short review

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Evidence-based follow-up in renal cell carcinoma

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Summary The optimal surveillance strategy in renal cell carcinoma after curative resection or ablation is a field of ongoing research. This review discusses the evidence behind routine follow up, duration of follow up, imaging modality and intervals as well as surveillance after local ablative therapy. The recommendations and differences of major guidelines are outlined as well. A risk based approach is advocated taking into account both tumor and patient specific characteristics.

Keywords Renal cell carcinoma · Surveillance · Follow up · RECUR database · Risk adapted

Take home message

Regarding imaging interval and total follow-up duration, surveillance protocols should be risk based, taking into account both tumor characteristics as well as patient's age and comorbidities. Cross-sectional imaging is preferred over conventional imaging.

Introduction

After curative surgery for renal cell carcinoma (RCC) routine follow-up consists of clinical evaluation, laboratory tests for renal function and thoracoabdominal imaging. This allows recognition of postoperative complications, monitoring of renal function, and early detection of recurrent disease. Since all proposed follow-up protocols are based on retrospective studies, the optimal surveillance strategy remains for debate. The most important findings of recent studies regarding follow-up in RCC are discussed in this review.

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Rationale for follow-up

The main rationale for follow-up is the belief that early detection of disease improves outcomes by the possibility of initiating therapy when tumor load is still low. Indeed, several studies indicate that patients benefit from early detection of asymptomatic recurrence [1, 2]. Based on recurrence site, number of lesions, estimated aggressiveness of the disease, and time from nephrectomy patients may receive local therapy directed against metastasis. Since a significant portion of patients experience single metastasis or oligometastatic disease at the time of recurrence—with a high percentage having solely pulmonary recurrence—metastasectomy or ablative therapies are viable treatment options with the chance of inducing long-term remission or even cure. Along with studies examining outcomes after local recurrence [3, 4], this was demonstrated by an analysis of the RECUR database [1]. Of 286 patients experiencing disease recurrence, almost two thirds were detected when still asymptomatic. Roughly one fourth of all patients received local treatment (mostly metastasectomy) and of these, one third were alive without disease at the time of analysis. These data suggest that a significant number of patients profit substantially from routine follow-up and application of local therapies. Furthermore, patients with asymptomatic recurrence—which would be rarely discovered without surveillance—demonstrate longer overall survival than patients with symptomatic disease relapse [1, 2]. A possible downside of regularly performed imaging is the detection of lesions unrelated to RCC in the

Table 1 Risk scores and their components for predicting survival/recurrence [7–9]

	TNM stage	Fuhrman grade	ECOG status	Symptoms	Histological tumor necrosis	Histologic subtype
Leibovich score	x	x	–	x	x	–
UISS	x	x	x	–	–	–
MSKCC	x	–	–	x	–	x

UISS University of California Los Angeles Integrated Staging System, *MSKCC* Memorial Sloan-Kettering Cancer Centre, *TNM* tumor node metastasis, *ECOG* Eastern Cooperative Oncology Group

need of invasive diagnostic procedures to rule out malignancy [5].

Recurrence risk

The overall rate of recurrence after primary resection is about 20–30% and highly depends on clinicopathological features [1, 5, 6]. Several validated risk scores are available and can be used for predicting recurrence risk. The most commonly used are the Leibovich score [7], the University of California Los Angeles Integrated Staging System (UISS) [8], and the Memorial Sloan-Kettering Cancer Center (MSKCC) postoperative prognostic nomogram [9]. These scores categorize patients as low-, intermediate-, or high-risk for recurrence depending on combinations of TNM stage, Fuhrman grade, ECOG status, symptoms at presentation, presence of tumor necrosis and/or histologic subtype (Table 1). Multiple retrospective studies have shown that the 5-year risk of recurrence is as high as 60% in high-risk patients and as low as 7–10% in patients of the low-risk group. Median time to recurrence also heavily depends on the calculated risk group, ranging from around one year in high-risk patients to about three years in low-risk patients [1, 6]. However, it is important to note that even low-risk patients may experience recurrent disease after more than 5 years of follow-up [10]. Recurrence pattern also depends on risk category. While the most common site of distant recurrence is lung metastasis in all patients, higher-risk patients tend to develop metastasis more frequently in the abdomen in comparison to low-risk patients [6]. Thus, surveillance protocols need to take into account the estimated overall risk as well as probable site and timing of recurrence based on the patient's risk category.

Duration of follow-up

Two large retrospective analysis pointed out that late recurrence (5–15 years) occurs in 6–11% of patients who remained disease free for the first 5 years of follow-up. Higher tumor stage by histology, lymphovascular invasion, and Fuhrman grade 3/4 are independent risk factors for developing late recurrence [10, 11]. In 2014, the National Comprehensive Cancer Network (NCCN) and American Urological Association (AUA) recommended mandatory imaging of the chest and abdomen for only 3 years in low-risk patients and for 5 years in intermediate- to high-risk patients. This recommendation was evaluated by a retrospective analysis of 3651 patients who underwent primary resection. It was shown that if these guidelines were strictly followed, approximately one third of disease recurrences would have been missed [12]. Therefore, independent of risk group, follow-up for more than 5 years seems advisable in all patients with an adequate life expectancy. Analysis of the RECUR database points out that patients in the low- and intermediate-risk group aged >75 years have a higher risk of dying due to other causes than due to recurrent disease. On the other hand, patients in the high-risk group exhibit independent of age a higher risk of dying due to disease recurrence than because of other causes. Follow-up duration based on recurrence risk and risk of death due to other causes was investigated by Stewart-Merrill et al. [13]. In their study, the risk of non-RCC death competing with the risk of disease recurrence was investigated in more than 2500 patients. Patients were stratified by age, Charlson comorbidity index (CCI; ≤1 and ≥2), pathologic stage, and relapse location. This analysis resulted in a timetable listing age-, CCI-, stage-, and relapse location-specific time points when risk of death due to other causes exceeds the risk of recurrent disease. Interestingly, for patients with pT1Nx-0 tumors and a CCI ≥2 the risk of non-RCC death is already higher than the risk of disease recurrence starting at 30 days after surgery, highly questioning any need for follow-up. Conversely, in patients with node-positive disease, the risk of non-RCC death does not exceed the risk of recurrence even after 20 years, suggesting that even longer follow-up then usually recommended may be of value [13]. The time point when risk of non-RCC death is higher than the risk of recurrence is of tremendous importance when determining the duration of surveillance. At that specific time point, age- and non-RCC-related comorbidities pose a greater impact on survival than RCC. In clinical practice, this study provides useful information for everyday decision making as it helps tailoring follow-up duration to patient-specific characteristics. To conclude, the duration of follow-up should not solely be based on risk of recurrence estimated by tumor characteristics but also on age, comorbidities, and ultimately life expectancy of the patient.

Table 2 European Association of Urology 2019 surveillance schedule [29]

	6 months	1 year	2 year	3 years	>3 years
Low risk	US	CT	US	CT	CT every other year
Intermediate/high risk	CT	CT	CT	CT	CT every other year

US abdominal ultrasound, *CT* computed tomography of chest and abdomen, alternatively use magnetic resonance imaging for the abdomen

Table 3 National Comprehensive Cancer Network 2019 recommendations for follow-up after partial or radical nephrectomy [30]

		First 3 years	3 to 5 years	>5 years
Stage I[a]	Abdominal	Baseline CT/MRI (preferred) or US within 3–12 months after surgery then annually	Annually as clinically indicated	Annually as clinically indicated
	Chest	Annual CXR or CT	Annual CXR or CT	As clinically indicated
Stage II or III[b]	Abdominal	Baseline CT/MRI then CT/MRI (preferred) or US (US is category 2B for stage III) every 3–6 months	CT/MRI (preferred) or US (US is category 2B for stage III) annually	As clinically indicated
	Chest	Baseline CT then CT (preferred) or CXR every 3–6 months	CT (preferred) or CXR annually	As clinically indicated

CT computed tomography, *MRI* magnetic resonance imaging, *US* ultrasound, *CXR* chest X-ray

[a]A more rigorous imaging schedule or modality can be considered if positive margins or adverse pathologic features (such as sarcomatoid, high-grade [grade 3/4], positive margins)

[b]Additional imaging (i.e., bone scan, brain imaging): as symptoms warrant

Imaging interval

Determining the optimal imaging frequency is quite challenging due to the lack of comparative studies. Specific recommendations for imaging intervals are based on retrospective evaluations which assessed site and time until recurrence stratified by patient- and tumor-specific characteristics. Patients are typically categorized as low-, intermediate-, or high-risk based on the earlier mentioned scoring systems. Due to their lower overall risk of recurrence and less aggressive disease, low-risk patients require less frequent imaging than intermediate- or high-risk patients. One analysis of the RECUR database indicates that in the first 5 years of follow-up, more frequent imaging as recommended by the 2017 EAU guidelines (imaging at 6 months, 12 months and then yearly until 5 years) has no positive influence on overall survival [14]. In particular, no difference in regards to survival could be shown between patients undergoing the recommended number of imaging procedures and those in whom less than 75% or more than double of the proposed follow-up images were obtained. Although striking, the study has limitations such as the possible diluting effect by extensive use of conventional imaging (53% in this study) as well as the retrospective nature of the analysis. Therefore, the imaging interval should be based on established follow-up protocols taking into account the timing, site, and overall risk of recurrence. We suggest more frequent imaging in high-risk patients (3–6 monthly in the first 2–3 years) and less frequent imaging in low-risk patients (annually after performing a baseline postoperative scan). Because the recurrence risk declines over time, less frequent imaging is needed in long-term follow-up (annually to every other year).

Imaging modality

The most commonly used imaging modalities for follow-up are chest X-ray (CXR), abdominal ultrasound, and computed tomography (CT). There are two studies which examined the usefulness of CXR in T1 RCC [15, 16]. Both concluded that due to the low diagnostic yield and test specificity combined with a low-risk of disease recurrence, CXR is of low clinical value in low-risk disease. Conventional imaging of the chest for stage T1-3N0 was evaluated by another study, showing that only 7 out of 19 patients experiencing a pulmonary recurrence were detected while asymptomatic with CXR; translating into a detection rate of 0.85% of all performed images [17]. These results correlate well with current recommendations of major guidelines which prefer CT over CXR.

Major guidelines prefer cross-sectional imaging (CSI)—CT or magnetic resonance imaging (MRI)—over ultrasound for abdominal imaging due to its higher diagnostic yield. However, there is no trial indicating that this leads to clinically relevant improved outcomes. In fact, the opposite is suggested by an analysis of the RECUR database which investigated whether more CSI during follow-up leads to longer survival after detection of recurrence [18]. Patients were divided into having received more or less than 50% of their total number of imaging tests performed by CSI. In the low- and intermediate-risk group more recurrences were detected if >50% of imaging was CSI during routine follow-up with statistical significance

Table 4 American Urological Association 2013 follow-up protocol [31]

		First 3 years	3 to 5 years	>5 years
Low risk	Abdominal	Baseline CT or MRI within 3–12 months after surgery then yearly imaging (US, CT or MRI) may be performed	–	–
	Chest	Annual CXR	As clinically indicated	As clinically indicated
Moderate to high risk	Abdominal	Baseline CT or MRI within 3–12 months after surgery then 6-monthly imaging (US, CT or MRI)	Annual US, CT or MRI	Optional
	Chest	Baseline CT within 3–6 months after surgery then 6-monthly CXR or CT	Annual CXR or CT	Optional

CT computed tomography, *MRI* magnetic resonance imaging, *US* ultrasound, *CXR* chest X-ray

reached in the intermediate-risk group. However, no difference in overall survival could be shown between patients stratified by CSI usage. Due to its retrospective nature, caution needs to be applied when implementing these results into clinical practice.

The usefulness of whole body MRI was evaluated by a small study in 28 patients [19]. MRI was more accurate in diagnosing musculoskeletal metastasis but less sensitive for pulmonary manifestations compared to CT. Given the importance of detecting pulmonary recurrence in RCC follow-up, CT of the chest cannot be exchanged by MRI. For abdominal imaging, MRI represents a valid alternative to CT with the advantage of less radiation exposure at the expense of higher costs.

In clinical practice, using different imaging modalities for chest and abdomen is inconvenient and impractical and therefore should be reserved for younger patients when reduction of radiation exposure is warranted. Due to higher diagnostic yield when compared to conventional imaging, we suggest CT of the chest, abdomen, and pelvis as the standard imaging technique.

Fluorodeoxyglucose positron emission tomography (FDG PET)/CT exhibits both high sensitivity and specificity (85–90%) for diagnosing metastasis as well as relapse to the renal bed [20, 21]. Compared to CT, it is more accurate in diagnosing musculoskeletal metastasis and small but aggressive lesions (e.g., lymph nodes) [22]. With the advantage of scanning the whole body in just one procedure the drawbacks for routine clinical practice are the higher costs and increased radiation exposure. We advise reserving FDG PET for unclear lesions detected by other imaging studies.

Bone lesions are typically osteolytic and usually cause symptoms. Since a bone scan has difficulties in detecting osteolysis, its routine performance in asymptomatic patients is discouraged [23]. Routine brain imaging is also not recommended in patients without symptoms suggestive of cerebral metastasis.

Surveillance after ablative therapies

Conflicting evidence exists whether cryoablation or radiofrequency ablation are equally effective to partial nephrectomy in small (T1a) tumors [24]. This is especially true in regard to local recurrence and cancer-specific survival warranting more intensive follow-up. Moreover, due to the absence of histological workup, the possibility of treatment failure after ablative therapy must be excluded by imaging studies. Residual tumor at the treatment site is detected in the majority of cases within 3 months but can stay occult for a prolonged period of time [25, 26]. Thus, more frequent abdominal imaging is needed in the first 1–2 years of surveillance. The suggested follow-up protocol by most authors is abdominal CT or MRI at 3, 6, 12, 18, and 24 months and annually thereafter [25–28]. Thoracic imaging should be applied as in low-risk patients treated by surgery.

Guidelines

The most influential guidelines come from the European Association of Urology (EAU), European Society for Medical Oncology (ESMO), NCCN (all updated in 2019) and AUA (published 2013). While the EAU published a very specific guidance (Table 2), NCCN (Table 3) and AUA (Table 4) recommendations are less strict and allow for more variation [29–31]. ESMO provides only rough guidance by stating that yearly CT scans of chest and abdomen are probably sufficient in low-risk patients, while 3–6 monthly imaging should be performed in high-risk patients for the first 2 years. No statement on the duration of follow-up is given [32].

NCCN and AUA advocate 3–6-monthly (NCCN)/6-monthly (AUA) imaging for 3 years in high-risk patients and annual imaging in low-risk patients. The EAU advises to perform imaging twice in the first year, yearly for the next two years and then every other year independent of risk group. With the exception of the AUA guideline, all expert groups prefer CSI over conventional imaging.

As reflected in these guidelines and other proposed follow-up protocols [33, 34], we agree on using a risk-based follow-up approach. We suggest using CT of chest and abdomen as the standard imaging procedure in time intervals as proposed by the NCCN or AUA guideline. To our opinion, the recommended imaging interval by the EAU in the first 3 years is too

long to capture recurrence early. The duration of follow-up should be guided not only by tumor-specific risk factors, but also by the patient's age and comorbidities, as outlined earlier.

Conclusion

Recent findings shed some light on the unanswered questions of optimal follow-up and help to improve existing protocols. The uncertainties regarding imaging intervals and modalities due to the lack of high-quality data is best reflected by the divergent recommendations of major guidelines. Therefore, beside standardized protocols, clinical judgement as well as patient preferences play an important role in the follow-up of RCC.

Conflict of interest K. Mayrhofer and D. Niedersüß-Beke declare that they have no competing interests.

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