

Update on the management of T1 renal cortical tumours

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There are a range of treatment strategies for the management of patients with small incidental renal cortical tumours including active surveillance, radiofrequency ablation, cryotherapy, radical nephrectomy and partial nephrectomy. A large number of such tumours are benign and might therefore be over-treated with radical nephrectomy.

There are emergent short-term oncological and clinical outcomes for cryotherapy and radiofrequency ablation, and recent studies have illustrated the benefits of partial nephrectomy for minimizing the risk of progression to chronic kidney disease. The outcomes of these different treatment methods are discussed.

KEYWORDS

Renal cortical tumour, small renal mass, active surveillance, radiofrequency ablation, cryotherapy, partial nephrectomy, radical nephrectomy

INTRODUCTION

The widespread use of cross-sectional and ultrasound imaging has led to the detection of a greater number of incidental renal cortical tumours (RCTs). Those that measure <7 cm at their widest are classified as clinical T1 tumours. Traditionally, these tumours have been associated with very favourable oncological outcomes when treated by open radical nephrectomy (ORN), which was formerly the 'gold standard' treatment. However, the rapid development of new surgical techniques, particularly laparoscopic radical nephrectomy (LRN), open partial nephrectomy (OPN), laparoscopic partial nephrectomy (LPN) and, most recently, robotic assisted LPN have superseded ORN as the treatment of choice for most uncomplicated RCTs. A number of less invasive thermoablative strategies have also been developed and are under evaluation. As ~20% of RCTs are benign [1], a further 25% are less aggressive (papillary and chromophobe) forms of renal cell carcinoma (RCC) [2] and only 54% are conventional clear cell RCC [3], there has been renewed interest in the natural history of RCTs. This has, in turn, resulted in the adoption of an active surveillance approach in selected patients. In this review article, the rationale and existing clinical evidence for each of the main therapeutic methods available for the management of T1 RCTs will be considered.

ACTIVE SURVEILLANCE OF RCTs

There is a group of patients for whom curative surgery would either be inadvisable or very challenging. Such patients include the elderly with multiple medical comorbidities, those with a solitary kidney or severe renal impairment, or those with multiple bilateral renal masses. Previous studies have evaluated the clinical outcomes of active surveillance in such patients [4,5]. There are several important clinical factors that must be considered before recommending active surveillance, including the natural history of RCTs, clinical predictors for high-risk or metastatic disease, and the outcomes of patients who subsequently undergo delayed intervention.

Perhaps the greatest anxiety facing the patient and their urologist when contemplating active surveillance is the potential for disease progression. Several factors may help to stratify risk of such progression occurring. Studies have shown that larger tumours are more likely to be high grade, clinically understaged and to have synchronous metastasis [6–10]. Histopathological high grade (G3/4) might be present in only 4–7% of tumours <2 cm in diameter, but present in 14–25% of 3–4 cm tumours [6,7] (Table 1). Furthermore, high grade RCC might be present in up to 39% of clinical T1b (4–7 cm) tumours [8] and in up to

58% of tumours >7 cm (T2). Tumours may be clinically understaged (for pT3a or more) in only 3–4% of tumours <2 cm, but in 12–36% of 3–4 cm tumours [6,7]. Initial tumour size is also useful for predicting the risk of synchronous metastasis, with the risk being around 4% for tumours <2 cm, 7% for 3.1–4 cm tumours, 18% for 6.1–7 cm tumours [11], and 45% for tumours ≥10 cm [9] (Table 1). Overall, the probability for synchronous metastasis might be 5.6% for T1a compared with 14.2% for T1b tumours [11].

A meta-analysis has shown that the rate of metastatic progression of RCTs (mean size 2.6 cm) was only 1% (three out of 286 lesions), during a mean follow-up of 34 months [4]. The rate of metastatic progression for T1b tumours appears to be greater than for T1a tumours, perhaps 3.2–11% [10,12], and both cancer-specific and overall survival appears reduced in patients with T1b tumours than in those with T1a tumours [12].

Most studies report an overall tumour growth rate of 0.06–0.28 cm/year [4,5], although there is no correlation between initial tumour size and subsequent growth, yet 26–33% of tumours show no growth under active surveillance [13]. Moreover, growth kinetics have been shown to be a poor marker for underlying pathology, with a similar incidence of malignancy in tumours with zero net

TABLE 1 Clinicopathological outcomes of renal cortical tumours based on size

	Renal tumour diameter				Reference
	≤2 cm	2–3 cm	3–4 cm	4–7 cm	
Pathological outcome (% tumours)					
G3/4	7.1	9	14	–	Pahernik <i>et al.</i> (2007) [6]
	–	4.7*	25.5	–	Remzi <i>et al.</i> (2006) [7]
	13.3	12.5	20.9	39	Frank <i>et al.</i> (2003) [8]
pT3 a/b	3	5.1	12.1	–	Pahernik <i>et al.</i> (2007) [6]
	4.2	14.9	35.7	–	Remzi <i>et al.</i> (2006) [7]
Synchronous metastasis (% tumours)	3	2.6	6	–	Pahernik <i>et al.</i> (2007) [6]
	–	2.4*	8.4	–	Remzi <i>et al.</i> (2006) [7]
	4.3	4.9	7.1	14.2	Lughezzani <i>et al.</i> (2009) [11]

*for ≤3 cm.

growth, compared with enlarging tumours [13]. Radiologically stable tumours must therefore be interpreted with caution when counselling patients.

The primary concern with active surveillance is the potential denial of curative treatment through delayed intervention. Several studies have examined the results of delayed intervention, although the mean time interval to aggressive treatment tends to be relatively short (12–26 months) [12,14,15]. Kouba *et al.* [14] did not report any upstaging of the tumours, however Crispen *et al.* [15] reported a 6% upstaging that did not appear to alter the oncological outcome. Although the overall 5-year survival rate in elderly patients with comorbidities under active surveillance is low (43%), the cancer-specific survival rate is much greater at 93%. Furthermore, substantially higher cancer-specific survival rates are found in patients with tumours <4 cm [12].

The risks and benefits of active surveillance can be difficult to quantify when counselling patients because the long-term outcome of this approach has yet to be determined. Patient numbers and duration of follow-up has been limited in most series to date, and there is variation in reported rates of metastatic progression between different studies, with rates as high as 6% in some series [5]. Pathological confirmation might only be available in 46% of cases [4,16] and analysis of cancer-specific survival and progression rates is fraught with error resulting from such selection bias. Furthermore, most observational study

cohorts predominately include elderly patients, in whom tumour growth kinetics and rates of pathological confirmation and subsequent surgical intervention tend to be lower than in younger patients [14,16]. The studies pertaining to active surveillance have a marked selection bias before the retrospective analysis and their findings must be interpreted with caution and cannot be applied to a general population.

Active surveillance in elderly and comorbid patients appears to be a reasonable option for small renal masses because these patients are more likely to die from other causes [12]. However in younger patients, including those with a solitary kidney, renal impairment or bilateral tumours, active surveillance may not be a viable management option even for radiologically stable masses as these have malignancy rates similar to those of enlarging masses [13]. The issues should therefore be discussed appropriately with patients on an individual basis. Furthermore, delayed intervention might result in tumour progression to higher stage disease [15] which, in turn, might alter survival.

THERMOABLATIVE THERAPIES

To reduce operative morbidity associated with partial or radical nephrectomy, minimally invasive probe-based thermoablative strategies have been developed and employed in the management of small renal masses. The two most commonly used therapies are cryoablation, which relies on repeated freeze-thaw cycles to effect cell death, and

radiofrequency ablation (RFA), which causes coagulative necrosis by tissue heating. Several centres have reported their experience with these techniques but the data must be interpreted with a degree of caution for several reasons. Firstly, study populations and length of follow-up are limited for both techniques. Secondly, there is a lack of consensus on optimum treatment and follow-up protocols resulting in wide variation in technique and follow-up imaging. Thirdly, the definition of treatment success between different series varies. As yet there is no randomized controlled trial comparing cryoablation with RFA, or comparing either technique with conventional surgical procedures or active surveillance. Nevertheless, early results are promising and may support the paradigm of thermoablation in selected patients.

RFA

Radiofrequency ablation uses monopolar radiofrequency currents passed through needle electrodes to generate heat in the target tissue, resulting in dessication and ultimately, coagulative necrosis. Temperatures in the range of 50 to 100°C are typically employed in the clinical setting [17]. This direct cytotoxic effect may be augmented by ischaemia resulting from vascular damage. RFA is commonly performed by percutaneous insertion of probes under CT guidance, although open and laparoscopic RFA are also used.

Reported results of RFA series have been limited by either small cohorts or short follow-up. However, Levinson *et al.* [18] did report the outcome for 31 patients who underwent RFA for RCTs (mean 2 cm) with a mean follow-up of 61.6 months. Only 18 of these patients had pathologically confirmed RCC and the overall recurrence-free survival rate was 90.3%. However, the overall survival rate was 71% with nine patients dying of non-RCC related causes, indicative perhaps of the general levels of comorbidity in this patient population.

The results of RFA in a larger series of 125 RCTs, biopsy proven for RCC, was reported in 2007 with a much shorter mean follow-up period of 13.7 months [19]. RFA was deemed successful if there was no residual contrast enhancement of the lesion on subsequent CT scan, and 93% of treatments resulted in this outcome.

Two other large case series with intermediate follow-up have been reported in recent years. In one series of 94 RFA procedures in 78 patients [20], recurrence-free survival rate was 96.8% after a mean follow-up of 25 months. Only 75% of these tumours, however, were biopsy-proven RCCs. In another series of 100 RFA procedures on 85 patients [21], 90% of tumours had been successfully ablated with a mean follow-up of 2.3 years. Of particular note was the fact that all small (<3 cm) tumours but only 25% of larger tumours (>5 cm) had been successfully ablated.

Follow-up imaging is commonly employed to determine the success of RFA, but may be difficult to interpret. RFA-treated lesions may not 'shrink' radiographically as coagulative necrosis progresses so other features, such as lack of contrast enhancement, are of paramount importance.

CRYOABLATION

Cryoablation involves the placement of a probe into a renal tumour with formation of an ice ball at the probe tip by means of liquid nitrogen or argon. This rapid freezing results in protein denaturation and cell membrane destruction. The size of the iceball can be monitored intraoperatively by means of a thermocouple or ultrasound device and usually two freeze-thaw cycles are employed [22]. The probe may be placed either laparoscopically or percutaneously. The laparoscopic approach allows careful probe deployment as well as the opportunity for real time visual and ultrasonic monitoring of the ice ball. Several laparoscopic series of cryoablation have been reported in the literature.

After a minimum 3-year follow-up in 56 patients (36 RCC on pre-cryo biopsy) [23], a 75% reduction in cryolesion size and a 98% cancer-specific survival in patients with sporadic tumours was observed. Of particular note was the fact that in 10 patients with a solitary kidney there was little effect on renal function. Another series comprising open and laparoscopic cryoablation procedures in 48 patients demonstrated a cancer-specific survival rate of 100% [24].

The percutaneous approach may be utilized for some RCTs, but may not be feasible for tumours located near the renal hilum or in the upper pole. There has been no prospective

study comparing laparoscopic to percutaneous cryoablation although a retrospective analysis has shown that the laparoscopic approach is slower and associated with a higher complication rate [25].

Weight *et al.* [26] reported their experience of 88 patients who underwent percutaneous RFA and 176 patients who underwent laparoscopic cryoablation. Recurrence or metastatic disease occurred in 12 patients (14%) from the RFA group and 11 patients (6%) from the cryo group. A further 13 patients (15%) from the RFA group and 6 (3%) from the cryo group had positive biopsy after treatment. This results in an overall failure rate of 29% in the RFA group and 9% in the cryoablation group. Furthermore at 6 months follow-up there was poor correlation between imaging and biopsy in the RFA group with six of 36 patients (24%) with negative imaging having positive biopsies. All 60 patients in the cryoablation group with negative imaging had benign biopsies. This lack of correlation between imaging and biopsy is concerning and warrants further investigation.

A meta-analysis [27] of 47 studies in which patients underwent either RFA (775 cases) or cryoablation (600 cases) has recently been published. There was no significant difference in mean patient age, tumour size or duration of follow-up. However, a greater number of the cryoablation patients underwent pre-treatment biopsy and surgery via the laparoscopic route. The main findings were a local progression rate that was significantly higher after RFA than cryoablation (12.9% vs 5.2%), and a greater need for repeat ablation with RFA than cryoablation (8.5% vs 1.3%). Although metastasis was seen more commonly after RFA, the difference did not reach statistical significance in this meta-analysis.

ROLE OF PERCUTANEOUS BIOPSY

It would seem germane to discuss the role of percutaneous renal biopsy as it is being increasingly used in the management of patients being considered for either active surveillance or thermoablative therapies. This is partly due to a rising incidence of incidental lesions found on imaging studies, and partly due to the realization that 18–20% of clinical stage T1 masses are benign [6,7,28,29] and

therefore over-treated with surgery. Since 2001, the technical failure rate of renal biopsy has been reported to be ≈5%, the indeterminate histology rate to be as little as 4%, the false negative rate to be <1%, and diagnostic accuracy to be >92% for cancer diagnosis and histological subtype [28]. The minor complication rate is ≈5%, the major complication rate <1%, and no case of tumour seeding has been reported since 1994 [28]. However not all studies echo these findings. Weight *et al.* [24] reported an indeterminate rate of 20% and 35%, and a benign rate of 9% and 24% for lesions treated by RFA and cryotherapy respectively. It is of some concern that four out of 19 patients with malignancy on post-treatment biopsy had benign biopsies before thermoablative treatment. Tumour heterogeneity and sampling error are the major causes of diagnostic inaccuracy, but it is hoped that future developments in molecular analyses will improve the accuracy further [28,29].

RADICAL NEPHRECTOMY

Surgery has the most durable oncological outcome compared with any other management for patients with RCTs. Radical nephrectomy was the original 'gold standard' [30] and worldwide is still the most widely used curative procedure for T1 renal tumours [31,32]. ORN has largely been superseded by LRN, the advantages of the laparoscopic approach being reduced blood loss, reduced analgesic requirements, shorter hospital stay and a quicker return to work [33–35]. The major complication rate for LRN is around 6% (largely haemorrhage), and the conversion rate 4–7% in experienced hands [32,36]. The oncological outcomes of both LRN and ORN are equivalent with 5-year disease-free, cancer-specific and actuarial survival of typically 91–94%, 94–98%, and 81–85% for laparoscopic nephrectomy [37–39].

However, despite the oncological efficacy of radical nephrectomy, recent studies show an increased incidence of chronic kidney disease (CKD) [40], cardiovascular events [41], overall mortality [41,42], and a reduced quality of life [43] for patients undergoing this procedure compared with those undergoing partial nephrectomy for small T1a renal tumours. It is apparent that up to 26% of these patients have pre-operative CKD and the 3-year probability of developing new onset mild (GFR <60 mL/min) or moderate (GFR <45 mL/min)

CKD is 20% and 5% respectively for partial nephrectomy, and 65% and 36% respectively for radical nephrectomy [40]. Radical nephrectomy was shown to be an independent risk factor for new-onset CKD on multivariate analysis and might be associated with an increased risk of overall mortality (hazard ratio [HR] 1.38, relative risk [RR] 2.16) and 1.4 times higher rate of cardiovascular events compared with partial nephrectomy [41,42]. CKD was also a significant leading predictor for death from any cause (HR1.59). These recent findings have implications for patients with small renal tumours depending on the type of procedure they are currently undergoing. Radical nephrectomy is still carried out for over 80% of T1 tumours worldwide, and it is therefore recognized that partial nephrectomy is substantially under-used at present [31,32].

PARTIAL NEPHRECTOMY (NEPHRON-SPARING SURGERY)

Partial nephrectomy is an established curative procedure for small renal tumours [30,44] with the advantage of renal functional preservation. Indications for nephron-sparing surgery might be absolute (single functioning kidney), relative or elective, and the procedure might be carried out via open access or laparoscopically. OPN might be technically more demanding than radical nephrectomy with a complication rate of 7.5% or more, mainly because of a slightly higher perioperative haemorrhage rate (3.1%) and a 4.4% urinary fistula rate [46]. The oncological outcomes of OPN are equivalent to radical nephrectomy for small T1a renal tumours (<4 cm) with 10-year cancer-specific survival over 95% in large series [47], and are also equivalent for T1b tumours (4–7 cm) in experienced centres [47–50]. The positive margin rate appears to be 0.8–6.8%, but only 4% of patients with positive margins develop a local recurrence at 30 months [47].

Laparoscopic partial nephrectomy (LPN) offers patients the same advantages over OPN as LRN [51] but it is technically challenging surgery which requires advanced laparoscopic skills. LPN is associated with a higher rate of major intraoperative complications (renal parenchymal haemorrhage), and postoperative urological complications, including urinary leak and peri-renal haematoma [51,53]. The learning curve for this procedure is long, and reports suggest

that laparoscopically adept surgeons might need to perform up to 200 cases before their complication rates equate with international benchmarks from established units [47,52–56]. Complication rates for this procedure might be as high as 24–33% in the first 90–200 cases and might include bowel injury, splenic injury and renal failure [53,54,57]. Once this learning curve has been surmounted the rates for overall complications (21%), haemorrhage (3–5%), urinary leak (4%), and medical complications (10%) appear to be equivalent for both laparoscopic and open partial nephrectomy [47]. The 5-year oncological outcomes of laparoscopic partial nephrectomy are now being reported and appear to be equivalent to open partial nephrectomy, with 91–97% 5-year disease-free survival [47,58,59]. In large series the positive surgical margin rate appears to be 2.4% [47], although positive margin status does not appear to impact negatively on recurrence rate, cancer-specific survival or overall survival at 3 years [60,61]. More recently, intermediate term outcomes have been reported which suggest that laparoscopic partial nephrectomy might have the same oncological control as radical nephrectomy for tumours >4 cm, but with superior renal functional recovery [62].

Factors predicting a lower GFR following partial nephrectomy include pre-existing low GFR, solitary kidney, age, tumour size and longer warm ischaemic interval [45,63]. Duration of warm ischaemic time is the most important modifiable risk factor for renal impairment and the average ischaemic time for laparoscopic partial nephrectomy is 10 min longer than for OPN [45,64]. Warm ischaemia beyond 20 min has a substantial negative impact on nadir GFR [63]. Recently, this warm ischaemic time has been reduced to levels of OPN (to 14 min) through the early unclamping of the renal pedicle after initial parenchymal suture placement. This reduction appears to have no negative impact on mean blood loss, total operative time, re-intervention rate or hospitalization period in experienced hands [65,66]. However, to date, cold ischaemia has not been reproducibly performed successfully in a laparoscopic partial nephrectomy series. Studies reproducing the cold ischaemia of open series are awaited. Furthermore, with OPN, ischaemia can sometimes be avoided completely, unlike with LPN when cross-clamping of the renal artery is always required.

IMPORTANT CONSIDERATIONS FOR SURGERY

The aim of any extirpative cancer surgery is to achieve excellent oncological outcome whilst minimizing morbidity. Although radical nephrectomy achieves the former, the recent literature has shown that patients undergoing this procedure for small renal tumours have a greater incidence of new-onset CKD and may have a higher overall long-term mortality compared with patients undergoing partial nephrectomy [5,40–42]. Partial nephrectomy has equivalent oncological control for T1a tumours by open or laparoscopic access [47], and for T1b tumours by experienced surgeons [47–50,62]. Furthermore, the underlying pathology appears to be benign in 17–25% of such resections [47], indicating that such patients would be surgically over-treated by any surgical procedure, with the additional risks of CKD and, possibly, greater long-term mortality.

With such information, it would seem logical for partial nephrectomy to be widely used but this is not the case [45]. In the UK and Canada partial nephrectomy still accounts for <10% of all nephrectomies performed [32,67]. There are a number of factors which may account for this. OPN is more technically challenging than radical nephrectomy [47] and laparoscopic partial nephrectomy is even more so, requiring advanced laparoscopic skills with a very long learning curve [47,52–56]. It is clear that acquisition of considerable experience is required before complication rates approach those of international centres, perhaps up to 200 cases for laparoscopic partial nephrectomy. In the UK there were only 162 registered partial nephrectomies in 2008 [32] and the experience might be two cases per year in practising hospitals [68] and fewer than 10 cases per year in centres [69]. There are therefore major hurdles to overcome to accrue such expertise before these operations can become offered routinely.

In expert hands, LPN appears to offer excellent outcomes with renal preservation for tumours <4 cm despite the issue of warm ischaemia. If intraoperative complications are encountered in centres with more modest expertise, then a choice would be to convert either to OPN or LRN. The former offers renal preservation, the latter a more rapid hospital recovery and return to work. If LPN cannot be offered locally, then there appears to be a strong

argument for carrying out elective OPN instead of LRN. The number of patients currently undergoing this procedure is very low, and the recently recognized advantages of nephron-sparing surgery might well alter surgical practice with a reduction in LRN in exchange for OPN until such expertise in LPN is gained.

CONCLUSIONS

It can be seen that the choice of therapeutic methods for RCTs has never been wider. Given the lack of prospective randomized controlled trials comparing one form of treatment over another, other factors such as the patient's performance status and local surgical expertise will be important when advising a patient on the most appropriate course of action. It seems inevitable that the paradigm of surgery which seeks to maximize remaining renal function will become increasingly relevant in an aging population, and thus the days of widespread ORN or LRN for T1 RCTs might be numbered. Ultimately, the choice of treatment for the patient with a RCT needs to be individualized, with the aim being to achieve maximum cancer care with preservation of renal function whenever possible.

CONFLICT OF INTEREST

None declared.

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Abbreviations: RCT, renal cortical tumour; ORN, open radical nephrectomy; LRN, laparoscopic radical nephrectomy; OPN, open partial nephrectomy; LPN, laparoscopic partial nephrectomy; RFA, radiofrequency ablation; CKD, chronic kidney disease.