeSH] major topic), *surgical procedures*, *minimally invasive* (MeSH major topic), *nephron-sparing surgery*, *cryoablation*, *radiofrequency ablation*, *surveillance*, and *watchful waiting*. Search was limited to English-language papers. Further references were identified from the reference list of retrieved articles. Because few randomised studies were available, most of the conclusions were drawn from case series or comparative cohort studies, both prospective and retrospective.

3. Evidence synthesis

3.1. Active surveillance

SRMs (<4 cm) are commonly detected in elderly patients or those with significant comorbidities. These patients have a higher risk of perioperative mortality and morbidity after treatment and a limited life expectancy that often appears to exceed the risk of cancer progression. A significant proportion (up to 20%) of these SRMs are benign when biopsied or removed [5,6]. No more than about 20–25% of SRMs have potentially aggressive characteristics [5,6]. Even when SRMs are confirmed to be RCC, most have slow growth rates and infrequently metastasize during the first few years after diagnosis [7,8]. These issues are important arguments to support an initial surveillance period for selected patients and reserve treatment for progression. AS of SRMs is now increasingly performed in carefully selected patients with an emerging experience to support this management option [6,9–15]. Some authors [6] believe that AS strategies should be limited to patients with tumours ≤ 3 cm because several studies have shown increased aggressive potential of renal masses with a diameter >3 cm [5,6,16]. In general, however, <4 cm is used to conform to stage T1a for RCC. Data of surveillance series reveal that most untreated localised renal tumours grow slowly (mean growth rate: 0.06–0.21 cm/yr) and have little tendency to metastasize, at least in the first few years

[10,14,15]. However, there is no correlation between tumour size and growth rate. Prospective AS series including 82 patients with 84 renal masses and 178 patients with 209 renal masses confirmed that most renal masses grow slowly and carry a low metastatic potential (1.2% and 1.1%, respectively) [8,17]. Mason et al. reported a mean annual renal mass growth rate of 0.25 cm/yr. Renal masses <2.45 cm were growing more slowly than masses >2.45 cm [17]. Kunkle et al. revealed that 26–33% of renal tumours followed by AS do not grow at a median follow-up of 29 mo. Importantly, these tumours with zero growth rates had similar rates of malignancy compared with growing lesions (83% and 89%, respectively; $p = 0.56$). The authors concluded that growth rate does not correlate with prognosis [11]. Kouba et al. found a more rapid growth in younger patients (≤ 60 yr) (0.77 cm vs 0.26 cm/yr) [18]. Therefore surveillance is currently not recommended in fit and young patients [7]. A meta-analysis of small AS series has shown a metastatic progression rate of only 1% (3 of 286 lesions) during a mean follow-up of 34 mo [10]. The low rate of metastatic progression in most AS series may be influenced by the short follow-up as well as the benign histology of a number of solid renal masses, the small tumour size, and the retrospective nature of the studies. Imaging characteristics do not provide a reliable prognostic factor for progression at this time [19]. No parameter was able to predict progression or overall prognosis [10,16]. A more refined preoperative diagnostic evaluation, in particular needle biopsy, is needed for defining the management of SRMs [19] and can help in selecting patients suitable for AS [20]. However at this time, the whole body of literature is insufficient to recommend biopsy for SRMs [21]. The identification of clinical, imaging, and molecular markers of disease progression, as well as further research on the role of biopsy, is needed to improve the selection of patients for AS. Until reliable prognostic parameters are formally identified, one must recognise there is a small but nonnegligible risk of developing metastatic disease in patients with SRMs followed expectantly. Surveillance requires excellent patient compliance and rigorous follow-up with contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Delayed intervention should be restricted to tumours that show fast growth during observation and have a higher risk of progression to metastatic disease. Delayed intervention >1 yr after diagnosis does not seem to exacerbate the prognosis for later metastatic RCC [14,18,22]. Larger tumours >3 or 4 cm in diameter with rapid growth are at risk of progression to metastatic disease and should be treated proactively.

AS is an acceptable management option for SRMs that should be discussed with all patients. AS should be a first management option for SRMs <4 cm in unfit patients or those with limited life expectancy (grade C) [14,23,24]. Delayed intervention should be undertaken in tumours that show fast growth during AS (grade C) [6,25]. Patients should be counselled about the small but nonnegligible risk of tumour progression during the observation period, possible loss of the opportunity for NSS, lack of curative salvage

therapies if metastatic disease develops, limitations of renal mass biopsy, lack of long-term data on surveillance, and the need for follow-up imaging and compliance. Renal mass biopsy enhanced by molecular profiling holds promise for assessing aggressive potential [26]. Further research will be required to define the usefulness and limitations of this approach to improve the selection of patients for AS.

3.2. Radical nephrectomy

Radical nephrectomy (RN) includes the removal of the tumour-bearing kidney and has been the traditional approach for localised RCC in patients with a normal contralateral kidney. Adrenalectomy and regional lymphadenectomy may be performed at the time of RN, but no strong recommendation can be made in this respect [27–29]. During the last decade, the status of RN has been called into question because of several factors including (1) equal oncologic efficacy as partial nephrectomy (PN) for renal tumours <4 cm [30,31] and tumours between 4 and 7 cm [32,33], (2) increased incidental detection of SRMs (<4 cm) with a significant proportion of benign tumours (up to 20%) [1], (3) possibility of late recurrence of RCC in the contralateral kidney, and (4) a higher risk of new-onset chronic kidney disease (CKD) or worsening of CKD following RN that leads to more cardiovascular events and worse survival [34–37]. Compared with PN, RN was associated with decreased OS in young patients (<65 yr) [38]. RN might no longer be regarded as the gold standard treatment for SRMs and should be reserved for patients with massive renal tumours in whom partial PN is not an option [34].

3.2.1. Open radical nephrectomy

Open radical nephrectomy (ORN) can be performed by a transperitoneal or extraperitoneal approach. Indications for ORN include **locally advanced renal tumours with invasion in the perirenal fat and adrenal gland (T3a), invasion in the vena renalis or vena cava (T3b and c), tumours that extend into the adjacent organs (T4), and** probably also those tumours that will undergo an extensive large lymph node dissection [39].

In a prospective randomised European Organisation for Research and Treatment of Cancer (EORTC) phase 3 study comparing open partial nephrectomy (OPN) with ORN in small renal tumours (≤ 5 cm), Van Poppel et al. found a perioperative blood loss <0.5 l and severe haemorrhage (>1 l) in 96.0% and 1.2% of patients treated with ORN, respectively. Pleural damage and spleen damage were respectively seen in 9.3% and 0.4% of ORN patients [40]. Blom et al. reported that lymph-node dissection had no impact on the complication rate. The most common adverse events in patients treated with ORN without and with lymph node dissection, respectively, were bleeding (6.5% vs 9.4%), pleural damage (5.1% vs 4.4%), and infection (5.7% vs 5.2%). Less common adverse events were bowel damage, embolism, and lymph fluid drainage [28].

3.2.2. Laparoscopic radical nephrectomy

In centres with laparoscopic expertise, ORN has largely been superseded by laparoscopic radical nephrectomy (LRN). The

choice of the transperitoneal or retroperitoneal approach has no impact on the efficiency and safety of the LRN procedure [41,42]. A recent study confirmed similar oncologic outcomes for both approaches [43]. LRN is reserved for stage T1 and T2 tumours that warrant complete removal of the kidney and without strict limitations for tumour size [44]. Complications are mainly vascular and are low in the hands of an experienced surgeon. Compared with the open approach, LRN is associated with significantly less blood loss, a significantly lower dose of analgesic agents during the postoperative course, and a significantly shorter hospital stay [45]. Some authors report that a minimum experience of 50 procedures is necessary to reduce the risk of major complications [46]. Three studies showed that LRN provides survival outcomes equivalent to those of ORN in patients with low-stage renal tumours [47–49]. LRN and robotic RN for localised renal tumours (T1–2N0M0) had comparable oncologic and operative outcomes. Robotic RN was associated with longer operative time and increased cost. There were no remarkable advantages of robotic RN observed over LRN [50]. No consensus currently exists on surveillance guidelines after surgical extirpation of RCC. Most follow-up strategies after RN are currently based on tumour stage alone but tend to include more histologic prognostic factors in the future to tailor surveillance to the individual patient.

RN should be limited to those cases where the tumour is not amenable to NSS. Routine extended lymph node dissection in patients with detectable lymph nodes does not improve survival and can be restricted to staging purposes (grade A). Adrenalectomy should only be considered in selected cases in which there are risk factors for adrenal involvement (grade B). In centres with laparoscopic expertise, ORN has largely been superseded by LRN. There are no significant differences in oncologic outcome between LRN and ORN. However, LRN has benefits over ORN in terms of morbidity. Therefore, LRN should be the standard of care for T1 and T2 tumours, provided it is performed in an advanced laparoscopic centre by an experienced surgeon and NSS is not applicable (grade B). No consensus currently exists on the follow-up strategies after RN.

3.3. Partial nephrectomy

PN includes the complete removal of a localised renal tumour while maintaining as much normal renal parenchyma as possible. Advantages of PN are preservation of renal function, a reduced risk of CKD, and avoidance of overtreatment of benign renal masses by nephrectomy. PN in solitary kidneys with limited ischaemia time results in minimal changes in long-term renal function [51]. Moreover, Lesage et al. showed a better quality of life after PN than after RN [52]. A significant concern with the use of PN for RCC is the potential risk of local recurrence in the ipsilateral kidney due to incomplete resection. However there are now several reports demonstrating low rates of recurrence following PN (0–10%) and even lower recurrence rates (1–3%) when performing PN for tumours <4 cm [53]. Many so-called local recurrences are not due to incomplete

removal but are rather de novo tumours, such as multifocal papillary RCC. A second concern is the occurrence of positive surgical margins. Analysis of the available literature reveals that frozen sections or final pathologic examination of the margins have minimal clinical significance and that a normal tissue margin of just 1 mm when performing PN may be sufficient to prevent local recurrence and disease progression from RCC [53]. A recent multicentre comparative study showed equivalence of standard PN and simple enucleation [54]. A multi-institutional survey on the use of LPN ($n = 855$ cases) in the United States and Europe revealed that 2.4% of cases had positive surgical margins [55]. Although negative surgical margins should always be the goal in any oncologic procedure, including PN, positive surgical margins appear to have a negligible impact on survival [56]. During the development phase there were initial concerns with the use of LPN as related to a somewhat longer warm ischaemia time (WIT) and increased risk of major postoperative complications such as urinary leakage and haemorrhage [57]. Therefore the decision to perform an OPN or LPN depends on the experience of the individual laparoscopic surgeon. Hilar clamping minimises blood loss and allows precise tumour excision and renal reconstruction in a nearly bloodless field. Today, there is no consensus about the clamping technique to be used (artery only vs artery and vein). Thompson et al. reported that when vascular clamping during NSS is necessary, efforts should be made to limit WIT to 20 min and cold ischaemia to 35 min to avoid increased risk of chronic renal insufficiency and acute renal failure [58]. Recently, an early unclamping technique was suggested by which only the initial parenchymal suturing is performed with the hilum clamped while sutured renorrhaphy is performed in the unclamped revascularised kidney. This resulted in a reduction of WIT by >50% (13.9 vs 31 min; $p < 0.0001$). The current mean WIT <14 min is lower than or similar to that in contemporary OPN series [59]. Other authors have confirmed these findings [60–62]. Nevertheless, the safe maximum duration of WIT remains debatable. Recently, a novel zero ischaemia technique was presented for LPN and robotic LPN for substantial renal tumours in 15 patients. The first results are promising [63]. If an ischaemia time >20 min is anticipated, cold ischaemia should be instituted up front at the start of PN. Cold ischaemia with ice slush [64] should be kept as short as possible, ideally within 35 min [65]. For surface cooling, slush ice can be applied to the clamped kidney for 20–25 min. A safe cold ischaemia time for a maximum of 35 min has been described in several studies [58,66,67]. Other methods to induce cold ischaemia are arterial and ureteral perfusion [68–71]. PN without ischaemia should be used when technically feasible in patients with a solitary kidney [72]. A study that used the Modification of Diet in Renal Disease equation to determine the estimated glomerular filtration rate (eGFR) in 101 patients who underwent LPN showed that renal function impairment was more than two-fold higher in patients with WIT >40 min than in the other groups ($p = 0.077$) [73]. However, a recent paper suggested that the known detrimental effects of warm ischaemia garnered from the

open kidney surgery literature may be mitigated during LPN by pneumo, resulting in no renal functional advantage for either technique [74]. The use of haemostatic agents and glues during LPN in 18 centres ($n = 1347$ cases) in the United States and Europe was shown to be routine in most centres performing LPN (in 77.4%). The rates of postoperative haemorrhage requiring transfusion and urine leakage rates were low in this survey (2.7% and 1.9%, respectively) [40]. Finally, there is the concern about the long-term oncologic data and the risk of complications. A randomised prospective phase 3 trial was conducted (EORTC 30904) comparing OPN and ORN in 541 patients with tumours ≤ 5 cm and a normal contralateral kidney. Oncologic equivalence of PN and RN could not be shown definitively [75] but is seen in nonrandomised studies (5-yr and 10-yr cancer-specific survival (CSS) rates up to 98.5% and 96.7%) [76] and now generally accepted. The percentage of patients with progression and renal cancer death in the EORTC 30904 study is very small and cannot explain any possible OS differences between the two treatment arms [75]. OPN might be technically more demanding than ORN. A previous report of the EORTC 30904 study revealed that the complication rate with OPN is slightly higher than with ORN [40]. Presence of a solitary kidney, prolonged WIT, and increased intraoperative blood loss were found to be independent risk factors on multivariate analysis for the development of postoperative complications after LPN [77]. The new tumour scoring systems as proposed by Ficarra et al. and Kutikov et al. may be extremely helpful in standardising measurements and allowing comparisons among series [78,79].

3.3.1. Open partial nephrectomy

OPN is the nephron-sparing modality with the largest clinical experience and the longest follow-up. Importantly, unlike ablative treatment options, OPN allows definitive pathologic identification (ie, stage, grade, and histology) and proof of complete resection. The standard indications for NSS according to the European Association of Urology guidelines are divided into the following categories: (1) absolute (anatomic or functional solitary kidney), (2) relative (functioning opposite kidney that is affected by a condition that might impair renal function in the future), and (3) elective (localised unilateral RCC with a healthy contralateral kidney). Relative indications also include patients with hereditary forms of RCC who are at high risk of developing a tumour in the contralateral kidney in the future [80]. Because more SRMs are detected now, elective PN has been adopted more frequently for the treatment of such tumours. During the last decade **elective PN has become the gold standard for the treatment of T1a tumours (<4 cm) in patients with a normal contralateral kidney [31,81]. When PN is performed in carefully selected patients in specialised centres, indications can be expanded to include T1b tumours (4–7 cm) [32,33, 82–91].** A recent small study revealed that PN can be safely performed and provide effective tumour control for selected patients with renal tumours ≥ 7 cm [92].

Lee et al. compared RN and OPN for T1a tumours and found equivalent oncologic results at 5 yr (disease-free

survival of 96%) with no local recurrences [31]. A recent population-based analysis confirmed the cancer-specific mortality equivalence between PN and RN for T1aN0M0 RCC and showed virtually perfect cancer-specific mortality free rates (97.5%) even in older patients [93]. Several studies indicate that elective PN can achieve similar oncologic outcomes as RN for select T1b tumours [32,33,82,86, 89,91,94,95]. Convincing data show equivalence of PN and RN for cancer control and superiority of PN in terms of preserving renal function, preventing CKD and subsequent long-term cardiac morbidity and mortality, and improving OS [35]. Therefore patients with T1 renal tumours should undergo PN whenever technically feasible. The expanding role of PN is the topic of a recent paper in *European Urology* [96]. In a comparative population-based study that analysed the rate of PN versus RN for clinically localised RCC (Surveillance Epidemiology and End Results data 1989–2004), the use of PN decreased with increasing tumour size and increased age and increased with more contemporary years of surgery (all $p < 0.001$) [97].

3.3.2. Laparoscopic partial nephrectomy

Over the years, OPN has been the reference standard nephron-sparing procedure. Today, at centres lacking advanced laparoscopic expertise, OPN remains the first nephron-sparing treatment option. However, at centres with the requisite minimally invasive expertise, LPN is now a routine procedure, with similar perioperative and long-term outcomes as OPN, albeit with a significantly decreased patient complication profile. As such, current indications for LPN have been expanded to include most renal tumours previously reserved for open surgery [98]. Studies report that LPN is feasible in central and hilar tumours [98–101]. LPN and OPN provide similarly excellent oncologic outcomes for localised RCC [66,67,102,103]. Several specific operative modifications developed to improve the laparoscopic techniques, and the increased experience of laparoscopic surgeons during the last decade has resulted in a significantly reduced complication rate of LPN that now seems similar to that of OPN [59,77,104]. Early results with robotic PN demonstrate that it is clinically comparable with LPN [105]. Larger LPN and robotic PN series with longer follow-up, possibly in a randomised fashion, are needed. Robotic techniques may increase penetration of minimally invasive PN into the community.

NSS should be a primary consideration in all patients with localised SRMs. This is based on the information that, in patients with a clinical T1 renal tumour, PN provides equivalent local tumour control as RN while minimising development of new-onset CKD or worsening of existing CKD (grade B). As such, PN is the established treatment for T1a tumours (<4 cm) and an emerging standard treatment for T1b tumours (4–7 cm) provided that the operation is technically feasible and the tumour can be entirely and adequately removed (grade B). Any tumour-free surgical margin following PN appears sufficient to prevent local recurrence and disease progression from RCC (grade B). In balancing the therapeutic decision between PN and RN, the individual patient's performance status, comorbidities,

and renal function should be carefully weighed. At present, PN is seriously underused, although it is often feasible even for a centrally located tumour or a tumour in the renal hilum when performed by an experienced surgeon. Contemporary LPN outcomes are similar to contemporary OPN outcomes, given adequate minimally invasive expertise. Future research should focus on decreasing the technical complexity of LPN and finding newer techniques of eliminating or reducing ischaemia. In the ultimate analysis, saving nephrons is the more important goal, which supersedes its technical approach, open or laparoscopic. Nonavailability of minimally invasive expertise must prompt OPN, not LRN.

3.4. Energy ablative therapies for localised renal cell carcinoma

Cryosurgery and radiofrequency ablation (RFA) by open, laparoscopic, or percutaneous approaches are promising minimally invasive nephron-sparing treatment options for localised RCC for most small (mainly <3.0 cm) low-grade renal tumours in patients who are at high surgical risk. There is no consensus on the maximum tumour size for ablation. Some authors find 3 cm appropriate as maximum tumour size for cryoablation [106] and RFA [107]; others suggest a limitation of 3.5 cm [83] or 4 cm [108] above which success rates substantially fall. It is indicated for small incidentally found renal cortical tumours in elderly patients, patients with a genetic predisposition to multiple tumours, and patients with a solitary kidney or bilateral tumours [109]. Potential advantages of ablative procedures are reduced morbidity, shorter hospitalisation, faster convalescence, preservation of renal function, lower costs, and the ability to treat patients who are at high risk for surgery [110]. However, no randomised comparisons have been performed between the outcome of ablative techniques and RN or PN. A primary concern in relation to thermal ablative therapies is the higher local recurrence rate with cryoablation and RFA when compared with surgical excision in a recent meta-analysis (4.6%, 7.9%, 2.7%, and relative risks [RRs] of 7.45, 18.23, and 1.0, respectively) [111]. A second concern is the controversy over the validity of the radiographic definition of postablative success [112]. Recent data showed that 46.2% patients (6 of 13 patients) who showed no enhancement on radiographic imaging after RFA demonstrated viable tumour cells at a 6-mo postablation biopsy [112]. Another weakness is the absence of histopathologic confirmation of complete tumour destruction and negative surgical margins [83]. In contrast, Raman et al. reported that absence of viable renal carcinoma in biopsies performed >1 yr following RFA confirms the reliability of axial imaging [113]. Finally, ablative procedures may preclude or complicate subsequent surgical salvage due to perinephric fibrosis [83]. These concerns underscore the need for the meticulous selection of patients who today may be potential candidates for thermal ablation.

3.4.1. Cryoablation

Cryoablation causes tumour destruction by rapid freeze and thaw cycles. At present, >75% of the reported renal

cryoablation treatments have been applied through an open or laparoscopic approach. Percutaneous image-guided techniques have been used much less frequently [114]. Finley et al. showed a lower complication rate after percutaneous cryoablation versus after laparoscopic cryoablation (22.2% vs 40%). They considered percutaneous cryoablation the treatment of choice for posterior, lateral, and select anterior renal lesions ≤ 3 cm [115]. A more recent retrospective review in a single tertiary referral centre reported a higher complication rate for percutaneous cryoablation, although most of these complications were mild and transient. However, on multivariate analysis the chosen ablative approach (laparoscopic or percutaneous) was not associated with the risk of complications [116]. Current 3-yr laparoscopic cryoablation data offer CSS rates of 98% [117,118] and 100% [119] and an OS of 89% [117]. Davol et al. reported a 5-yr CSS rate of 100%. The cancer-free survival rate after a single cryoablation procedure was 87.5% and improved to 97.5% after a repeat procedure [120]. Mean renal tumour size in these studies was <2.7 cm. Three and 5-yr survival data are promising and indicate that renal cryoablation could be a good alternative in appropriately selected patients who are considered unsuitable for PN or AS. Recently, Aron et al. reported on 80 patients with a minimum 5-yr follow-up after laparoscopic cryoablation for an SRM, including 92% 5-yr disease-specific survival and 84% OS in the 55 patients with biopsy-proven RCC. Of these 55 patients, 11 (14%) had recurrence. The same study showed that cryoablation has minimal impact on renal function. The eGFR before versus after treatment was 66 versus 59 ml/min per 1.73 m^2 [121]. A multi-institutional review by Johnson et al. demonstrated that cryoablation has a low complication profile when used to treat small renal tumours (13.7%; minor 12.2%, major 1.4%) [122]. The most common complication was pain or paraesthesia at the probe insertion site (7.2%). More recently, Laguna et al. prospectively collected multi-institutional data on laparoscopic renal cryoablation with ultrathin probes in 144 patients. Perioperative negative outcomes including conversion occurred in 17% of cases. Complications according to the Clavien system occurred in 15.5% of the cases; however, most of the complications were Clavien grade 1 or 2. Increasing tumour size, the presence of cardiac conditions, and female gender were associated with a higher risk of developing a complication. The authors confirmed the tumour size cut-off of 3.4 cm as an adequate predictor of negative outcomes. This study confirms the relative safety of laparoscopic cryoablation [123]. Recently, the midterm oncologic and functional results were reported. A total of 92 patients (100 tumours; mean size: 2.5 cm, 53.7% RCC) were treated with ultrathin cryoprobes in 95 sessions. The estimated mean recurrence-free survival time was 47.8 mo. The 3-yr OS and recurrence-free survival rates in patients with RCC were 86.1% and 91.8%, respectively. Renal function was preserved in 84.5% of patients with normal preoperative eGFR [124]. Laparoscopic cryoablation can be considered a safe and intermediate-term effective method to treat SRMs [125]. No cases of collecting system injury or serious haemorrhagic complications were identified in a

recent study evaluating 67 CT-guided percutaneous cryoablation procedures of renal masses with ice ball overlap of the renal sinus [126]. Synchronous cryoablation is also relatively safe and feasible for patients with multiple ipsilateral renal lesions that could be very challenging to address with an extirpative approach [127]. Larger tumours, those with endophytic growth pattern [128] and renal lesions that make broad-based contact with the renal sinus [129], may be at increased risk of relapse after laparoscopic cryoablation. For each 1-cm increase in tumour size there was a four-fold increase in the probability of local recurrence [128].

3.4.2. Radiofrequency ablation

RFA causes tumour coagulation by converting the radiofrequency waves to heat, resulting in thermal tissue damage [110]. Patient demographics and selection criteria for RFA are similar as for cryoablation treatment, mainly for older and high surgical risk patients and tumours with diameter <3 cm. Gervais et al. treated 100 tumours in 85 patients by percutaneous RFA and showed that small-size tumours (<3 cm) and exophytic tumours were predictive factors for complete coagulation. All small (<3 cm) tumours but only 25% of larger tumours (>5 cm) had been successfully ablated [107]. A meta-analysis by Kunkle and Uzzo demonstrated that patients treated with RFA may require reablation more frequently than those treated with cryoablation (8.5% vs 1.3%, respectively) [114]. Most of the RFA cases were percutaneous where retreatment and conservative ablation zone sizes are feasible with minimal morbidity. Compared with cryoablation, a large proportion of tumours managed with RFA had unknown or indeterminate pathology (42.8% vs 17.7%) [111], which could lead to an overestimation of the actuarial specific CSS rates for RCC. RFA can be performed percutaneously or laparoscopically under ultrasound, CT, or MRI guidance. Currently, about 94% of the reported renal RFA treatments have been performed through the percutaneous approach [114], mostly under CT scan guidance. Although the percutaneous approach is less invasive, RFA and cryoablation reablation rates are significantly higher when a percutaneous approach is used and seemed to correlate with surgeon speciality (interventional radiologist or urologist) [130]. After 94 RFA procedures in 78 patients, recurrence-free survival was 96.8% after a mean follow-up of 25 mo (68% were RCC). Mean tumour size was 2.4 cm [131]. After 34 percutaneous RFA procedures for SRMs (mean size: 2.0 cm), the overall recurrence-free survival was 90.3% at a mean follow-up of 61.6 mo and 79.9% for pathologically confirmed RCC at a mean follow-up of 57.4 mo [132]. Zagoria et al. reported that percutaneous RFA achieved complete ablation after one session in all 95 RCCs <3.7 cm and in only 14 of 30 RCCs >3.7 cm [133]. A recent study including 41 patients reported that RFA can result in durable oncologic control for RCCs <4 cm. There were no recurrences when RCCs <4 cm were treated [134]. The results of a recent study treating 208 patients with 243 SRMs over 7.5 yr indicated a minimal risk of disease recurrence beyond 3 yr after RFA. The overall 5-yr recurrence-free survival rate was 93% (90% for 160 patients

who had biopsy-proven RCC [135]. RFA appears to have minimal impact on renal function. The median GFR before and after RFA in a retrospective analysis of 63 healthy patients with small renal cortical tumours was 76.3 and 74.3 ml/min per 1.73 m² [136]. A multi-institutional review of Johnson et al. demonstrated that RFA has a low complication profile when used to treat small renal tumours (8.3%; minor 6.0%, major 2.2%) [122]. The most common complication was pain or paraesthesia at the probe insertion site (3.0%). There are currently no prospective studies comparing cryoablation with RFA or with other forms of NSS. Currently, CSS rates of cryoablation and RFA are relatively similar (97–98%, respectively [137]. A recent meta-analysis by Kunkle and Uzzo compared the outcome of cryoablation ($n = 600$; 65% laparoscopically) and RFA ($n = 775$; 94% percutaneously). Cryoablation was associated with a lower reablation rate (1.3% vs 8.5%), lower local tumour progression rate (5.2% vs 12.9%), and fewer metastases (1.0% vs 2.5%; $p = 0.06$) than RFA. Pretreatment biopsy was performed more frequently in the cryoablation group (82.3% vs 62.2%) [114]. In another meta-analysis by Kunkle et al, cryoablation was also associated with lower rates of local recurrence and metastatic progression (4.6% vs 11.7% and 1.2% vs 2.3%) compared with RFA [111]. The meta-analyses were flawed in that they consisted of retrospective series each with their own selection biases [138,139]. Furthermore, RFA was primarily performed percutaneously (compared with laparoscopic cryoablation) where incomplete treatment and reablation is more commonly acceptable because retreatment is easier to perform. Because follow-up after ablative therapy lacks histopathologic confirmation of tumour destruction, some centres prefer to add postablation biopsies to radiographic imaging [117]. Current imaging techniques are limited to monitor recurrences, and postablation biopsies are encouraged when recurrence or incomplete ablation is suspected or as routine in all cases [112]. Existing follow-up criteria are not well defined and should be more precise and standardised based on radiologic and histologic factors. Weight et al. tried to determine a correlation between imaging findings and histopathology after probe ablative procedures. They demonstrated a poor correlation between post-RFA radiographic imaging and post-RFA biopsy results and an excellent correlation between the radiographic findings after cryoablation and subsequent percutaneous biopsy of the treated lesions. In this study, 6 of 13 patients (46.2%) who showed no enhancement on radiographic imaging after RFA demonstrated viable tumour cells at a 6-mo post-RFA biopsy. The 6-mo postablation biopsy reduced the success rate of RFA from 85% to 64.8% [112].

Cryoablation and RFA are reasonable minimally invasive treatment options for most small (mainly <3 cm) low-grade renal tumours in patients who are at high surgical risk, who are not candidates for AS, and who accept the need for long-term radiographic surveillance after ablation. Retrospective noncontrolled studies suggest that cryoablation may be associated with a lower reablation rate and local recurrence rate compared with RFA. However, variables such as

surgical approach (laparoscopic vs percutaneous), renal parenchyma reserve, anaesthesia (general vs sedation), and physician performing the procedure (surgeon vs radiologist) can strongly influence these rates. Percutaneous tumour core biopsy with or without fine-needle aspiration should always be performed before ablation to define histology. Posttreatment biopsies may be necessary when recurrence or incomplete ablation is suspected. There is an urgent need for pre- and postoperative algorithms, strong, uniform, and explicit indications, and a standard consensus for follow-up schedules in the use of ablative therapies, which is nonexistent at this moment. When deciding on thermal ablation, it is important to counsel patients regarding the slightly increased risk of local recurrence and the potential need for retreatment when compared with surgical excision. Counselling about thermal ablation should further include the absence of established radiographic measures of postablative success, the potential for difficult surgical salvage therapy due to perinephric fibrosis if tumour progression developed, and the substantial limitations of the existing literature on thermal ablation. Larger tumours beyond a diameter of 3 or 4 cm and those with irregular form or infiltrative growth pattern may be associated with increased risk of recurrence when treated with thermal ablative therapies.

At this time, there are insufficient long-term data available to make adequate comparisons between ablative techniques. Therefore ablative therapies should be reserved for carefully selected high surgical risk patients with SRMs <4 cm (grade C).

3.4.3. Novel treatment modalities of renal masses

To date, the use of other minimally invasive techniques, such as high-intensity focused ultrasound, radiosurgery, microwave thermotherapy, laser interstitial thermal therapy, and pulsed cavitation ultrasound should be considered experimental. Further studies are required to determine their oncologic and functional role in the management of localised RCC.

3.5. Meta-analysis of active surveillance, partial nephrectomy, cryoablation, and radiofrequency ablation studies

The meta-analysis of Kunkle et al. [111] including 99 studies representing 6471 tumours illustrates that PN, cryoablation, RFA, and AS are viable approaches to the management of SRMs. Compared with PN, current data demonstrate a significantly higher incidence of local tumour recurrence following cryoablation and RFA with cryoablation predominantly performed laparoscopically resulting in less local tumour progression than RFA generally performed percutaneously (RRs: 1.00, 7.45, 18.23, respectively). However, no statistical differences were detected in progression to metastatic RCC regardless of treatment option (PN, cryoablation, or RFA) or absence of treatment (AS) (RRs: 1.00, 1.24, 3.21, 0.11, respectively). These data raise concern over a possible overtreatment bias for SRMs [111]. Delayed intervention for SRMs appears to be a safe treatment strategy in selected patients.

4. Conclusions

Currently, no hard recommendations can be made against a given treatment modality for localised SRMs because of the limitations of the current studies. To allow better comparisons between treatment options for localised RCC, future studies should be prospectively designed, have identical selection criteria, standardised treatment protocols, and consistent follow-up strategies using markers of clinical success, and ideally they should be conducted in a randomised way. In addition, as newer treatment options become available, future studies should include quality-of-life and cost-efficacy outcomes. The choice of treatment for the patient with localised RCC needs to be individualised, and preservation of renal function without compromising the oncologic outcome should be the most important goal in the decision-making process. The patient's performance status and surgical expertise will be important factors when advising a patient about the most appropriate treatment option.

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Study concept and design: Van Poppel, Becker, Cadeddu, Gill, Janetschek, Jewett, Laguna, Marberger, Montorsi, Polascik, Osamu Ukimura, Zhu.

Acquisition of data: Van Poppel, Becker, Cadeddu, Gill, Janetschek, Jewett, Laguna, Marberger, Montorsi, Polascik, Osamu Ukimura, Zhu.

Analysis and interpretation of data: Van Poppel, Becker, Cadeddu, Gill, Janetschek, Jewett, Laguna, Marberger, Montorsi, Polascik, Osamu Ukimura, Zhu.

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