Canadian Urological Association guidelines for followup of patients after treatment of non-metastatic renal cell carcinoma

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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 eleventh 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 (SHD-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 or radical nephrectomy) 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 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 multicenter studies and well-designed controlled studies.[19] There are no randomized trials of surveillance strategies, but an evidence based approach to follow up 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 database was conducted. The searches were limited to English language publication. The main search terms used to identify eligible studies from database combined patient terms (renal or kidney carcinoma/tumour/neoplasm/cancer), intervention terms (radical nephrectomy, partial nephrectomy, 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 recommendations 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 3 major topics: rationale for surveillance, prognostic variables, and 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 renal cell carcinoma.

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, radiologic imaging, and serum biochemistry testing.

Chronic kidney disease (CKD) is recognized as a public health problem worldwide with prevalence between 8 and 16%, and potentially associated with progression to end-stage renal disease (ESRD), cardiovascular disease and increased mortality rates.[21,22] Decreased kidney function refers to a decreased glomerular filtration rate (eGFR less than 60ml/min/1.73m^2), which is usually estimated (eGFR) using serum creatinine and one of several available equations.[23] Huang et al, showed in a retrospective study that 26% of patients with solitary small renal mass (≤ 4cm) surgically managed had CKD on the basis of Modification of Diet in Renal Disease equation.[24] Several retrospective studies have demonstrated impairment of renal function after treatment for RCC; radical nephrectomy (RN) is a significant risk factor for the development of CKD.[25-27] Renal function decreases post-operatively and usually improves over time until a new baseline is achieved in approximately 3 to 6 months.[28] 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/1.73m^2 or progressive CKD develops after surgery, especially if associated with proteinuria (Level of evidence: 2; Grade B).**[29-31]

Radiologic 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 radiologic 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 radiologic imaging such as CT since theoretically it can be associated with an increased risk of secondary malignancies.[32,33] Furthermore, a risk-adapted approach may also decrease the cost of surveillance on the health care system.[34-36] Early diagnosis of local and contralateral kidney recurrence (incidence < 2%) is useful since the majority of these patients can be cured with treatment **(Level of evidence 4; Grade C).**[37-39] Risk factors for ipsilateral renal recurrence are positive surgical margins, tumour multifocality, higher tumour stage, and higher tumour grade.[40] 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.[41-43] 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 of evidence 4; Grade C).**

Prognostic variables

Predictors of disease relapse after surgical extirpation can be classified into anatomical (TNM classification system), histological, clinical, and molecular.[44,45] Tumour grade, local extent of the primary tumour, presence of nodal metastasis, and histological subtype are predictors of the disease relapse **(Level of Evidence 3)**.[41,46-48] 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, tumour with elements of sarcomatoid and rhabdoid dedifferentiation exhibit higher metastatic potential. Localized chromophobe and papillary RCC type 1 portend a better prognosis.[49,50] Fuhrman nuclear grade is another important histological prognostic where higher grade is associated with worse prognosis in clear cell RCC **(Level of Evidence 4)**.[51-53]

Clinical factors associated with prognosis include performance status (ECOG), the presence of symptoms (localized or systemic), cachexia, anemia, platelet count, elevated erythrocyte sedimentation rate, and primary tumour characteristics (tumour size, histologic coagulative necrosis, DNA ploidy) have also been shown to be associated with outcome **(Level of Evidence 4)**.[41, 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 pathologic 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).**[59-65]

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 nonmetastatic renal cell carcinoma is risk stratified based on pathologic 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 being 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 nonrandomized cohorts with long-term followup. **To evaluate recurrence in the lung, routine chest x-ray is recommended. In higher risk patients, CT of the chest may be performed due to the higher sensitivity of this test compared to chest x-ray (Level of evidence 5; Grade D). 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 of evidence 4; Grade C). CT head or bone scan is not routinely recommended unless clinically indicated (Level of evidence 4; Grade C).** Magnetic resonance imaging (MRI) has presented acceptable accuracy to detect musculoskeletal and lymph node metastases, however, lower sensitivity to detect pulmonary metastases when compared to CT.[70] 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-computerized tomography (PET-CT) is a nuclear imaging modality with the ability to characterize molecular processes noninvasively during a fast whole-body scan. ^{18}F-fluorodeoxyglucose (FDG) is the most common PET-CT radiotracer used in 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 5 years following RN.[73,74] Among several series, the local recurrence for T1 lesions is approximately 2%. Local recurrence is more common for larger tumours following partial nephrectomy or tumour ablation compared to radical nephrectomy.

A population-based study showed occurrence of metastases or local recurrence in 5% of patients with T1a and 15% for T1b during 5 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 3 and 4 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 ± 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 postnephrectomy recurrence in the lungs, abdomen, and bone was approximately 6 years, 8 years, and 12 years, respectively.[75-78] In a cohort from a single center, most kidney cancer patients treated for lung metastasis were diagnosed with metachronous lesions with the following features: 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 pateints.[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 5 years after nephrectomy for localized RCC can occur in 2% to 10% of patients, and some cases after 9 years from the initial treatment. Most recurrences are distant rather than local.[82-84] The largest study evaluating relapse after 5 years following nephrectomy demonstrated lymphovascular invasion, Furhman grade 3 or 4, and pathologic 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% 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.[36]
Recommended surveillance (Table 1) will include blood biochemistry and chest x-ray (CXR) annually following surgery. Abdominal CT, MRI or US is recommended at 24 and 60 months (Level of evidence 4; Grade C). Ultrasound is less sensitive than CT, however its use justifiable and cost effective in patients with a minimal risk of abdominal recurrence and lower body mass index (BMI). **Followup is the same for partial nephrectomy for < 4 cm lesions since the local recurrence rates in this population are similar to radical nephrectomy (Level of evidence 2; Grade B).** CT abdomen at 3-12 months postoperative for patients treated with partial nephrectomy to evaluate the residual baseline renal appearance is optional **(Level of evidence 4; Grade C).** Radiographic screening for brain and bone metastases is not recommended in asymptomatic patients **(Level of evidence 4; Grade C). Routine imaging beyond 5 years is optional and can be risk-adapted (Grade D).**

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 al[75] reported 35% recurrence rate after mean followup duration of 5 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 25.5 ± 23.9).[79] Among several studies regarding RCC surveillance, the latest post-nephrectomy recurrence in the lungs, abdomen, and bones was approximately 8 years, 8 years, and 12 years, respectively.[75-78] **Recommended surveillance (Table 1) will include clinical assessment, blood biochemistry, and CXR (or chest CT) every 6 months for 3 years then yearly. Abdominal CT, MRI or US recommended at 12, 24, 36, 60 months (Level of evidence: 4; Grade C).** Routine imaging beyond 5 years is at the discretion of the treating physician.

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 28% of patients developed recurrence after a median of 13.9 months (range 10-68.3).[86] In a multi-institutional cohort of 176 patients with pathological T3 disease (pT3), 26% of patients developed recurrence (24% of patients developed metastatic disease and 2% of patients developed an isolated local recurrence) after median followup 22.6 months (range 0.2 - 75). Lung (70%), bone (39%), and lymph nodes (30%) were the most common sites of metastases.[87] The recurrence rate for these group of patients was 15%, 30%, and 53% within 1, 3, and 5 years.[88] Among several studies regarding RCC surveillance, the latest postnephrectomy recurrence in the lungs, abdomen, and bone was approximately 12 years, 6 years, and 5 years, respectively.[75-78] The presence of lymph node metastases is associated with dismal prognosis[89] 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) within 3 months after surgery and every 6 months for 3 years then yearly. Abdominal CT or MRI recommended at 6, 12, 18, 24, 36, 60 months then every 2 years (Level of evidence: 4; Grade C). In cases of lymph node positive disease, abdominal CT or MRI is recommended at 3 and 6 months, then every 6 months for 3 years then yearly (Level of evidence 4; Grade C).**

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 partial nephrectomy, and multifocal, bilateral RCC or patient preference.[91,92] Patients who have undergone ablation therapy due to RCC should be followed with contrast-enhanced radiologic imaging (MRI or CT) to assess for residual enhancing disease and post procedure complication. The success of this procedure is

defined by two types of imaging findings which are related to the zones of decreased perfusion, and the signal intensity (at MRI imaging), or attenuation (at CT).[93] Ablated tumour may be larger than the pre-treatment size in the imaging promptly performed after the procedure due to extension of treatment beyond of its margin. After thermal ablation, the zone of ablation is usually seen as an area of hypoattenuation on computed tomography and is generally hypointense at T2-weighted magnetic resonance imaging and iso - to hyperintense at T1-weighted imaging relative to renal parenchyma. The ablation zone frequently involutes over time. Residual tumour after thermal ablation is most common at the margin of the ablation zone and often seen as nodular or crescent-shaped areas of contrast enhancement.[94] Renal tumours successfully treated with RFA demonstrate no contrast enhancement. However, they do not regress significantly in size.[95] Meanwhile, renal tumours successfully treated with cryoablation may demonstrate reduction in size or complete resolution, or scar formation.[93] Definition of successful after RFA for small renal masses based only in radiographic imaging has provoked some debate. Nevertheless, radiologic imaging has remained the main tool to follow patients after ablation therapy. Meta-analysis evaluating cryoablation and RFA showed local tumour recurrence in 13% of patients and 2% of patients developed metastasis.[96] A cohort of cT1a patients treated with RFA demonstrated good response in 74% of patients whereas 8% had partial response and 18% failure response within mean 30.6 months of followup (range 4 - 60).[97] Large single center series have shown failure rate of approximately 10% to cryoablation and radiofrequency.[98,99] Several series has shown postoperative complications after ablation to treat RCC, ranges from 11% to 23% **(Level of evidence 3).**[100-102] Matin et al. reviewed treatment and followup information of 616 patients from 7 institutions who underwent RFA or cryoablation for renal masses, and reported that most incomplete treatments (70%) were detected within the first 3 months following treatment.[103] **Recommended surveillance for ablated cT1a lesions (Table 1) will include clinical assessment, blood biochemistry, abdominal imaging (CT or MRI) at 3, 6, and 12 months then annually thereafter for up to 5 years. Chest x-ray recommended annually during followup (Level of evidence 4; Grade C). If pretreatment biopsy demonstrated oncocytoma and imaging post ablation shows treatment success, routine imaging beyond one year is not recommended (Level of evidence 5; Grade D).**

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Figures and Tables

Table 1. Followup post-surgical resection

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

Followup beyond 60 months, refer to text for more details. *For high- and very high-risk patients, consider an extended individualized followup. HX & PE: history and physical examination. Blood test: 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.