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ORIGINAL ARTICLE

Impact of routine imaging in the diagnosis of recurrence for patients with localized and locally advanced renal tumor treated with nephrectomy

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Abstract

Objective Modalities of surveillance to detect recurrence after nephrectomy for localized or locally advanced renal tumor are not standardized. The aim was to assess the impact of surveillance scheme on oncological outcomes.

Methods Patients treated for localized or locally advanced renal tumor with total or partial nephrectomy between 2006 and 2010 in an academic institution were included retrospectively. According to the University of California Los Angeles Integrated Staging System (UISS) protocol, follow-up was considered adequate or not. Symptoms, location and number of lesions at recurrence diagnosis were collected. Recurrence-free, cancer-specific and overall survivals were estimated using the Kaplan–Meier method and compared with the log-rank test. Cox proportional hazards regression models were calculated to identify prognostic factors.

Results A total of 267 patients were included. Median follow-up was 72 months. Recurrence rate was 23.2% (62/267 patients). Recurrences were local (16%), single metastatic (23%), oligo-metastatic (15%) or multi-metastatic (46%). 72.6% of the recurrences occurred within the 3 years after surgery. No recurrence was diagnosed by chest X-ray or abdominal ultrasound. One hundred and twenty-one patients had inadequate follow-up. They had similar recurrence-free survival, cancer-specific survival and overall survival as patients with adequate follow-up. In multivariable analysis, the presence of multi-metastatic lesions was an independent prognostic factor of worse cancer-specific mortality after recurrence diagnosis (HR = 10.15, 95% CI: 2.29–44.82, $p = 0.002$).

Conclusion Role of chest X-ray and abdominal ultrasound for the detection of recurrences is limited. Rigorous follow-up according to the UISS protocol does not improve oncological outcomes. Follow-up schedules with less frequent imaging should be discussed.

Keywords Renal tumor · Follow-up · Recurrence · Survival · Tomography

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Introduction

20 to 30% of patients undergoing surgery for non-metastatic renal tumor will eventually experience either a local or distant recurrence at 5 years [1]. Consequently, appropriate and early identification of recurrences following nephrectomy is essential in these patients.

Numerous postoperative surveillance schedules have been proposed to predict recurrence of the disease [2–5]. In theory, the justification for this follow-up is based on early detection of recurrent or metastatic disease that subsequently translates into a survival benefit. However, no comparative study has ever addressed whether follow-up after treatment of renal tumor improves survival. Moreover, these algorithms have been developed from historical cohorts of patients and some have never been validated in modern cohorts.

The UISS (UCLA (University of California Los Angeles) Integrated Staging System) score was proposed to guide patient follow-up [6]. Based on T stage, N stage, tumor grade [7] and ECOG-PS [8], this system has been used for the creation of high-risk (HR), intermediate-risk (IR) and low-risk (LR) groups to stratify patients according to their probability of survival and tumor recurrence. According to the level of risk, a specific follow-up is planned especially type and frequency of imaging examination [4].

The purpose of this work was to assess the impact of surveillance modalities and scheme on the detection of recurrence and oncological outcomes in a modern cohort of patients with localized renal tumor treated with partial or radical nephrectomy.

Methods

Study design

The charts of all patients who underwent radical or partial nephrectomy for renal tumor from 2006 to 2010 in an academic department of urology were retrospectively reviewed. Patient demographic and pathological tumor characteristics were collected. Patients with benign lesions ($n=38$) or metastases at the time of diagnosis ($n=45$) were excluded. Patients with positive surgical margins ($n=2$) or missing data for definitive pathology or follow-up ($n=3$) were also excluded.

Follow-up protocol

Follow-up modalities were determined according to the surgeon's discretion. For each patient, the rhythm of monitoring and the type of imaging (chest X-ray, chest computerized tomography (CT) scan, abdominal ultrasound, abdominal CT scan or magnetic resonance imaging (MRI)) were collected. By comparing the monitoring rhythm and the type of imaging performed with those recommended in the UCLA UISS surveillance protocol [4], two types of follow-up were defined: "adequate" and "inadequate". The follow-up was considered "adequate" when it corresponded precisely to the recommendations of the UCLA UISS surveillance protocol (supplementary data). On the other hand, as soon as imaging examinations were spaced or less informative than those recommended, the follow-up was considered "inadequate". Thus, a delay of more than 3 months in the completion of a recommended imaging examination was considered as a deviation from the protocol of surveillance.

Definition of recurrence

Recurrence was defined as the development of a new mass at least 30 days after surgery, confirmed by clinical findings, pathological specimens or radiological reports. The first recurrence for each patient was considered as event, and all other recurrences were censored to prevent double counting. Recurrence-free survival (RFS) was defined as the time from surgery to recurrence (either local or metastasis). Recurrence was defined as a local recurrence (renal recurrence after partial nephrectomy or lymph node recurrence in the retroperitoneum after radical nephrectomy) or metastasis. Metastatic recurrence was defined according to the number of metastases on imaging: single metastatic, oligo-metastatic (up to 3 metastatic lesions) or multi-metastatic. Symptomatic and asymptomatic recurrences were distinguished. The type of initial imaging that led to the diagnosis of recurrence (ultrasound, X-ray, CT scan or MRI) was specified.

Treatment of recurrence

Patients with local recurrence were eligible for new surgery. Surgery could also be proposed to patients with a single metastasis or to oligo-metastatic patients, depending on the site of recurrence and the possibilities of resection. Systemic treatment may be associated. For multi-metastatic patients or those not eligible for surgical treatment, a systemic treatment could be introduced. The therapeutic decision was at the discretion of the surgeon and the oncologist.

Statistical analysis

Continuous variables were reported as medians and interquartile ranges (IQRs), and categorical variables were reported as proportions. Recurrence-free survival, cancer-specific survival and overall survival were estimated using the Kaplan–Meier method and compared between groups

with the log-rank test. Univariable and multivariable analyses using the Cox regression model were performed to identify prognostic factors of oncological outcomes after recurrence diagnosis. Statistical analyses were performed using Stata 14.1 statistical software (Stata, College Station, TX, USA). All tests were two-sided with a significance level at $p < 0.05$.

Results

Patients' and tumors' characteristics

We identified 267 patients who met the criteria for study inclusion. Patients' and tumor's characteristics are summarized in Table 1. Median age at diagnosis was 60 years (IQR 50–71). Median tumor size was 5.5 cm (IQR: 3–7). Clear cell RCC was the most common histological subtype of RCC (79%). There were 163 (61%) patients with pT1 lesions, 24 (9%) with pT2 and 80 (30%) with pT3 or higher-stage tumors.

Characteristics of recurrence

Pattern of recurrence

Recurrence was reported in 62 patients (23.2%) during median 72-months (IQR 51–92) follow-up. Ten were local recurrences (16.4%), 14 were single metastatic recurrences (22.9%), 9 were oligo-metastatic recurrences (14.8%), and 29 were multi-metastatic (45.9%). The recurrence was symptomatic in 12 patients (20%) and asymptomatic in 50 patients (80%). The sites of recurrence were lungs ($n = 28$), lymph nodes ($n = 19$), pancreas ($n = 4$), brain ($n = 4$), bone ($n = 4$), liver ($n = 3$) and adrenal gland ($n = 2$).

Time to recurrence

The median time to recurrence diagnosis was 24.5 (12–54) months. According to UISS score, the median time to recurrence was 26.5, 29 and 7 months for patients for low, intermediate and high UISS score, respectively. 72.6% of recurrences occurred within the first 3 years, and 14.5% of the recurrences were diagnosed after 5 years of follow-up (Fig. 1). At 5 years, recurrence-free survival (RFS) in the overall population was 80%. At 5 years, RFS for UISS scores 1, 2 and 3 was 96, 71 and 57%, respectively (Fig. 2).

Imaging studies and follow-up modalities

In our cohort, no recurrence was diagnosed with abdominal ultrasound or chest X-Ray.

The follow-up was considered inadequate in 121 patients and adequate in 146 patients. RFS was similar in both groups (log rank, $p = 0.93$) (Fig. 3a). Similar cancer-specific survival (CSS) (Fig. 3b) and overall survival (OS) (Fig. 3c) were observed as well (log-rank test = 0.46 and 0.91, respectively).

Survival following identification of recurrence

After recurrence, 4-year CSS was 53%. CSS was similar among patients with adequate and inadequate follow-up; 4-year CSS was 52% and 51% (Fig. 4a, log-rank test, $p = 0.76$). Patients with symptoms at recurrence diagnosis had lower CSS: 4-year CSS was 28% in patients with symptoms at recurrence diagnosis and 60% in asymptomatic patients. However, difference of CSS among the groups was not statistically significant (Fig. 4b, log-rank test, $p = 0.07$). Among patients with local, metastatic, oligo-metastatic and multi-metastatic recurrence, 4-year CSS was 100, 83, 50 and 31%, respectively (Fig. 4c, log-rank test, $p < 0.0001$).

In univariable analysis, the presence of multi-metastatic lesions at recurrence diagnosis was an independent prognostic factor of worse CSM (HR = 8.70, 95% CI: 2.01–37.72, $p = 0.004$). A similar trend was observed regarding the presence of symptoms at diagnosis and CSM (HR = 2.05, 95% CI: 0.91–4.58, $p = 0.082$). The type of surveillance did not affect CSM (HR = 1.13, 95% CI: 0.53–2.42, $p = 0.76$). In multivariable analysis, only the presence of multi-metastatic lesions at recurrence diagnosis was an independent prognostic factor of worse CSM (HR = 10.15, 95% CI: 2.29–44.82, $p = 0.002$) (Table 2).

Discussion

We retrospectively reviewed our recent cohort of patients treated with radical nephrectomy or partial nephrectomy for local or locally advanced renal tumor and followed for a minimum of 5 years. In this large contemporary cohort, we hereby report an overview of the recurrence characteristics and demonstrate that infringements to a strict protocol of follow-up do not impact oncological outcomes.

We first reported that one-fifth of our patients had disease recurrence. This rate is comparable to the 5-year recurrence rate of 27.6% reported in the original UISS validation series [4]. Recent series, in Swedish and Dutch cohorts, reported similar rates [9, 10]. In our study, nearly 50% of patients had partial nephrectomy. This is much more than in the Swedish, Dutch and UISS series, which included 12.3, 20 and 30% of patients treated with partial nephrectomy, respectively. The rate of tumor stage T1 was similar among all studies. The high rate of partial nephrectomy at our institution can be explained by a central effect and an up-to-date management

Table 1 Population characteristics

	Total		Partial nephrectomy		Radical nephrectomy	
No. pts	267		130		137	
Age, years (IQR)	60.2	(50–71)	57.7	(48–68)	62.4	(57–74)
Gender, *n* (%)						
Female	98	(36)	52	(40)	46	(34)
Male	169	(64)	78	(60)	91	(66)
ECOG score, *n* (%)						
0	191	(71.5)	104	(80)	87	(63.5)
1	37	(13.9)	8	(6.2)	29	(21.1)
2	1	(0.4)	0	(0)	1	(0.7)
Unknown	38	(14.2)	18	(13.8)	20	(14.6)
Tumoral size, cm (IQR)	5.57	(3–7)	3.84	(2.1–4)	7.21	(5.5–11)
Surgical approach, *n* (%)						
Open	175	(65.5)	93	(71.5)	82	(59.9)
Laparoscopic	92	(34.5)	37	(28.5)	55	(40.1)
RCC histological subtypes, *n* (%)						
Clear cells	213	(79.8)	103	(79.2)	110	(80.3)
Papillary	36	(13.5)	17	(13.1)	19	(13.9)
Chromophobe	18	(6.7)	10	(7.7)	8	(5.8)
Fuhrman grade, *n* (%)						
1	12	(4.5)	11	(8.5)	1	(0.7)
2	131	(49.1)	81	(62.3)	50	(36.5)
3	98	(36.7)	35	(26.9)	63	(46)
4	24	(9)	2	(1.5)	22	(16.1)
Unknown	2	(0.7)	1	(0.8)	1	(0.7)
pT stage, *n* (%)						
T1	163	(61.1)	117	(90)	46	(33.6)
T2	24	(9)	6	(4.6)	18	(13.1)
T3	78	(29.2)	7	(5.4)	71	(51.8)
T4	2	(0.7)	0	(0)	2	(1.5)
pN stage, *n* (%)						
N0/Nx	262	(98.1)	130	(100)	132	(96.4)
N1	1	(0.4)	0	(0)	1	(0.7)
N2	4	(1.5)	0	(0)	4	(2.9)
Necrosis present, *n* (%)	93	(34.8)	27	(20.8)	66	(48.2)
UISS Score, *n* (%)						
Low	105	(39.3)	80	(61.5)	25	(18.3)
Intermediate	140	(52.5)	49	(37.7)	91	(66.4)
High	22	(8.2)	1	(0.8)	21	(15.3)
Leibovich score, *n* (%)						0
1	130	(48.7)	99	(76.2)	31	(22.6)
2	78	(29.2)	28	(21.5)	50	(36.5)
3	58	(21.7)	3	(2.3)	55	(40.2)
Unknown	1	(0.4)	0	(0)	1	(0.7)
Recurrence, *n* (%)	62	(23.2)	13	(10)	49	(35.8)
Recurrence type, *n* (%)						
Local	10	(16.4)	6	(4.6)	4	(2.9)
Single metastasis	14	(22.9)	1	(0.8)	13	(9.5)
Oligo-metastatic	9	(14.8)	3	(2.3)	6	(4.4)
Multi-metastatic	29	(45.9)	3	(2.3)	26	(19)
Symptoms at recurrence, *n* (%)	12	(20)	2	15.4%	10	20.4%

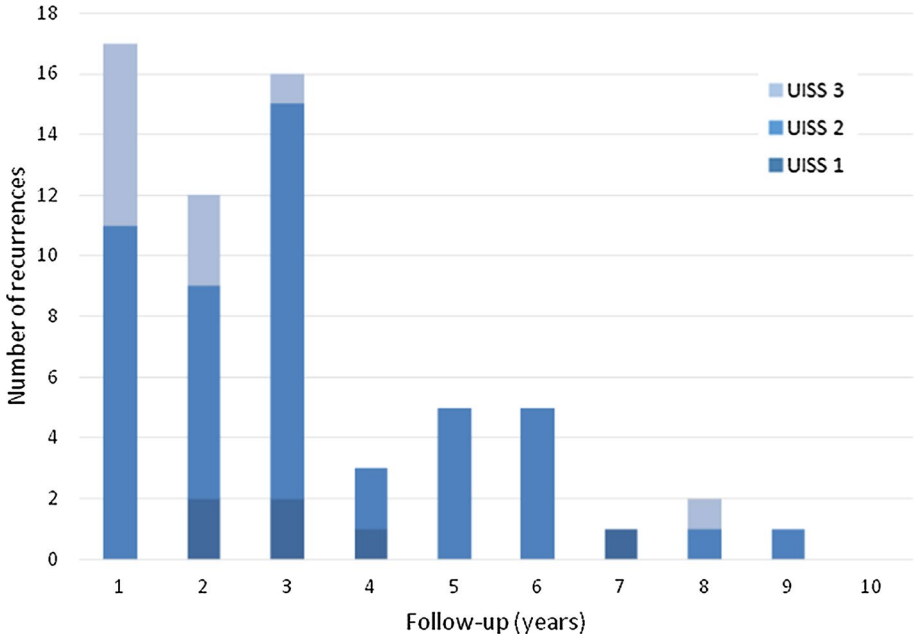

Fig. 1 Number of recurrences during follow-up according to UISS score groups

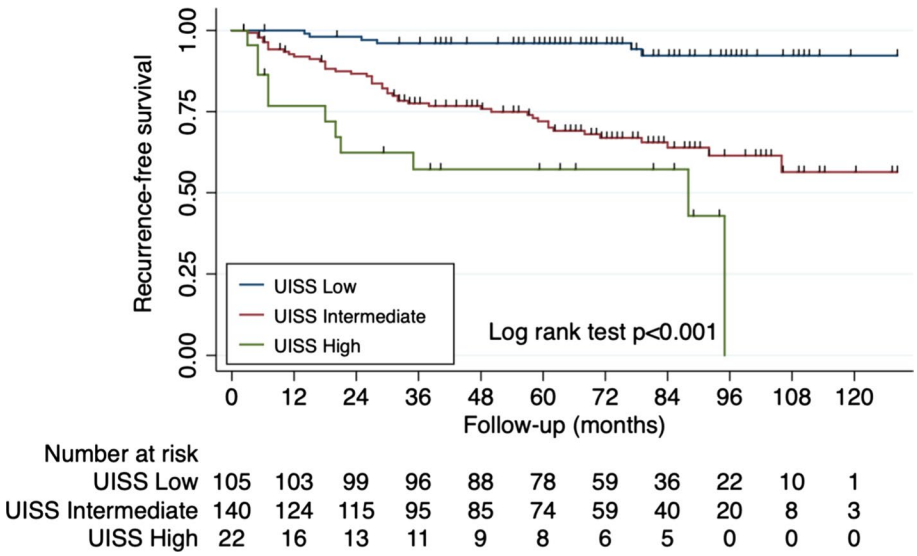

Fig. 2 Kaplan–Meier curves show probability of recurrence stratified by UISS risk category

of low-stage disease [11]. This management may have been associated with an increased risk of local recurrence. However, in our series, only 16% of the recurrences were local and patients treated with partial nephrectomy had no more local recurrences (6/130) than those treated with enlarged nephrectomy (4/137). These observations confirm that, as seen in a recent series [12], even with the widespread of partial nephrectomy, most of the recurrences remain metastatic.

In our study, median time to recurrence varies according to tumor characteristics. Therefore, the higher the tumor stage, the lower the median time to recurrence [13, 14]. This is in agreement with the results published by Levy et al. [15], which reported median delays of 56, 24, 21 and 11 months for stages T1 to T4, respectively. These observations warrant the tailoring of surveillance schedule to tumor characteristics and justify the use of prognostic tools and scores, such as UISS group scores [2–5]. However, considering UISS scores in our recent cohort, from low to high risk, we observed that the median delays were 26.5, 29 and 7 months for patients with low, intermediate and high risks, respectively. In the original UISS series [4], the median delays were 28.9, 17.8 and 9.5 months. The earlier median time in our low-risk group compared to intermediate group may be explained as follows. Our series included much more patients treated with partial nephrectomy than the original one (50% vs 30%). A higher proportion of patients were treated with partial nephrectomy in the low-risk group. The risk of local recurrence on

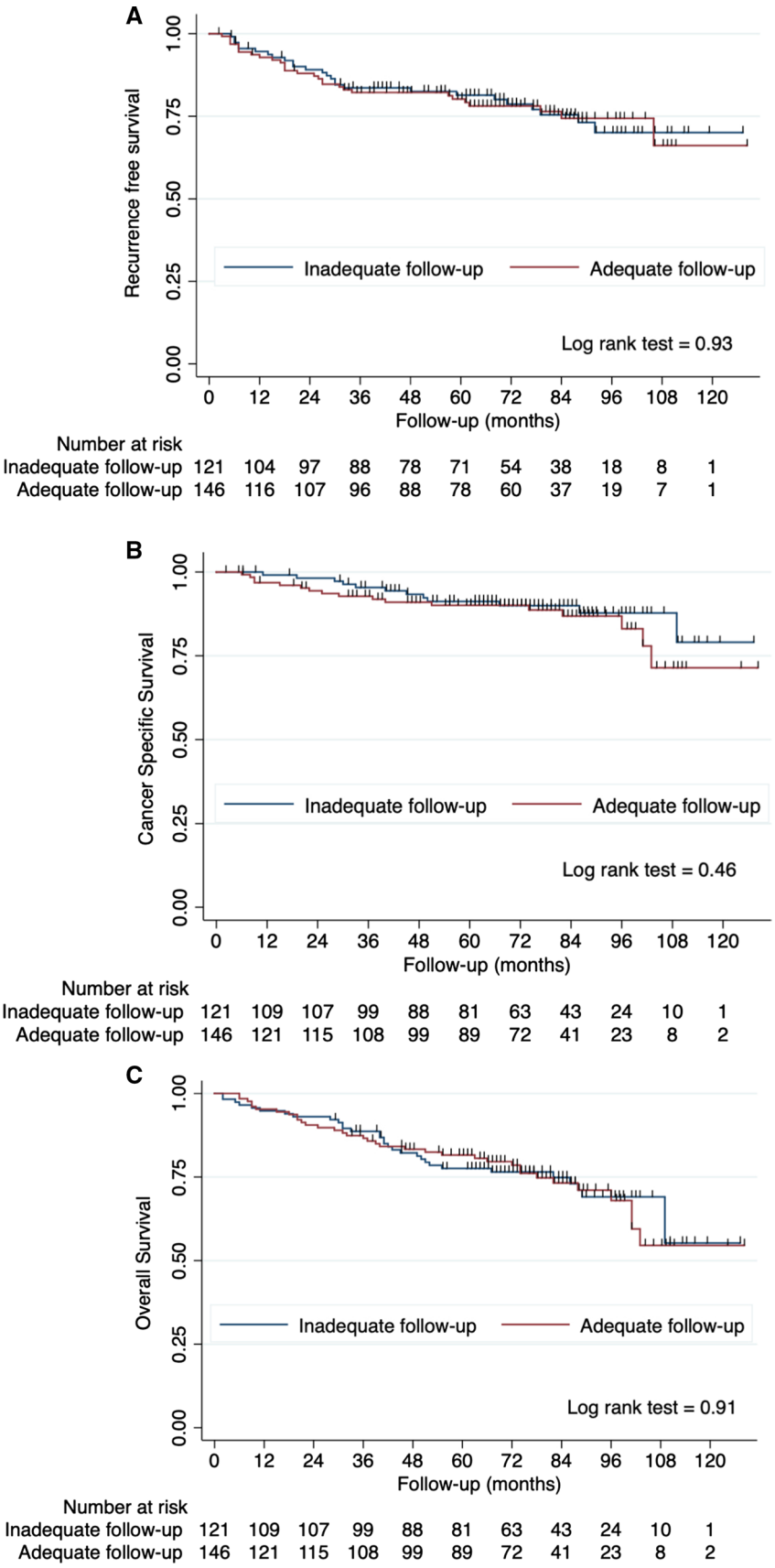

Fig. 3 Survival according to follow-up: recurrence-free survival (**a**), cancer-specific survival (**b**), overall survival (**c**)

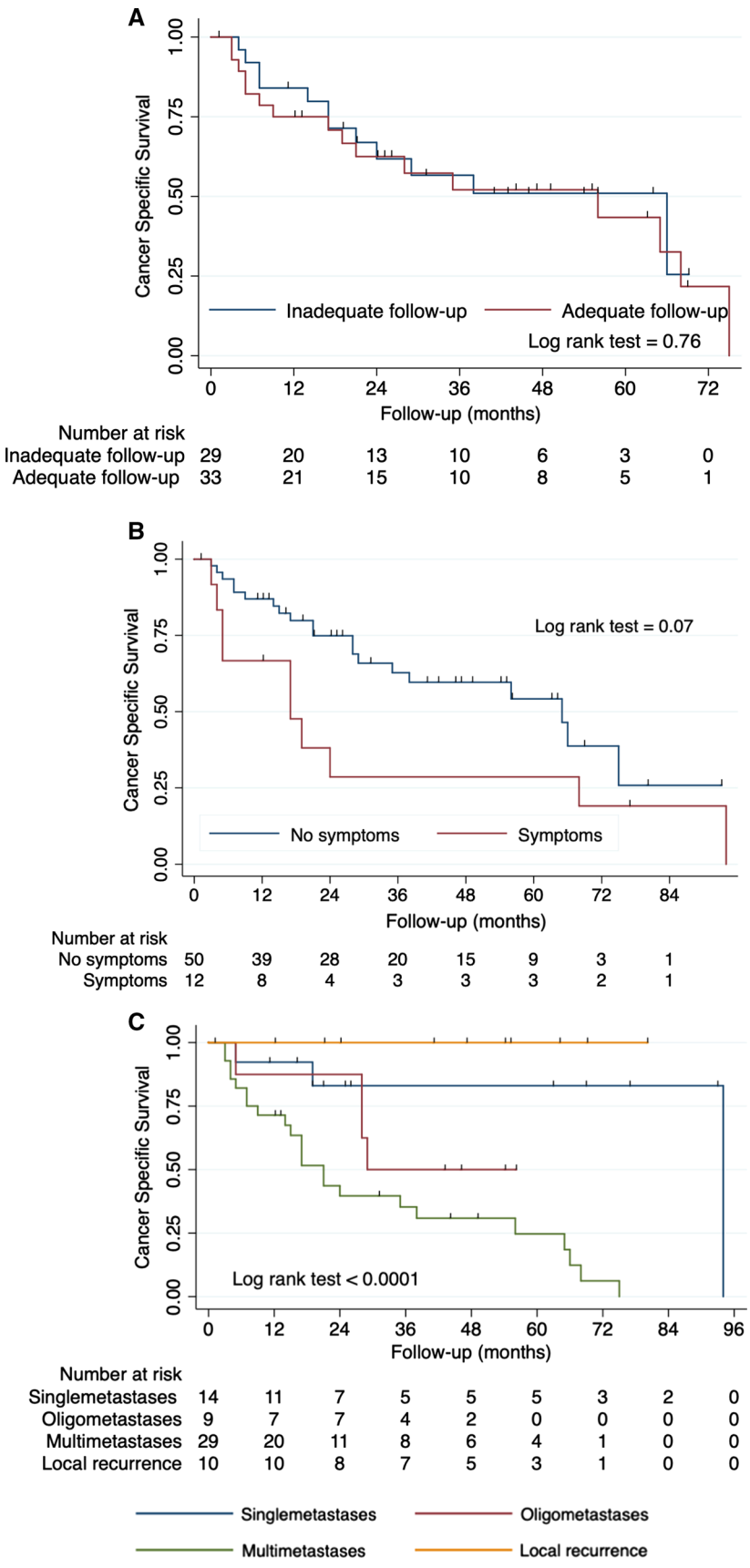

Fig. 4 Cancer-specific survivals after recurrence diagnosis according to initial follow-up (**a**), symptoms at diagnosis (**b**), and type of recurrence (**c**)

Table 2 Cox regression analysis for prediction of cancer-specific mortality in 62 patients with recurrence after nephrectomy for renal tumor

	CSM					
	Univariable			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age at recurrence diagnosis	1.03	0.99–1.06	0.12			
Gender (male vs female)	1.34	0.60–3.02	0.48			
Symptoms at recurrence diagnosis	2.05	0.91–4.58	0.082	1.82	0.79–4.21	0.162
pT stage						
T1	Ref.	Ref.	Ref.			
T2	0.67	0.08–5.47	0.71			
T3	1.47	0.62–3.50	0.39			
T4	5.94	0.68–51.64	0.11			
pN + status	0.76	0.18–3.20	0.71			
Histological subtype						
Clear cells	Ref.	Ref.	Ref.			
Papillary	1.49	0.56–3.94	0.43			
Chromophobe	1.98	0.58–6.74	0.28			
Type of recurrence						
Single metastasis	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Oligo-metastases	4.25	0.74–24.41	0.104	5.4	0.88–32.92	0.067
Multi-metastases	8.70	2.01–37.72	0.004	10.15	2.29–44.82	0.002
Inadequate follow-up	1.13	0.53–2.42	0.76			

the resection bed or in the ipsilateral kidney was greater in this group and may have shortened time to recurrence.

With a median follow-up of 72 months, most of the recurrences were diagnosed within the first 3 years of follow-up. Thus, the median time to diagnosis of recurrence was relatively short. These results are in accordance with the original study by Lam et al. and other recent published studies [4, 9, 16]. In our experience, almost all high-risk patients according to the UISS score experienced recurrence within 3 years. These results call for close monitoring during the first postoperative years, especially in this group. However, we reported that 14.5% of all recurrences were diagnosed after 5 years of follow-up. Therefore, late recurrences may not be considered exceptional. In 2011, Kim et al. [17] published a series of more than 1400 patients with no recurrence during the first 5 years of postoperative follow-up. After this initial monitoring of 5 years, the authors reported a total of 235 recurrences (16.2%). In a cohort of 254 patients followed more than 10 years after surgery, Antonelli et al. [18] showed that 5% of the patients had recurrence after 10 years. In our series, these late recurrences mainly concerned patients with intermediate risk according to the UISS score, while only one patient with a low risk experienced recurrence after 4 years. If the global rate of recurrence after 5 years justifies prolonged monitoring of patient with renal tumor after surgery, a reduction or even a stop of follow-up for low-risk patients should also be considered.

Most of the recurrences we observed were lung metastases. Therefore, the sensitivity of the thoracic imaging is a considerable stake for the detection of recurrence. We observed that lung metastases were only detectable on chest CT. Previous chest X-rays were not contributive in these patients. This strong argument supports the recommendations of the EAU [19] (as opposed to the AUA recommendations [20]) and the complete abandonment of the chest X-ray as a surveillance examination during follow-up after renal carcinoma. Recently, Canvasser et al. [21] highlighted the highly debatable performance of this imaging examination in the detection of asymptomatic recurrences in patients with a low-risk tumor (stage T1a): out of 258 patients, 3 patients had recurrence on lungs and only one was diagnosed by chest X-ray. The benefit of chest X-ray is also limited according to Doornweerd et al. [22]: 221 patients treated for T1-3 N0 M0 renal tumor were followed with regular chest X-rays. Nineteen patients experienced lung recurrence, and only 7 patients were diagnosed on chest X-rays. Similarly, none abdominal recurrence was diagnosed by ultrasound in our series. If the use of non-irradiating or easily accessible imaging examinations is an attractive option, our results show that their diagnostic performance in this indication is limited. It is therefore advisable to privilege more informative imaging examinations (CT and MRI) compared to X-rays and ultrasounds.

To schedule the follow-up of our patients, we commonly use UCLA's UISS prognostic score. It is a fairly

simple tool that incorporates established prognostic factors such as tumor stage, Fuhrman grade and ECOG score. In contrast, the score proposed by the MSKCC (Kattan) does not include the tumor grade according to Fuhrman [2]. The SSIGN, Leibovich (Mayo Clinic) and Karakiewicz scores [23] require the integration of 5 prognostic factors, limiting its use in routine practice. Our analysis on the score itself confirms the association with the risk of recurrence. But according to our results, strict follow-up according to UCLA-based UISS recommendations did not significantly shorten recurrence diagnosis, whatever UISS group the patient belonged to. Therefore, similar cancer-specific and overall survivals were observed among patient with "inadequate" surveillance compared to those strictly followed. To our knowledge, this is the first study to assess the relationship between follow-up modalities and specific survival. Our results demonstrate that strict adherence to UISS protocol does not improve diagnostic performance and does not shorten initiation of an effective therapeutic management. These observations may warrant a reduction of the imaging examinations during follow-up without compromising oncological outcomes. However, we also demonstrated that the symptomatic character and the type of recurrence (oligo- and especially multi-metastatic) were associated with worse survivals. Thus, although follow-up can certainly be alleviated, it is necessary that this follow-up allows the diagnosis of recurrence when asymptomatic and stage is limited (local recurrence or single metastasis). As previously discussed, if imaging examinations may be spaced, CT and MRI should be preferred.

Our study has many limitations in particular as it is retrospective and monocentric. It does not take into account the therapeutic strategy initiated after tumor recurrence which may influence specific survival. Finally, inadequate follow-up represents very different monitoring modalities and does not reflect standard protocols to come up with new recommendations.

Conclusion

The performance of chest X-ray and abdominal ultrasound for the detection of recurrences after nephrectomy for renal tumor is limited. Strict adherence to the UISS protocol of follow-up does not improve oncological outcomes. These results may justify follow-up schedules after nephrectomy with wider intervals regarding routine imaging and the preference to highly informative imaging examination.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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