Chapter 16
Posttreatment Surveillance for Renal Cell Carcinoma

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Introduction

Following the treatment of renal cell carcinoma (RCC), 20–38% of patients with localized tumors will experience disease progression [1, 2]. The most common sites of recurrence are pulmonary (52–64%) and osseous (9–15%), in addition to the pancreas (3–7%), liver (5–11%), distant lymph nodes (4–7%), brain (7%), adrenal gland (10%), and other sites (3–33%) [3]. Local recurrences to the renal fossa, ipsilateral adrenal gland, and regional lymph nodes are relatively rare, occurring in 0.8–3.6% of patients [4–7]. Prompt recognition of recurrence and progression of RCC is proposed to be of benefit in cases of local recurrence, as the most effective treatment appears to include locally directed therapy (i.e., cytoreductive surgery or ablation) which is more easily administered to less extensive foci of disease [4]. It is worth noting, however, that although early detection of asymptomatic metastatic RCC is thought to be worthwhile, the degree of clinical benefit remains to be determined.

Overall the 5-year recurrence-free survival for RCC ranges from 41.9% to 97.8% [3]. While the highest degree of risk for recurrence appears to be within the first 5 years following treatment, this risk varies substantially according to both disease characteristics such as stage and grade and treatment-related factors including surgical approach, utilization of nephron-sparing strategies, and surgical margin status [8, 9]. Additionally, time to recurrence varies between different anatomical

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locations. For example, the median time to pulmonary, osseous, and brain metastases for a pT2 RCC are 31, 24, and 11 months, respectively [8].

Posttreatment surveillance for recurrences is a cornerstone of the management of patients with RCC and is based on the premise that identification of both local and distant asymptomatic recurrences can permit the prompt initiation of treatment of relapses, with the goal of improving cancer-specific survival. Furthermore, posttreatment surveillance permits early detection of renal function deterioration and timely referral to nephrology as indicated. The rationale for surveillance for RCC relapse after initial definitive treatment is therefore to permit timely initiation of treatment, with the goal of extending survival.

In this chapter, we review published risk stratification tools for patients with RCC who have undergone surgical treatment. In addition, we summarize and compare contemporary posttreatment surveillance guidelines. Finally, we evaluate the limitations of contemporary guidelines as well as identify challenges in optimizing posttreatment surveillance.

Risk Prognostication: Assessing Risk of Relapse at the Time of Treatment

As noted, the risk of relapse following treatment varies considerably according to tumor biology, patient-specific, and treatment-related factors. Recommendations regarding the intensity of posttreatment surveillance vary according to risk prognostication, underscoring the importance of accurately characterizing a patient's risk for relapse at the time when a surveillance strategy is undertaken.

Tumor-specific Prognostic Factors

Tumor Size

Among patients with small renal masses (i.e., <4 cm in diameter), there is conflicting evidence regarding whether tumor size is associated with malignant versus benign histology [10, 11]. However, there is a strong association between increasing tumor size and risk of RCC recurrence. Among patients with localized RCC who have undergone extirpation, local recurrence-free survival and metastasis-free survival decreases significantly with each 1 cm in size of the tumor [12].

Tumor Stage

The American Joint Commission on Cancer tumor-node-metastasis (TNM) staging system is the universally accepted system utilized to describe RCC, incorporating tumor size as well as the extent of local infiltration and distant lymphatic and metastatic involvement to characterize the anatomic extent of the disease [13]. Validation

studies of earlier versions of the TNM system for kidney tumors [14, 15] have resulted in refinements of prior version, leading to the current iteration which includes a subclassification within T2 cancers based on a tumor size cutoff of 10 cm (T2a ≤ 10 cm and T2b > 10 cm), inclusion of both perirenal fat involvement and renal vein tumor thrombus in the T3a stratum, and classification of patients with ipsilateral adrenal disease T4 cancer. Independent validation of this system has been performed in large retrospective single- and multi-institutional cohorts [16, 17]. The estimated 10-year cancer-specific survival for patients treated with either radical or partial nephrectomy according to the primary tumor classifications using the updated TNM staging system was 96%, 80%, 66%, 55%, 36%, 26%, 25%, and 12% for pT1a, pT1b, pT2a, pT2b, pT3a, pT3b, pT3c, and pT4, respectively [17].

Collecting System Invasion

Invasion of the renal collecting system by RCC is independently associated with an increased risk of RCC recurrence [18]. A meta-analysis of 17 pooled studies demonstrated a 2.3-fold increased risk of RCC in patients with collecting system invasion and increased risk of cancer-specific mortality, especially in patients with stage T1-2 cancers, leading the authors to suggest that RCC patients with urinary collecting system invasion may warrant more intense surveillance following treatment [18].

Tumor Grade

The Fuhrman nuclear grading system was first described in 1982 and up until recently was widely used for the grading of RCC [19]. In this system, a nuclear grade of 1 to 4 is assigned according to a combination of nuclear size, irregularity, and nucleolar prominence. Fuhrman nuclear grade is independently associated with increased risk of recurrence [20–22]. There are, however, several limitations to the Fuhrman grading system including challenges related to incorporating the three scored components into a single grade and the fact that nuclear atypia is frequently noted in indolent chromophobe tumors. In light of these limitations, the International Society of Urological Pathology (ISUP) now recommends that grading should be based solely on nucleolar prominence and only be applied to cases of clear cell and papillary RCC [23].

Histologic Subtypes of Renal Cell Carcinoma

As mentioned in earlier chapters in this book, RCC is comprised of multiple distinct histologic variants, each of which is associated with variable metastatic potential and oncologic outcomes. The most common subtype is clear cell RCC (75%), followed by papillary RCC (10%), chromophobe RCC (5%), clear cell papillary RCC (1–4%), collecting duct RCC (1%), and rare variants such as Xp11 translocation tumors and mucinous tubular and spindle cell tumors [24]. In a contemporary population-based series of 17,605 surgically treated RCC patients, Keegan et al.

observed that the prevalence of advance disease at diagnosis (pT3/pT4, N1, or M1) varied considerably between the histologic variants: 28% of patients with clear cell RCC compared to 82.8% of patients with sarcomatoid, 55.7% of collecting duct, 17.6% of papillary, and 16.9% of patients with chromophobe RCC. On multivariable analysis, compared to clear cell RCC, chromophobe histology was associated with decreased all-cause mortality, while collecting duct and sarcomatoid histology were independently associated with increased mortality (HR 2.97 and 2.26, respectively) [25].

Other Histologic Features Associated with Increased Risk of Posttreatment Relapse

Microvascular invasion (MVI) is another pathologic feature that is associated with risk of RCC recurrence [23, 26, 27]. Dall'Oglio and colleagues demonstrated that the 5-year disease-free survival was 27.2% (95% confidence interval [CI] 14.9–50.3%) for patients with MVI compared to 87.1% (95% CI 79–95%) for patients without MVI in a retrospective series of 230 patients [28]. In a large meta-analysis including nearly 15,000 patients, MVI was found to be independently associated with a 2.7-fold increased risk of local recurrence (HR = 2.75, 95% CI 1.97–3.83), a 1.6-fold increase in the risk of metastasis (HR = 1.62, 95% CI 1.095–2.40), and 2.1-fold increase in the risk of cancer-specific mortality (HR = 2.09, 95% CI 1.53–2.86) [27].

Sarcomatoid differentiation describes an aggressive and highly lethal variant of RCC [29]. These tumors are characterized by spindle-like cells with high cellularity and cellular atypia and comprise approximately 5% of cases of RCC [30]. In a series of 206 patients with sarcomatoid RCC, nearly half of patients presented with synchronous metastatic disease and 70% of those without metastases at the time of surgery developed distant relapse [31].

Lymphovascular invasion (LVI) is identified in 5–20% of patients with RCC, with a higher prevalence among cases of locally advanced disease (pT3–pT4) [32]. Patients with organ-confined RCC found to have LVI has been observed to have similar oncologic outcomes to patients with locally advanced tumors [32].

Coagulative tumor necrosis is associated with adverse clinicopathologic and molecular features in RCC [23, 33] and is associated with increased risk of disease recurrence and cancer-specific death [22, 34, 35]. The most recent ISUP recommendations included the statement that, for clear cell RCC, the presence or absence of tumor necrosis should be included in routine pathology reports given its association with oncologic outcomes [23]. Conversely, there is conflicting evidence regarding the prognostic utility of necrosis in nonclear cell histologies; thus this recommendation is not applied to all RCC morphotypes [36].

Prognostic Nomograms and Risk Scores

Several risk models incorporating a variety of prognostic factors have been developed to further improve the postsurgical risk stratification of patients with RCC [21, 33, 35–41].

One example of a risk stratification tool is the *Cindolo Recurrence Risk Formula* [37], which generates a risk of tumor recurrence on the basis of tumor size at the time of treatment and the presence or absence of symptoms related to the tumor at diagnosis. A score is generated according to the formula [1.28 × presentation (asymptomatic, 0; symptomatic, 1) + 0.13 × clinical size]. For scores ≤1.2, the 5-year disease-free survival was 93% compared to 68% for a score > 1.2 [37].

Another risk stratification tool is the *Kattan nomogram* which incorporates histologic subtype, tumor size, 2002 TNM classification, and the presence or absence of symptoms [38]. The predictive accuracy of this nomogram has subsequently been validated in contemporary practice using the 2010 TNM staging system [39].

The *Leibovich prognosis score* (PROG score) [40] estimates the risk of progression to metastatic RCC after radical nephrectomy. This algorithm utilizes pathological T stage (pT1–pT4), regional lymph node spread (pNx-pN2; 2002 TNM criteria), tumor size (<10 or ≥10 cm), nuclear grade (1–4), and presence of histological tumor necrosis (yes or no). After scoring, patients can be stratified into three risk groups: low (0–2), intermediate (3–5), and high (≥6), with a 5-year metastasis-free survival rates of 97.1%, 73.8%, and 31.2%, respectively.

The *Mayo Clinic SSIGN score* [22] is another validated prognostication system that predicts cancer-specific survival for patients with clear cell RCC after radical nephrectomy. This system utilizes the same features as the Leibovich algorithm to assess survival except for the inclusion of metastasis: the pathological T stage (pT1-pT4), regional lymph node spread (pNx-pN2), M stage (pM0 or pM1; 2002 TNM criteria), tumor size (<5 or ≥5 cm), nuclear grade (1–4), and presence of histological tumor necrosis (yes or no). Patients with a SSIGN score of 0–1, 5, and ≥10 have 5-year cancer-specific survivals of 99.4%, 65.4%, and 7.4%, respectively. Zigeuner and colleagues provided evidence for the external validation of the SSIGN score through a retrospective multivariate analysis of 1862 patients [41]. Recently, Parker and colleagues validated the SSIGN score in a contemporary cohort of surgically treated RCC patients, confirming that the c-index was preserved across 3600 patients treated with radical nephrectomy from 1970 to 1998 (the development cohort) and those treated with either radical or partial nephrectomy from 1999 to 2010 [35]. The authors observed that the c-index was preserved across the three cohorts (*c*-index = 0.82, 0.84, and 0.82, respectively) [35].

The *Karakiewicz nomogram* [42] was developed using data from 2530 patients treated with either radical or partial nephrectomy for renal cortical tumors. The nomogram incorporates the 2002 TNM stages, tumor size, Fuhrman grade, histologic subtype, local symptoms, age, and sex to generate predictions for cancer-specific survival. This nomogram was externally validated in an additional 1422 patients, demonstrating 88.8% accuracy at 10 years [42].

The University of California Los Angeles Integrated Staging System (UISS) [41] is a prognostication system that predicts overall survival in patients with any histological subtype of kidney cancer after surgical resection. Patients are stratified into five categories (I–V) based upon the TNM staging system (1997 TNM criteria), Eastern Cooperative Oncology Group (ECOG) performance status, and Fuhrman grade. Risk groups are further differentiated based upon local versus metastatic disease. Patients categorized as UISS I, II, III, IV, and V have a 5-year overall survival rate of 94%, 67%, 39%, 23%, and 0%, respectively. The UISS algorithm can be broadly used to assess treatment outcomes, determine the need for adjuvant therapy, and assess eligibility for future clinical trials [1, 43, 44].

Treatment-Associated Factors

Oncologic Outcomes Following Partial vs. Radical Nephrectomy vs. Thermal Ablation

For pT1a renal cortical tumors (<4 cm, confined to the kidney), management strategies include partial nephrectomy (PN), radical nephrectomy (RN), thermal ablation, or active surveillance [44, 45]. The comparative effectiveness of definitive treatments has focused predominantly on cancer-specific survival, renal function preservation, and comparison of complications rates [46], while, at this time, there is relatively limited data available regarding patient-reported quality of life outcomes. A recent meta-analysis regarding the management of localized kidney cancer concluded that, regarding oncologic outcomes, comparisons of RN versus PN demonstrated relatively equivalent oncologic outcomes for T1a, T1b, and T2 tumors [46]. In contrast, when comparing PN to thermal ablation, this analysis found a higher local recurrence rate with ablation. However, when repeat treatment for residual tumor following initial thermal ablation was taken into account, there was no significant difference in recurrence risks between PN and thermal ablation.

Positive Surgical Margins

Among patients treated with PN, the prognostic implications of *positive surgical margins* are a subject of debate. Following PN, positive surgical margins are detected in 1.7–10% of patients [47–49]. In a population-based sample, positive surgical margins have been associated with increased all-cause mortality following PN (HR = 1.34, 95% CI 1.01, 1.78) [49]. Similarly, in a large multi-institutional cohort of 1240

patients with a median follow-up of only 33 months, positive surgical margins were associated with a twofold increase in the risk of local recurrence [48]. However, when these results were stratified into high risk (pT2–pT3; Fuhrman grades III–IV) versus low-risk disease (pT1, Fuhrman grades I–II), positive surgical margins were associated with increased risk of local relapse among high-risk patients, but not those with low-risk disease on multivariable analysis (HR = 7.48, 95% CI 2.75–20.34 vs. HR = 0.62, 95% CI 0.08–4.7). Conversely, a multicenter Korean study of 1831 patients with a median follow-up of 32.5 months did not identify any difference in local recurrence-free survival on the basis of positive margin status [47].

Positive surgical margins following RN are reported in 0.8–2.3% of cases [22, 50, 51] and are associated with a risk of local recurrence of 3.5–6.3% [52]. Approximately 4% of patients with positive surgical margins have been observed to ultimately develop metastases; however, surgical margin status has not been found to be independently associated with metastasis-free survival or cancer-specific survival after adjusting for other relevant confounding factors [53, 54].

At this time, guidelines from both the American Urological Association (AUA) [45] and Eastern Association of Urology (EAU) [44] acknowledge the potential for increased risk of RCC relapse in the setting of positive margins and recommend that these patients be surveilled according to the high-risk protocols.

With respect to vascular margin status, while gross tumor at the vein margin may be identified in up to 32% of patients treated with RN [52, 55], microscopic disease at the vascular margin is reported in 18.4% of cases with venous tumor thrombus [55, 56]. Abel and colleagues reviewed a series of 256 patients with RCC and venous tumor thrombus and identified local recurrence in only 2 patients (0.8%) [55]. On multivariable analysis, the authors reported that positive vascular margins were independently associated with an increased risk of local recurrence, but not with systemic recurrence or cancer-specific mortality. Similar findings have been reported by Liu and colleagues who noted that, among patients with venous tumor thrombus, the risk of relapse following nephrectomy is most strongly associated with the degree of the tumor thrombus extent, while the positive vascular margins were not associated with either disease progression or survival [56].

Summary of Established Surveillance Guideline Statements

Posttreatment surveillance is a fundamental component in the treatment and care of patients with RCC. Appropriate surveillance allows urologists to assess for local or distant recurrence, postoperative complications, and renal function. Established guidelines from the AUA [45], Canadian Urological Association (CUA) [57], EAU [44], and National Comprehensive Cancer Network (NCCN) [58] all emphasize the importance of posttreatment surveillance but with minor variations (i.e., imaging modalities, surveillance timeline, risk stratification, etc.). What follows is a summary of the most current recommendations for posttreatment surveillance of RCC from each governing body as of the writing of this text. Table 16.1 provides a summary of the various schedules of examinations recommended by each guideline committee.

Table 16.1 Summary of the recommended surveillance schedules following treatment of localized renal cell carcinoma by guidelines committee

Guideline statement (last updated)	Risk group/treatment approach	Recommended testing	Months after treatment									
			3	6	12	18	24	30	36	48	60	72
AUA (2013)[c]	***Thermal ablation***[d]	*History and physical examination*[a]	X	X	X		X		X	X	X[o]	
		Laboratories[b]	X	X	X		X		X	X	X[o]	
		Chest surveillance			XR		XR		XR	XR	XR	
		Abdominal surveillance	CT or MRI	CT or MRI	CT or MRI		CT or MRI		CT or MRI	CT or MRI	CT or MRI[o]	
	Low-risk (pT1 Nx-0) Partial nephrectomy	*History and physical examination*[a]	X				X		X[o]			
		Laboratories[b]	X				X		X[o]			
		Chest surveillance	XR				XR		XR[o]			
		Abdominal surveillance	Baseline CT or MRI within 3–12 months				CT, MRI, or US[p]		CT, MRI, or US[o,p]			
	Low-risk (pT1 Nx-0) Radical nephrectomy	*History and physical examination*[a]	X				X		X[o]			
		Laboratories[b]	X				X		X[o]			
		Chest surveillance	XR				XR		XR[o]			
		Abdominal surveillance	Baseline CT or MRI				CT, MRI, or US[p]		CT, MRI, or US[o,p]			
	Moderate/high risk (pT2–pT4 Nx-0, pT1–pT3 N1, pT)	*History and physical examination*[a]	X		X	X	X	X	X	X	X[o]	
		Laboratories[b]	X		X	X	X	X	X	X	X[o]	
		Chest surveillance	CT or MRI		XR/CT	XR/CT	XR/CT	XR/CT	XR/CT	XR/CT	XR/CT[o]	
		Abdominal surveillance	Baseline CT or MRI		CT, MRI, or US	CT, MRI, or US	CT, MRI, or US	CT, MRI, or US	CT, MRI, or US	CT, MRI, or US	CT, MRI, or US[o]	

Guideline statement (last updated)	Risk group/treatment approach	Recommended testing	Months after treatment									
			3	6	12	18	24	30	36	48	60	72
CUA (2008)[e,f]	***pT1***	*History and physical examination*			X		X		X	X	X	X[o]
		Laboratories[h]			X		X		X	X	X	X[o]
		Chest surveillance			XR		XR		XR	XR	XR	XR[o]
		Abdominal surveillance (partial nephrectomy)	CT[p]		US		US		US	US	US	US
		Abdominal surveillance (radical nephrectomy)					CT or US				CT or US[o]	
	pT2	*History and physical examination*		X	X		X		X	X	X	X[o]
		Laboratories[h]		X	X		X		X	X	X	X[o]
		Chest surveillance		XR	XR	XR	XR	XR	XR	XR	XR	XR[o]
		Abdominal surveillance			CT or US				CT or US		CT or US[o]	
	pT3	*History and physical examination*		X	X		X		X	X	X	X[o]
		Laboratories[h]		X	X		X		X	X	X	X[o]
		Chest surveillance		XR	XR	XR	XR	XR	XR	XR	XR	XR[o]
		Abdominal surveillance		CT	CT	CT	CT		CT	CT	CT	CT[r]
	pTany N1	*History and physical examination*	X	X	X		X		X	X	X	X[g]
		Laboratories[h]	X	X	X		X		X	X	X	X[g]
		Chest surveillance	XR	XR	XR	XR	XR	XR	XR	XR[f]	XR[f]	XR[g]
		Abdominal surveillance	CT	CT	CT	CT	CT		CT	CT	CT	CT[g]

(continued)

Table 16.1 (continued)

Guideline statement (last updated)	Risk group/treatment approach	Recommended testing	Months after treatment									
			3	6	12	18	24	30	36	48	60	72
EAU (2016)[i]	***Low risk (radical nephrectomy or partial nephrectomy only)***	*History and physical examination[j]*										
		Laboratories[j]										
		Chest surveillance			CT				CT		Ct[q]	
		Abdominal surveillance		US	CT		US		CT	US	Ct[q]	
	Intermediate risk (radical/partial nephrectomy, thermal ablation)	*History and physical examination[j]*										
		Laboratories[j]										
		Chest surveillance		CT	CT		CT			CT	CT[r]	
		Abdominal surveillance		CT	CT		CT		US	CT	CT[r]	
	High risk (radical/partial nephrectomy, thermal ablation)	*History and physical examination[j]*										
		Laboratories[j]										
		Chest surveillance		CT	CT		CT		CT	CT	CT[r]	
		Abdominal surveillance		CT	CT		CT		CT	CT	CT[r]	

Guideline statement (last updated)	Risk group/treatment approach	Recommended testing	Months after treatment									
			3	6	12	18	24	30	36	48	60	72
NCCN (2016)[l]	***Thermal ablation***	*History and physical examination*		X	X	X	X		X	X	X	
		Laboratories[m]		X	X	X	X		X	X	X	
		Chest surveillance			XR or CT		XR or CT		XR or CT	XR or CT	XR or CT	
		Abdominal surveillance	CT or MRI		CT, MRI, or US		CT, MRI, or US		CT, MRI, or US	CT, MRI, or US	CT, MRI, or US	
	pT1 Nx-0 Partial nephrectomy	*History and physical examination*		X	X		X		X	X	X	
		Laboratories[m]		X	X		X		X	X	X	
		Chest surveillance			XR or CT		XR or CT		XR or CT[o]			
		Abdominal surveillance	CT, MRI, or US			CT, MRI, or US[p]		CT, MRI, or US[o,p]				
	pT1 Nx-0 Radical nephrectomy	*History and physical examination*		X	X		X		X	X	X	
		Laboratories[m]		X	X		X		X	X	X	
		Chest surveillance			XR or CT		XR or CT		XR or CT[o]			
		Abdominal surveillance	CT, MRI, or US[o]									
	pT2–pT3 Nx-0 or pT1–pT3 N1 or pT4 Nx-1 Radical nephrectomy	*History and physical examination*[n]	X	X	X	X	X	X	X	X[o]		
		Laboratories[m]	X	X	X	X		X	X	X[o]		
		Chest surveillance[n]	XR or CT		XR or CT	XR or CT	XR or CT	XR or CT	XR or CT	XR or CT	XR or CT[o]	
		Abdominal surveillance[n]	CT or MRI		CT, MRI, or US	CT, MRI, or US	CT, MRI, or US	CT, MRI, or US	CT, MRI, or US	CT, MRI, or US	CT, MRI, or US[o]	

(continued)

Table 16.1 (continued)

XR chest X-ray, *CT* computed tomography, *US* abdominal ultrasound

[a]History and physical exam directed at detecting progression or metastases

[b]Basic laboratories to include BUN/creatinine, UA, estimated glomerular filtration rate. Complete blood count, lactate dehydrogenase, liver function tests, alkaline phosphatase, and calcium to be used at the discretion of the physician. The AUA guidelines stipulate that progressive renal insufficiency should prompt referral to nephrology

[c]Pelvic imaging, spine MRI, bone scan to be performed as clinically indicated

[d]The panel recommends against further radiographic imaging for any patients with pathologically confirmed benign histology before or at the time of treatment and have radiographic confirmation of treatment effect and no complications

[e]Recommendations for follow-up after partial nephrectomy or radical nephrectomy only. No recommendations given for follow-up after thermal ablation

[f]Chest X-ray may be alternated with chest CT

[g]Annual surveillance is recommended to continue

[h]Laboratory studies include complete blood count, serum chemistries, and liver function tests

[i]Risk stratification utilizing one of the multifactor prognostic nomograms discussed in section "Treatment-Associated Factors". Surveillance includes evaluation of renal function and cardiovascular risk

[j]There is no commentary in the most recent update to the EAU recommendations regarding the frequency of non-imaging-based surveillance including clinic visits or laboratory examinations

[k]Optional after radical nephrectomy only

[l]Pelvic CT or MRI, CT or MRI of the head, MRI of the spine, bone scan as clinically indicated

[m]Comprehensive metabolic panel with other tests as indicated

[n]Every 3–6 months for 3 years and then annually for years 4 and 5

[o]Ongoing follow-up at the physician's discretion

[p]Optional after baseline

[q]Patients to be discharged

[r]Follow-up thereafter every 2 years

American Urological Association (AUA)

The AUA guidelines regarding follow-up for clinically localized renal neoplasms were most recently updated in 2013 [45]. These guidelines provide recommendations for follow-up stratified according disease stage and the treatment modality undertaken. Each individual guideline is graded according to the strength of underlying evidence (from highest to lowest) as a standard, recommendation, option, clinical principle, or expert opinion.

The AUA specifies that patients undergoing follow-up for treated or observed renal cortical tumors should be followed with a history and physical examination that is directed toward identifying signs and symptoms of metastatic spread or local recurrence. Standard laboratories recommended include blood urea nitrogen and creatinine to assess renal function as well as urine analysis. The guidelines specify that additional laboratory evaluations such as a complete blood count, lactate dehydrogenase, liver function tests, and calcium level should also be considered and utilized at the discretion of the treating physician. In terms of optimal imaging for relapses in the chest, the AUA preferentially recommends chest X-ray (CXR) rather than X-ray computed tomography (CT) due to a lower rate of false-positive and benign findings that may result in unnecessary invasive evaluation.

The AUA makes the recommendation that patients with progression of renal insufficiency on follow-up evaluations should be referred for consultation by nephrology. Adjunct studies including bone scan and neurologic cross-sectional imaging (i.e., CT or magnetic resonance imaging [MRI]) are only recommended in the setting of symptoms suggestive of metastases to the bone (e.g., elevated alkaline phosphatase, bone pain, and/or findings of bony neoplasm on other surveillance studies) or central nervous system (e.g., acute neurological signs or symptoms), respectively. Additionally, it is the expert opinion of the AUA guideline panel that positron emission tomography should not be utilized in the follow-up of RCC at this time due to lacking data regarding the sensitivity and specificity of this imaging modality in this setting. Finally, the AUA currently recommends against the routine use of molecular biomarkers in posttreatment RCC surveillance due to a lack of clear clinical benefit at this time.

Canadian Urologic Association (CUA)

The CUA guidelines were last published in 2008 for surveillance following PN or RN for RCC, with an expected update pending at the time of this writing [57]. Follow-up according to the CUA guidelines is stratified by pathologic tumor stage. The guidelines specify that CXR should be the standard imaging modality for evaluation of pulmonary relapse. The authors stipulate that chest CT may be performed instead; however, they cite insufficient evidence to suggest a benefit for universal

preferential use of chest CT over CXR. With respect to abdominal imaging, the panel recommends utilization of CT of the abdomen, however, patients with pT1 or pT2 RCC may also be followed with abdominal ultrasound (US). As recommended by the AUA guidelines, CT of the head and bone scan are only reserved for situations where symptoms are suggestive of brain or osseous relapse. The routine laboratory panel recommended by the CUA includes a complete blood count, serum chemistry panel, and liver function tests. Finally, the CUA panel recommends surveillance out to 6 years following definitive treatment.

European Association of Urology (EAU)

The EAU guidelines [44] differ from the prior guideline statements in that they recommend risk stratification into low-, intermediate-, and high-risk disease according to available clinical risk stratification models such as those detailed earlier. No preference, however, is given to any specific model. Contrary to the other guideline statements, the EAU cite evidence regarding the poor sensitivity of CXR for detecting small pulmonary metastases [44, 59] and therefore specify CT as the preferred imaging modality for relapse in the chest. MRI of the chest is recommended as an alternative to minimize radiation exposure. Similar to the recommendations put forth by the AUA panel, the EAU guidelines advise against the routine use of positron emission tomography and bone scintigraphy due to limited sensitivity and specificity. In terms of duration of follow-up, the EAU recommends that low-risk patients may be discharged from surveillance at 5 years after definitive treatment, whereas patients with intermediate- and high-risk disease, or any patient treated with thermal ablation, are recommended to undergo continued surveillance on a biennial basis.

National Cancer Control Network (NCCN)

The NCCN guidelines are stratified by disease stage and treatment modality [58], with a surveillance framework that is similar to the recommendations proposed by the AUA. The NCCN reiterates that no single follow-up plan is appropriate for every patient and therefore recommends modification of follow-up according to the treating physician's judgment. Recommendations are made up to 5 years following treatment; however, due to the potential for relapse after 5 years [60], the NCCN recommends consideration of follow-up after 5 years according to clinician discretion.

With respect to which imaging studies are recommended, the NCCN guidelines state that CT of the abdomen with or without pelvic CT and CXR are considered essential baseline studies [58]. In terms of screening for metastases, pulmonary imaging is mandated. While the panel acknowledges that chest CT is more accurate than CXR for the assessment of pulmonary metastases, the guidelines do not give preference to one modality over the other.

Review of Guidelines, Stratified by Tumor Stage/Risk Category and Treatment Modality

Low-Risk Patients (pT1 N0/x) Following Surgical Resection (RN or PN)

For clinically localized disease, the majority of the guidelines recommend less intensive postoperative surveillance due to the decreased risk of recurrence [44, 45, 57, 58]. The AUA guidelines [45] specify that for low-risk patients (pT1, N0, Nx) treated with PN or RN, an initial physical examination with basic laboratory studies should be performed at 6 months posttreatment and then annually for 3 years. Baseline abdominal imaging (CT or MRI) is recommended within 3–12 months after surgery. While patients treated with PN are recommended to undergo further abdominal imaging (US, CT, or MRI) annually for 3 years, additional abdominal imaging after RN is recommended at the discretion of the physician. Chest imaging is recommended annually for 3 years to assess for pulmonary metastases.

The CUA [57] specifies that surveillance following PN or RN for T1 RCC should include a history and physical exam and labs including complete blood count, chemistries, liver function tests, and CXR on an annual basis. For pT1 lesions treated with RN, abdominal imaging in the form of either CT or abdominal ultrasound, with consideration for alternating the two, is recommended at 2 years and 5 years. For pT1 lesions treated with PN, the panel gives the option of obtaining a CT at 3 months to assess the residual disease and gives consideration to the option of annual abdominal US.

For patients with low-risk disease treated surgically with PN or RN, the EAU [44] recommendations include US of the kidneys and renal fossa at 6 months, followed by alternating CT of the chest, abdomen, and pelvis with US on an annual basis until 5 years following treatment, at which time the patients are discharged from further surveillance.

The NCCN [58] recommendations following surgery for T1 RCC are similar, including a history and physical and comprehensive metabolic panel every 6 months for the first 2 years and then annually through year 5. Abdominal imaging using US, CT, or MRI is recommended within 3–12 months of PN and annually for 3 years.

Intermediate to High Risk (pT2-pT4, N0, Nx or any Stage, N1) Following Surgical Resection

For intermediate- to high-risk patients treated with RN, more intensive surveillance is recommended due to the increased risk of both local recurrence and development of systemic metastases [44, 45, 57, 58]. The AUA [45] and NCCN [58] recommend a postoperative history and physical exam and basic laboratories every 6 months for 3 years and then yearly for years 4 and 5 after surgery. Baseline chest and abdominal cross-sectional imaging (CT or MRI) is recommended within the first 3–6 months. Surveillance imaging (US, CXR, CT, or MRI of the abdomen) is obtained every 6 months for 3 years and then annually until year 5. After 5 years, further imaging

may be performed at the discretion of the physician and should be performed if symptoms are suggestive of recurrence or metastatic spread.

The CUA guidelines [57] similarly recommend a CXR every 6 months, extending out to 6 years, but recommend lower-intensity abdominal surveillance, recommending either CT or abdominal US at 1, 3, and 5 years for T2 tumors. For T3 tumors, cross-sectional imaging (CT or MRI) is favored and recommended every 6 months through year 2 and then at years 4 and 6. Finally, for patients with node-positive disease, CXR and CT of the abdomen are recommended every 6 months through 6 years following surgery.

For patients with clinically risk-stratified high-risk disease, the EAU recommends CT of the chest/abdomen and pelvis at 6 months and 12 months, then yearly until 5 years, and every other year thereafter [44]. Among patients with intermediate-risk disease, the panel cites the option of ultrasound rather than CT at year 3.

Follow-Up After Thermal Ablation

Relapse following thermal ablation is reported in 2–10% of patients [45, 46, 61]. The AUA guideline panel [45] adopted a standardized definition of post-thermal ablation "treatment failure or local recurrence." This is defined as a visually enlarging neoplasm or new nodularity in the same area of prior treatment and may be identified by enhancement of the renal mass on posttreatment imaging with contrast or failure of the renal mass to regress in size over time, as well as by new satellite, nodules along the port-site or needle track, or a biopsy-proven recurrence.

Follow-up after thermal ablation otherwise follows a similar schedule to that recommended for after PN for low-risk disease, extended out to 5 years. Specifically, the panel recommends a history and physical exam, labs, and cross-sectional abdominal imaging (CT or MRI) at 3 and 6 months to determine treatment success and then annually for surveillance for 5 years and thereafter according to the clinician's assessment of individualized patient risk.

Importantly, it is a central tenant of the AUA recommendations that all patients under consideration for ablation undergo a biopsy prior to treatment to confirm that the renal cortical mass represents an RCC [45]. However, for patients who were treated with thermal ablation for a pathologically confirmed benign tumor, with radiographic evidence of treatment success without evidence of treatment complications, no further radiologic assessment is recommended. The panel provided expert opinion that patients with treatment failure within 6 months should be offered the alternatives of observation, repeat treatment, or definitive surgical extirpation and that any evidence of recurrence within an ablated neoplasm should prompt consideration of biopsy.

The EAU guidelines specify that patients with RCC treated with thermal ablation should be followed according to the regimens specified for either intermediate- or high-risk disease [44]. According to these guidelines, high-risk patients should be surveilled with CT or MRI of the chest, abdomen, and pelvis at 6 months and then

yearly for 5 years, while intermediate-risk patients may substitute US for cross-sectional imaging at year 3. After 5 years, patients are recommended to undergo CT or MRI of the chest, abdomen, and pelvis every 2 years, indefinitely.

Evaluation of the Available Guidelines for Surveillance After Definitive Treatment for RCC

Limitations of the Available Guideline Statements

In the guideline statements from the AUA, CUA, EAU, and NCCN, it is acknowledged that no single follow-up regimen can be considered universally appropriate. This is echoed by the European Society for Medical Oncology (ESMO) which advocates for a follow-up strategy that incorporates both patient- and disease-specific risk factors and possible treatment options that may be employed in the setting of potential relapse [62].

In 2014, Stewart and colleagues evaluated the ability of the available AUA and NCCN surveillance guidelines to identify local and systemic relapse following surgical treatment for M0 RCC in 3651 patients from a single center [60]. With a median follow-up of 9 years, the authors observed recurrences in 1088 (29.8%) patients. The 2014 NCCN recommendations had recently been updated prior to the study, adopting a similar risk-adapted surveillance strategy, similar to the 2013 AUA recommendations. If the then-contemporary 2014 NCCN guidelines were followed, 742 recurrences (68.2%) would have been detected. Similarly, the 2013 AUA guidelines would have identified 728 (66.9%) of recurrences (Fig. 16.1). In the same paper, the authors presented a comparison of the relative costs of the two guideline-

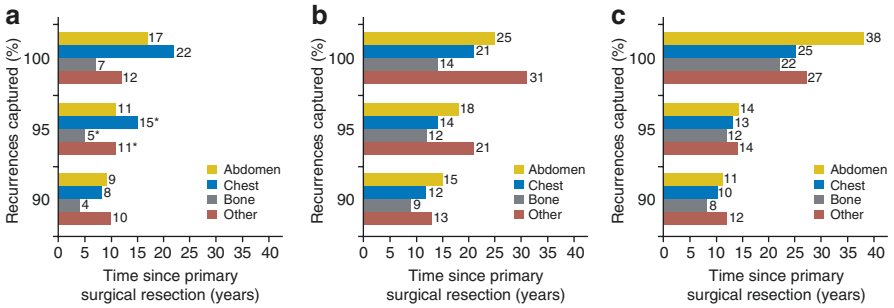

Fig. 16.1 Total duration of surveillance required to capture 90%, 95%, and 100% of recurrences stratified by the American Urological Association risk groups and recurrence locations: (**a**) low risk after partial nephrectomy, (**b**) low risk after radical nephrectomy, and (**c**) moderate/high risk. (*) Estimated duration of surveillance as a result of the few recurrences in these groups. (From Stewart et al. [60]. Reprinted with permission. ©(2018) American Society of Clinical Oncology. All rights reserved)

based surveillance strategies compared to a continued surveillance strategy that would have captured 95% of all recurrences. For example, for a patient with a pT1 renal mass treated with PN, complete surveillance as recommended by the NCCN in 2014 would have resulted in 2014 Medicare costs totaling $2131.52 compared to $1738.31 if the 2013 AUA guidelines were followed. However, to capture 95% of all recurrences, surveillance costs would be estimated to total $9856.82. Importantly, these costs did not include indirect costs such as clinic visits, lost wages related to time away from work for the patient or their family members. These findings led the authors to call for improved surveillance algorithms, balancing both patient benefit and health-care costs.

Radiation-Related Harms with Surveillance

In addition to taking the health-care costs into consideration when evaluating surveillance protocols, the potential harms of more intensive surveillance must also be considered. While intensive surveillance may capture more recurrences over time, the potential harm of the cumulative radiation dose incurred must be considered and should be discussed with patients as part of the shared decision-making around recommending an optimal surveillance strategy. As discussed in the 2013 AUA guidelines [45], the carcinogenic potential of relative low-dose (<100 mSv) radiation is extrapolated from analysis of the survival of Japanese survivors of the atomic bomb exposed to intermediate (>100 mSv). These extrapolations rely on the linear no-threshold model, which assumes that there is risk for biological damage (increase in the risk of carcinogenesis) at any dose of radiation [63]. For reference, the average CXR is associated with an estimated radiation dose of <0.1 mSv, compared to 1–10 mSv for abdominal CT without contrast or abdominal radiograph and 10–100 mSv for abdominal CT scans with and without contrast. At this point, there is indirect evidence demonstrating increased risk of developing cancer following exposure to low levels of radiation at doses that would be expected with the surveillance CT scans recommended in the guidelines discussed herein [64]. This increasing understanding of the potential risks associated with CT scanning has generated new low radiation dose scanning protocols and increasing reliance on imaging modalities that do not utilize ionizing radiation [65]. As stated in the 2013 AUA guidelines, “it is prudent to limit the use of CT to clinical indications in which the benefit is felt to outweigh the risks” [45].

In addition to radiation exposure, both CT and MRIs administered with contrast involve risks related to hypersensitivity and allergies, as well as potential complications in patients with renal insufficiency. Capogrosso and colleagues demonstrated a lacking consensus regarding surveillance due to clinician heterogeneity in post-treatment follow-up and imaging modalities [66]. The authors recommend that a standardized evidence-based protocol is still needed with a goal of limiting radiation exposure, minimizing unnecessary costs, and ensuring early detection of tumor recurrence.

The Guidelines in Practice

When real-world evaluations of surveillance patterns and uptake of the various guideline strategies are undertaken considerable variation is noted. For example, Sohn and colleagues identified 7603 patients treated for RCC in the Surveillance, Epidemiology, and End Results database and reported on both adherence to the AUA surveillance guidelines as well as the association between more intensive surveillance and oncologic outcomes [67]. Dividing patients into relatively abbreviated follow-up periods of only 15 (short) and 30 (intermediate) months, the authors noted that more than 40% of the patients in the short follow-up cohort did not undergo any chest imaging. Similarly, more than 50% of the intermediate interval cohort did not undergo chest imaging and over 30% of all patients did not undergo any surveillance imaging following definitive treatment. The authors also assessed whether compliance with the AUA guidelines was associated with cancer-specific survival and noted that adherence to imaging follow-up per the AUA guidelines was not associated with improved outcomes compared to no imaging at all.

Alternative Surveillance Strategies

Indeed, it is challenging to demonstrate a survival benefit related to the intensity of post-RCC surveillance. As noted above, survival is ultimately the product of disease-specific, patient-specific, and both initial and salvage treatment-related factors, which may manifest differently within a single patient. Furthermore, lead-time bias, which results in a lengthening of apparent survival simply related to earlier detection of recurrences, confounds assessment of the relative benefit of more intensive surveillance strategies.

As such, no one follow-up strategy can be recommended over any other due to the paucity of comparative studies pitting surveillance strategies against one another. Furthermore, and perhaps more importantly, there are limited data to support the fact that treatment of asymptomatic recurrences captured on surveillance confers a survival benefit compared to treatment of recurrences detected related to symptoms alone. In some patients, metastatic RCC may be asymptomatic with a relatively indolent course. Park and colleagues reported on outcomes in 58 patients in whom first-line systemic therapy for metastatic RCC was deliberately deferred, with a median time to progression in 12.4 months [68]. Systemic therapy was ultimately initiated at the time of progression after a period of active surveillance, with objective response rates to systemic therapy that were similar to historical controls. Additionally, in a prospective phase 2 trial, Rini and colleagues demonstrated that treatment-naïve, asymptomatic patients with metastatic RCC can undergo active surveillance prior to beginning system therapy in 48 patients [69]. The authors found that increasing numbers of the International Metastatic Database Consortium adverse risk factors and a greater number of metastatic sites were associated with a

shorter period of surveillance. Conversely, in an assessment of RCC retroperitoneal recurrence size after surgical treatment, Thomas and colleagues observed that the maximal diameter of the retroperitoneal recurrence was independently associated with risk of cancer mortality, suggesting the potential benefit of earlier detection of relapse among patients who were candidates for cytoreductive surgery [70].

Alternative surveillance strategies have been proposed to meet the objective of improving the efficiency and efficacy of posttreatment surveillance, incorporating different risk-stratifying algorithms including factors such as DNA ploidy, tumor size, and stage [71]. Lam and colleagues proposed an alternate strategy using the UISS nomogram for risk stratification, including stage, Fuhrman grade, and performance status [72]. Alternatively, Siddiqui and colleagues recommended incorporation of histologic subtype in risk stratification [73].

Williamson and colleagues proposed a surveillance protocol that unifies recommendations from the existing guideline statements from the AUA, CUA, EAU, and NCCN [74]. Briefly, the authors recommend that following treatment (RN, PN, or thermal ablation) for low-risk/T1 renal tumors, follow-up should be initiated at 3 months with a history and physical exam, CT, and labs. Then patients may be followed by yearly US or CT through 3 years with a final US or CT at 5 years. For chest surveillance, the authors recommend annual CXR with a chest CT at 3 and 5 years. For intermediate- and high-risk disease, the authors propose a baseline abdominal CT at 3 months, and then alternating abdominal US with CT at 6 months, and then every 6 months for 3 years, and annually for years 4 and 5. For chest surveillance, it was proposed that CXR and chest CT could be alternated at the same intervals as the abdominal imaging.

Ultimately, however, these strategies and the available existing guidelines might be considered to fall short in that they do not account for patient-specific risk stratification and the competing risks of noncancer morbidity. Specifically, there are no recommendations for how clinical guidelines should be modified for a specific patient according to his or her comorbidity burden, age, or other patient-specific factors that a physician might wish to weigh when considering how to personalize a surveillance strategy.

To address this knowledge gap, Stewart-Merrill and colleagues developed a novel surveillance schedule incorporating the changing risk of site-specific cancer relapse over time stratified by disease stage, age, and comorbidity [9]. According to this strategy, a patient's risk of RCC recurrence, stratified by pathologic stage, and relapse site is presented graphically in the context of their risk of non-RCC death stratified by age and Charlson comorbidity index (Fig. 16.2). This methodology permits assessment of the individualized point at which a patient's competing risks of non-RCC death exceed the risk of recurrence, at which point, further surveillance may be considered to have relatively limited benefit. Table 16.2 presents comparisons of the durations of the variable risk-stratified individualized surveillance durations. To date, however, this protocol has yet to be externally validated or compared to the current recommended guidelines.

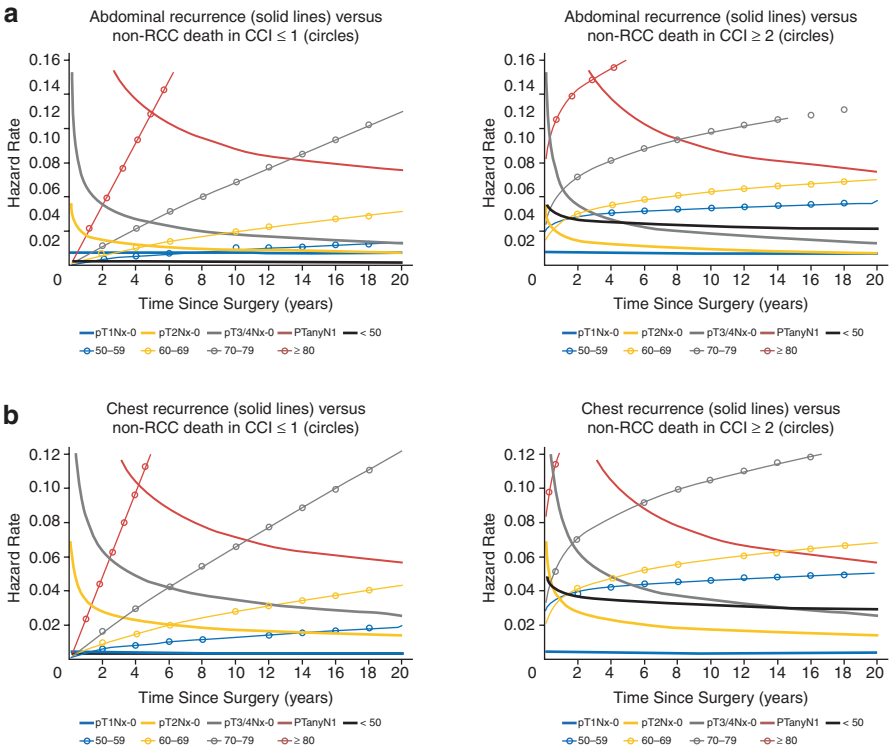

Fig. 16.2 Weibull models illustrating the time points at which the risk of non-RCC death exceeds the risk of recurrence. Decreasing hazard rates of recurrence over time are stratified by stage and relapse location (solid lines; [**a**] abdomen, [**b**] chest, [**c**] bone, and [**d**] other sites) . These are compared to increasing hazard rates of non-RCC death over time stratified by age and Charlson Comorbidity Index (CCI) groups (circles; 1 or 2). Age-, CCI-, stage-, and relapse location-specific time points (in years) were estimated when risk of non-RCC death exceeded the risk of recurrence. (From Stewart-Merrill et al. [9]. Reprinted with permission. ©(2018) American Society of Clinical Oncology. All rights reserved)

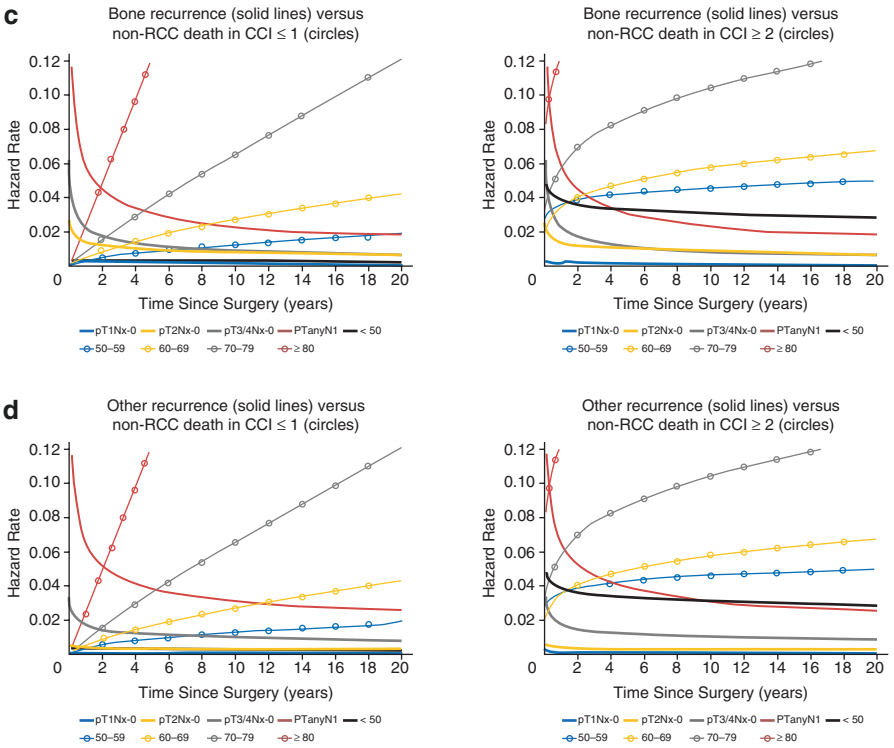

Fig. 16.2 (continued)

Conclusions

At the present time, there are multiple guidelines available to direct posttreatment surveillance of RCC. However, considerable variation exists between these recommendations. A patient's posttreatment risk of relapse may vary considerably with factors related to tumor biology, the individual patient, and mode of treatment. Prognostic multivariable nomograms and models may be helpful in assessing a patient's individual risk of local relapse and oncologic outcomes, which can then guide a physician in defining the most appropriate surveillance strategy for a patient. Contemporary surveillance guidelines proposed by the AUA, CUA, EAU, and NCCN are consistent in their goal of ensuring early relapse recognition; however, they differ regarding patient risk stratification methodology, surveillance frequency, and imaging modalities utilized. At the time of writing this chapter, there is no consensus in terms of recommending one strategy for posttreatment surveillance over another. While more intense surveillance may permit earlier identification of relapses, increased frequency and duration of surveillance may be associated with greater harm from cumulative radiation exposure, potential direct and indirect health-care costs, and quality of life impact for the patient. Ultimately, optimization of posttreatment surveillance requires

Table 16.2 Age-, Charlson Comorbidity Index-, and relapse location-specific time points at which the risk of death from causes other than renal cell carcinoma exceeds the risk of recurrence of renal cell carcinoma in years

		Time point in years by age group (years) and Charlson comorbidity index at which the risk of non-RCC death exceeds the risk of RCC recurrence after surgical treatment									
		< 50 years		*50–59 years*		*60–69 years*		*70–79 years*		*≥80 years*	
Stage group	**Relapse location**	*CCI ≤ 1*	*CCI ≥ 2*	*CCI ≤ 1*	*CCI ≥ 2*	*CCI ≤ 1*	*CCI ≥ 2*	*CCI ≤ 1*	*CCI ≥ 2*	*CCI ≤ 1*	*CCI ≥ 2*
pT1 Nx-0	*Abdomen*	>20	–	7	–	2.5	–	1.5	–	0.5	–
	Chest	>20	–	1	–	1	–	0.5	–	–	–
	Bone	0.5	–	0.5	–	0.5	–	0.5	–	0.5	–
	Other	–	–	–	–	–	–	–	–	–	–
pT2 Nx-0	*Abdomen*	>20	0.5	10.5	0.5	5	0.5	2.5	0.5	1	–
	Chest	>20	0.5	14	1	6	1	3	0.5	1.5	–
	Bone	>20	–	6.5	–	3	–	1.5	–	1	–
	Other	>20	–	2.5	–	2	–	0.5	–	0.5	–
pT3/pT4 Nx-0	*Abdomen*	>20	5	19.5	3	9	2.5	5	1.5	2	0.5
	Chest	>20	14	>20	5.5	12.5	4.5	6	1.5	2.5	1
	Bone	>20	0.5	7.5	0.5	4	0.5	2.5	0.5	1.5	–
	Other	>20	0.5	10	0.5	5.5	0.5	2	0.5	1	–
pTany N1	*Abdomen*	>20	>20	>20	>20	>20	>20	13	8	5	3
	Chest	>20	>20	>20	>20	>20	14	10.5	5.5	4.5	2
	Bone	>20	4.5	20	3	9	2.5	4.5	1	2	0.5
	Other	>20	>20	>20	10.5	13	4.5	6.5	2	2.5	1

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Abbreviations: *CCI* Charlson Comorbidity Index

Dash mark "—" represents that the risk of non-RCC death exceeded the risk of recurrence starting at 30 days following surgery, which may be suggestive of the fact that surveillance may not be indicated in these situations

shared decision-making between the patient and the physician. Future work is needed to improve risk stratification strategies and to better understand the risks and benefits of varying approaches to posttreatment surveillance.

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