

## Surgical management of renal cell carcinoma: Canadian Kidney Cancer Forum Consensus

Ricardo A. Rendon, MD, FRCSC,\* Anil Kapoor, MD, FRCSC,<sup>†</sup> Rodney Breau, MD, FRCSC,<sup>§</sup> Michael Leveridge, MD, FRCSC,<sup>‡</sup> Andrew Feifer, MD, FRCSC,<sup>‡</sup> Peter C. Black, MD, FRCSC,<sup>‡</sup> Alan So, MD, FRCSC,<sup>‡</sup> on behalf of the Kidney Cancer Research Network of Canada

\*Department of Urology, Dalhousie University, Halifax, NS; <sup>†</sup>Department of Surgery, Division of Urology, McMaster University, Hamilton, ON; <sup>§</sup>Division of Urology, University of Ottawa, Ottawa, ON; <sup>‡</sup>Departments of Urology and Oncology, Queen's University, Kingston, ON; <sup>‡</sup>Credit Valley Hospital, Mississauga, ON; <sup>‡</sup>Department of Urologic Sciences, University of British Columbia, Vancouver, BC

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### Epidemiology

The Canadian Cancer Society estimated 5900 new cases of renal cell carcinoma (RCC) and 1750 related deaths in Canada in 2012.<sup>1</sup> RCC is the sixth and eleventh most common cancer diagnosed in Canadian men and women, respectively, and its incidence has been rising by about 2.3% per year, including the period from 2005 to 2009.<sup>2</sup> Much of this rise is attributed to incidental detection via abdominal imaging for other causes. Most of these RCCs have been small renal masses (SRMs), defined as solid-appearing masses less than 4 cm in maximum diameter.<sup>3,4</sup>

Hereditary RCC syndromes are well-described, but account for a minority of incidental findings. Other well-recognized risk factors include cigarette smoking, obesity, hypertension and chronic renal failure.<sup>5-7</sup>

### Evaluation

#### Primary evaluation and investigations

- Thorough history
- Physical examination
- Laboratory evaluation
  - Complete blood count (CBC), renal function
  - Liver function (transaminases)
  - Markers of bone disease (alkaline phosphatase and corrected calcium)
  - Markers of prognosis in patients with advanced disease (Lactic acid dehydrogenase [LDH], platelets, calcium, neutrophils, hemoglobin)
  - Urine cytology in central tumours

The initial evaluation of patients with RCC begins with a thorough medical history. Within the history, the identification of risk factors for RCC should be assessed, including history of smoking, hypertension, previous renal masses, as well as a family history of renal tumours or genetic disorders associated with RCC. You should also assess the patient's symptoms, including pain (bony and flank) and gross hematuria. New onset coughing or other respiratory issues may suggest pulmonary metastases and new neurologic symptoms may suggest cerebral metastases. The performance status should be evaluated.

Physical examination should include blood pressure, as well as abdominal examination for masses and assessment for cervical lymphadenopathy and lower extremity edema, which may suggest inferior vena cava (IVC) involvement. Neurologic exam should be performed if there is any suggestion of cerebral or spinal metastases.

Laboratory evaluation includes a complete blood count (CBC), and renal function studies (creatinine, estimated glomerular filtration rate [eGFR]). Liver function testing (alanine transaminase [ALT], aspartate aminotransferase [AST]) and markers of bony disease (serum alkaline phosphatase and corrected calcium) should also be assessed.<sup>8</sup> In patients with advanced disease, laboratory features that are associated with worse overall survival include anemia, hypercalcemia, neutrophilia, thrombocytosis, and elevated LDH.<sup>9</sup> For central masses, urine cytology may be valuable to differentiate urothelial cell carcinoma from RCC.

## Staging

- Primary tumour:
  - Triphasic abdominal/pelvic computed tomography (CT) without and with intravenous contrast.
  - Abdominal magnetic resonance imaging (MRI), if contrast allergy or renal insufficiency or CT suggests caval thrombus and level cannot be determined.
  - Consider Doppler ultrasound to assess the extent of tumour involvement of the IVC.
- Metastatic evaluation
  - Chest X-ray, consider CT chest if ≥stage T2.
  - Bone scan, if clinically indicated or elevated alkaline phosphatase and serum calcium.
  - Brain CT or MRI if large volume metastatic disease.

## Radiologic examination and staging

With staging accuracy of over 90%, CT imaging is the imaging of choice of renal masses.<sup>10,11</sup> Enhancement of renal tumours, defined as an attenuation increase of 10 to 20 Hounsfield units (HU) on post-contrast images, is an important determinant of the malignant potential of a renal mass.<sup>12</sup> The evaluation of CT image includes staging of the primary tumour, determination of lymphadenopathy, abdominal metastatic disease and characterization of the contralateral kidney. Abdominal MRI is an alternative to assess renal masses for pregnant patients and those with a contrast allergy, and decreased renal function. As well, MRI is another tool to evaluate IVC tumour involvement with a sensitivity of almost 100%.<sup>13</sup> Doppler ultrasound is also a valuable tool to determine the extent of tumour involvement of the IVC.<sup>14</sup>

A chest imaging with chest x-ray to determine metastases is usually adequate, but a chest CT may be useful in patients who are symptomatic or are at high risk of metastases (>stage T2). In patients with compromised renal function, bilateral or multifocal disease, an isotope renogram may be useful for surgical planning and patient counselling. Moreover, patients with bony pain or elevated alkaline phosphatase and/or serum calcium should receive a bone scan to rule out bony metastases. A CT or MRI of the head may be valuable in patients with suspicion of brain metastases in cases with neurologic symptoms or large volume metastatic disease. Although positron emission tomography (PET) has no role in the primary assessment of RCC, its role in advanced RCC and assessment of tumour recurrence is evolving.<sup>15-17</sup>

## Bosniak Classification of renal cysts

Initially described in 1986, the Bosniak Classification of renal cystic lesions is still used to ascertain the risk of malignancy.<sup>18</sup> A CT or MRI can be used to classify renal cystic lesions as per the Bosniak Classification.<sup>19</sup>

**Category I** cysts are simple benign cyst with a hairline thin wall that does not contain septa, calcification or solid

components. It measures as water density and does not enhance with contrast material. These cysts do not need follow-up.<sup>19</sup>

**Category II** cysts are benign cysts that might contain a few hairline thin septa. Fine calcifications might be present in the wall or septa. These cysts also include uniformly high-attenuation lesions (hyperdense cyst) of <3 cm that are sharply marginated and do not enhance. These cysts do not need follow-up.<sup>19</sup>

**Category IIF** cysts might contain more hairline thin septa. Minimal enhancement of a hairline thin septum or wall can be seen and there might be minimal thickening of the septa or wall. These cysts might contain calcification that might be nodular and thick, with no contrast enhancement. There are no enhancing soft-tissue elements. Totally intrarenal non-enhancing high-attenuation renal lesions of ≥3 cm are also included in this category. These lesions are generally well-marginated. Between every 6 to 12 months, these cysts require follow-up with ultrasound or CT to ensure stability of solid components.<sup>20,21</sup> Risk of malignancy with Category IIF cysts is less than 10%.<sup>22</sup>

**Category III and IV** cysts both enhance and carry a much greater risk of harbouring RCC. Category III cysts contain thickened irregular or smooth walls or septa in which measurable enhancement is present. Close to 65% of these cysts may be benign, and can include hemorrhagic cysts, chronic infected cysts, and multi-loculated cystic nephroma.<sup>18</sup> Category IV cysts have all the criteria of category III and also contain enhancing soft-tissue components independent of the septum.<sup>18</sup> These cysts are usually malignant (92%) and require treatment.<sup>23</sup>

## Pretreatment prediction of tumour histology

### Predictive tools

- Nomograms and Classification trees may be used to predict pretreatment histology of renal masses less than 4 cm in diameter.

Although most renal masses >4 cm are malignant, determining the cancer risk of smaller tumours can be challenging (Table 1, Table 2, Table 3, Table 4).<sup>24-26</sup> Several authors have constructed statistical tools to predict benign and malignant histology in SRMs to aid providers in counselling patients about treatment options. One example is a patient and disease characteristic-based classification tree with an accuracy of 89%.<sup>27</sup> A subsequent accuracy of 74% was maintained when classification tree was externally validated.<sup>28</sup> The advantage of a classification tree is its ease of use, as it closely correlates with a clinicians' thought process making it more likely to be used clinically.

Other groups have developed nomograms to determine

**Table 1. AJCC TNM Staging System for kidney cancer: Primary tumour**

TX	Primary tumour cannot be assessed.
T0	No evidence of primary tumour.
T1	Tumour ≤7 cm in greatest dimension, limited to the kidney.
T1a	Tumour ≤4 cm in greatest dimension, limited to the kidney.
T1b	Tumour >4 cm but not >7 cm in greatest dimension, limited to the kidney.
T2	Tumour >7 cm in greatest dimension, limited to the kidney.
T2a	Tumour >7 cm but ≤10 cm in greatest dimension, limited to the kidney.
T2b	Tumour >10 cm, limited to the kidney.
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia.
T3a	Tumour grossly extends into the renal vein or its segmental (muscle containing) branches, or tumour invades perirenal and/or renal sinus fat but not beyond Gerota fascia.
T3b	Tumour grossly extends into the vena cava below the diaphragm.
T3c	Tumour grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava.
T4	Tumour invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland).

AJCC: American Joint Committee on Cancer; T: primary tumour; N: regional lymph nodes; M: distant metastasis. Taken from Edge SB, American Joint Committee on Cancer.<sup>24</sup>

**Table 2. AJCC TNM Staging System for kidney cancer: Regional lymph nodes**

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastases in regional lymph node(s).

AJCC: American Joint Committee on Cancer; T: primary tumour; N: regional lymph nodes; M: distant metastasis. Taken from Edge SB, American Joint Committee on Cancer.<sup>24</sup>

**Table 3. AJCC TNM Staging System for kidney cancer: Distant metastasis**

M0	No distant metastasis.
M1	Distant metastasis.

AJCC: American Joint Committee on Cancer; T: primary tumour; N: regional lymph nodes; M: distant metastasis. Taken from Edge SB, American Joint Committee on Cancer.<sup>24</sup>

**Table 4. AJCC TNM Staging System for kidney cancer: Anatomic stage/prognostic group**

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T1 or T2	N1	M0
	T3	N0 or N1	M0
IV	T4	Any N	M0
	Any T	Any N	M1

AJCC: American Joint Committee on Cancer; T: primary tumour; N: regional lymph nodes; M: distant metastasis. Taken from Edge SB, American Joint Committee on Cancer.<sup>24</sup>

the risk of benign and malignant disease for SRMs.<sup>29,30</sup> Lane and colleagues used age, gender, radiological size at diagnosis, symptoms at presentation and smoking history to develop a nomogram with an accuracy of 0.64.<sup>29</sup> Kutikov and colleagues developed a nomogram using the R.E.N.A.L. nephrometry scoring system with an area under the curve (AUC) of 0.76 in predicting malignancy and 0.74 in predicting low and high grade.<sup>30</sup> The nomogram's ability to predict tumour grade (Fuhrman) has been externally validated,<sup>31</sup> but the nomogram predicting malignancy has not been externally validated. Mullins and colleagues used R.E.N.A.L. nephrometry scoring to predict malignancy by subdividing the score in low (4-6), intermediate (7-9) and high risk (10-12). They found that an increased risk of malignancy in intermediate and highly complex masses.<sup>32</sup> A subgroup analysis of SRMs (<4 cm) showed that intermediate complex masses were more likely malignant than low and highly complex SRMs.

### Biopsy of the localized renal mass

- Biopsy of SRMs for histologic characterization is an option and may guide treatment decisions.
- Biopsy of a renal mass or metastatic site in the setting of metastatic disease is important in guiding systemic therapy. In patients undergoing cytoreductive nephrectomy before systemic therapy, or surgical resection of metastatic site, a biopsy may not be necessary.
- Percutaneous biopsy is associated with a low risk of complications.
- Biopsy should be reserved for patients in whom the results might change management.

The last 15 years have seen the establishment of percutaneous biopsy in the workup of SRMs. Classical indications for renal mass biopsy include the identification of metastatic deposits, lymphomatous infiltration or an infectious etiology to an imaging abnormality; more recently, there has been a focus on the histologic determination of SRMs. Numerous series have been published that establish a diagnostic rate of between 62% and 96%, with a mean of 83%.<sup>33-40</sup> The series with the highest reported yield included second biopsies after a first inconclusive biopsy.<sup>34</sup> Among diagnostic biopsies, benign masses were identified in 20% to 42% of cases. This is congruent with surgical series assessing the histology of resected SRMs.<sup>41</sup> The largest published series to date is from Canada, and noted an 81% diagnostic rate; and a 20% incidence of benign histology.<sup>34</sup>

Comparison to pathologic specimens is not the rule in SRM biopsy series or practice; nonetheless, the reported concordance is high. Tumour classification on biopsy has been confirmed at extirpation in 73% to 98% of cases.<sup>33,39,42,43</sup> Concordance of Fuhrman grading between biopsy and surgical specimens has not been as robust. An identical grade may be found in 32% to 70% of cases.<sup>33,43,44</sup>

In the case of a non-diagnostic initial biopsy, it may be

expected that a diagnosis can be made with repeat biopsy, and that the rate of malignancy remains high. Leveridge and colleagues found that 83% of repeat biopsies were diagnostic, and 80% of these were malignant.<sup>34</sup> Laguna and colleagues identified cancer in 71% of repeat biopsies, and 78% of all cases with a non-diagnostic initial biopsy.<sup>45</sup> Thus, an indeterminate initial biopsy should not be taken as reassurance regarding the malignant potential of the mass.

Safety has also been reported favourably in the literature. Since 2000, the reported complication rate has been 2.4%.<sup>46</sup> There has been only a single case report of biopsy tract seeding with RCC in the past decade. In this case, there was suspicion of seeding in the perirenal fat on the partial nephrectomy specimen.<sup>47</sup> No cases of clinical recurrence or metastatic disease in a biopsy tract have been published in recent years.

It is essential to identify tumour histology in the setting of metastatic disease, both to confirm that metastatic sites represent tumour spread (and not a second primary tumour) and to classify the histologic subtype as a guide to systemic therapy. In many cases in which cytoreductive nephrectomy will have been performed, the primary histology is known and widespread metastatic disease can comfortably be assumed to be similar. If cytoreductive nephrectomy is not performed prior to planned initiation of systemic therapy, percutaneous biopsy may help to guide therapy. Poorly differentiated cancer in the renal mass or metastatic sites may occasionally present a diagnostic challenge. Abel and colleagues assessed over 400 biopsy specimens in patients with metastatic disease.<sup>44</sup> They found that in 26.8% of cases, a biopsy of metastatic sites showed unspecified cancer that could not confirm RCC. Overall, RCC was clearly identified in only 65% of cases. This large cohort study also found 96% concordance between a diagnosis of clear cell RCC on biopsy and subsequent surgical excision.

In the setting of oligometastatic disease, the link between primary and secondary masses cannot be assumed reliably. Limited data are available with regards to the role of percutaneous biopsy in this setting.

## Treatment options

The recommended treatment of T1a RCC has evolved with the incorporation of level-1 evidence and larger observational studies into clinical practice. Previous guidelines recommended partial nephrectomy (PN) as first-line therapy for pT1a RCC, and several recent studies also support the ongoing use of PN,<sup>48,49</sup> with a growing focus on the technical feasibility of minimally invasive approaches.<sup>50-55</sup> From a population health perspective, PN may still be underutilized,<sup>56</sup> despite its association with a lower risk of long-term renal dysfunction<sup>57-59</sup> compared to radical nephrectomy (RN), while providing similar oncologic outcomes.<sup>60,61</sup> Tumour enucleation, regardless of the approach for exophytic lesions, seems to offer equivalent outcomes to PN when a negative surgical margin is established.<sup>62</sup> PN may also be associated with a lower risk of long-term cardiovascular events.<sup>63-65</sup> Laparoscopic or robotic-assisted laparoscopic PN can result in comparable surgical and oncologic outcomes in the hands of experienced surgeons.<sup>66,67</sup> While the impact of a positive surgical margin on subsequent disease outcome has not definitively been shown to adversely affect survival outcomes, a negative surgical margin is always the goal of any nephron-sparing procedure. It is also a required metric of surgical quality of care.<sup>68,69</sup>

A recent European Organization for Research and Treatment of Cancer (EORTC) trial evaluated overall survival and time to cancer progression in 541 patients randomized to PN or RN for T1-T2N0 lesions suspicious for RCC,<sup>70</sup> but also supported noninferiority of PN. The results indicated an overall survival advantage for patients undergoing RN, contrary to previously reported retrospective data. When pathologically eligible patients were evaluated, the differences in survival were less pronounced, and the RN was no longer statistically superior. PN did demonstrate maintenance of renal function with a slightly higher risk of perioperative complications. This study has somewhat tempered enthusiasm for PN in the elective setting, despite the overwhelming evidence for PN in medical renal disease.<sup>71</sup> However, numerous shortcomings of this study (such as premature study closure, baseline and cross-over related patient comorbidity imbalances, low statistical power, variable surgical technique and parenchymal sparing) have rendered its interpretation problematic. A further prospective investigation should be able to shed light on the role of PN versus RN in this and other populations.

The use of image-guided ablative technologies in the management of T1a RCC is widely accessible in Canadian institutions. Despite the lack of long-term recurrence and survival data, radiofrequency ablation (RFA) or cryotherapy performed either percutaneously under image guidance or laparoscopically, is a viable management option in patients with tumours less than 3 cm in diameter, with infrequent complications;

### Stage T1aN0M0

- Partial nephrectomy recommended. This can be done via open/laparoscopic/robotic procedures.
- Pure or robot-assisted laparoscopic partial nephrectomy with experienced surgeons (transperitoneal or retroperitoneal).
- Consider laparoscopic radical nephrectomy for tumours not amenable to partial nephrectomy.
- Consider probe ablation by radiofrequency (RFA) or cryotherapy in patients with high surgical risk. A biopsy should be obtained before or at the time of ablation.
- Consider active surveillance in the elderly or infirm.

they do, however, have a slightly higher risk of local recurrence compared to PN.<sup>72-74</sup> Currently, patients considered for ablative approaches are those with severe medical comorbidities precluding surgical extirpation, or in patients with multiple bilateral lesions, possibly due to underlying genetic predispositions (Birt-Hogg-Dubé syndrome, Von Hippel-Lindau disease). Several technologies and approaches are differentially used with success, although long-term oncologic outcomes are not yet available.<sup>75,76</sup> Pre-treatment or concomitant biopsy in these cases is recommended.<sup>77</sup>

### Active surveillance

- The long-term safety of initial active surveillance with delayed treatment for progression is not yet established. However, it is an alternative for managing SRMs that are asymptomatic and characteristic of RCC on imaging in the elderly and/or infirm. It is not yet recommended for the young and fit.
- Follow-up must include serial imaging.

Active surveillance for SRM lesions has gained widespread acceptance owing to strong clinical research demonstrating safety in select patient populations.<sup>78,79</sup> Canadian experience with active surveillance has been documented, and has been associated with low risk of metastasis.<sup>80</sup> This group also demonstrated a growth rate of 0.13 cm/year, which did

#### Stage T1bN0M0

- PN (open/laparoscopic/robotic) in cases where technically feasible
- Laparoscopic RN should be offered if a PN is not feasible
- Open RN if laparoscopic surgery not possible.

not correlate with histology in a subgroup of patients with histologically confirmed RCC. Lesions <4 cm with elevated growth rates have increased the risk of local or systemic progression and should be considered for definitive extirpation or ablation.<sup>79,81</sup> Data suggest that lesions greater than 2.45 cm in diameter are more likely to have accelerated growth rates.<sup>82</sup> An emerging and safe trend may be routine biopsy in patients with SRM to confirm malignant histology. Active surveillance is a viable option after histological confirmation of RCC and may help to further risk-stratify patients for management or tailoring of follow-up imaging.<sup>83,84</sup> Despite the low risk of metastasis, the documented potential of systemic (1.1%) or local progression (12%) merits consideration when counselling patients.<sup>80,85</sup> Management of SRM in elderly patients has also been investigated in several series, and active surveillance has been associated with a greater overall survival compared to active surgical or ablative therapy.<sup>86,87</sup> The selection of active surveillance as a validated treatment option is supported by the literature. It should be considered for patients with significant comorbid medical disease and for elderly patients.

The use of PN for T1bN0M0 cases was supported initially for patients with solitary kidneys or with renal function-endangering medical comorbidity.<sup>88</sup> However, with the technical advancement in the field, supported by clinical research and the rising global impact of medical renal disease,<sup>71</sup> PN has been applied in patients with normal contralateral kidneys.<sup>89</sup>

Although PN is safe, oncologically equivalent to RN, and offers an effective means to prevent surgically induced renal dysfunction,<sup>90-92</sup> randomized data have modified enthusiasm for PN for T1b lesions to a greater degree than lesions under 4 cm.<sup>70,93</sup> Despite the aforementioned study limitations, the positive comparative overall survival of RN compared to PN in the T1b population in an intent-to-treat analysis is noteworthy, and may raise uncertainty about the efforts to expand PN for patients with larger and more complex tumours in the elective setting.

Nevertheless, the expertise required to perform PN in larger tumours is growing in many tertiary care institutions,<sup>94</sup> but the general uptake is still modest.<sup>95</sup> Recent studies have shown similar outcomes for open PN and minimally invasive PN.<sup>96</sup> Minimally invasive approaches to PN for tumours between 4 and 7 cm present a further surgical challenge, but are certainly feasible and effective in experienced hands.<sup>97-99</sup> Although many patients with positive surgical margins do not experience local relapse, there may be a greater importance in attaining a negative surgical margins in larger lesions, related to greater risks of higher grade tumours. Several important technical advances have enabled laparoscopic surgeons to maintain acceptable ischemia times.<sup>50,100,101</sup>

If a PN is not feasible, a laparoscopic RN is the surgery of choice and is preferred to open RN, secondary to improvements in postoperative recovery, pain, and return to normal activity.<sup>102,103</sup> When LRN is not feasible, open PN is preferred. Ablative modalities are not recommended for these tumours due to the high rate of incomplete ablation in lesions greater than 4 cm.<sup>104-106</sup>

#### Stage T2N0M0

- RN – open/laparoscopic/robotic
- PN – open/laparoscopic/robotic

Patients with tumours larger than 7 cm have traditionally been managed with laparoscopic or open RN,<sup>107,108</sup> although open RN remains an option for patients not suitable for laparoscopic RN. Both minimally invasive and open approaches have been associated with equivalent cancer-specific outcomes,<sup>109,110</sup> with a potential for fewer perioperative complications.<sup>111</sup> Robotic RN in selected cases is feasible.<sup>54,108,112,113</sup> The role of extended PN for tumours greater than 7 cm is controversial, and the consideration of such highly selected cases should be limited to experienced surgeons.<sup>114-116</sup>

**Stage T3**

- RN – open, laparoscopic or robotic assisted
  - Resection of vascular thrombus when applicable (usually open)
  - Resection of all gross disease including hilar or retroperitoneal extension
- PN may be attempted in highly selected cases by experienced surgeons.

Patients with tumours greater than 7 cm should raise suspicion of involvement of peri-renal tissues, such as Gerota's fascia or renal sinus fat.<sup>117</sup> Current TNM staging reflects the higher rate of disease recurrence with peri-renal tissue involvement.<sup>118-122</sup> Other series have not supported universal upstaging for all locally advanced tumours, and suggest variable survival differences based on sites of regional tumour extension.<sup>123,124</sup> In many cases, T3 disease can only be pathologically determined based on pathologic evidence of muscular venous branch invasion, which has been associated with an adverse prognostic impact.<sup>125-127</sup> Some investigators use MRI to help to preoperatively identify muscular venous branch invasion.<sup>128</sup> Technical considerations regarding the optimal surgical approach may be modified based on disease stage, the presence or level of vascular tumour thrombus, and the feasibility of negative margins.<sup>129,130</sup> Open or laparoscopic RN is the management option of choice, with most tumour thrombi necessitating an open approach. PN (open or laparoscopic) is feasible in highly selected patients in the hands of experienced renal surgeons.<sup>51</sup> Ipsilateral involvement of the adrenal gland from upper pole tumours portends a more guarded prognosis, with recent upstaging to T4 on the most recent TNM classification.<sup>131</sup>

**Management of the IVC and renal vein thrombus**

- In the presence or absence of distant metastases, tumour thrombus should be resected if technically feasible in appropriately selected patients
- It is recommended that these operations be performed in a centre with experience and with an availability of a multidisciplinary team as these complex procedures have significant risk of morbidity and mortality.

About 4% to 10% of all RCCs involve the IVC, with a smaller subset extending to the right atrium. RCC with intravascular disease at any level is associated with higher-grade disease and a worse prognosis.<sup>127,132</sup> Distant lymph node or metastatic disease is more common in this population.<sup>133</sup> Renal vein involvement may be visualized with CT, MRI or Doppler ultrasound.<sup>134,135</sup> Nephrectomy and tumour thrombectomy in the absence of metastasis may provide durable disease response with acceptable morbidity.<sup>136</sup> Tumour thrombectomy with cytoreductive nephrectomy in the metastatic setting should be considered for all patients secondary to the poor outcome associated with untreated intravascular disease.

Statistical prediction tools and patient scoring criteria may help better select patients who may derive maximum benefit from these procedures.<sup>137,138</sup> Expertise and advanced surgical planning are necessary, and referral to high volume centres is recommended due to the possibility of requiring vascular reconstruction, or access to cardiothoracic and hepatobiliary surgical support.<sup>139-141</sup>

Appropriately selected cases can be managed via minimally invasive approaches using innovative approaches to manage vascular thrombi.<sup>142-147</sup>

The advent of vascular endothelial growth factor targeted therapies has challenged the role of cytoreductive nephrectomy, but less so in patients with intravascular thrombus.<sup>148-150</sup> The survival benefits of multimodality approaches are in need of prospective evaluation, but current data suggest a primary role for surgical resection of tumour vascular thrombi in patients with metastatic disease.

**Special considerations****Role of adrenalectomy**

- The ipsilateral adrenal gland should be preserved at the time of the nephrectomy provided it appears normal on imaging and there is no sign of direct tumour invasion.

The incidence of ipsilateral adrenal involvement is 1.9% to 7.5%.<sup>151</sup> Current evidence does not support adrenalectomy in all patients with localized RCC. Disease-specific survival (5- and 10-year) and recurrence-free survival are equivalent regardless of whether ipsilateral adrenalectomy is performed in cases in which the gland does not appear to be involved.<sup>152</sup> CT imaging has been shown to have as high as 99.4% specificity and a 99.4% negative predictive value.<sup>153</sup> Metastatic disease to the ipsilateral adrenal gland as the only site of metastatic spread is low at 0.7% to 2%.<sup>154</sup> Ipsilateral adrenalectomy may be performed for patients with abnormal imaging, advanced stage (T3-4), or upper pole tumours greater than 7 cm.

**Role of lymphadenectomy**

- Routine lymphadenectomy at the time of RN or PN is not routinely recommended in patients with clinical N0 disease.
- Lymphadenectomy is recommended in patients with clinical N1M0 disease.
- Lymphadenectomy may be performed for diagnostic purposes in patients with clinical N1M1 disease.

Regional lymph-node dissection combined with RN has a minimal effect in operative time, morbidity or mortality in an EORTC trial of 772 clinically node-negative patients ran-

domized to regional lymphadenectomy or not at the time of nephrectomy.<sup>155</sup>

There is no demonstrated survival benefit to resection of clinically negative regional nodes. In patients with clinically enlarged nodes and no evidence of distant metastatic disease, single-institution, retrospective series indicate that resection of these nodes may result in a survival benefit.<sup>84,156,157</sup>

### Role of neoadjuvant therapy in kidney cancer

- Currently there is no role for neoadjuvant therapy outside of a clinical trial.

Neoadjuvant therapy is defined as pre-surgical medical treatment for patients undergoing definitive surgical resection of their kidney cancer with curative intent (i.e., non-metastatic disease). In theory the goals of neoadjuvant therapy for locally advanced disease are to reduce the risk of recurrence, reduce the size of tumours to make unresectable tumours resectable, reduce the rate of positive surgical margins, make PN more feasible, or to simplify the resection of venous thrombus.

Most of the data on the impact of neoadjuvant therapy on the primary tumour are extrapolated from studies on metastatic RCC.<sup>158</sup> Sorafenib has been evaluated in the neoadjuvant or pre-surgical setting in patients with stage II or higher RCC awaiting nephrectomy. In this non-randomized study of 30 patients, a reduction in size was seen in 77% of patients with a median decrease in size of 9.6%.<sup>159</sup> Other similar studies have shown a small decrease in size with neoadjuvant therapy.<sup>160-162</sup>

A potential benefit of neoadjuvant therapy is to make an unresectable lesion resectable; however, surgical resectability is subjective and poorly defined.<sup>163,164</sup> In the modern era, fewer than 1% of cases are unresectable and, given that striking responses in the primary lesion are rare, this is unlikely to have a significant role.<sup>158</sup>

Silberstein and colleagues examined the use of neoadjuvant sunitinib in 12 patients prior to PN. After tyrosine-kinase inhibitor (TKI) therapy, the average tumour size decreased from 7.1 to 5.6 cm. All attempted PNs were successful with negative margins.<sup>165</sup> Other studies demonstrate that PN is feasible after TKI therapy, but they do not provide efficacy data to support the use of systemic therapy prior to PN.<sup>158</sup>

Neoadjuvant therapy has been studied in patients with IVC thrombus to assess if it can downsize the thrombus and improve surgical resectability. A retrospective study was done with 25 patients with level II or higher thrombus who were treated with targeted molecular therapies. Thrombus height increased in 7 patients, decreased in 11 patients and remained unchanged in 7 patients.<sup>166</sup> At this time the data do not support the use of neoadjuvant therapy for tumour thrombus and further studies are needed.

Most studies have shown that preoperative therapy is safe, although a mild increase in wound complications has been observed. There are potential advantages to neoadjuvant therapy in locally advanced disease, however, currently the data are limited and further investigation is needed.

### Role of pre-surgical therapy in advanced kidney cancer

- Currently there is no role for pre-surgical therapy outside of a clinical trial.

Pre-surgical therapy is defined as preoperative medical therapy in patients with locally advanced or metastatic RCC prior to cytoreductive RN. There are several potential advantages. Pre-surgical therapy may alleviate symptoms related to RCC before surgery and may downsize the primary tumour to facilitate subsequent resection. Pre-surgical therapy will help to identify patients with refractory disease who are unlikely to benefit from cytoreduction and therefore may avoid surgery.

Pre-surgical therapy to downsize primary tumours was assessed in a prospective trial using sunitinib for 12 to 18 weeks prior to nephrectomy. The response rate was 14% and the overall effect on the size of the primary tumour was modest.<sup>167</sup> The pre-surgical therapy currently available does not have a significant role in downsizing the primary tumour.

The utility of pre-surgical therapy to identify patients with refractory disease who may be spared a nephrectomy and the risks associated with surgery remains undemonstrated.<sup>158,168</sup> Evidence to help support the use of pre-surgical therapy was demonstrated in a phase II pre-surgical study that examined the role of bevacizumab. The authors found a median progression-free survival of 11 months and a median overall survival of 25.4 months.<sup>161</sup> The authors noted this was comparable to post-surgical treatment.

Postoperative complication rates tend not to increase after pre-surgical medical therapy. One study compared complications within 12 months in patients who received pre-surgical systemic therapy against those who had a cytoreductive nephrectomy initially. Pre-surgical treatment was not associated with an increase of severe surgical complications (Clavien 3 or more) on multivariate analysis. However, an increase in wound complications was observed.<sup>169</sup> The role of pre-surgical therapy requires further investigation. There are currently a number of phase II trials ongoing. Two phase III trials are assessing the impact of sunitinib prior to cytoreductive nephrectomy, the EORTC (SURTIME) and European CARMINA trial.<sup>170</sup> Results of these trials are expected within the next 3 to 5 years.

## Role of adjuvant therapy in kidney cancer

- Currently there is no role for adjuvant therapy outside of a clinical trial.

Adjuvant therapy is defined as postoperative medical therapy after surgical resection with definitive curative intent. The aim of adjuvant therapy is to decrease the risk of cancer recurrence in patients with features indicative of intermediate- or high-risk for recurrence. In patients with kidney cancer, high-risk features for recurrence include high grade (Fuhrman's Grade 3 or 4), high T-stage (>T2b), unfavourable histology, and nodal involvement.

Currently the standard of care after resection of intermediate or high-risk kidney cancer is watchful waiting. Radiotherapy, cytotoxic chemotherapy, immunotherapy, and antiangiogenic therapies have been studied in the adjuvant setting.<sup>158</sup> Multiple studies have demonstrated no benefit to adjuvant radiation.<sup>171,172</sup>

Immunotherapy has been studied in the adjuvant setting without evidence of benefit.<sup>173-176</sup> A randomized controlled study used interferon as an adjuvant treatment in 247 patients with stage II or III RCC did not demonstrate a significant improvement in overall survival ( $p = 0.86$ ) and event-free survival ( $p = 0.11$ ).<sup>173</sup> Another phase III randomized controlled prospective study used IL-2 in the adjuvant setting and did not show a benefit.<sup>176</sup> The only study to demonstrate an advantage with adjuvant treatment is one that used an autologous RCC vaccine. This study demonstrated an improved progression-free survival of 77.4 versus 67.8% ( $p = 0.039$ ) at 5 years.<sup>177</sup> However, the study had significant methodological flaws and other vaccine studies have not shown a benefit.<sup>158</sup>

We are still awaiting the results from several trials examining adjuvant therapy. The REC.2 ASSURE trial, comparing postoperative sunitinib versus sorafenib versus placebo in patients at high risk for recurrence, completed accrual in 2012 and the results are expected in 2015. The S-TRAC trial is a phase III trial where patients with high-risk RCC are randomized to 1 year of sunitinib or placebo. The results are expected in 2017. The SORCE trial is a phase III randomized double-blind study comparing sorafenib to placebo in patients with resected intermediate- to high-risk RCC. The PROTECT trial is a randomized, double-blind, placebo-controlled phase III trial. The trial evaluates the efficacy and safety of pazopanib versus placebo as adjuvant therapy for patients with localized or locally advanced RCC following nephrectomy. It is currently in progress and the estimated completion date is 2017.

## T4NOMO (Local tumour extension to adjacent organs without metastatic disease)

- RN with resection of adjacent organs if feasible.

The only treatment modality with potential to achieve cure with T4 disease is surgical resection.<sup>178</sup> The goal of surgery is to remove all known disease, with possible concomitant resection of involved organs, such as the adrenal gland, liver, pancreas, diaphragm, and bowel. It is recommended that these cases are performed at high volume centres with a multidisciplinary surgical team. Even with complete resection, 5-year survival is poor and the oncological benefits of surgery should be carefully considered in the context of surgical morbidity.<sup>124,179-181</sup> A significant proportion of these patients will have occult lymph node metastases, and regional lymphadenectomy should therefore be considered for adequate pathologic staging.<sup>178,182,183</sup> Pre-surgical systemic treatments are experimental and phase III trials evaluating adjuvant systemic agents are ongoing.

## TanyN+MO (Radiographic and clinical evidence of lymph node enlargement)

- RN and regional lymphadenectomy

There are no randomized trials assessing the effect of lymphadenectomy for patients with RCC and clinical lymphadenopathy. However, a subset of patients with regional lymph node metastases will be cured, or experience prolonged survival following surgery.<sup>141</sup> Enlargement of regional lymph nodes in RCC is often not due to metastases.<sup>155,184</sup> Therefore, lymphadenectomy provides important prognostic information for these patients.

## T-any N-any M+ (Distant metastases at the time of renal tumour diagnosis)

- Cytoreductive nephrectomy unless contraindicated
- Complete metastatectomy should be considered in select patients with few surgically resectable metastases
- Clinical trial

There are no randomized trials assessing the effect of complete surgical resection versus cytoreductive nephrectomy followed by systemic therapy versus systemic therapy without nephrectomy. Since systemic therapy is not curative, complete surgical resection can be considered in selected patients. In published cohorts, a subset of patients will be cured or experience prolonged survival following complete resection of synchronous metastases.<sup>185-191</sup> This strategy can sometimes spare patients of prolonged periods of time from



the toxicity of systemic therapy. Favourable prognostic factors include a limited number of metastatic sites, a limited number of metastases, and location of metastases (adrenal, pancreas, and lung).<sup>192</sup> The potential benefits of complete resection of synchronous metastases should be balanced with the known surgical risks.<sup>192</sup> Metastatectomy should also be considered for palliation in symptomatic patients.<sup>193</sup>

### Cytoreductive nephrectomy (Role of nephrectomy in patients with metastatic RCC)

- Cytoreductive nephrectomy is recommended in patients presenting with metastatic RCC unless contraindications are present.
- Clinical trial

Meta-analysis of 2 randomized controlled trials reveals that nephrectomy combined with immunotherapy prolongs survival compared to immunotherapy alone for patients who present with metastatic RCC (median survival 13.6 months vs. 7.8 months).<sup>194</sup> The greatest benefit of nephrectomy is experienced in healthy patients (ECOG [Eastern Cooperative Oncology Group] 0 or 1) with a low volume of metastatic disease and absence of critical brain metastases. Nephrectomy may provide palliative benefits in patients with pain and hematuria and a small percentage of patients will experience spontaneous regression of metastases following nephrectomy.<sup>195,196</sup> There are no completed randomized trials on the use of nephrectomy in the targeted therapy era. However, the ongoing use of cytoreductive nephrectomy is supported by the fact that most patients (>90%) enrolled in clinical trials for molecular targeted treatment had a nephrectomy,<sup>197,198</sup> and observational studies of contemporary patients reveal an association between nephrectomy and prolonged survival.<sup>199</sup>

Several studies have helped identify patients least likely to benefit from cytoreductive nephrectomy.<sup>200-202</sup> Cytoreductive nephrectomy exclusion factors can be categorized into patient, metastatic, and histologic factors. Patient factors include poor performance status (ECOG >1) and age greater than 75. Metastatic factors include >25% of total tumour volume in metastatic sites, central nervous system metastases, liver metastases, symptomatic metastases and distant lymph node metastases. Histologic factors include non-clear-cell histology and sarcomatoid features. Recent studies have also suggested laboratory studies, such as serum albumin and lactate dehydrogenase, may help predict prognosis and thus help determine which patients would be most appropriate for cytoreductive nephrectomy.<sup>203,204</sup>

### The role of metastatectomy in patients with distant recurrence

- Resection of metastatic tumours should be considered for well selected patients

There are no randomized trials comparing metastatectomy to systemic treatments. However, among patients who develop metachronous metastases following nephrectomy, about one-third are eligible for metastatectomy<sup>205</sup> and several large cohorts report long-term survival for a subset of patients after complete resection of metastases.<sup>185-192</sup> Isolated metastases to the lung,<sup>206-211</sup> bone,<sup>193,212-215</sup> pancreas,<sup>216</sup> and adrenal glands<sup>217,218</sup> have the most favourable prognosis. Based on available observational data, patients most likely to benefit from metastatectomy are those diagnosed with metastases over 2 years following nephrectomy, those with isolated metastases, and those with favourable metastatic locations.<sup>192</sup> In all scenarios, the potential benefits of surgery must carefully weighed against the inherent operative risks.<sup>192</sup>

### Follow-up of RCC

#### Active surveillance

- Optimal follow-up regimen is unclear.
- Regular surveillance of the primary tumour is recommended, initially at 3 to 6 months then followed yearly (CT, ultrasound, MRI).
- Chest x-ray should be performed yearly to screen for pulmonary metastases.
- Duration of follow-up should be tailored to individual patient risk factors.

Active surveillance in SRMs (<3.0-4.0 cm) is an option for patients with significant comorbidities or reduced life expectancy. In this population, about 20% to 30% of SRMs are benign, while 70% to 80% are low-grade, and renal biopsy may help to identify benign tumours from malignant ones, as well as to differentiate low-grade from high-grade tumours.<sup>34,219,220</sup> These patients should be followed with regular imaging to assess for changes in tumour size. Patients must be warned of a risk of <2% of metastases, as shown in multiple prospective studies.<sup>34,82,220</sup> The optimal follow-up protocol is not known, but regular surveillance is recommended to ascertain growth and metastases.<sup>154</sup> Abdominal imaging (CT, ultrasound, MRI) should be obtained at 3 to 6 months to ascertain a growth rate, followed by yearly imaging.<sup>34,82,220</sup> As well, chest x-rays should be performed yearly to screen for pulmonary metastases.<sup>34,82,220</sup> Duration of follow-up should be tailored to individual patient risk factors and life expectancy.

## Needle ablation treatments

- Optimal follow-up regimen is unclear.
- Regular surveillance of the primary tumour is recommended, initially at 3 to 6 months followed every 6 months to 1 year (CT, ultrasound, MRI).
- Chest x-ray should be performed yearly to screen for pulmonary metastases.
- Duration of follow-up should be tailored to individual patient risk factors.

Ablative therapies to treat SRMs are an option for patients with SRMs that are <3.0 to 4.0 cm or who do not wish to undergo surgery or who have comorbidities that make them unsuitable for surgery.<sup>221-223</sup> Most data for use of ablative therapy in renal cancer are derived from either cryotherapy or RFA. These treatments should be performed in centres where the interventional radiologists have significant experience. As well, discussion between the urologist and radiologist at a multidisciplinary conference is ideal. Biopsy at the time of ablative therapy should be performed to aid in future management and follow-up in these patients. A post-treatment biopsy should be performed upon confirmation of enhancing areas seen in follow-up imaging studies.

Re-treatment may be required in 2% to 10% of patients and progression may occur in up to 13% of patients.<sup>223</sup> Close follow-up is thus required and consideration of surgical intervention should be considered if progression occurs. Abdominal imaging (CT, ultrasound, MRI) at first at 3 to 6 months followed by imaging every 6 to 12 months should be performed to ascertain tumour growth and progression.<sup>221-223</sup> As well, yearly chest X-rays should be performed to screen for pulmonary metastases.<sup>221-223</sup> The duration of follow-up should be tailored to individual patient risk factors and life expectancy.

## Post-surgical resection

A follow-up regimen should be established based on the risk of recurrence. Tumours with higher stage and higher Fuhrman grade have a higher and earlier risk of recurrence. Several follow-up guidelines are available. The recommended Canadian Urological Association guidelines for the follow-up of post-surgical resection have been adopted (Fig. 1).<sup>224</sup>

	Months Post-op									
	3	6	12	18	24	30	36	48	60	72
<b>pT1</b>										
Hx & PE			x		x		x	x	x	x
Blood test			x		x		x	x	x	x
CXR			x		x		x	x	x	x
CT or U/S abd					x				x	
<b>pT2</b>										
Hx & PE		x	x	x	x	x	x	x	x	x
Blood test		x	x	x	x	x	x	x	x	x
CXR		x	x	x	x	x	x	x	x	x
CT or U/S abd			x				x		x	
<b>pT3</b>										
Hx & PE		x	x	x	x	x	x	x	x	x
Blood test		x	x	x	x	x	x	x	x	x
CXR		x	x	x	x	x	x	x	x	x
CT abd		x	x	x	x		x		x	
<b>pTxN+</b>										
Hx & PE	x	x	x	x	x	x	x	x	x	x
Blood test	x	x	x	x	x	x	x	x	x	x
CXR	x	x	x	x	x	x	x	x	x	x
CT abd	x	x	x	x	x	x	x	x	x	x

Hx & PE: history and physical examination  
 Blood test: include complete blood count, serum chemistries, and liver function tests  
 CXR: can be alternated with chest CT  
 CT abd: can be alternated with abdominal ultrasound in pT1-2N0 patients  
 \* -if patient is symptomatic or abnormal blood test, earlier radiologic investigations may be indicated  
 -follow-up beyond 72 months, refer to text for more details

**Fig. 1.** Canadian Urological Association (CUA) recommendations for the follow up of patients after radical or partial nephrectomy. Reprinted from reference 15 with permission of the CUA.

## Low risk patients (pT1, N0, Nx)

Post-surgical follow-up of patients should be tailored to individual patient risk factors. In low-risk patients, a baseline postoperative abdominal scan (CT, MRI or ultrasound) should be performed within 24 months following surgery. In patients undergoing PN, a CT or MRI may provide better imaging to rule out recurrence in the surgical field. Optimal frequency of repeat imaging in low-risk patients is uncertain, but may be discontinued after 3 to 5 years of normal imaging since most recurrences occur in this time period.<sup>205</sup> All patients with low-risk disease should receive a yearly chest x-ray to screen for pulmonary metastases for the first 3 to 6 years.

## Moderate to high-risk patients (pT2-4N0 Nx or any stage N+)

In moderate- to high-risk patients, the frequency of abdominal imaging is increased. Patients should undergo a baseline postoperative abdominal scan (CT or MRI) within 6 months following surgery with frequency of repeat imaging based on individual risk factors. Follow-up should occur for at least 5 years.<sup>205</sup> Moreover, patients should have a chest CT or chest x-ray yearly for 5 years.

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**Correspondence:** Dr. Ricardo A. Rendon, Queen Elizabeth II Health Sciences Centre, Room 210, 5-South, Victoria Building, 1276 South Park St., Halifax, NS B3H 2Y9; fax: 902 492-2437; [rendon@dal.ca](mailto:rendon@dal.ca)