

Follow-up guidelines after radical or partial nephrectomy for localized and locally advanced renal cell carcinoma

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Introduction and objectives

Renal cell carcinoma (RCC) comprises approximately 2% of all malignancies. It is the seventh most common cancer and tenth most common cause of cancer-related deaths among men.¹ Risk factors for RCC include smoking, obesity, and hereditary conditions associated with a mutation in the von-Hippel-Lindau gene (level 2).^{2,3} Surgical resection (radical or partial nephrectomy) remains the only effective therapy for clinically localized RCC. Publications that address surveillance after surgical extirpation are based on retrospective analysis, including some larger multicentre studies and well-designed controlled studies.⁴ Randomized prospective studies are sparse, rendering it difficult to obtain qualified evidence-based data. Although there is no clear consensus on surveillance after surgical extirpation for patients with RCC, this document attempts to provide some clarity and guidance for the practicing urologist based on the current literature. Where possible, levels of evidence and grades of recommendations are provided employing the modified Oxford Centre for Evidence-based Medicine scheme.

Rationale for surveillance

Surveillance after surgery allows the urologist to monitor for post-operative complications, renal function, local recurrence, recurrence in the contralateral kidney and development of metastasis. Renal function and post-operative 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 is recommended particularly in patients with compromised renal function prior to surgery or significant increase

in creatinine after surgery (Grade B).⁵ Early diagnosis of local and contralateral kidney recurrence (incidence < 2%) is useful since the most effective treatment is surgical resection (level 3).^{6–8} Recurrence in the kidney is associated with positive surgical margins, multifocality and grade. Tumors that develop in the contralateral kidney can be treated with nephron-sparing surgery when detected at a small size. Patients who underwent surgery when local recurrences became symptomatic have a higher rate of incomplete resection of recurrence, positive surgical margins and poorer survival.⁹ Extensive tumor recurrence reduces the possibility of complete surgical resection, which is standard therapy for patients with local recurrence or resectable solitary metastasis (level 2). Furthermore, an early diagnosis of disease relapse may enhance efficacy of systemic therapy if the tumor burden is low. Hence, this supports the rationale for surveillance of patients to detect recurrences and metastases early (Grade B).

Prognostic variables

Predictors of disease relapse after surgical extirpation include RCC subtypes, tumor grade, local extent of the primary tumor, and presence of nodal metastasis (level 2).¹⁰ As such, these variables should be noted because they contribute important prognostic information. RCC with collecting duct carcinoma, medullary carcinoma and tumor with elements of sarcomatoid dedifferentiation exhibit higher metastatic potential.^{11,12} Localized chromophobe and papillary RCC portend a better prognosis. Other potential risk factors include performance status (ECOG), the presence of symptoms (localized or systemic), cachexia, anemia, platelet count, and primary tumor characteristics (tumor size, histologic coagulative necrosis, DNA ploidy) (level 3).^{13–16}

Molecular markers including carbonic anhydrase IX, vascular endothelial growth factor, hypoxia inducible factor, Ki67, p53, PTEN, E-cadherins and others have demonstrated potential utility as prognostic markers (level 3). No molecular marker is currently recommended for utilization in the routine clinical setting. Several prognostic models have been published and externally validated.^{13,15,17} However, more extensive analysis in prospective randomized controlled studies are needed to prove superiority over the stage-specific strategy. The use of integrated prognostic system or nomograms is not routinely recommended although these tools may be useful for enrolling patients in clinical trials.

Surveillance

The intensity of radiological surveillance for patients will vary depending on the risk of developing recurrence or metastases. Intensity and type of surveillance will be tailored according to a risk-adapted approach. Most contemporary surveillance protocols have been formed on stage-based

stratifications (Fig. 1). The Canadian guidelines for surveillance after nephrectomy for nonmetastatic renal cell carcinoma will be based on pathologic stage. Since the other previously-mentioned factors have been shown to be prognostic mostly in single center institutions, the incorporation of such factors to help tailor patients to more or less stringent follow-up protocols will be at the discretion of the treating physician (Grade C).

In the absence of randomized studies, conclusions will be based on large nonrandomized cohorts with long-term follow-up (level 3). To evaluate recurrence in the lung, routine chest x-ray is recommended. CT of the chest may be performed instead; however there is insufficient evidence to suggest a benefit in this setting (Grade C). To evaluate abdominal recurrences, CT of the abdomen is recommended, particularly in cases of tumor-associated symptoms; an abdominal ultrasound may be performed for lower risk patients (pT1 and pT2) (Grade C). CT head or bone scan is not routinely recommended unless clinically indicated.

		Figure 1. Months Post-op									
		3	6	12	18	24	30	36	48	60	72
pT1											
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	
pT2											
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	
pT3											
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	
pTxN+											
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

Recurrence patterns for pT1 tumors

Among several series, the local recurrence for pT1 lesions is very low (< 2%). Levy et al⁹ reported 7% recurrence rate at median follow-up of 39 months with a median time to recurrence of 38 months (range 18–67 mo). Majority of recurrences were in the lung and no recurrences were found in the abdomen. None of the pulmonary recurrences were symptomatic. Similarly, the Canadian group has shown that median time to recurrence was 35 months (range 2–93) and only 0.9% of patients recurred at 13, 66, and 93 months in the renal fossa and were asymptomatic.¹⁸ Several other reports showed similar findings.^{10,12,19–21} Among several studies regarding RCC surveillance, the latest postnephrectomy recurrence in the lungs, abdomen, and bone was 67, 97, and 144 months, respectively.^{9,12,18,20} Recommended surveillance will include clinical assessment, blood biochemistry, and chest x-ray every year. Abdominal CT recommended at 24 and 60 months (Grade C). Follow-up is the same for partial nephrectomy for < 4 cm lesions since the local recurrence rates in this population is similar to radical nephrectomy (Grade B). CT abdomen at 3 months post-op for patients treated with partial nephrectomy to evaluate the residual renal appearance is optional (Grade D). Annual abdominal ultrasound for patients post partial nephrectomy is optional (Grade D).

Recurrence patterns for pT2 tumors

Several series have reported recurrences after a median time of 25–32 months.^{9,12,18,20} Levy et al reported 27% recurrence rate at a median follow-up of 53 months with a time to recurrence of 32 months (range 3–115 mo). Only 2 patients developed metastasis within 6 months post-op. The Canadian group reported a median time to recurrence of 25 months (range 3–95 mo) and 50% were asymptomatic.¹⁸ Among several studies regarding RCC surveillance, the latest postnephrectomy recurrence in the lungs, abdomen, and bone was 96, 92, and 144 months, respectively.^{9,12,18,20} Recommended surveillance will include clinical assessment, blood biochemistry, and chest x-ray every 6 months for 3 years then yearly. Abdominal CT recommended at 12, 36, 60, 84, and 108 months (Grade C).

Recurrence patterns for pT3 tumors

Levy et al reported 39% recurrence rate at a median follow-up of 31 months with a median time to recurrence of 17 months (range 2–88 mo). Stephenson et al reported a median time to relapse of 14 months and 9 months for pT3a and pT3b tumors.¹⁸ Among several studies regarding RCC surveillance, the latest postnephrectomy recurrence in the lungs, abdomen, and bone was 138, 79, and 65 months, respectively.^{9,12,18,20} Recommended surveillance will include clinical assessment, blood biochemistry, and chest x-ray every 6 months for 3 years then yearly. Abdominal CT recommended at 6, 12, 18, 24, 36, 60 months then every 2 years (Grade C).

Recurrence patterns of pTxN+ tumors

Canfield et al reported a 70% recurrence rate at a median follow-up of 17.7 months with a median time to recurrence of 4.9 months.²² Saidy et al²³ reported a 64% recurrence rate at a mean follow-up of 39 months with a median time to recurrence of 9 months. Most disease will recur within the first year and > 90% by 3 years. Most common sites of recurrences in order of decreasing frequency were retroperitoneal lymph nodes, lung, liver, bone, renal fossa, pelvis, and brain. Similar results are shown by the UCLA group.²⁴ Recommended surveillance will include clinical assessment, blood biochemistry, chest x-ray, and CT of the abdomen/pelvis at 3 and 6 months, then every 6 months for 3 years then yearly (Grade C).

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