Postoperative Surveillance Protocols for Renal Cell Carcinoma

17

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Introduction

Cancers of the kidney and renal pelvis accounted for approximately 3–5 % of all malignancies diagnosed in the United States in 2012, with 65,150 new cases and 13,680 deaths expected in 2013 [1]. The majority of these cancers are renal cell carcinomas (RCC). The incidence of RCC continues to rise, increasing by 2 % per year, in part secondary to the increasing use of abdominal imaging resulting in the incidental finding of renal masses. Despite the potential advantage of identifying and treating asymptomatic patients at earlier disease stages, one third of patients will eventually develop local or distant recurrence following surgical extirpation [2–4].

Prognosis of patients with untreated recurrent disease is poor, with 5-year survival rates of 3–9 % [5, 6]. If identified early, however, metastasectomy with or without systemic therapy has been shown to improve overall survival [7–10]. Therefore, the use of surveillance to effectively identify those at risk for recurrence is of paramount importance.

This chapter reviews the recurrence patterns of RCC and the prognostic factors associated with risk of recurrence as a rationale for the establishment of surveillance protocols. Although there is no single consensus on the optimal guidelines for follow-up, there are several evidence-based recommendations and reviews that are currently being used in the postoperative setting, following radical and partial nephrectomy, and ablative therapies for RCC.

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Natural History of RCC and Recurrence Patterns

Renal cell carcinoma originates from the proximal tubular epithelium and typically grows slowly, forming discrete focal lesions. Local disease progression occurs by invasion through the renal capsule into Gerota's fascia and further local extension to surrounding structures. In addition, renal cell carcinoma spreads to distant sites through both hematogenous and lymphatic routes. Lung, bone, and liver are the most commonly affected, although RCC can also metastasize to the brain, contralateral kidney, adrenal gland, and soft tissues [11]. Involvement of lymph nodes without distant metastases is uncommon, although disease progression can be unpredictable secondary to the variable lymphatic drainage of the kidneys [12].

Distant Recurrence

Lung

The most common site of metastasis from RCC is the lung, with a reported incidence of 3–16 %

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[13–17]. Median time to development of pulmonary recurrence is correlated with tumor stage, with an earlier time to recurrence for higher stage disease. One series reports the median time to metastasis to be 53 months for pT1 disease, 31 months for pT2 disease, and 14 months for pT3 disease. In this same observational study, none of the patients with pT1 disease were symptomatic at diagnosis of recurrence, 11 % with pT2 disease were symptomatic, and only 9 % with pT3 disease presented with symptoms [14].

Symptoms associated with pulmonary metastasis include pleuritic chest pain, hemoptysis, cough, dyspnea, and weight loss. Multiple other studies have confirmed the low rates of symptomatic lung recurrences, with pulmonary lesions being found in over 90 % of asymptomatic patients with metastases undergoing routine surveillance imaging [16, 18, 19].

A meta-analysis reviewing post-nephrectomy pulmonary metastasis reports the latest pulmonary lesion discovered at 67 months for pT1 tumors, 97 months for pT2 tumors, and 138 months for pT3 tumors, emphasizing the importance of surveillance up to at least 5 years postoperatively, and ideally longer [14–16, 20].

The high percentage of asymptomatic recurrences for all stages of disease has led to recommendations for routine chest imaging in the form of CXR or CT chest for all stages of disease with emphasis on the first 3–5 years postoperatively.

Bone

Bone metastasis occurs in approximately 2–8 % of all patients after nephrectomy for RCC and comprises 16–27 % of patients with recurrent disease [14–16, 19]. Although reported to be less common for patients with pT1 disease (0–25 %), bone metastasis for patients with pT2 and pT3 disease occurs in 17.6–45 % and 16–26.5 %, respectively. Recurrence is at a median time of 39 months for pT1 disease, 24–40 months for pT2 disease, and 7–20 months for pT3 disease [14–16, 20].

As with pulmonary metastasis, tumor stage is correlated with median time to recurrence. In contrast to pulmonary recurrence, however, most patients with bone metastasis present with symptoms. Bone pain is reported in 67–90 % of patients and alkaline phosphatase levels are elevated in 33–55 % [14, 19, 20]. In a study by Shvarts et al., 68 % of patients with bone metastasis were also found to have extraosseous metastasis and 95.5 % had an ECOG performance status of one or more [21]. Given these data, routine surveillance with nuclear scintigraphy is not warranted in the absence of symptoms or an elevated alkaline phosphatase level.

Liver

The reported incidence of liver metastasis is between 1 % and 7 %. It is rarely reported for patients with pT1 disease, with an incidence of 0 in several studies [14–16, 20]. In one series, an incidence of 12 % is reported for patients with pT2 disease and 9 % for pT3 disease, with a median time to recurrence of 53–83 months and 5–67 months, respectively [14, 20]. Most patients (pT2: 60–100 %; pT3: 73–100 %) were diagnosed after presenting with abdominal pain and/or elevated liver function tests (LFTs).

Brain

Brain metastasis occurs in 2–4 % of all patients after nephrectomy [19].

Data derived from a meta-analysis by Skolarikos et al. report the incidence of brain metastasis for pT1 tumors to be from 0 % to 12 %. However, the 12 % was derived from a single study in which one patient with pT1 disease in a cohort of eight developed brain metastasis [14]. For pT2 and pT3 disease, the reported incidence ranges from 0 % to 15 % and from 4 % to 11 %, respectively. All patients who developed brain metastasis presented with symptoms such as headache, mental status change, or other neurologic deficits [14–16, 20]. For this reason, routine imaging has not been recommended in the absence of focal or new onset neurological symptoms.

Lymph Nodes

Development of new lymph node metastasis was identified in up to 25 % of patients with pT2 and pT3 disease. In all cases, patients were asymptomatic, diagnosed by routine CT scans, and found to have concomitant sites of recurrent disease [14, 16].

Local Recurrence After Radical Nephrectomy

Local recurrence involving the renal fossa, ipsilateral adrenal gland, or axial musculoskeletal anatomy is rare and incidence varies between 3 % and 27 %, depending on the literature reviewed [14, 22, 23]. A retrospective study from the Mayo Clinic followed 1,737 node-negative patients who underwent nephrectomy for RCC. They reported a 1.8 % incidence of isolated renal fossa recurrence at 5 years, with only 60 % of those patients being symptomatic upon diagnosis [24]. Margulis et al. [25] reviewed 2,945 patients who had a radical nephrectomy with curative intent and reported an isolated local recurrence in 54 (1.8 %) of those patients. Local recurrence was defined as any RCC, proven by pathology evaluation, localized in the renal fossa, ipsilateral adrenal gland, or ipsilateral retroperitoneal lymph nodes. In line with the Mayo series, 61.2 % of patients were symptomatic (28 patients with local symptoms and five with systemic symptoms) at presentation. In this population, the authors identified five risk factors that portend poor prognosis: size >5 cm, positive surgical margins, presence of sarcomatoid elements, abnormal LDH, and abnormal alkaline phosphatase. Patients with none of these risk factors ($N=34$) had median survival of 111 months. Patients with only one risk factor ($N=9$) had median survival of 40 months, while patients with more than one risk factor ($N=11$) had median survival of only 8 months after resection. As noted, tumor size was one of the poor prognostic indicators, suggesting that earlier detection of such recurrence could lead to improved resectability and achieving negative surgical margins, decreased surgical morbidity, and ultimately improved survival.

Recurrence After Partial Nephrectomy

Historically, there was a concern of increased risk of local recurrence in the ipsilateral kidney following partial nephrectomy. However, multiple studies over the past decade have found recurrence rates to be similar to radical nephrectomy despite utilization of a nephron-sparing approach. A study from the Cleveland Clinic reviewed 327 patients who underwent partial nephrectomy and demonstrated a local recurrence rate of 4 % and a metastatic recurrence rate of 7.6 % over 55.6 months [13]. A follow-up study from the same group observed 107 patients over 10 years and found no local recurrence for patients with localized pT1 and pT2 disease. For patients with pT3a and pT3b disease, local recurrence rates were 10 % and 12 %, respectively. Distant metastatic disease occurred in 2 %, 29 %, 0 %, 33 %, and 53 % of patients with pT1a, pT1b, pT2, pT3a, and pT3b, respectively [26].

In more recent years, the size threshold for renal masses amenable to partial nephrectomy has been expanded to include masses up to 7 cm and in some cases >7 cm, when technically feasible and clinically indicated. The feasibility of partial nephrectomy in larger renal masses has come with concern regarding long-term oncological outcomes [27]. The group from the Mayo Clinic studied 5-year survival rates for patients with renal masses 4–7 cm who underwent either partial or radical nephrectomy. They concluded that after controlling for stage, grade, tumor necrosis, and histological subtype, there was no statistical difference in cancer-specific survival or distant-metastatic-free survival for those undergoing partial or radical nephrectomy [28].

Aside from the influence of size on recurrence patterns after partial nephrectomy, the effect of positive surgical margins (PSMs) has also been recently investigated. A study conducted by Memorial Sloan-Kettering Cancer Center and the Mayo Clinic reviewed 1,344 patients who underwent partial nephrectomy at one of these institutions between 1972 and 2005 [29]. A total of 77 patients (5.5 %) were noted to have PSMs. Of the entire cohort, 39 patients had local recurrence and 57 had progression to metastatic disease. For patients with PSMs, the 5-year freedom from local recurrence was 98 % and from metastatic progression 95 %. There was no significant difference in freedom from local recurrence or metastatic progression between patients with positive surgical margins and patients with negative surgical margins [29]. A retrospective

multi-institutional review collected data from 26 centers throughout Europe and North America and reported similar results [30]. They identified 119 positive surgical margins following partial nephrectomy. A negative surgical margin cohort was obtained from a multi-institutional database and was matched for surgical indication, tumor size, and Fuhrman grade. There was no difference in recurrence-free survival between patients with negative surgical margins and those with positive surgical margins. Rates of cancer-specific survival and overall survival were comparable for both groups [30].

Collectively, these data indicate that recurrence and survival rates are similar following partial and radical nephrectomy regardless of tumor size and positive surgical margins. As such, contemporary surveillance strategies for the two groups have not markedly differed.

Surveillance Following Radical or Partial Nephrectomy

Rationale for Surveillance

According to observational data from the National Cancer Data Base for patients diagnosed with RCC between 2001 and 2002, the current 5-year overall survival rates are 81 % for stage T1, 74 % for T2, 53 % for T3, and 8 % for T4 [31]. Given that adjuvant therapy has not been proven to be beneficial to date, early detection of metastatic disease is imperative to improving clinical outcomes. In early stages, chest and abdominal metastases are usually asymptomatic, with symptoms only appearing in advanced stages [14]. In patients with surgically resectable metastases, early intervention in the absence of symptoms when complete resection is still possible could result in higher survival rates (reviewed in [32]). The Mayo Clinic recently reported that complete metastasectomy confers a cancer-specific survival (CSS) advantage in patients who present with multiple synchronous and asynchronous metastatic lesions. Alt et al. reviewed 887 patients who underwent nephrectomy for renal cell carcinoma and were diagnosed with metastatic disease [33]. One hundred twenty-five patients underwent complete surgical metastasectomy and were found to have an improved median CSS compared to patients who did not undergo metastasectomy (4.8 vs.1.3 years). Patients with pulmonary metastasis who underwent complete surgical resection had a 5-year CSS of 73 % versus 19 % for those who did not have complete resection. Patients with multiple, nonpulmonary lesions also benefited from complete resection compared to those who did not undergo complete resection (5-year CSS of 32.5 % vs. 12.4 %). A survival advantage was seen following metastasectomy for both patients with localized disease who developed synchronous or asynchronous metastasis and patients who initially presented with metastatic disease and then developed asynchronous metastasis [33].

Components of Surveillance

There is currently no consensus on the optimal surveillance protocol following surgical resection or ablative therapy for the treatment of RCC. Historically, surveillance has included history, physical examination, laboratory work, and periodic chest and abdominal imaging studies at intervals based on established recurrence patterns.

A thorough history and physical examination is important for promptly identifying signs and symptoms that suggest disease recurrence and warrant further investigation. Constitutional symptoms such as fever, weight loss, and fatigue are concerning for metastatic disease. A complete review of systems should be performed to identify the presence of pleuritic chest pain, dyspnea, hemoptysis, epistaxis, abdominal pain, flank pain, bone pain, change in mental status, or focal neurologic deficits. Physical exam findings such as a palpable abdominal mass and groin, supraclavicular or axillary lymphadenopathy, and lower extremity swelling are also concerning for metastatic disease and should elicit further workup.

Current National Comprehensive Cancer Network (NCCN) guidelines recommend lab work to include a urinalysis, complete blood count (CBC), coagulation profile, and a comprehensive

metabolic panel (CMP), which consists of liver function studies, lactate dehydrogenase (LDH), calcium, electrolytes, BUN, and creatinine.

Routine blood work plays a prognostic role in surveillance of oncological as well as non-oncological parameters. Motzer et al. identified that a lactate dehydrogenase level >1.5 times the upper limit of normal, a hemoglobin level < lower limit of normal, a corrected serum calcium level >10 mg/dl, a Karnofsky performance score ≤70, and an interval of less than 1 year from the original diagnosis to start of systemic therapy predicted short survival in patients with advanced renal cell carcinoma. In this study, patients with three or more of these factors had a poor prognosis, with a median survival of 5 months, and a 1-, 2-, and 3-year survival rate of 20 %, 6 %, and 2 % [34]. Patients with elevated liver function studies should be evaluated with abdominal imaging and those with elevated alkaline phosphatase should receive a nuclear bone scan to evaluate for metastatic disease.

Aside from monitoring lab work that relates to oncological outcomes, it is also important to follow kidney function parameters including creatinine, estimated glomerular filtration rate (eGFR), and urinalysis. Chronic kidney disease (CKD) is defined as eGFR < 60 mL/min or the presence of factors that suggest kidney damage, such as albuminuria or abnormal renal imaging, occurring for 3 months or greater [35]. CKD has been shown to be associated with a higher risk of morbidity and mortality [36]. Early identification of worsening serum creatinine, eGFR, and development of proteinuria identifies patients who are developing chronic kidney disease following surgery and allows for early referral to a nephrologist, who will work with the patient to control medical comorbidities and optimize renal function.

Prognostic Factors Influencing Recurrence

Early recommendations for surveillance have been guided mostly by the correlation of tumor stage with time to recurrence and site of recurrence [14–16, 20]. The likelihood of developing metastatic disease has been shown to be greatest in the first 3 years after nephrectomy and directly correlates with tumor stage. In one series, the risk of metastatic disease was 7.1 % for those with T1 disease, 26.5 % for T2 disease, and 39.4 % for T3 disease [14]. Chae et al. reviewed patterns of tumor recurrence in 194 patients and found that 21 % of patients recurred in a mean time of 17 months. Eighty-three percent of those who recurred were diagnosed within the first 2 years after surgery and the rate of recurrence was higher for patients with tumor size of >5 cm [37].

Over the last decade, data has emerged that supports the addition of other important prognostic factors to models that predict postoperative recurrence of RCC. In 2001, Kattan and colleagues at Memorial Sloan-Kettering Cancer Center (MSKCC) constructed a nomogram to predict 5-year disease-free survival rates following radical or partial nephrectomy. In addition to tumor stage, tumor size, histology, and symptomatic presentation were analyzed for 601 patients and determined to be important prognostic factors influencing disease recurrence [38].

Tumor size has been demonstrated to be an independent predictor of disease-free survival [39–41]. Five-year survival rates in one publication were reported to be 84 % for tumors less than 5 cm, 50 % for tumors 5–10 cm, and 0 % in tumors greater than 10 cm [42]. In a follow-up study, the MSKCC group also confirmed the importance of tumor size in predicting disease recurrence independent of pathological stage [43].

Histology by itself has also been shown in several studies to predict disease-specific survival. Of the four subtypes of RCC, chromophobe RCC confers a better prognosis than conventional (clear cell) RCC or papillary RCC [44]. Papillary type II, however, has been shown to independently predict poor survival [45, 46]. The presence of sarcomatoid dedifferentiation on final pathology indicates poor prognosis and has been utilized in risk stratification algorithms to predict disease recurrence [47, 48].

The MSKCC group published an externally validated postoperative nomogram in 2004 that analyzed a cohort of 701 patients diagnosed specifically with clear cell RCC. The prognostic

factors in this nomogram included tumor size, symptomatic presentation, pathologic stage, Fuhrman grade, presence of necrosis, and presence of microvascular invasion [43]. Both Fuhrman grade and microvascular invasion were predictive of disease-free survival on multivariate analysis.

Other literature has also confirmed the importance of Fuhrman grade, microvascular invasion, and necrosis in predicting disease recurrence [39, 49, 50]. The group from Mayo Clinic constructed a scoring system, SSIGN, based on tumor stage, tumor size, Fuhrman grade, and presence of tumor necrosis. All four factors were predictive of cancer-specific survival on multivariate analysis and used in an algorithm to predict clinical outcomes [49].

Authors from the University of California Los Angeles (UCLA) demonstrated the importance of the Eastern Cooperative Oncology Group (ECOG) performance status score in predicting overall survival. Based on stage, grade, and ECOG performance status, they established a risk classification system predicting 2- and 5-year survival rates [51]. This model was later used to create a surveillance strategy that has been recommended by the NCCN and is widely used today [22].

A preoperative nomogram from MSKCC and Mayo Clinic was published in 2008 that was developed after reviewing clinicopathologic factors and outcomes of 2,517 patients. Gender, symptomatic presentation, lymphadenopathy by imaging, tumor necrosis, and tumor size were used to create a preoperative nomogram predicting disease-free recurrence at 12 years [50].

Other nomograms and predictive tools have been previously reported and will be the subject of a separate chapter in this book.

Surveillance Following Radical or Partial Nephrectomy in Patients with Sporadic RCC

Since the early 1990s, multiple investigators have used their institutional databases to put forth recommendations for postoperative surveillance for patients with RCC. These will be described in detail in this section and summarized in Table 17.1.

In 1994, Montie et al. proposed a 5-year surveillance protocol that included physical exam, laboratory studies, and CXR every 6 months, as well as an abdominal CT at 12, 24, and 48 months, independent of pathologic stage after nephrectomy [52]. While more metastases are potentially detected using this unselected schedule, one has to keep in mind the cost-effectiveness of such an approach, as well as potential radiation risk.

In 1995, in order to subselect surveillance tools based on stage, Sandock and colleagues [16] from Case Western Reserve University retrospectively reviewed 137 patients without nodal or metastatic disease at presentation who underwent radical nephrectomy between 1979 and 1993. Nineteen patients were pT1 and had no recurrence at a mean follow-up of 44.4 months. Eighty-two patients were pT2 and 15.9 % recurred at mean of 29.5 months. Thirty-six patients were pT3 and 52.8 % recurred at mean of 22 months. Of those patients who experienced recurrence, chest metastases occurred in 53.8 % (7 of 13) of patients with pT2 and 63.2 % (12 of 19) with pT3. For patients with pT2 and pT3 disease, 71 % (5 of 7) and 75 % (9 of 12), respectively, were specifically symptomatic with dyspnea, cough, hemoptysis, and/or pleuritic chest pain. Abdominal metastases occurred in 38.5 % (5 of 13) of patients with pT2 and 42.1 % (8 of 19) of patients with pT3. Twelve of these 13 patients with abdominal metastases (liver 8, local 3, both 2) had signs or symptoms of metastatic disease. Bone metastases developed in 38.5 % (5 of 13) patients with pT2 and 26.4 % (5 of 19) patients with pT3, and all ten patients with bone metastases presented with bone pain that prompted further workup. Brain metastases developed in two patients with pT2 and four patients with pT3. In all six patients, brain metastases were symptomatic with headaches or mental status changes. Lymphadenopathy occurred in 25 % (3 of 13) patients with pT2 and 25 % (5 of 19) patients with pT3, and all eight recurrences were not isolated, but were associated with other findings.

Table 17.1 Surveillance guidelines after partial or radical nephrectomy

	Clinical assessment (history, physical exam, laboratory studies)	Chest X-ray	Abdominal CT
pT1			
Sandock [16]	Not specified	Not recommended	Not recommended
Hafez [13]	Yearly	Not recommended	Not recommended
Levy [14]	Yearly	Yearly	Not recommended
Ljunberg[a] [15]	Not recommended	Not recommended	Not recommended
Mickish [54]	Every 6 months for 3 years, then yearly from years 3–5	Every 6 months for 3 years, then yearly from years 3–5	Not recommended
Stephenson [56]	Yearly	Yearly	Not recommended
Kassouf [59]	Yearly	Yearly	At years 2, 5 (optional at 3 months)
pT2			
Sandock [16]	Every 6 months for 3 years, then yearly	Every 6 months for 3 years, then yearly	Not recommended
Hafez [13]	Yearly	Yearly	Every 2 years
Levy [14]	Every 6 months for 3 years, then yearly	Every 6 months for 3 years, then yearly	At years 2, 5
Ljunberg[b] [15]	At 3 and 6 months, then every 6 months until 3 years, then yearly	At 3 and 6 months, then every 6 months until 3 years, then yearly	Not recommended
Mickish [54]	Every 6 months for 3 years, then yearly from years 3–5	Every 6 months for 3 years, then yearly from years 3–5	Not recommended
Stephenson [56]	Yearly	Yearly	Not recommended
Kassouf [59]	Every 6 months for 3 years, then yearly	Every 6 months for 3 years, then yearly	12, 36, 60, 80, 108 months
pT3			
Sandock [16]	Every 6 months for 3 years, then yearly	Every 6 months for 3 years, then yearly	Not recommended
Hafez [13]	Yearly	Yearly	Every 6 months until 2 years, then every 2 years
Levy [14]	At 3 and 6 months, then every 6 months until 3 years, then yearly	At 3 and 6 months, then every 6 months until 3 years, then yearly	At years 2, 5
Ljunberg [15]	At 3 and 6 months, then every 6 months until 3 years, then yearly	At 3 and 6 months, then every 6 months until 3 years, then yearly	At 6 and 12 months (optional)
Mickish [54]	Every 6 months for 3 years, then yearly from years 3–10	Every 6 months for 3 years, then yearly from years 3–10	Every 6 months for 3 years, then yearly from years 3–10
Stephenson [56]	Every 6 months for 3 years, then yearly	Every 6 months for 3 years, then yearly	At 6, 12, 24, and 36 months, then every 2 years
Kassouf [59]	Every 6 months for 3 years, then yearly	Every 6 months for 3 years, then yearly	At 6, 12, 18, 24, 36, 60 months, then every 2 years
UCLA risk groups [22]			
Low risk	Yearly	Yearly for 5 years	At years 2, 4
Intermediate risk	Every 6 months for 3 years, then yearly until 10 years	Every 6 months for 3 years, then yearly until 10 years	At years 1 and 2, then every 2 years for 10 years
High risk	Every 6 months for 3 years, then yearly until 10 years	Every 6 months for 3 years, then yearly until 10 years	Every 6 months for 2 years, then yearly until 5 years, then every 2 years until 10 years
Nodal disease	At 3, 6, 12, 18, 24 months then yearly	At 3, 6, 12, 18, 24 months then yearly	At 3, 6, 12, 18, 24 months then yearly

[a]Includes pT1 tumors <5 cm, pT1 diploid, and pT2 diploid
[b]Includes pT1 >5 cm aneuploid/ploidy not assessed or pT2 aneuploid/ploidy not assessed

Most recurrences (85 %) occurred in the first 3 years after radical nephrectomy. From the authors' dataset, only 1 of the 137 patients they studied benefited from routine CT scan. The authors concluded that bone scans and CT scans should not be routinely performed and that follow-up should include only a history and physical in patients with pT1 disease. For patients with pT2 and pT3 disease, they recommended a history, physical examination, liver function tests, and chest X-rays every 6 months for the first 3 years, then yearly thereafter.

In 1997, Hafez et al. from Cleveland Clinic reported oncological outcomes for 327 patients who underwent partial nephrectomy prior to December 1994. Mean follow-up was 54 months and recurrence developed in a total of 38 patients (11.6 %). Thirteen patients (4 %) had local recurrence of which seven also had distant metastatic disease. Twenty-five patients (7.6 %) presented with metastatic disease in the absence of local recurrence. Incidences for local recurrence and metastatic disease by stage were 0 and 4.4 % for T1, 2.0 and 5.3 % for T2, 8.2 and 11.5 % for T3a, and 10.6 and 14.9 % for T3b. Local recurrence was most often diagnosed from 6 to 24 months and after 48 months. Based on these data, the authors recommended that all patients should undergo a yearly history, physical exam, and lab work. No imaging was recommended for patients with T1 disease since risk of recurrence was found to be low; however, a yearly chest X-ray was recommended for patients with T2 and T3 disease as metastasis to the lung was more common in these groups. Occasional follow-up every 2 years with CT abdomen was suggested for patients with T2 disease, and since local recurrence is highest in T3 disease, the authors recommend CT abdomen every 6 months for the first 2 years and then every 2 years thereafter [13].

In 1998, Saidi and colleagues [53] from Columbia University reported on 45 patients that were enrolled in an adjuvant autolymphocyte therapy trial for N+M0 high-risk patients. Twelve patients were T2, 30 were T3, and 3 were T4. Sixty-four percent recurred after radical nephrectomy (29 of 45) at a mean of 14.9 months. Fourteen recurred in the retroperitoneal nodes at 13.9 months, 11 in the lung at 14.4 months, 5 in the liver at 14.9 months, 5 in bone at 11.9 months, 4 in the mediastinal nodes at 11.8 months, 3 in the renal fossa at 6.9 months, and 2 in the brain at 20.7 months. Of those who had disease progression, 31 % did so by 6 months, 59 % by 12 months, 83 % by 24 months, and 93 % by 36 months. As such, the authors recommended routine chest X-ray and CT abdomen at least every 6 months for the first 3 years and then yearly. Given that this study involved very high-risk patients (node positive), the follow-up recommended cannot be necessarily applied to the general population of patients with renal cell carcinoma treated with surgery.

In 1998, Levy and colleagues [14] from MD Anderson Cancer Center proposed postoperative surveillance guidelines stratified by stage and based on 286 patients that were surgically treated for renal cell carcinoma without nodal or distant metastases between 1985 and 1994. At a median follow-up of 23 months, 68 patients developed metastatic disease in a total of 92 sites. Eight of 113 patients with pT1, 17 of 64 patients with pT2, and 43 of 109 patients with pT3 developed metastases at a median of 38 months, 32 months, and 17 months, respectively. Sixty-four percent (59 of 92) of the metastases were asymptomatic (32 detected on chest X-ray and 12 on routine laboratory studies). Only six patients (9 %) had an isolated intra-abdominal metastasis without associated symptoms. All brain metastases presented with neurological symptoms that prompted further evaluation. In the eight pT1 patients with recurrent disease, 4 were in the chest (lung), 2 in bone, and 1 each in brain and uvula. In the 17 pT2 patients with recurrence, 9 were in the chest (lung), 5 in the abdomen (liver 2, lymph node 1, adrenal 1, pancreas 1), 3 in bone, and 1 in brain. In the 43 pT3 patients, 18 were in the chest (lung – 18 % diagnosed <6 months after surgery), 10 in the abdomen (local 4, liver 4, adrenal 2), 7 in bone, five in lymph nodes (detected on physical examination), and 3 in brain. Eleven of the pT3 patients were diagnosed with metastases <6 months after surgery. The authors suggested starting with abdominal CTs no earlier than 24 months after surgery, as in their experience,

all 344 CT scans done in the first 24 months of surveillance did not yield any useful information. The authors recommended history, physical exam, laboratory studies, and chest X-ray at 12, 24, 36, 48, and 60 months after surgery for pT1, history, physical exam, laboratory studies, and chest X-ray at 6, 12, 18, 24, 30, 36, 48, and 60 months and CT abdomen at 24 and 60 months for pT2. Recommended follow-up for pT3 was similar to pT2, with the addition of history, physical exam, laboratory studies, and chest X-ray at 3 months after surgery.

In 1999, Ljungberg and colleagues [15] from Umea University in Sweden developed a surveillance protocol based on stage, tumor size, and DNA ploidy. They retrospectively reviewed 187 patients with no clinical nodal or distant metastases treated with radical nephrectomy between 1982 and 1997. Fifty-six patients developed a total of 98 metastases at a median of 14.5 months after radical nephrectomy. Thirty-seven were in the chest (lung), 24 were bone, 21 were intra-abdominal (11 liver, 7 local or retroperitoneal, 3 abdominal), 4 were brain, 3 were skin, and 9 in other sites. In 43 % of the 56 patients, the metastases were discovered in the first year, in 70 % in the first 2 years, in 80 % in the first 3 years, and in 93 % in the first 5 years after surgery. Seven percent (5 of 70) of patients with T1 experienced a recurrence at a median of 40 months; however, all these patients had tumors larger than 5 cm in size. Fourteen percent (6 of 43) of patients with pT2 recurred at median of 8 months, 55 % (26 of 48) of patients recurred at median of 12 months, and 73 % (19 of 26) recurred at a median of 15 months. Of the 11 recurrences in patients with pT1 and pT2, 6 were in the lung (only one symptomatic) and 5 were in bone (all symptomatic). In patients with pT3, only 1 of 24 lung recurrences was symptomatic, while all 10 bone and all 5 liver, and both liver recurrences were symptomatic. Patients with pT1–T2 homogenously diploid tumors did not experience a recurrence, while ploidy did not affect patient outcomes in patients with stage pT3. Based on these findings, the authors recommend no follow-up for patients with pT1 tumors <5 cm, pT1 diploid, and pT2 diploid. Physical examination, laboratory studies, and chest X-ray at 3, 6, 12, 18, 24, 30, 36, 48, and 60 months were recommended for patients with pT1 >5 cm aneuploid/ploidy not assessed or pT2 aneuploid/ploidy not assessed, and a similar follow-up as the latter category with the addition of optional CT abdomen and bone scan at 6 and 12 months for patients with pT3 or N1 disease.

In 2001, Mickish and colleagues [54] from Erasmus University Rotterdam reviewed multiple publications [13, 14, 16] and established a follow-up protocol. For patients with pT1 and pT2 disease, the authors recommended history, physical exam, laboratory studies, and a chest X-ray every 6 months for the first 3 years, then yearly until year five. Abdominal CT was not recommended for this group. More intense follow-up for a longer period of time was recommended for patients with pT3 disease. A clinical assessment, chest X-ray, and abdominal CT were recommended every 6 months for the first 3 years then yearly up to 10 years [54].

In 2003, Frank and colleagues [55] from the Mayo Clinic retrospectively reviewed 1,864 patients treated with partial or radical nephrectomy in the absence of distant metastases and defined recurrence locations into four major categories: chest, abdomen, bone, and brain. Sixteen percent (300 patients) recurred in the chest at a median of 1.6 years, 10 % (185 patients) recurred in the abdomen at a median of 1.7 years, 7 % (134 patients) recurred in bone at a median of 1.5 years, and 4 % (81 patients) recurred in the brain at a median of 2.5 years. The authors then used analyses that included different combinations of risk factors (positive surgical margins, tumor stage, nodal status, size >10 cm, nuclear grade, tumor necrosis, sarcomatoid features, cystic architecture, and multifocality) to devise scoring systems that predicted the risk of metastases into each of these four locations. One important finding, in line with other studies, is that 98.2 % of brain metastases and 90.5 % of bone metastases were symptomatic at presentation, obviating the need for routine surveillance for these sites in the absence of specific symptoms. The authors, however, did not recommend a particular surveillance schedule based on these findings and recommended that the clinician should decide on the

appropriate follow-up scheme on an individual basis that considers the scoring system as well as individual patient characteristics such as age and comorbidities, among others.

In 2004, Stephenson and colleagues [56] retrospectively reviewed 495 patients who underwent partial or radical nephrectomy in five Canadian centers. Sixty-seven patients had a recurrence after surgery (63 distant and 12 local) and only four patients had an isolated local recurrence. Sixteen of 303 patients with pT1 relapsed at a median of 35 months, with 15 of these relapses being solitary. Thirteen patients had symptoms with or without a chest recurrence that would have been found on physical examination or chest X-ray. There were three asymptomatic (2 after partial nephrectomy, 1 after radical nephrectomy) and 1 symptomatic abdominal recurrences. Fourteen of 84 patients with pT2 recurred at a median of 25 months. All these 14 patients had symptoms with or without a chest recurrence, and only 10 of 14 recurrences were solitary. Twenty-three of 74 patients with pT3a recurred at 14 months (only 16 recurrences were solitary), and 14 of 34 patients with pT3b recurred at 8 months (only 8 recurrences were solitary). Based on their findings, the authors recommended annual history, physical examination, and chest X-ray in patients with pT1 or pT2 disease. They recommended that patients with pT3a or pT3b should be followed every 6 months for the first 3 years with history, physical examination, chest X-ray, and then annual follow-up, while obtaining CT abdomen at 6, 12, 24, and 36 months after surgery, and then every 2 years afterwards.

In 2005, Lam and colleagues from the University of California Los Angeles [22] developed a postoperative surveillance protocol based on the UISS – an integrated risk stratification model that incorporates the 1997 TNM staging, Fuhrman grade, and ECOG status into five categories – that has been shown to predict outcomes in patients post nephrectomy for RCC [51] (Fig. 17.1). This UISS model has been validated in subsequent studies [57, 58]. In this retrospective study [22], 559 patients with nonmetastatic RCC treated between 1988 and 2003 were reviewed and risk stratified according to the established UISS model (low risk, intermediate risk, high risk, and node positive). Recurrence patterns were then analyzed and a surveillance protocol was constructed based on their findings. 92.8 % of patients had localized disease and 70 % underwent radical nephrectomy. Median follow-up was 26 months (Fig. 17.2). Patients identified as low risk ($N=196$) had an overall 5-year recurrence rate of 9.6 %, with a median time to recurrence of 28.9 months. 87.5 % (7 of 8) had a solitary recurrence. The chest was the most common site of recurrence in the low-risk group accounting for 75 % of the overall recurrences in this cohort. Recurrence was most common in the first 3 years following nephrectomy with a median time to recurrence of 23.6 months. No pulmonary recurrences were diagnosed after 5 years. Abdominal recurrences comprised 37.5 % of the recurrences with a median time to recurrence of 32 months. None of the abdominal recurrences in the low-risk group occurred before 20 months or after 5 years. For the intermediate risk group ($N=251$), the 5-year recurrence rate was 38.2 % at median time of 17.8 months. 40.5 % (25 of 62) had solitary recurrence, 77.4 % of the recurrences were discovered in the chest, and 58.1 % in the abdomen. 41.7 % of patients with chest metastasis were diagnosed in the first year, and of those, 70 % were diagnosed between 6 months and 1 year post nephrectomy. Fifty-eight percent of the abdominal recurrences were diagnosed within the first year, of which 66.6 % were discovered between 6 months and 1 year after nephrectomy. 44 % of the bone recurrences occurred within the first year, while 33 % occurred after 5 years. Brain recurrences in this group were rare. Patients classified as high risk ($N=72$) had a 5-year recurrence rate of 58.1 % at a median time of 9.5 months. 74.2 % (23 of 31) of the recurrences were solitary. The chest was the most frequent site of recurrence accounting for 45.5 % of the recurrences. 50 % of chest recurrences were diagnosed in the first year and 42.8 % of those within the first 6 months after surgery. 7 % of the chest recurrences were found on routine imaging after 5 years of follow-up. Abdominal recurrences including renal fossa, liver, and other abdominal organs together comprised 68.2 % of recurrences.

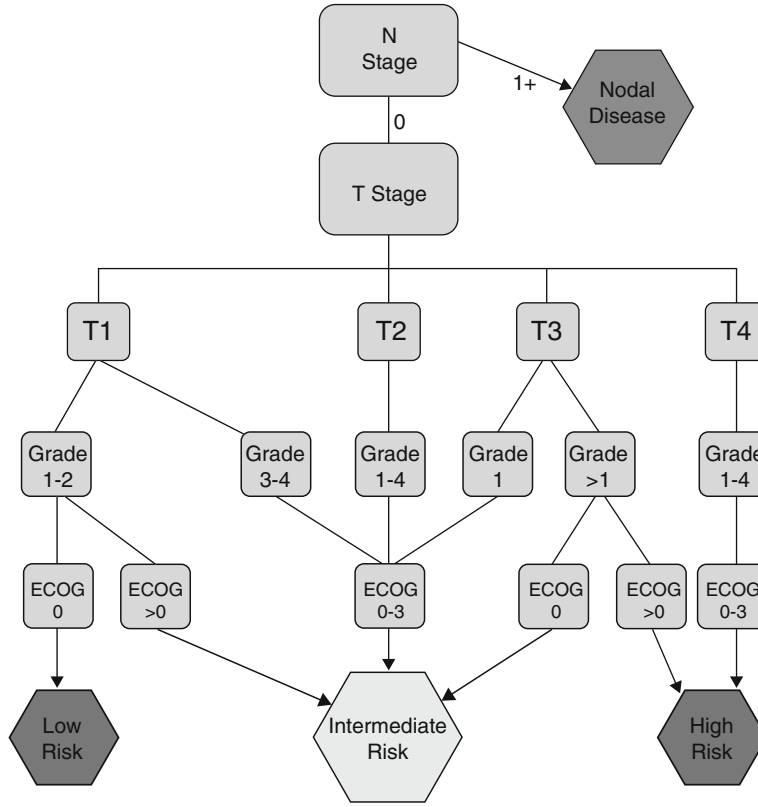

Fig. 17.1 Flow chart for UISS risk group assignment of patients with localized and locally advanced RCC. Progress from top to bottom using 1997 UICC N stage and T stage, Fuhrman grade, and ECOG-PS (Reprinted from Lam et al. Postoperative surveillance protocol for patients with localized and advanced renal cell carcinoma based on a validated prognostic nomogram and risk group stratification system. J Urol. 2005;174(2):466–72, with permission from Elsevier)

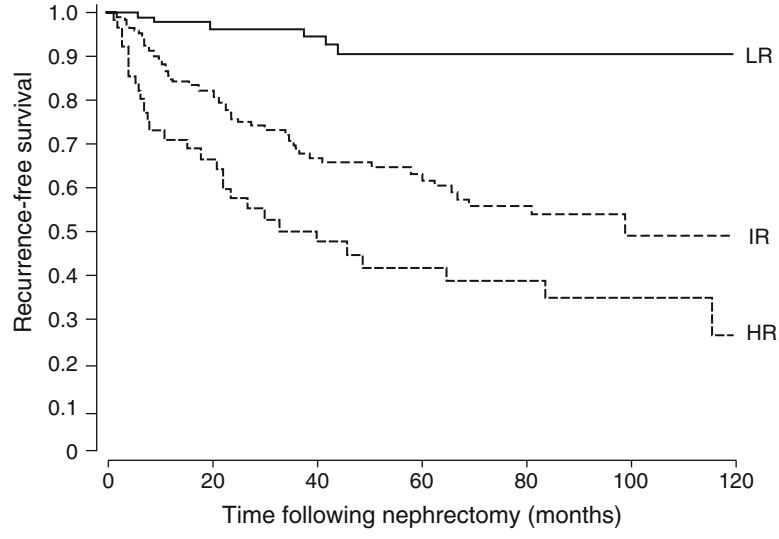

Fig. 17.2 Kaplan-Meier estimate of recurrence-free survival following nephrectomy among UISS risk groups (Reprinted from Lam et al. Postoperative surveillance protocol for patients with localized and advanced renal cell carcinoma based on a validated prognostic nomogram and risk group stratification system. J Urol. 2005;174(2):466–72, with permission from Elsevier)

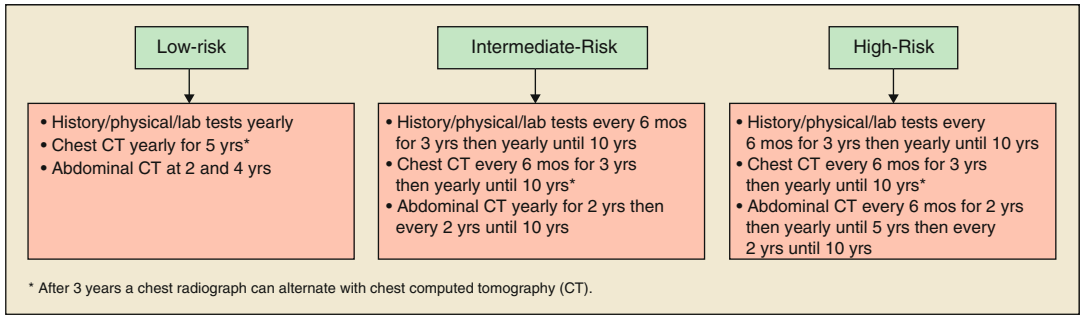

Fig. 17.3 Surveillance protocol following nephrectomy for localized renal cell carcinoma using the University of California Los Angeles Integrated Staging System (Copyright © MedReviews®, LLC. Reprinted with permission of MedReviews®, LLC. Chin AI et al. Surveillance strategies for renal cell carcinoma patients following nephrectomy. Rev Urol. 2006;8(1):1–7. *Reviews in Urology* is a copyrighted publication of MedReviews®, LLC. All rights reserved)

Of these, 62 % occurred within the first year and 61.5 % of those within the first 6 months. Only 5 % of abdominal recurrences were diagnosed after 5 years. Patients with lymph node-only metastasis experienced a 64 % 5-year recurrence after surgery. Of those who recurred, 58.8 % had a chest recurrence and 76.5 % had an abdominal recurrence. In patients who recurred in the chest, recurrence occurred in 25 %, 12.5 %, 25 %, and 37.5 % at months 0–3, 3–6, 6–12, and 12–24 after surgery, respectively. In patients who recurred in the abdomen, recurrence occurred in 28.6 %, 21.4 %, and 28 % at months 0–3, 3–6, and 12–24 after surgery, respectively. Based on these data, a surveillance protocol was constructed [19], outlining the optimal follow-up for patients post nephrectomy as risk stratified according to the UISS model (Fig. 17.3).

In 2005, Chae and colleagues from ASAN Medical Center in Korea retrospectively reviewed 194 patients treated with surgery [37]. Twenty-one percent of patients experience disease recurrence at a mean of 17 months. Tumor recurred within 2 years after surgery in 34 (83 %) patients. Disease recurrence occurred in the lung in 29, bone in 13, nephrectomy bed in 7, brain in 6, mediastinal lymph nodes in 5, liver in 5, contralateral kidney in 4, and the neck in 2. Patient with tumors >5 cm, stage III, or Fuhrman grade 3–4 had a higher risk of recurrence. With the lung being the most common site of metastasis in their series, the authors recommended that CT chest should be done every 6 months during the first 2 years after surgery and then annually for 2 years in patients with a high risk for tumor recurrence [37].

In 2009, Kassouf and colleagues from McGill University reviewed multiple series [2, 13–16, 20] before establishing the Canadian Urological Association guidelines for postoperative surveillance after nephrectomy [59]. The authors decided on a stage-based protocol to include a yearly history, physical exam, laboratory studies, and a chest X-ray for patients with pT1 disease. They recommend abdominal CT in this group at years 2 and 5, with an optional abdominal CT at 3 months and/or optional abdominal ultrasound yearly for patients who underwent partial nephrectomy. For patients with pT2 disease, history, physical exam, laboratory studies, and a chest X-ray were recommended every 6 months for 3 years and then yearly. Abdominal CT was recommended in this group at 12, 36, 60, 84, and 108 months postoperatively. Guidelines recommend the same follow-up in regard to clinical assessment and chest X-ray in patients with pT3 disease; however, abdominal CT should be done at 6, 12, 18, 24, 36, 60 months and then continue every 2 years. For patients with node-positive disease, the authors recommended clinical assessment, chest X-ray, and abdominal CT at 3 and 6 months, every 6 months for 3 years, and then yearly [59].

In 2009, Siddiqui and colleagues from the Mayo Clinic [60] updated their prior surveillance

Table 17.2 Postoperative surveillance guidelines based on histological subtype – Siddiqui [60]

	Clinical assessment (history, physical exam, laboratory studies)	Chest X-ray	Abdominal CT or US
Clear cell RCC			
Low risk	Yearly	Every 6 months for 2 years, then yearly until 10 years	CT at 18, 24, 30 months then year 5, 7, 10; US at year 3, 4, 6, 8, 9
Intermediate risk	Yearly	Every 3 months for 3 years, then yearly until 10 years	CT at 6, 9, 12, 15, 24, 27, 30, 48 months then yearly until 10 years; US year 3
High risk	Yearly	Every 3 months for 1 years, then at 24 and 30 months	CT every 3 months for 2 years, then every 6 months for 1 years, then yearly until 10 years
Papillary RCC			
Low risk	Yearly	Not recommended	CT at year 1,2; US at 6, 9 months
Intermediate risk	Yearly	At 12, 18, 30, 33, 36 months then yearly until 10 years	CT year 3; US 6, 24 months then every 2 years
High risk	Yearly	At 6, 9, 12, 18, 24 months	CT at 6, 9, 12, 18, 24, months then every 2 years
Chromophobe RCC			
Low risk	Yearly	Not recommended	Not recommended
Intermediate risk	Yearly	Not recommended	CT at year 3, 7; US at year 5, 10
High risk	Yearly	At 6, 9, 15 months	CT at 3, 6 months and at year 7; US at year 3, 5, 10

protocol and included histologic subtype as one of the additional risk factors for recurrence (in addition to the previously reported 1,864 patients, the authors added 357 patients with papillary and 118 patients with chromophobe RCC). As such, tumor stage, grade, nodal status, margin status, and tumor necrosis were accounted for when recommending specific follow-up protocols. In addition, the authors recommended particular imaging at specific time intervals (Table 17.2), which was not provided in the prior manuscript in 2003 [55].

The recently updated 2012 National Comprehensive Cancer Network guidelines reflect a modified surveillance approach based on panel consensus [61]. The panel has updated the recommendation that the first follow-up should commence at an interval of 2–6 months following nephrectomy rather than 4–6 months as was stated in the 2011 version. Also the specific type of imaging recommended was modified to read "chest and abdominal imaging," leaving the choice of imaging modality at the discretion of the clinician. Follow-up laboratory studies now include the addition of lactate dehydrogenase (LDH) to the comprehensive metabolic panel. In summary, NCCN currently recommends follow-up surveillance every 6 months for 2 years, then annually for 5 years, to include a complete history and physical exam as well as a comprehensive metabolic panel and LDH. At 2–6 months postoperatively, chest and abdominal imaging should be completed and then should be ordered as indicated. Although the NCCN guidelines do not make reference to when these imaging studies are indicated, they do discuss that no single follow-up is appropriate for all patients. The panel also suggests that contemporary surveillance protocols such as the UCLA integrated scoring system (UISS) can allow for a more selective use of imaging modalities at appropriate intervals based on individual risk stratification [61] (Figs. 17.4 and 17.5).

Surveillance for Hereditary RCC

Patients with familial forms of renal cell carcinoma have a high risk of recurrence and often

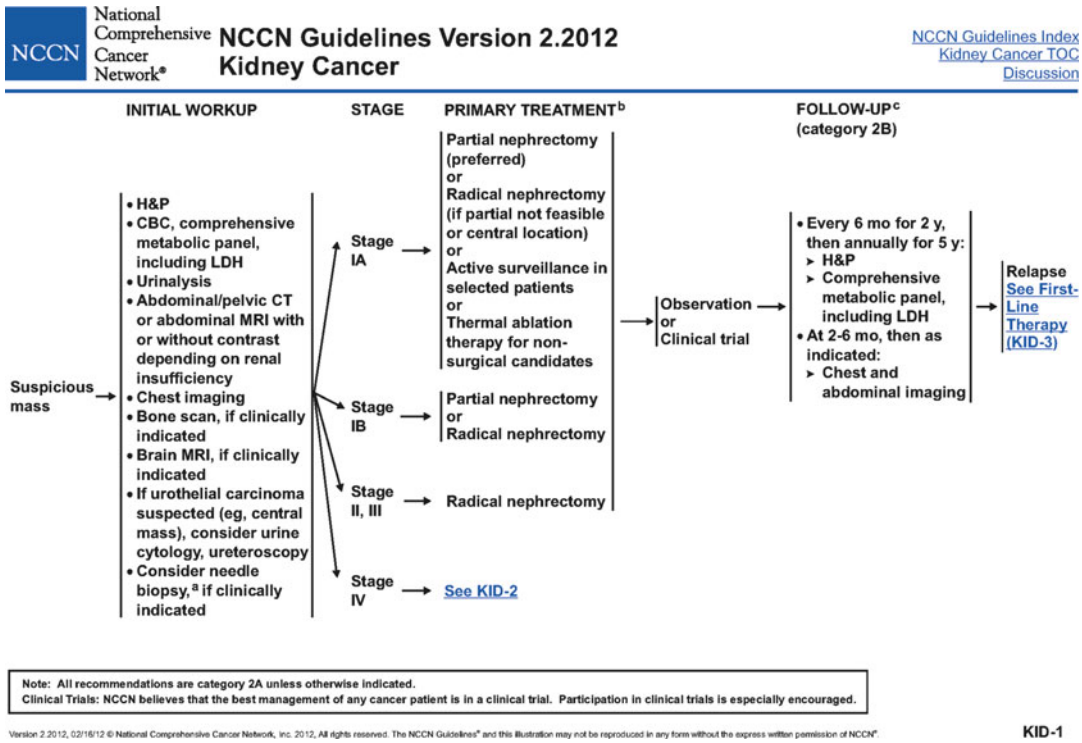

Fig. 17.4 **a** Biopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide surveillance, cryosurgery, and radiofrequency ablation strategies. **b** See Principles of Surgery (KID-A). **c** No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient and tumor characteristics. Alternate follow-up schemes have been proposed

require multiple nephron-sparing surgeries to treat their disease process. Steinbach et al. [62] conducted a multi-institutional study that reviewed 65 patients with von Hippel-Lindau (VHL) disease. Sixteen patients underwent radical nephrectomy and 49 underwent partial nephrectomy with a mean follow-up of 68 months. 51 % of patients who underwent partial nephrectomy had local recurrence in the ipsilateral kidney at a mean follow-up of 99 months and required further surgical intervention. Given the high risk of recurrence in patients with hereditary forms of RCC and the potential for multiple further surgeries, the relationship between tumor size and risk of developing metastatic disease was evaluated. Duffey et al. [63] reported metastatic disease occurring in 27 % of patients who had renal masses >3 cm, whereas no patients with tumors <3 cm were found to have evidence of metastasis. Therefore, active surveillance in this patient population has been recommended without surgical intervention until the largest tumor size approaches 3 cm. In patients who are diagnosed specifically with VHL, screening for other manifestations of their disease process is also warranted. The NIH recommends checking urinary catecholamines every 1–2 years from age 2, yearly ophthalmoscopy starting from birth, contrast-enhanced MR imaging of the brain and spine every 2 years starting at age 11 and then every 3–5 years from age 60, abdominal ultrasound yearly from age 11, and then CT abdomen every 1–2 years after age 20 [64].

Surveillance Following Ablative Therapies for RCC

As an increasing number of elderly patients with multiple medical comorbidities are diagnosed

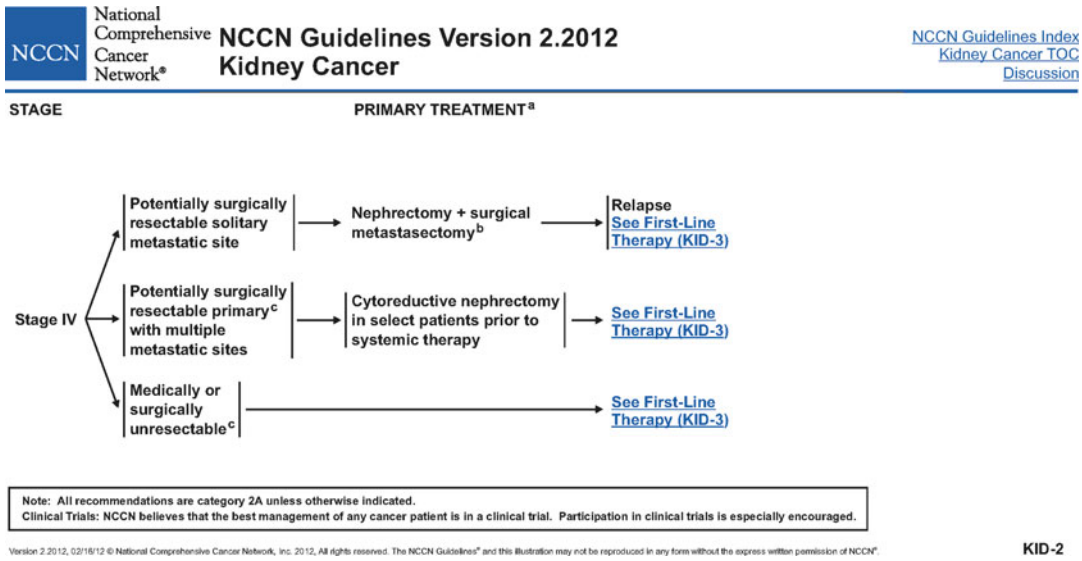

Fig. 17.5 **a** See Principles of Surgery (KID-A). **b** No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient and tumor characteristics. Alternate follow-up schemes have been proposed. **c** Individualize treatment based upon symptoms and extent of metastatic disease

with renal masses, minimally invasive nephron-sparing ablative therapies have become more popular as an alternative to partial nephrectomy. Ablative technologies include radiofrequency ablation (RFA), cryoablation, microwave, high-intensity focused ultrasound, laser interstitial thermotherapy, and radiotherapy [65–68].

The two most established ablative modalities being utilized for the definitive treatment of small renal masses are RFA and cryoablation. Data exist to support good short-term cancer control following ablative therapy, and recent literature reports promising intermediate-term outcomes [31, 69–73]. Oncological success following ablative therapy is defined as a lack of contrast enhancement and absence of tumor growth on follow-up CT or MRI imaging. Currently, a universal protocol for post-ablation imaging is undefined. Surveillance strategies following ablative therapies for RCC are therefore at the discretion of the individual physician and vary based on the institution or according to individual patient characteristics.

Radiofrequency Ablation

Contrast imaging with CT or MRI is used post ablation to monitor oncological success of treatment. Initially following therapy, the lesion visualized on CT is slightly larger. Over time, the lesions decrease in size at a rate slower than seen in lesions treated with cryoablation [74]. Unenhanced areas seen on CT correlate with tissue necrosis, and often, a hyperattenuating halo around the defect can also be seen [75]. On MRI, the lesion is also initially larger with some minimal decrease in size over time, when compared to the original tumor size. T2-weighted images reveal the ablation defect to be hypointense, and on T1, it appears hyperintense relative to the renal cortex. There can also be a slight rim of enhancement seen initially on contrast-enhanced T1-weighted imaging; however, this becomes barely present after 3 months. Any persistent enhancement on gadolinium-enhanced MRI after 3 months or increase in tumor size is consistent with residual disease until proven otherwise [75, 76].

Despite promising data reporting favorable oncological outcomes, some studies have questioned the effectiveness of radiofrequency ablation. Rendon et al. compared pathological outcomes after RFA in ten patients with a mean tumor size of 2.4 cm. Partial or radical nephrectomy was performed in four patients with five renal masses immediately following intraoperative RFA of the renal mass. Six patients underwent percutaneous RFA and then delayed nephrectomy 7 days later. Pathologic evaluation of the nephrectomy specimens revealed residual viable tumor in 4 of 5 specimens in the acute group and 3 of 6 specimens in the delayed group [77]. The group from Cleveland clinic also investigated the presence of residual viable tumor following RFA. They discovered that 46 % of patients in their cohort had a positive biopsy 6 months following RFA despite the lack of enhancement demonstrated on CT or MRI [78]. The discrepancy between radiographic imaging and pathologic findings following RFA has made it difficult to determine the success of therapy based on imaging alone. However, accurate interpretation of the pathologic specimen has also been questioned and surmised to be time dependent (i.e., not all positive pathology following RFA indicates true presence of disease). RFA causes heat fixation of tumor cells – a process that preserves atypical cellular architecture and delays degeneration, making it difficult to distinguish treatment effect from viable tumor [79]. The time period in which cellular degeneration is complete is debated in the literature and further study is needed to reconcile these inconsistencies. Most investigators agree that biopsies should be done at least 6 months after RFA, when clinically indicated, to minimize false-positive results and avoid misinterpretation. However, there are currently no guidelines to support routine biopsy following RFA when recurrence or residual disease is not suspected radiographically [78].

Cryoablation

Since cryoablation does not uniformly freeze the lesion, most clinicians use a 1 cm margin beyond the tumor edge to ensure the entire tumor reaches the critical temperature for successful treatment [80]. Unlike RFA, histologic evaluation post cryoablation reveals a fibrotic scar with inflammatory changes, and there is no preservation of tumor or normal renal parenchymal cellular architecture [31].

On CT imaging immediately following cryoablation, the lesion appears as a larger hypoattenuating defect. Over time, lesions decrease in size at a rate faster than that of RFA-treated lesions. Cryoablated tumors appear isointense to hyperintense on T1-weighted MR images and hypointense on T2 images [75]. It is not uncommon to see complete resolution of the ablation defect on follow-up imaging. Rukstalis et al. described 20 of 23 patients as having complete resolution of the treated mass or small residual scar on MRI at 3 months [81]. Gill et al. reported a 75 % reduction in defect size over 3 years, with no evidence of scar detected in 38 % of patients [82].

As many institutions began to incorporate minimally invasive ablative therapies into their treatment modalities for small renal masses, the accuracy of follow-up imaging to detect disease recurrence and the optimal timing of surveillance came into question. As with radiofrequency ablation, several groups set out to validate the definition of radiographic success following cryoablation. Weight et al. [78] investigated the correlation of radiographic imaging and histopathology following ablative therapy for renal masses. One hundred percent of the cryoablation cohort who had no evidence of enhancement on post-ablation imaging also had negative biopsies. A total of six positive biopsies were obtained from the cryoablation cohort, and all of these came from tumors that demonstrated some degree of enhancement. Peripheral enhancement was observed in 26 lesions at 6 months follow-up, and of those, only two yielded positive biopsies. There were 11 centrally enhancing lesions identified on imaging at 6 months and positive biopsies were found in four of those patients. The sensitivity of central enhancement on 6-month follow-up to predict a positive biopsy following

Table 17.3 Examples of surveillance protocols following ablative therapy of renal masses

	Preferred imaging modality and schedule	Technology used and year started	Access route	Routine biopsy on follow-up
Case Western Reserve University	MRI Week 2, month 3, 6, 9, 12, then biannually	RFA, 1999	Percutaneous	No
Cleveland Clinic	MRI Day 1, month 1, 3, 6, 12 then yearly	Cryoablation, 1999; RFA, 2002	Percutaneous; laparoscopic	Yes, at 6 months
Fox Chase Cancer Center	CT Month 1, 3, 6, 12, then every 6 months	RFA and cryoablation, 2002	Percutaneous and laparoscopic	No
Massachusetts General Hospital	CT Month 1, 3, 6, and 12, then every 6–12 months	RFA, 1998	Percutaneous	No
M. D. Anderson Cancer Center	CT Month 1, 3, 6, 12, then every 6–12 months	RFA, 2001; cryoablation, 2002	Percutaneous and laparoscopic	No
Southwestern Medical Center	CT Week 6, month 6, 12, then yearly	RFA, 2001	Percutaneous and laparoscopic	No
Wake Forest University	CT Month 2, 8, then every 6 months	RFA, 2000	Percutaneous	No

Reprinted from Matin et al. Residual and recurrent disease following renal energy ablative therapy: a multi-institutional study. J Urol. 2006;176(5):1973–77, with permission from Elsevier

cryoablation was 77.8 %, with 95 % specificity, 63.4 % PPV, and 97.7 % NPV [78].

A series by Beemster et al. concluded that at 6 months following cryoablation, persistent rim enhancement occurred in 20 % of cryolesions with a size reduction of 38 % despite negative histopathological diagnosis. The rim enhancement disappeared on further follow-up imaging, and the authors concluded that persistent rim enhancement is common in the first few months following cryoablation, and routine biopsies are not justified [83].

Recommendations for Surveillance Following Radiofrequency Ablation or Cryoablation

Given the variation in follow-up protocols after ablative therapy and the lack of a universal surveillance strategy, Matin et al. conducted a multi-institutional study with the objective of providing evidence-based recommendations [84]. In this retrospective review of data from seven institutions (Table 17.3), recurrence patterns were reviewed for 616 patients who underwent RFA or cryoablation. Residual disease was defined as enhancement seen on the first CT or MRI following ablative therapy. Recurrent disease was any enhancement demonstrated after an initial negative imaging study. Residual or recurrent disease occurred in a total of 63 patients, 55 of 410 (13.4 %) undergoing RFA and 8 of 206 (3.9 %) undergoing cryoablation. Approximately 70 % of residual or recurrent disease was detected within the first 3 months of surveillance imaging and 92 % was detected within the first year of surveillance following ablative therapy. Of the 63 patients who had residual or recurrent disease, 46 underwent salvage ablative therapy and 37 patients had no further evidence of disease on follow-up imaging. Metastasis-free survival for the patients who had recurrent or residual disease following ablative therapy was 97.4 % at 2 years. Survival did not differ based on type of approach (laparoscopic vs. percutaneous) or ablative modality utilized (RFA vs. cryoablation) [84].

Based on these findings, a minimum schedule of 3–4 imaging studies was recommended in the first year following ablative therapy for renal masses. A CT scan or MRI without and with intravenous contrast is recommended in month 1, 3, 6 (optional), and 12.

The Future of Surveillance

The Incorporation of Molecular Markers into Surveillance Strategies

In the current era of targeted therapy, research efforts have focused on the molecular biology of renal cell carcinoma and the impact of individual molecular markers on diagnosis, prognostication, and surveillance. Several prognostic algorithms exist based on clinicopathologic factors that predict disease progression and survival with acceptable accuracy [85]. The addition of molecular markers to clinicopathologic factors has been shown, in limited studies, to improve accuracy of these prognostic models.

Many molecular biomarkers have been identified and demonstrated to predict cancer-specific survival as well as disease progression in patients with renal cell carcinoma. To name a few, Nogueria and Kim provide a thorough review on all prognostic molecular markers [86] and Crispen et al. evaluated the markers IMP-3, CXCR3, p53, survivin, cIAP1, B7-H1, and B7-H4 that specifically predict disease progression following nephrectomy [87]. However, these are not in routine clinical use and are mainly limited to research studies. On the other hand, clinically available markers, such as C-reactive protein, have been shown to have potential in identifying patients at risk of recurrence after definitive surgery [88] and should be further validated in external cohorts. Other studies have evaluated that biomarkers are prognostic factors and will be covered in a separate chapter.

Despite the valuable prognostic information that molecular markers confer, they also have several limitations in clinical practice. The majority of biomarkers that have been identified require histopathologic examination of the tumor specimen. In addition, the cost, reproducibility, need for special expertise, commercial availability of the antibodies, and lack of large-scale external validation limit the use of these biomarkers in clinical practice at present. Future research efforts should focus on identifying important molecular markers in the serum or urine that could potentially play a valuable role in identifying early diagnosis of disease recurrence as well as measure response of individuals to systemic therapy [85].

Use of F-18 Fluorodeoxyglucose Positron Emission Tomography in Surveillance and Reducing Risk of Radiation Exposure

Computed tomography (CT) without and with intravenous contrast is the most common imaging modality being utilized in the postoperative setting for surveillance of disease progression in patients with renal cell carcinoma. With the number of diagnostic CT scans dramatically increasing in the United States over the past several decades, there has been growing concern over radiation exposure and risk of developing a secondary malignancy [89, 90]. The National Council on Radiation Protection and Measurements (NCRP) reported that radiation exposure associated with medical technology has risen sixfold since the 1980s from 0.5 to 3.0 mSv [91]. In 2007, Brenner et al. estimated that as many as 1.5–2 % of cancers could be a result of radiation from CT scans [89]. In response to these worrisome trends, the Food and Drug Administration (FDA) launched an initiative in 2010 to reduce radiation exposure from medical imaging and increase patient awareness about the risks of frequent exposure [91].

As the effort to minimize radiation exposure has been emphasized, and in search of more sensitive imaging modalities, several studies have investigated the use of alternative imaging modalities for surveillance. The use of F-18 fluorodeoxyglucose positron emission tomography (PET scan) has been investigated in preoperative setting with various results. While some groups have found it to be equally sensitive as CT imaging in detecting malignancy in the primary tumor, other groups have demonstrated the sensitivity of PET scans to be inferior [92, 93]. Use of

PET scan to detect lymph node-positive disease has been shown to be superior to CT imaging, and these results suggest the use of PET scan may be more valuable as an adjunctive role in surveillance [93, 94]. A study by Nakatani et al. recently evaluated the potential clinical value of FDG-PET in the postoperative period to detect disease recurrence. They reviewed 28 scans in 23 patients who underwent a PET scan in addition to CT following nephrectomy for renal cell carcinoma. PET scan identified 17 true positive cases and two false positives. Metastatic lesions were correctly identified in all but four cases. Overall sensitivity, specificity, accuracy, PPV, and NPV were 81 %, 71 %, 79 %, 90 %, and 56 %. This group also demonstrated 5-year survival rates of 46 % for patients with positive PET scans versus 83 % for those with negative PET scans [95]. When compared to CT scan alone, the authors concluded that PET scan had little impact on therapeutic decisions. Although the results are promising, further studies are needed to validate these findings and determine the value of this modality in surveillance.

In addition to limiting radiation exposure with PET/CT scan, MRI scans can be alternatively used. However, the utility of MRI for postoperative surveillance has not been well studied or established and is not currently routinely used.

Cost of Surveillance

In the current economic climate, increasing health-care utilization and cost has been extensively scrutinized. The goal of an ideal surveillance protocol is to accurately detect the presence of disease progression in a timely fashion while minimizing the cost and radiation risk associated with unnecessary over imaging. Levy et al. reviewed the number and cost of CT scans performed 24 months following nephrectomy in 286 patients. A total of 344 CT scans were completed in the first 2 years following nephrectomy, 95 CT scans for patients with pT1 disease, 102 for patients with pT2 disease, and 147 for those with pT3 disease. Each CT was estimated to cost $1,200 for a total cost of $412,800 [14].

Dion et al. performed a cost-analysis comparison of two surveillance strategies in a Canadian cohort [96]. The authors compared the follow-up practices performed at their own institution with a projected cost of surveillance had they followed the 2009 Canadian Urological Association (CUA) guidelines. Mean follow-up was 31 months for 75 patients who had undergone nephrectomy for localized renal cell carcinoma. They concluded total medical costs, in Canadian dollars, were higher for their institutional strategy than the CUA guidelines ($181,861 vs. $135,054). Interestingly, when analyzing cost by tumor stage, the cost to survey patients with pT1 tumors at the authors' institution was more expensive than the calculated cost based on the CUA guidelines, whereas the cost to survey patients with pT3 tumors was more expensive as estimated by the CUA guidelines. This was likely secondary to over imaging patients with pT1 tumors who may have had little indication for CT scan with low risk of abdominal recurrence [96].

Siddiqui et al. [60] performed cost analysis comparing the Mayo surveillance protocol to a traditional scheme, as well as other published work [14–16, 22] using Medicare Part B reimbursement estimates. They reported that the Mayo algorithm was more expensive than stage-based algorithms for patients with clear cell RCC, while it resulted in more savings compared to traditional protocols and the UCLA protocol in patients with papillary and chromophobe RCC.

Conclusion

Patients with renal cell carcinoma are at risk of recurrence, even after definitive surgical therapy, and should be carefully, but rationally, monitored for prolonged duration to detect recurrences early enough to allow meaningful intervention that could lead to prolonged survival. While many current guidelines use loose recommendations for follow-up with much discretion left for individual urologists, it is clear that we need a risk-based approach, driven by evidence, in order to provide optimal postoperative surveillance for patients with renal cell carcinoma. Hopefully,

advances in genomic sciences and molecular markers can help us develop more robust and individualized follow-up schema for our patients in the future.

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