

## Canadian guidelines for the management of small renal masses (SRM)

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See related article on page 163.

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### Defintion of small renal mass

Small renal masses (SRMs), as a clinical entity, are defined as enhancing tumours <4 cm in diameter, with image characteristics consistent with stage T1aN0M0 renal cell carcinoma (RCC).<sup>1-5</sup> Most, but not all, SRMs are RCC. The assessment must exclude metastases, in which case the patient would be considered to have metastatic RCC with a small primary tumour (T1aN0M+).

### Introduction

The incidence of SRMs has increased with the widespread use of imaging and this, in turn, has increased the incidence of RCC. Mortality rates are not increasing, despite the rising incidence and increased treatment.<sup>6,7</sup> The established standard treatment for localized RCC has been radical nephrectomy.<sup>8</sup> More recently, partial nephrectomy has become the recommended treatment.<sup>9,10</sup> Results of surgical therapy are excellent, with over 90% disease-specific survival for stage T1a.<sup>11</sup> Probe ablation and active surveillance are alternative management strategies with similar efficacy.<sup>12</sup>

SRMs are frequent in the elderly and infirm, in whom the risk of treatment must be weighed against life expectancy

and malignant potential of the tumour.<sup>5</sup> About 20% to 25% of SRMs are benign.<sup>13</sup> Even if SRMs are malignant, most of them grow slowly. Most studies have reported that the rates of malignant pathology, higher grade, higher pathological stage, growth and the risk of metastasis increase with tumour size.<sup>14</sup> Small RCCs may be associated with metastatic disease at diagnosis in up to 8% of cases, so initial staging of all SRM patients is essential.<sup>15</sup> Based on current data, initial active surveillance (AS) with delayed treatment for local progression appears to be a relatively safe initial management strategy.

### Methods

We reviewed the literature from the electronic Medline database. Citations from included articles and review articles were manually searched by the chair (MJ) and a draft guideline was developed. This draft was reviewed by the guideline writing committee. Suggestions were incorporated and the final draft was approved by the same committee and submitted to the Canadian Urological Association (CUA) Guideline Committee for subsequent approval and promulgation in 2014. It is anticipated that this guideline will be reviewed and updated at regular intervals.

### Role of needle core biopsy of SRMs

The Kidney Cancer Research Network of Canada (KCRNC) Consensus after the January 2013 Canadian Kidney Cancer Forum describes needle biopsy for histologic characterization as an option that may guide treatment decisions and

that should be reserved for patients in whom the results might change management. Biopsy should be done at the time of probe ablation, if not before.<sup>9,16</sup> There is Canadian experience with needle core biopsy of SRMs.<sup>13,17</sup> Biopsy appears safe and at least 80% of first biopsies are diagnostic. Repeat biopsy may be considered. The frequent benign pathology found with excised SRMs and the lack of specificity in imaging have led to increasing acceptance of the role for pre-treatment biopsy.<sup>5,18</sup> Successful biopsy requires expertise in interventional imaging and pathology.<sup>12</sup> Multiple tumours may have different histology and tumour grade, so multiple and repeat biopsies may be required to accurately characterize tumour histology. However, biopsy is not yet a standard of care in Canada.

### Management options for SRMs

The Canadian Consensus for the management of early stage T1a RCC states the following options:<sup>16,19</sup>

- Partial nephrectomy is recommended – by open, laparoscopic or robotic-assisted laparoscopic means
- Laparoscopic radical nephrectomy is reserved for tumours not amenable to partial nephrectomy
- Probe ablation by radiofrequency or cryotherapy. A biopsy should be obtained before or at the time of ablation
- Active surveillance

### Partial nephrectomy

There is increasing concern about the use of nephrectomy, as opposed to nephron-sparing surgery or partial nephrectomy, for localized kidney cancer. While it has been considered the gold standard treatment for RCC, partial nephrectomy is increasingly being associated with a lower risk of long-term renal dysfunction and a reduction in overtreatment of benign tumours.<sup>20-23</sup>

The only level I evidence regarding oncological outcomes of partial nephrectomy compared to radical nephrectomy is controversial and was discussed during the Canadian Consensus meeting.<sup>16,24-27</sup> The EORTC (European Organization for Research and Treatment of Cancer) trial was underpowered and closed prematurely due to poor enrollment, despite a prolonged accrual. It is still generally believed that partial nephrectomy is not inferior to radical nephrectomy. Laparoscopic partial nephrectomy is increasingly available in Canada and experience with robot-assisted laparoscopic partial nephrectomy is also growing in Canada.<sup>28,29</sup> There is continued controversy about the role of intraoperative cooling and the optimal method and time limit for renal ischemia. It is generally accepted that minimizing warm ischemia is prudent, but we await the results of ongoing clinical trials.

Open partial nephrectomy is preferable to laparoscopic nephrectomy, when feasible. Partial nephrectomy can result in complications including bleeding, a need for transfusion, urinary fistula and acute changes in renal function. There is no consensus regarding the optimal surveillance after partial nephrectomy, but the 2008 CUA guideline by Kassouf and colleagues should be followed.<sup>16,30</sup>

### Thermal or probe ablation—radiofrequency ablation, cryotherapy

Percutaneous probe ablation is becoming more widely accepted and practiced, but it is important to have a biopsy before or at the time of treatment for follow-up planning and outcome analysis.<sup>31</sup> Morbidity is low and ablation can be performed on an outpatient basis without general anesthesia in a cost-effective manner. It is an attractive approach in elderly and infirm patients. Long-term follow-up with imaging is required and local recurrence occurs in up to 14% of patients.<sup>3</sup>

The definition of ablative success remains controversial, as many tumours are not biopsied pre-treatment. Complications are relatively uncommon and well-described, including transient pain, and damage to adjacent organs and the collecting system. Renal function appears to be well-preserved. Tumour location is the most important aspect of patient selection, with reduced success rates for endophytic central tumours. Laparoscopic approaches are unnecessary. Anterior tumours are approached laparoscopically at some centres, but partial nephrectomy should be considered if operative exposure is undertaken. Success rates decrease in tumours larger than 3 cm in diameter. Reports with longer term follow-up in a greater number of patients demonstrate good oncological efficacy in carefully selected patients and repeat treatments are possible.<sup>32,33</sup> Salvage surgery is technically difficult and usually requires nephrectomy. The clinical significance of reported outcomes is frequently weakened by the lack of biopsy and rate of re-treatment.

The number of centres offering ablation is limited and most centres focus on one method. Cryotherapy can be monitored during treatment by using ultrasound to visualize the ice ball, although experienced radiofrequency ablaters can see changes in the tumour and use impedance or temperature for monitoring.

### Active surveillance

All active surveillance studies of SRMs have relatively short follow-up, but low rates of progression, including a low rate of metastasis of 1% to 2%. Most are not biopsy proven to be cancer. Long-term follow-up is required to establish the safety of this approach in the young and fit patient. Prognostic factors for progression are poorly understood, but primary tumour growth rate is the most widely used trigger for delayed treatment.<sup>34</sup>

Active surveillance with regular radiographic follow-up should be a primary consideration for SRMs in elderly and/or infirm patients with multiple comorbidities that would make them high risk for intervention, and in those with limited life expectancy.<sup>26,29</sup>

For follow-up during the surveillance period, Rendon and colleagues suggested computed tomography (CT) or magnetic resonance imaging every 3 months in the first year, every 6 months in the next 2 years and every year thereafter.<sup>24</sup> This high number of CT scans was considered necessary to assure a safe surveillance strategy. However, in this regard, the recognized risk of radiation exposure due to multiple CT scans should be kept in mind. The optimum protocol and imaging modality are unknown at present, but ultrasound, with or without contrast, may provide adequate images for measurement.

## Summary

Needle core biopsy is increasingly performed, but is not yet the standard of care for histological characterization of SRMs. Partial nephrectomy is recommended for SRMs. Pure and/or robotic-assisted laparoscopic partial nephrectomy is an option at experienced centres. Laparoscopic radical nephrectomy is recommended for tumours not amenable to partial nephrectomy. Probe ablation is an alternative treatment, but a biopsy should be obtained before or at the time of ablation to guide follow-up. Experience with active surveillance is currently limited by short follow-up, but should be a primary consideration in the elderly and infirm.

**Competing interests:** Dr. Lacombe, Dr. Leveridge, Dr. Cagiannos, Dr. Evans and Dr. Haider declare no competing financial or personal interests. Dr. Jewett is a member of the Advisory Board for Pfizer. He has also received grants from Novartis, GSK and Pfizer. Lastly, he has participated in clinical trials with Novartis, GSK and Pfizer. Dr. Rendon is a member of the Advisory Board and the Speakers' bureau for Amgen, Astellas, Ferring and Janssen. Dr. Karakiewicz is partially supported by the University of Montreal Health Centre Urology Specialists, Fonds de la Recherche en Santé du Québec, the University of Montreal, Department of Surgery and the University of Montreal Health Centre (CHUM) Foundation. Dr. Tanguay is a member of the advisory board for Pfizer. He has also received grants from Pfizer, Novartis and GlaxoSmithKline. Dr. Kassouf is an Advisory Board member and a speaker for Amgen and Astellas. He has also received grants and honoraria from these companies. He is currently participating in unpaid clinical trials within the past 2 years. Dr. Kapoor is a member of the speakers' bureau for Pfizer Oncology and Novartis Oncology. Dr. Pautler is currently participating in a clinical trial with Astellas. Dr. Drachenberg has attended Advisory Boards for Astellas and Janssen and has been a speaker for Amgen and Actavis (formerly Watson). He has also been an investigator in clinical trials run by Cancer Care Manitoba (CCMB). Dr. Moore is a member of the advisory boards for Astella, Janssen, and Quest PharmaTech. He has also received a grant from and is participating in a clinical trial with Quest PharmaTech. Dr. Gleave is a member of the advisory boards for Oncogenex, Astra Zeneca, Janssen, and Astellas. He is also a member of the speakers' bureaus for Janssen and Astellas. He has received payment from Oncogenex, as cofounder. He has also received grants from Amgen, Janssen, Astellas, and AstraZeneca.

This paper has been peer-reviewed.

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## COMMENTARY

# Canadian guidelines for SRMs: How Canadian are they?

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See related article on page 160.

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Small renal masses (SRM) are encountered by most urologists as part of their routine clinical practice, which makes best practice statements or guidelines like those published in this month's *CUAJ* important in standardizing care.<sup>1</sup> While it is good for patients to have options, the management of SRMs has started to resemble that of localized prostate cancer – each patient and the treating physician have many potentially difficult choices to make, and there is an underlying concern for over-treatment.

The European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) have recently updated their kidney cancer guidelines including the management of SRMs.<sup>2,3</sup> The American Urological Association (AUA) published guidelines specifically on SRMs in 2009 and validated these in 2010.<sup>4</sup> Furthermore, the Kidney Cancer Research Network of Canada (KCRNC), which includes many of the same contributors who drew up these SRM guidelines, has developed best practice guidelines in the past.<sup>5</sup> The question therefore arises how these

new guidelines compare to other international guidelines, how they differ from the prior KCRNC consensus statement, and what makes them specifically Canadian. The answer to all these questions is: not much.

Specific Canadian content to the literature on the management of SRMs relates primarily to the utility of renal mass biopsy<sup>6-8</sup> and the adoption of active surveillance,<sup>9</sup> both of which we as a Canadian community of urologists would generally promote. However, neither of these components is emphasized particularly strongly in the current guidelines, reflecting a degree of uncertainty in their widespread adoption. With respect to these two issues, these guidelines do not read much differently than the AUA guidelines from 2010, which also recognize an increased role for biopsy and allow for active surveillance in older patients and those with significant medical comorbidities.<sup>4</sup> The EAU and NCCN guidelines do not really entertain the notion of SRM biopsy to decide on surgical intervention versus surveillance, but instead limit its scope to patients with metastatic disease, those on surveillance, or those undergoing ablation. The NCCN guidelines are more restrictive than these Canadian guidelines with respect to use of ablative procedures, and reserve these for patients who are explicitly not candidates for surgery. However, this represents a deviation of the

*Continued on page 213*