Introduction and objectives

Renal cell carcinoma (RCC) accounts for approximately 3% of all malignancies. RCC is about twice as common in males. It is the seventh most common cancer and 11th most common cause of cancer-related deaths among men.1,2 Cigarette smoking, obesity, and hypertension are the most well-established risk factors for sporadic RCC.3-6 Acquired cystic kidney disease (ACKD) is also a significant risk factor.7 Other studies have linked occupational exposure to RCC.8-9 As many as 5% of patients with RCCs are associated with germline mutations. There are a number of different hereditary diseases that are associated with RCC, including von Hippel-Lindau (VHL), hereditary papillary renal carcinoma (HPRC), Birt-Hogg-Dubé (BHD), hereditary leiomyomatosis renal cell carcinoma (HLRCC), succinate dehydrogenase kidney cancer (SDH-RCC), tuberous sclerosis complex (TSC), and Cowden’s disease.10-14 There are different options for management of patients with clinically localized renal masses suspicious for RCC, including active surveillance, ablation, and surgery. Comparing the non-surgical with the surgical approach (partial [PN] or radical nephrectomy [RN]) for small renal masses, the surgical approach may be associated with better oncological outcomes based on large observational studies;15-18 however, no prospective randomized studies have been completed.

Patients with newly diagnosed RCC are living longer after diagnosis, largely due to incidental diagnoses and subsequent migration to earlier stages of disease.4 Surveillance after treatment is important since some patients are at high risk of asymptomatic cancer recurrence and these recurrences may respond better to treatment if detected early.

Observation remains the standard of care after nephrectomy. Surveillance protocols after treatment of the primary RCC tumour focus on oncological control, functional preservation, and survivorship. Publications that address surveillance after surgical extirpation are based on retrospective analysis, including some larger multicentre studies and well-designed controlled studies.19 There are no randomized trials of surveillance strategies, but an evidence-based approach to followup can be achieved by assessing the timing and location of RCC recurrence in a risk-stratified manner. This updated guideline attempts to provide some clarity and guidance for the practicing urologist based on the current literature.

Methods

A systematic search of the PubMed and MEDLINE databases was conducted. The searches were limited to English-language publication. The main search terms used to identify eligible studies from the databases combined patient terms (renal or kidney carcinoma/tumour/neoplasm/cancer), intervention terms (RN, PN, nephron-sparing surgery, ablation), and followup. Where possible, levels of evidence (LE) and grades of recommendations (GR) are provided employing the International Consultation on Urologic Disease (ICUD)/World Health Organization (WHO) modified Oxford Centre for Evidence-based Medicine grading system.20 The level of evidence was summarized according to the following: Level 1: systematic review of randomized controlled trials (RCT); Level 2: individual RCT, including low-quality RCT; Level 3: controlled cohort; Level 4: case-control studies or case series; Level 5: expert opinion, mechanism-based reasoning. Based on these levels of evidence, we have graded recom-
mendations as follows: Grade A: usually consistent with Level 1 studies; Grade B: consistent with Level 2 or 3 studies or extrapolations from Level 1 studies; Grade C: Level 4 studies or extrapolations from Level 2 or 3 studies; Grade D: Level 5 evidence or inconsistent/inconclusive studies of any level.

The present guideline was organized into three major topics:

1. Rationale for surveillance
2. Prognostic variables
3. Stage-stratified surveillance recommendations

The main objective is to present the rationale and guide the post-treatment followup in patients with localized and locally advanced RCC.

1. Rationale for surveillance

Surveillance after treatment allows the urologist to monitor for postoperative complications, renal function, local recurrence, recurrence in the contralateral kidney, and development of metastases. Surveillance is usually accomplished with physical examination, radiological imaging, and serum biochemistry testing.

Chronic kidney disease (CKD) is recognized as a public health problem worldwide, with prevalence from 8–16%, and potentially associated with progression to end-stage renal disease (ESRD), cardiovascular disease, and increased mortality rates. Decreased kidney function refers to a decreased glomerular filtration rate (GFR <60 ml/min/1.73 m²), which is usually estimated using serum creatinine and one of several available equations. Huang et al showed, in a retrospective study, that 26% of patients with solitary small renal mass (≤4 cm) surgically managed had CKD on the basis of Modification of Diet in Renal Disease equation. Several retrospective studies have demonstrated impairment of renal function after treatment for RCC; RN is a significant risk factor for the development of CKD. Renal function decreases postoperatively and usually improves over time until a new baseline is achieved in approximately 3–6 months. The aim of renal function surveillance is to prevent or delay CKD and avoid dialysis. Renal function and postoperative complications are commonly assessed by history, physical examination, and measurement of serum creatinine and hemoglobin at 4–6 weeks post-surgery. Long-term monitoring of serum creatinine, eGFR, and proteinuria is recommended, particularly in patients with compromised renal function prior to surgery or significant decrease in eGFR after surgery.

Consideration for referral to a nephrologist if eGFR <45 ml/min/1.73 m² or progressive CKD develops after surgery, especially if associated with proteinuria (Level 2 evidence, Grade B recommendation).

Radiological imaging plays an important role at diagnosis for renal mass, as well as followup after treatment for RCC. Surveillance in patients after treatment of RCC should be adapted and based on known independent predictors of postoperative recurrence to optimize the use of radiological imaging. This understanding would avoid over-surveillance of patients at low risk for relapse and under-surveillance for those at high risk. It would also avoid unnecessary radiation exposure from radiological imaging, such as computed tomography (CT), since theoretically it can be associated with an increased risk of secondary malignancies. Furthermore, a risk-adapted approach may also decrease the cost of surveillance on the healthcare system. Early diagnosis of local and contralateral kidney recurrence (incidence <2%) is useful, since the majority of these patients can be cured with treatment (Level 4 evidence, Grade C recommendation). Risk factors for ipsilateral renal recurrence are positive surgical margins, tumour multifocality, higher tumour stage, and higher tumour grade. Tumours that develop in the contralateral kidney are more likely amendable to nephron-sparing treatments when detected earlier. Patients undergoing surgery for symptomatic recurrences have a higher rate of incomplete resection of recurrence, positive surgical margins, and worse survival compared to surgery without symptoms. Extensive tumour recurrence reduces the possibility of complete surgical resection, which is standard therapy for patients with local recurrence or resectable solitary metastasis. Furthermore, an early diagnosis of metastatic disease relapse may enhance efficacy of systemic therapy or allow for metastasectomy if the tumour burden is low. Therefore, this supports the rationale for surveillance of patients to detect recurrences and metastases early when they are more likely to be successfully treated (Level 4 evidence, Grade C recommendation).

2. Prognostic variables

Predictors of disease relapse after surgical extirpation can be classified into anatomical (TNM classification system), histological, clinical, and molecular. Tumour grade, local extent of the primary tumour, presence of nodal metastasis, and histological subtype are predictors of the disease relapse (Level 3 evidence). As such, these variables should be noted because they contribute to important prognostic information.

Histological subtype is a significant predictor of survival and recurrence, regardless of type of surgical resection or tumour stage. RCC with collecting duct carcinoma, medullary carcinoma, and tumour with elements of sarcomatoid and rhabdoid dedifferentiation exhibit higher metastatic potential. Localized chromophobe and papillary RCC type 1 portend a better prognosis. Fuhrman nuclear grade is another important histological prognostic value, where higher grade is associated with worse prognosis in clear-cell RCC (Level 4 evidence).

Clinical factors associated with prognosis include performance status (Eastern Cooperative Oncology Group...
[ECOG]), the presence of symptoms (localized or systemic), cachexia, anemia, platelet count, elevated erythrocyte sedimentation rate, and primary tumour characteristics (tumour size, histological coagulative necrosis, DNA ploidy) have also been shown to be associated with outcome (Level 4 evidence).\(^{31, 54-57}\)

Molecular markers, including carbonic anhydrase IX, hypoxia-inducible factor, Ki67, p53, phosphatase, and tensin homolog (PTEN), regulator of apoptosis Bcl-2, E-cadherins, C-reactive protein (CRP), microRNAs (miR-21 and miR-126), and others, have demonstrated potential utility as prognostic markers, and vascular endothelial growth factor (VEGF) as predictive biomarker.\(^{58}\) Higher level of PD-L1 expression has been linked with a negative prognostic factor in RCC. The role of molecular markers in RCC is expansive and can range from aiding pathological diagnosis, understanding the histogenesis of renal tumour, classifying new entities, and choosing appropriate therapy in patients who present with advanced disease, to the more investigative arena of elucidating predictive and prognostic behaviour of renal neoplasm. **However, use of molecular markers is not recommended in the routine clinical setting (Grade C recommendation).**\(^{59-65}\)

### 3. Surveillance

Intensity and type of surveillance should vary depending on the risk of developing recurrence or metastases. The Canadian guidelines for surveillance after nephrectomy for non-metastatic RCC is risk-stratified based on pathological stage, but some patients may benefit from more or less intensive surveillance based on other risk factors presented above. There are several nomograms and scoring systems that combine different prognostic factors.\(^{66-69}\) They classify patients into risk of relapse, progression, and survival. Although some of these nomograms have already been validated, they have not been widely used in routine clinical practice. Most of them are used to enrol patients in clinical trials. In the absence of randomized studies, surveillance recommendations are based on large, non-randomized cohorts with long-term followup. **To evaluate recurrence in the lung, routine chest x-ray (CXR) is recommended. In higher-risk patients, CT of the chest may be performed due to the higher sensitivity of this test compared to CXR (Level 5 evidence, Grade D recommendation).** To evaluate abdominal recurrences, CT of the abdomen and pelvis is recommended, particularly in cases of tumour-associated symptoms; an abdominal ultrasound may be performed for lower-risk patients (pT1 and pT2) (Level 4 evidence, Grade C recommendation). CT head or bone scan is not routinely recommended unless clinically indicated (Level 4 evidence, Grade C recommendation). Magnetic resonance imaging (MRI) has presented acceptable accuracy to detect musculoskeletal and lymph node metastases, but lower sensitivity to detect pulmonary metastases when compared to CT.\(^{60}\) MRI can be used to reduce radiation exposure from x-ray and CT during followup after treatment for renal cancer, since MRI does not involve the use of ionizing radiation. The use of gadolinium-based contrast agent in the MRI should be handled with caution because there is a slight chance of developing nephrogenic systemic fibrosis, mainly in patients with severe renal failure. Positron emission tomography (PET)-CT is a nuclear imaging modality with the ability to characterize molecular processes non-invasively during a fast whole-body scan. \(^{18}\)F-fluorodeoxyglucose (FDG) is the most common PET-CT radiotracer used in the urology field. FDG PET-CT has a lower sensitivity compared to enhanced CT for primary diagnosis of renal masses. However, \(^{18}\)F-Sodium fluoride PET-CT may have an advantage over conventional modalities in bone and musculoskeletal metastases. It is more sensitive at detecting RCC skeletal metastases than bone scintigraphy or CT.\(^{71, 72}\) **Currently, PET-CT is not a standard exam for diagnosis, staging, or surveillance in RCC.**

**Recurrence patterns for pT1 tumours (low-risk)**

Cohort studies have shown less than 7% of patients develop recurrences. The mean time to recurrence is 56 months and almost half of all recurrences are detected beyond five years following RN.\(^{71, 74}\) Among several series, the local recurrence for T1 lesions is approximately 2%. Local recurrence is more common for larger tumours following PN or tumour ablation compared to RN.

A population-based study showed occurrence of metastases or local recurrence in 5% of patients with T1a and 15% for T1b during five years of followup after RN or PN. The incidence of distant metastases was higher than local recurrence, regardless of surgical approach. Concerning all stages of RCC, the most common locations of the first recurrence were lung (54%), lymph nodes (22%), bone (20%), and liver (15%).\(^{75}\) Other population-based studies have found similar results.\(^{76}\) Chin et al\(^{77}\) reported that tumour stage plays an important role in timing of recurrence, with T1 tumours generally recurring between three and four years following resection.

Similarly, a Canadian group has shown that median time to recurrence was 35 months (range 2–93) and only 0.9% had asymptomatic, isolated abdominal relapse at 13, 66, and 93 months postoperatively.\(^{78}\) Lam et al reported that following nephrectomy, median time to recurrence was 28.9 months (mean ± standard deviation [SD] 26.5±17.1); the median time for chest and abdominal recurrence was 23.6 and 32 months, respectively.\(^{79}\) Among several studies regarding RCC surveillance, the latest post-nephrectomy recurrence in the lungs, abdomen, and bone was approximately six, eight, and 12 years, respectively.\(^{75-78}\) In a cohort from a single centre, most kidney cancer patients treated for lung metastasis were diagnosed with metachronous lesions with the following fea-
tures: solitary mass, one affected lung, and measured more than 2 cm. Multivariate analysis confirmed a significant effect of radical surgery on the survival in these patients.80 Unlike metastases to the abdomen and thorax, metastases to brain and bone were symptomatic in 98.2% and 90.5%, respectively. These lesions become symptomatic quickly.81

In general, late recurrence beyond five years after nephrectomy for localized RCC can occur in 2–10% of patients, and in some cases after nine years from the initial treatment. Most recurrences are distant rather than local.82-84 The largest study evaluating relapse after five years following nephrectomy demonstrated lymphovascular invasion, Fuhrman grade 3 or 4, and pathological tumour stage >pT1 as independent predictors of late recurrence. In addition, late recurrence was approximately 2.6%, 5%, 9%, 10%, 11%, and 22% for T1a, T1b, T2a, T2b, T3a, and T3b, respectively.82

Regarding nephron-sparing surgery for RCC, a retrospective study showed 5.1% recurrence rate (2.7% pT1a and 12.7% pT1b); 61% of relapses were diagnosed within the first 24 months following surgery (median time to relapse was 14.3 months). Multifocal or bilateral lesions and pathological stage higher than T1a were independent predictors of relapse on multivariate competing risk regression analysis.16

Recommended surveillance (Table 1) will include blood biochemistry and CXR annually following surgery. Abdominal CT, MRI, or ultrasound (US) is recommended at 24 and 60 months (Level 4 evidence, Grade C recommendation). US is less sensitive than CT, however, its use is justifiable and cost-effective in patients with a minimal risk of abdominal recurrence and lower body mass index (BMI). Followup is the same for PN for lesions <4 cm, since the local recurrence rates in this population are similar to RN (Level 2 evidence, Grade B recommendation). CT abdomen at 3–12 months postoperative for patients treated with PN to evaluate the residual baseline renal appearance is optional (Level 4 evidence, Grade B recommendation). Radiographical screening for brain and bone metastases is not recommended in asymptomatic patients (Level 4 evidence; Grade C recommendation). Routine imaging beyond five years is optional and can be risk-adapted (Grade D recommendation).

Recurrence patterns for pT2 tumours (intermediate-risk)

Several series have reported recurrences after a mean time of 24–35 months (range 1–82).73-75 Dabestani et al75 reported 35% recurrence rate after mean followup duration of five years in a population-based study of patients with T2 disease who underwent RN or PN. Retrospective analysis of single institution with similar followup showed 16% of recurrence, diagnosed between 24 and 57 months after RN, and the lung was the main site of recurrence.85 The Canadian group reported a median time to recurrence of 25 months (range 3–95) and 50% were asymptomatic.78 Lam et al showed that median time to recurrence was 17.8 months (mean ± SD

Table 1. Followup post-surgical resection

<table>
<thead>
<tr>
<th>Months postop</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk (pT1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hx &amp; PE</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Blood test</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>CXR</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Abdominal CT/MRI/US</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Intermediate-risk (pT2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hx &amp; PE</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Blood test</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>CXR or Chest CT</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Abdominal CT/MRI/US</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>High-risk (pT3-4)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hx &amp; PE</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Blood test</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>CXR or Chest CT</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Abdominal CT/MRI</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Very high-risk* (pTxN+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hx &amp; PE</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Blood test</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>CXR or Chest CT</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Abdominal CT/MRI</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

*For high- and very high-risk patients, consider an extended individualized followup beyond 60 months (refer to text for more details). Blood tests: include blood count, serum chemistries, and liver function test. CXR: can be alternated with chest CT. Low-risk baseline CT at 3–12 months post-partial nephrectomy is optional. For ablation in cT1a tumours, surveillance is similar to low-risk disease except for abdominal CT/MRI at 3, 6, 12 months, then annually for up to 5 years. If patient is symptomatic or abnormal blood test, earlier radiological investigations may be indicated. CT: computed tomography; CXR: chest x-ray; HX & PE: history and physical examination; MRI: magnetic resonance imaging.
25.5±23.9). Among several studies regarding RCC surveillance, the latest post-nephrectomy recurrence in the lungs, abdomen, and bone was approximately eight years, eight years, and twelve years, respectively.75-78 Recommanded surveil-

Recurrence patterns for pT3/pT4 tumours and N+ (high-risk)

The median time to recurrence in this cohort is approximately 21 months (range 2–101).73 Dabestani et al reported recurrence rates of 42% and 47% for patients with T3 and T4 disease, respectively.75 Tumours classified as T3 generally recurred between 17 and 28 months.77 Lam et al presented in this group that median time to recurrence was 9.5 months (mean ± SD 21.9±26.2).79 Stewart et al reported among several studies regarding RCC surveillance, the latest post-nephrectomy recurrence in the lungs, abdomen, and bone was approximately twelve, six, and five years, respectively.75-78 The presence of lymph node metastases is associated with dismal prognosis,99 with a median survival of only 20.4 months.90 Recommended surveillance (Table 1) will include clinical assessment, blood biochemistry, and CXR (or chest CT) every six months for three years, then yearly. Abdominal CT, MRI, or US recommended at 12, 24, 36, and 60 months (Level 4 evidence, Grade C recommendation). Routine imaging beyond five years is at the discretion of the treating physician.

Followup after ablation

Ablation is an option to treat selected patients with small renal mass, usually patients with clinical T1a RCC. There are several settings where ablation can be an option or recommended, such as patients with high surgical risk, complex mass in a solitary kidney, prior PN, and multifo-

Guideline: Non-metastatic RCC followup
Competing interests: Dr. Kassouf has received grants/honoraria from Astellas, AstraZeneca, Janssen, Merck, and Roche. Dr. Fairey has been a speaker for J&J and Roche. Dr. Finelli has attended an advisory board with Merck. Dr. Leveridge has attended an advisory board for Amgen. Dr. Fairey has been a speaker for J&J and Roche. Dr. Finelli has attended an advisory board for Amgen. The remaining authors report no competing personal or financial interests.

This paper has been peer-reviewed.

References


17. Kassouf et al. Dr. Tanguay has attended advisory boards for Pfizer; and has received travel grants from Sanofi, Zeneca, Janssen, Pfizer, and Sanofi. Dr. So has been a speaker for Amgen, Astellas, and Pfizer; has received payment/grants/honoraria from Amgen, Astellas, AstraZeneca, Janssen, Pfizer, and Sanofi. Dr. So has been a speaker for Amgen, Astellas, and Janssen. Dr. Tanguay has attended advisory boards for Pfizer; and has received travel grants from Sanofi. The remaining authors report no competing personal or financial interests.
Kassouf et al


Correspondence: Dr. Wassim Kassouf, Division of Urology, McGill University Health Centre, Montreal, QC, Canada; wassim.kassouf@muhc.mcgill.ca