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The Impact of Histological Subtype on the Incidence, Timing, and Patterns of Recurrence in Patients with Renal Cell Carcinoma After Surgery—Results from RECUR Consortium

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Abstract

Background: Current follow-up strategies for patients with renal cell carcinoma (RCC) after curative surgery rely mainly on risk models and the treatment delivered, regardless of the histological subtype.

Objective: To determine the impact of RCC histological subtype on recurrence and to examine the incidence, pattern, and timing of recurrences to improve follow-up recommendations.

Design, setting, and participants: This study included consecutive patients treated surgically with curative intention (ie, radical and partial nephrectomy) for non-metastatic RCC (cT1–4, M0) between January 2006 and December 2011 across 15 centres from 10 countries, as part of the euRopEan association of urology renal cell carcinoma guidelines panel Collaborative multicenter consortium for the studies of follow-Up and recurrence patterns in Radically treated renal cell carcinoma patients (RECUR) database project.

Outcome measurements and statistical analysis: The impact of histological subtype (ie, clear cell RCC [ccRCC], papillary RCC [pRCC], and chromophobe RCC [chRCC]) on recurrence-free survival (RFS) was assessed via univariate and multivariate analyses, adjusting for potential interactions with important variables

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(stage, grade, risk score, etc.) Patterns of recurrence for all histological subtypes were compared according to recurrence site and risk criteria.

Results and limitations: Of the 3331 patients, 62.2% underwent radical nephrectomy and 37.8% partial nephrectomy. A total of 2565 patients (77.0%) had ccRCC, 535 (16.1%) had pRCC, and 231 (6.9%) had chRCC. The median postoperative follow-up period was 61.7 (interquartile range: 47–83) mo. Patients with ccRCC had significantly poorer 5-yr RFS than patients with pRCC and chRCC (78% vs 86% vs 91%, $p = 0.001$). The most common sites of recurrence for ccRCC were the lung and bone. Intermediate-/high-risk pRCC patients had an increased rate of lymphatic recurrence, both mediastinal and retroperitoneal, while recurrence in chRCC was rare (8.2%), associated with higher stage and positive margins, and predominantly in the liver and bone. Limitations include the retrospective nature of the study.

Conclusions: The main histological subtypes of RCC exhibit a distinct pattern and dynamics of recurrence. Results suggest that intermediate- to high-risk pRCC may benefit from cross-sectional abdominal imaging every 6 mo until 2 yr after surgery, while routine imaging might be abandoned for chRCC except for abdominal computed tomography in patients with advanced tumour stage or positive margins.

Patient summary: In this analysis of a large database from 15 countries around Europe, we found that the main histological subtypes of renal cell carcinoma have a distinct pattern and dynamics of recurrence. Patients should be followed differently according to subtype and risk score.

Introduction

Clear cell renal cell carcinoma (ccRCC) is the commonest histopathological subtype of renal malignancies and accounts for nearly 80% of all cases, followed by papillary (pRCC) and chromophobe (chRCC) renal cell carcinoma (RCC) in 10–15%, and 5% of tumours, respectively [1,2]. Although surgical resection is the standard of treatment for localised tumours, up to 40% of patients still experience disease recurrence, mainly in the first 5 yr after surgery [3–5]. Previous studies have identified several risk factors, including tumour-node-metastasis (TNM) stage, Fuhrman grade, and Eastern Cooperative Oncology Group performance status, as the most widely recognised prognostic factors in RCC [2,6]. Based on these findings, several prognostic models have been developed for the evaluation of the risk of metastasis or disease recurrence. However, until recent years, these risk groups were established for ccRCC only [7,8] or for all RCC subtypes considered collectively [9–11], ignoring the inherent association between individual histological subtypes and the significant survival differences in patients after radical surgery. Over the years, further prognostic models were developed for the non-ccRCC population, including the "GRade, Age, Nodes and Tumour" (GRANT) score for both ccRCC and non-ccRCC [12] and the VENUSS score for nonmetastatic pRCC [12,13]. A recent study by Leibovich et al [14] has generated specific prognostic models for all major histological subtypes. However, most of these studies did not compare the pattern of recurrence for each subtype regarding recurrence sites or whether they were diagnosed by routine follow-up imaging or symptoms. Despite the lack of well-designed prospective cohort studies, previous data suggest that early identification and treatment of RCC recurrence may improve cancer-specific survival (CSS) and overall survival in selected patients [15–17]. Thus, it is imperative to develop an effective risk-based surveillance strategy for the different subtypes that takes the sites of recurrences and the dynamics of their occurrence into account.

The objective of this study was to determine the impact of RCC histological subtype on recurrence-free survival (RFS). Our secondary objective was to examine the patterns, dynamics, and sites of recurrences for each histological subtype, relying on a large multi-institutional consortium focusing on follow-up after surgery (the euRopEan association of urology renal cell carcinoma guidelines panel Collaborative multicenter consortium for the studies of follow-Up and recurrence patterns in Radically treated renal cell carcinoma patients [RECUR]), to develop clinical practice recommendations on follow-up imaging strategies.

Patients and methods

Study population

Data were analysed from the RECUR database, a retrospectively collected registry of 3425 consecutive patients from 15 European centres, in 10 European countries [18,19]. All patients included in the cohort were treated with radical or partial nephrectomy between 2006 and 2011 for sporadic, nonmetastatic RCC. Patients with ccRCC were stratified into low, intermediate, and high risk of recurrence groups according to Leibovich score (LS), whereas the University of California Los Angeles Integrated Staging System (UISS) using TNM stage was applied for non-ccRCC. The final analysis included only patients with the final pathology of ccRCC, pRCC, or chRCC. The exclusion criteria included

metastatic disease upon diagnosis, hereditary disease increasing the risk for RCC (such as Von Hippel-Lindau, Birt-Hogg-Dubé syndrome, and hereditary papillary renal cell carcinoma), and death during or shortly after hospitalisation. Patients who were alive without disease at the last follow-up, which was <2 yr after surgery, were censored at the point of the last follow-up.

Definition of outcome measures

The primary outcome was tumour recurrence, measured as discrete incidence (%; expressed as overall recurrence and recurrence at specific sites, and number of lesions), RFS, and time to recurrence (TTR). Recurrence sites of metastases were specified as local ipsilateral, contralateral, or distant. In addition, recurrences were specified as solitary, oligometastatic (three or fewer at a single site), multiple (four or more at a single site), or disseminated (multiple sites), including the multidisciplinary tumour board opinion of the participating site to consider the recurrence as potentially "curable disease" amenable to focal therapy (metastasectomy, radiotherapy, and ablation) [18,19]. RFS was defined as the time from surgery to the recurrence of tumour, death, or end of follow-up. TTR (in months) was calculated as follows: "date of recurrence event – date of Surgery". Recurrence patterns were stratified based on symptoms upon detection of recurrence and based on whether recurrence detection was within regular follow-up [20]. In addition to analysing the sites of distant metastasis, these were divided into three localisation groups: thorax (lung, pleura, and mediastinal lymph nodes), abdomen (liver, pancreas, adrenal gland, contralateral kidney, and retroperitoneal lymph nodes), and other (bone, brain, and miscellaneous). For a site-based analysis, the localisation groups were as follows: only thoracic, only abdominal, or both (upon diagnosis of recurrence, two or more sites were involved, including both thoracic and abdominal locations).

Statistical analysis

Associations of RCC histological subtype with other clinicopathological features (ie, age, gender, pathological stage, nuclear grade, sarcomatoid differentiation, necrosis, risk score, vascular invasion, positive surgical margins [PSMs], and type of curative treatment) were evaluated using one-way analysis of variance for an analysis of continuous variables, and the Fisher exact test and chi-square test were used for categorical variables. Of note, tumour stage was handled as a continuous variable. Cox regression analysis was applied to define clinical and pathological parameters associated with recurrence. Independent variables were first analysed by univariate methods. A survival analysis was performed by the Kaplan-Meier method. Variables that were statistically significant by univariate analysis were included in a multivariate analysis using the Cox stepwise proportional hazard model. A p value of <0.05 was considered statistically significant. Statistical Package for Social Sciences (SPSS, version 25.0; SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

Out of a total of 3425 patients in the RECUR database, 3331 (97.3%) were eligible and were included in this study (Fig. 1). Of the eligible patients, 2565 (77%) were diagnosed with ccRCC, 535 (16.1%) with pRCC, and 231 (6.9%) with chromophobe chRCC. The median postoperative follow-up period was 61.7 (interquartile range [IQR]: 47–83) mo. Twenty-three patients in RECUR with non-ccRCC who were alive without disease at the last follow-up, which was <2 yr after surgery, were censored at the point of the last follow-up. The clinicopathological and surgical features for ccRCC, pRCC, and chRCC are summarised in Table 1.

Results of primary analysis for the entire cohort

Five-year RFS rates for the entire cohort stratified according to subtype were 78%, 86%, and 91% for ccRCC, pRCC, and chRCC, respectively ($p = 0.001$; Fig. 2). On univariate analysis, features associated with worse RFS included the stage, size, grade, necrosis, vascular invasion, PSMs, risk score, and histological subtype of the tumour (all $p < 0.001$; Supplementary Table 1). The variables that remained significant on multivariable analysis included tumour stage (hazard ratio [HR]: 1.34, confidence interval or CI [1.25–1.43]), size (HR: 1.061, CI [1.03–1.09]), nuclear grade (HR: 1.44, CI [1.28–1.61]), necrosis (HR: 1.75, CI [1.42–2.15]), vascular invasion (HR: 1.44, CI [1.15–1.8]), PSMs (HR: 3.3, CI [2.35–4.6]), and histological subtype (ccRCC vs pRCC: HR: 0.65, CI [0.43–0.97]; ccRCC vs chRCC: HR: 0.32, CI [0.13–0.76]; Supplementary Table 2). Separate analyses for both abdominal and thoracic recurrence showed similar results. For both anatomical areas, RFS was significantly poorer in ccRCC patients than in both pRCC and chRCC patients. On multivariable analysis, histological subtype was a significant factor for thoracic recurrences (HR: 4.6, CI [1.4–14.3]; HR: 3.6, CI [1.1–12]). Regarding the number of sites, 319 patients had a single-site recurrence, with the lung being the most common site (119 patients), followed by local recurrence and contralateral kidney recurrence in 51 and 40 patients, respectively. Single-site lymphatic spread was recorded in 21 patients (seven thoracic and 14 retroperitoneal); the highest rate of isolated lymphatic spread was seen in pRCC patients (17.2%), followed by 6% in ccRCC and 0% in chRCC. For CSS, 5-yr survival rates were 89%, 91%, and 96% for ccRCC, pRCC, and chRCC, respectively. On multivariable analysis, survival was associated with tumour stage, nuclear grade ($p < 0.001$ for both), size ($p = 0.005$), necrosis ($p = 0.016$), PSM ($p = 0.014$), and vascular invasion ($p = 0.025$); histological subtype was not a significant factor for death from RCC, probably due to the low number of events (249 vs 34 vs10 patients with ccRCC vs pRCC vs chRCC).

Results of subgroup analyses

Clear cell RCC

The primary metastatic pattern of patients with ccRCC is shown in Fig. 3. The most common site of recurrence was the lung in 50.4% of patients, followed by bone and

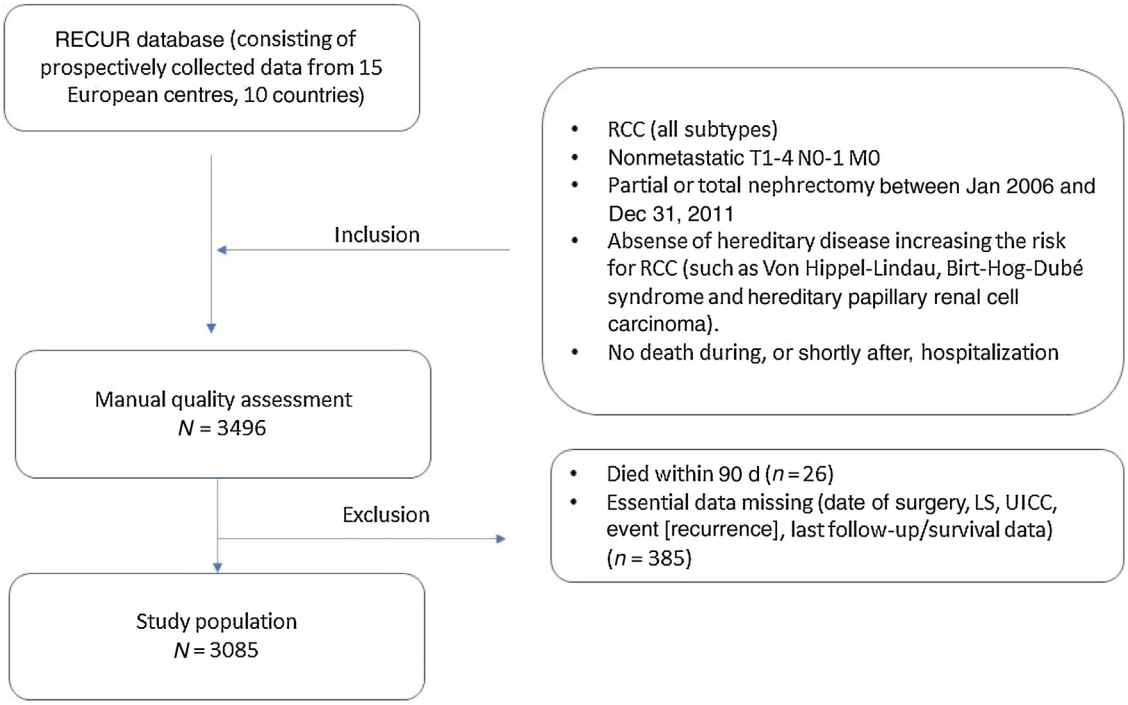


Fig. 1 – Flowchart demonstrating the inclusion and exclusion criteria for the present study. LS = Leibovich score; RECUR = euRopEan association of urology renal cell carcinoma guidelines panel Collaborative multicenter consortium for the studies of follow-Up and recurrence patterns in Radically treated renal cell carcinoma patients; RCC = renal cell carcinoma; UICC = Union Internationale contre le Cancer score.

Table 1 – Clinicopathological and surgical features for ccRCC, pRCC, and chRCC.

		ccRCC (*n* = 2565)	pRCC (*n* = 357)	chRCC (*n* = 231)
Age		62.9 ± 12	62.7 ± 12	59.6 ± 15
Gender	Male	1643 (64)	413 (77)	129 (56)
	Female	922 (36)	122 (23)	102 (44)
Surgery	RN	1673 (65)	265 (49.6)	133 (57.4)
	NSS	892 (35)	270 (50.4)	98 (42.6)
Side ^	Left	1112 (47.8)	230 (47.4)	96 (46)
	Right	1171 (50.4)	233 (48)	109 (52.4)
	Both	42 (1.8)	22 (4.5)	3 (1.4)
Size (cm)		5.5 ± 3.2	5.03 ± 3.7	5.9 ± 3.7
Stage ^	T1a	985 (38.6)	265 (49.7)	83 (36)
	T1b	644 (25.3)	129 (24.2)	65 (28)
	T2a	226 (9)	36 (6.8)	26 (11)
	T2b	77 (3)	33 (6.2)	17 (7.4)
	T3a	489 (19)	56 (10.5)	32 (14)
	T3b	97 (3.8)	9 (1.7)	6 (2.6)
	T3c	13 (0.5)	1 (0.2)	1 (0.4)
	T4	19 (0.7)	4 (0.8)	1 (0.4)
Grade ^	1	233 (9)	21 (4)	7 (3)
	2	1544 (60)	157 (29.3)	60 (26)
	3	618 (24)	81 (15)	35 (15.2)
	4	152 (6)	9 (1.7)	8 (3.5)
Sarcomatoid features ^		62 (2.4)	7 (1.3)	2 (0.9)
Tumour necrosis ^		791 (33.2)	209 (42.5)	57 (27)
Vascular invasion ^		378 (17.4)	43 (9.6)	21 (11.6)
PSM ^		84 (3.3)	25 (4.7)	10 (4.3)
Risk group ^	Low risk	1350 (54.3)	303 (57.3)	123 (53.5)
	Intermediate risk	686 (27.6)	100 (19)	38 (16.5)
	High risk	448 (18)	126 (23.8)	69 (30)

ccRCC = clear cell RCC; chRCC = chromophobe RCC; NSS = nephron-sparing surgery; pRCC = papillary RCC; PSM = positive surgical margin; RCC = renal cell carcinoma; RN = radical nephrectomy.

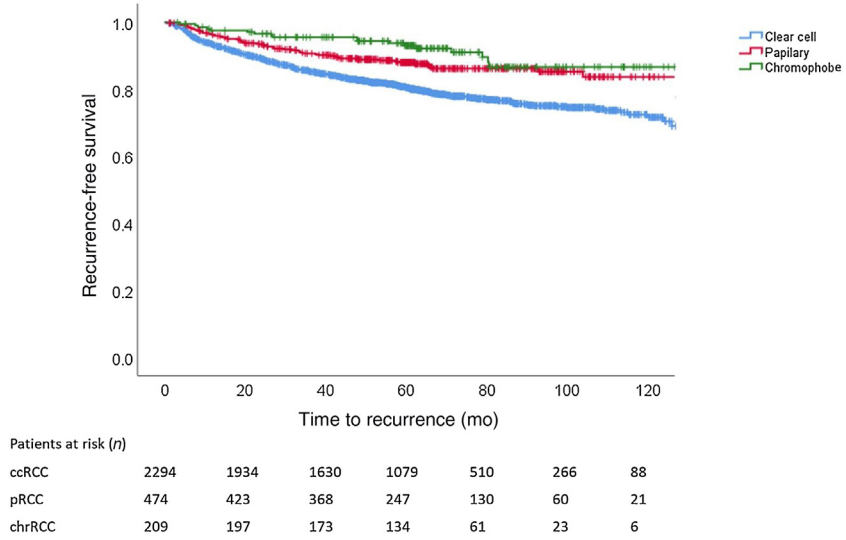


Fig. 2 – Recurrence-free survival in main histological renal cell carcinoma subtypes. ccRCC = clear cell RCC; chRCC = chromophobe RCC; pRCC = papillary RCC; RCC = renal cell carcinoma.

retroperitoneal lymph nodes in 16% and 15.7%, respectively (Fig. 4). On univariate analysis, features associated with worse RFS included tumour stage, size, grade, necrosis, vascular invasion, PSM, and risk score (all $p < 0.001$; Supplementary Table 1). The variables that remained significant on multivariable analysis included tumour stage (HR: 1.32, CI [1.2–1.42]), size (HR: 1.061, CI [1.03–1.09]), nuclear grade (HR: 1.65, CI [1.43–1.92]), necrosis (HR: 1.69, CI [1.35–2.11]), vascular invasion (HR: 1.35, CI [1.07–1.72]), and PSM (HR: 3.15, CI [2.13–4.6]; Supplementary Table 2). The median TTR was 21.2 (IQR: 7.9–41.1) mo, and 65 patients (13.5%) recurred after >5 yr from surgery. The 5-yr RFS for this subgroup was 78%. A log-rank test analysis showed a significantly increased risk of recurrence for each incremental risk group stratified by low, intermediate, and high risk, according to LS ($p < 0.001$; Fig. 5A). Further analysis based on these risk groups revealed a different pattern of recurrence in regard to site. While local and contralateral kidney recurrences were seen more often in patients with low-risk LS (27% and 23% of patients, respectively), intermediate- and high-risk patients were more likely to have recurrence in the lung and liver (58% and 17%, respectively). Regarding timing, the TTR for abdominal sites only was significantly longer than thorax recurrence only (31.1 ± 2.43 and 26 ± 1.8 mo, respectively, $p = 0.008$).

Papillary RCC

Among the 535 patients with pRCC, 59 (11%) recurred at a median of 19 (IQR: 8.5–41) mo following surgery. Upon diagnosis, 22% of the patients had a solitary lesion, whereas 37.3% were diagnosed with disseminated disease (Fig. 3). Similar to ccRCC, the most common site of recurrence was the lung in 35.8% of patients (Fig. 4), followed by retroperitoneal lymph nodes in 29.6% of patients. Among patients in this subgroup, the median TTR was 19 (IQR: 8.6–41.1) mo. Only nine patients (1.7%) had a recurrence after >5 yr. The observed RFS rate at 5 yr was 86%. On univariate analysis, variables associated with worse RFS included tumour stage, size, grade, vascular invasion, PSM, risk score (all $p < 0.001$), and necrosis ($p = 0.008$; Supplementary Table 1). The variables that remained significant on multivariable analysis included tumour stage (HR: 1.5, CI [1.27–1.8]), vascular invasion (HR: 3.62, CI [1.76–7.5]), and PSM (HR: 2.33, CI [1.01–5.4]; Supplementary Table 2). Patients were subsequently stratified based on the Union Internationale contre le Cancer score. Cox regression analysis ($p < 0.001$; Fig. 5B) presented a significantly increased risk of recurrence for each risk group. Given the similar pattern of recurrence, the groups of intermediate and high risk were combined for the following analysis. In the *low*-risk group, the contralateral kidney and lung were the most common sites of recurrence in 31.3% (five of 16 patients, in both), whereas for the *intermediate- to high*-risk groups, the lung (40%) and retroperitoneal lymph nodes (35.5%) were the most frequent sites. Similar to ccRCC, the majority (75.5%) of recurrences were diagnosed via regular follow-up, and 35.6% were detected due to symptoms.

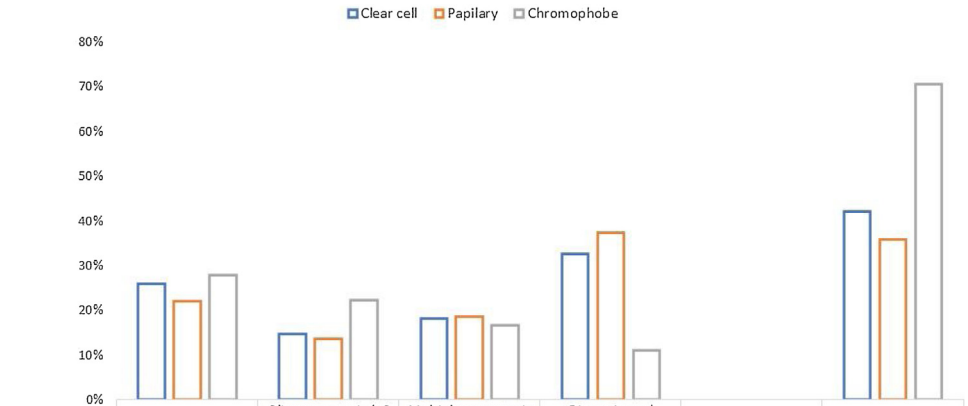
Chromophobe RCC

Among the 231 patients with chRCC, 19 (8.2) recurred, 27.8% were diagnosed with a solitary lesion, and two patients (11%) were diagnosed with disseminated disease (Fig. 3). The most common site of recurrence was bone in 29.4% of patients, whereas none of the patients experienced progression to the pancreas or mediastinal lymph nodes (Fig. 4). The variables that were found to be associated with worse RFS on univariable analysis included tumour stage, size, risk score ($p < 0.001$), grade ($p = 0.005$), necrosis ($p = 0.016$), and PSM ($p = 0.009$; Supplementary Table 1). The variables that remained significant on multivariable analysis included tumour stage (HR: 1.7, CI [1.3–2.3]) and PSM (HR: 5.4, CI [1.4–20.7]; Supplementary Table 2). The median

Table 2 – Published results on impact of histology on metastatic patterns in RCC.

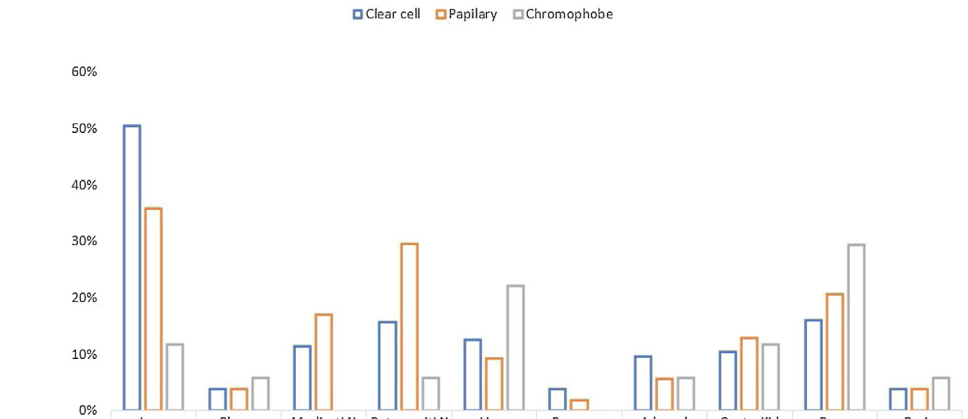
Study	Objective	Year	*N*	YOS	Median FU (mo)	Rec/met site	Main mets					
							ccRCC		pRCC		chRCC	
Hoffmann et al [22]	Site of mets in a met population [D]	2008	910	1970–2000	11.6 yr [*]		*N* = 853% of rec = NA [D]	Site	*N* = 39% of rec = NA [D]	Site	*N* = 18% of rec = NA [D]	Site
						Lung		53.6%		33.3%		33.3%
						Bone		25.3%		20.5%		16.7%
						Liver		9.7%		18%		33.3%
						LN		3.8%		10.3%		5.6%
Mai et al [24]	Compare met RCC according to subtype	2001	344	NA	NA		*N* = 283% of rec = 48.4% (*n* = 137)	Site	*N* = 48% of rec = 10.4% (*n* = 5)	Site	*N* = 13% of rec = 1/13	Site
						Lung		16.9%		20%		1/1
						Bone		10.6%				
						Liver		2.47%				
						LN		1.4%—IA, 2.47%—EA		80% (3—only RP); 1—RP & MED)		
Renshaw and Richie [25]	Site of mets in a met Population [D]	1999	82 pts; 119 rec [*]	1993–1997	20–38		*N* = 163 % of rec = 37.4% (*n* = 61)	Site	*N* = 76% of rec = 28.9% (*n* = 22)	Site	*N* = 25 % of rec = 28% (*n* = 7)	Site
						Lung		50.6%		9.1%		28.6%
						Bone		10.6%		9.1%		
						Liver		4.7%		13.6%		71.4%
						LN		9.4%		68.2%		
Noguchi et al [4]	Time-dependent changes in the relapse features	2018	1398	1985–2015	56.3		*N* = 1226% of rec = 17.7% (*n* = 217)		*N* = 89% of rec = 12/89		*N* = 53 % of rec = 5.7% (*n* = 3)	
						Lung		46.6%		20%		66.7%
						Bone		17.9%		25%		33.1%
						Liver		7.6%		10%		
						LN		6.5%		20%		
Beck [23]	Effect of histology, metastatic pattern, and DSS	2003	1057	1989–2002	33.2–43		*N* = 794% of rec = 11.96% (*n* = 95)		*N* = 157% of rec = 9/157		*N* = 106% of rec = 5.66% (*n* = 6)	
						Lung		62%		44%		50%
						Bone						
						Liver						
						LN		23%		22.2%		33%
Siddiqui et al [30]	Assess natural history of surgically treated RCC	2008	2339	1970–2000	8.1 yr		*N* = 1864% of rec = 37.55% (*n* = 700 rec)	185/700 abdominal, 300/700 thoracic	*N* = 357% of rec = 10.4% (*n* = 37)	37.6% abdominal, 32.4% thoracic	*N* = 118% of rec [*] = 11% (*n* = 13)	10/118 abdominal, 3/118 thoracic
						Lung						
						Bone						
						Liver						
						LN						
Motzer et al	Outcome data for non-ccRCC met Population [D]	2002	64	1985–2001	NA		NA		*N* = 18% of rec = NA [D]		*N* = 12% of rec = NA [D]	
						Lung				44%		17%
						Bone				33%		17%
						Liver				17%		25%
						LN				RP—56%		RP—33%
Narayan et al [29]	Evaluated patterns of relapse in non-ccRCC	2019	403	NA	6.2 yr		NA		*N* = 54% of rec = NA		*N* = 17% of rec = NA	
						Lung				33%		12%
						Bone				0%		12%
						Liver				7%		18%
						LN				Abd—39%		Abd—41%
Current study		2020		2006–2011	61.7		*N* = 2565% of rec = 18.8%		*N* = 357% of rec = 11%		*N* = 231% of rec = 8.2%	
						Lung		50.4%		35.8%		11.8%
						Bone		16%		20.8%		29.4%
						Liver		12.6%		9.3%		22.2%
						LN		15.7% (RP), 11.4% (MED)		29.6% (RP), 17% (MED)		5.9% (RP), 0% (MED)

Abd = abdominal; ccRCC = clear cell RCC; chRCC = chromophobe RCC; DSS = disease-specific survival; EA = extra-abdominal; FU = follow-up; IA = intra-abdominal; LN = lymph node; MED = mediastinal; met = metastasis/metastatic; NA = not available; pRCC = papillary RCC; pts = patients; RCC = renal cell carcinoma; rec = recurrence; RP = retroperitoneum; YOS = years of study.



	Solitary lesion	Oligometastasis (<3 SS)	Multiple metastasis (>4 SS)	Disseminated disease		Curable Dz
Clear cell	25.9%	14.8%	18.2%	32.6%		42.0%
Papilary	22.0%	13.6%	18.6%	37.3%		35.8%
Chromophobe	27.8%	22.2%	16.7%	11.1%		70.6%

Fig. 3 – Pattern of recurrence in clear cell, papillary, and chromophobe RCC. Dz = disease; RCC = renal cell carcinoma; SS = single site.



	Lung	Pleura	MediastLN	RetroperitLN	Liver	Pancreas	Adrenal	ContraKid	Bone	Brain
Clear cell	50.5%	3.9%	11.4%	15.7%	12.6%	3.9%	9.6%	10.5%	16.0%	3.9%
Papilary	35.8%	3.8%	17.0%	29.6%	9.3%	1.9%	5.7%	13.0%	20.8%	3.8%
Chromophobe	11.8%	5.9%	0.0%	5.9%	22.2%	0.0%	5.9%	11.8%	29.4%	5.9%

Fig. 4 – Site of recurrence in clear cell, papillary, and chromophobe RCC. ContraKid = contralateral kidney; LN = lymph node; MediastLN = mediastinal LN; RCC = renal cell carcinoma; RetroperitLN = retroperitoneal LN.

TTR was 37.4 (IQR: 11.1–64.6) mo. Of the 19 events, six (18.2%) recurred after >5 yr from surgery. The 5-yr RFS for this subgroup was 91%. Only three patients had recurrences in the thoracic region alone, nine in the abdomen and six in other regions (bone, brain, and miscellaneous). In one patient, the site of recurrence was unspecified. No subanalysis based on risk stratification was performed due to the low rate of recurrence. In regard to symptoms, 42.1% were symptomatic upon diagnosis and 58.5% were detected by regular follow-up (compared with 66.7% in the other subgroups).

Discussion

The RECUR database, a registry of 3400 consecutive patients with nonmetastatic RCC undergoing nephrectomy at 15 European centres, was developed by the European Association of Urology Renal Cancer Guideline Panel to inform recommendations for follow-up [2,19]. The novelty of RECUR in comparison with other registries [21] is that complete clinical data are available for further management and the outcome after a recurrence was detected.

To date, multiple stratification and risk assessment tools that have been recommended by various guidelines to evaluate the risk of progression or death in patients with RCC. Most of these models, however, are developed for patients with ccRCC alone or for all RCC subtypes considered as one [7,11]. The problem with the last option is that although both pRCC and ccRCC share some prognostic risk factors, such as grade or T stage, some of these may differ, such as tumour necrosis or vascular invasion [14], meaning that the aggressiveness of the disease may be defined adversely for different tumours;

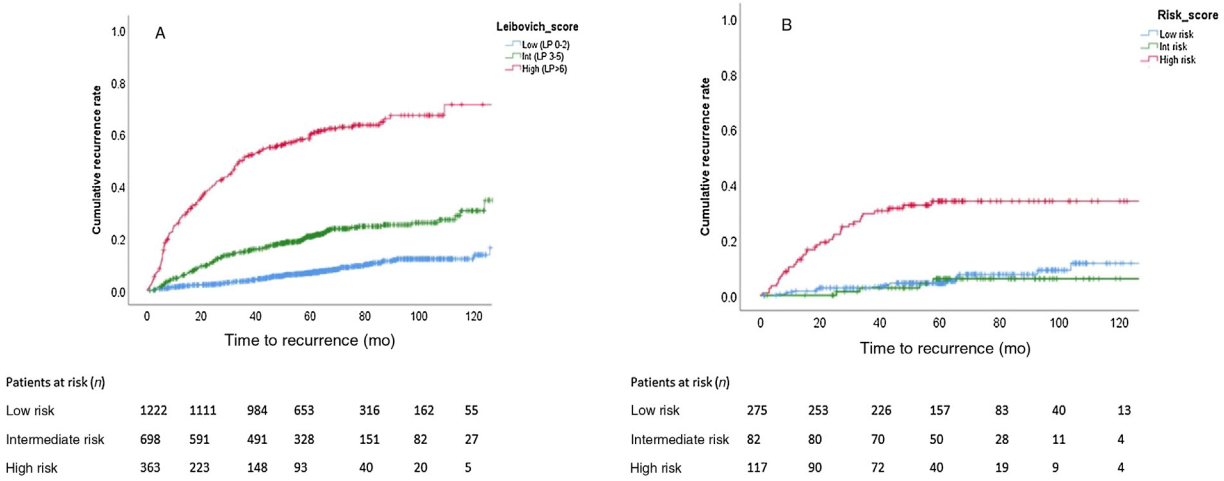


Fig. 5 – Kaplan-Meier curves for cumulative recurrence rates after treatment of initially localised ccRCC stratified by low-, intermediate-, and high-risk groups according to (A) Leibovich score for clear cell RCC and (b) UICC score for papillary RCC. ccRCC = clear cell RCC; RCC = renal cell carcinoma; UICC = Union Internationale contre le Cancer score.

hence, the follow-up should be tailored accordingly. The optimal way to follow patients is not only by recognising the high-risk ones early, but also by knowing where the recurrence may occur and when. To date, timing and duration of follow-up after treatment for RCC are debatable and inconsistent across guidelines. The overall recommendations rely mainly on the previously mentioned risk models and the treatment delivered, regardless of the histological subtype. Hence, identification of differences in location and dynamics of recurrence can lead to improved follow-up recommendations. Previous reports exist about the site of distant metastasis by histological subtype, with results of varying consistency (Table 2) [4,22,23]. Yet, most studies have been limited by small sample sizes and noncontemporary patient cohorts. Moreover, most of these studies only evaluated patients who had primary metastatic RCC (ie, M1 at the time of initial diagnosis) and did not mention the site of metastasis in those who recurred following treatment [22,24,25]. Therefore, in the current analysis, we attempted to expand on these previous studies in a large contemporary cohort of patients. Similar to previous studies, we found differences in the distribution of metastatic organ sites across each histological subtype.

In support of previous studies, patients with ccRCC were more likely to have metastasis to the lungs compared with other common sites. Patients with chRCC, on the contrary, not only have a low recurrence rate, but were also more likely to suffer from bone and liver metastases (five and four patients, respectively). Our findings concur with those of Renshaw and Richie [25] who found that all three metastatic events in the chRCC patient in their series occurred in the liver, as well as with those of Hoffmann et al [22] who found that the chRCC variant was significantly more likely to metastasise to the liver than ccRCC (33.3% vs 9.7%; Supplementary Table 2). Although the overall number of patients with recurrences in chRCC is small, the difference in recurrence sites is striking. Thus, due to the negligible thoracic recurrences among patients with chRCC, one may question routine computed tomography (CT) chest scans, while abdominal cross-sectional imaging could potentially be limited to chRCC patients with higher tumour stage and PSMs.

Previous reports have suggested that pRCC has a higher tendency for lymph node involvement [4,22,25], while others have noted a similar trend for all subtypes, especially when focusing on nonregional lymph node spread (Table 2) [26]. In the current analysis, patients with pRCC had a higher rate of lymph node metastasis, both regional and thoracic, than those with ccRCC and chRCC (Fig. 4). Moreover, patients with pRCC had the highest rate of solitary metastasis, exclusively to lymph nodes. This apparent tropism of lymphatic recurrence raises the question whether patients with intermediate- and high-risk pRCC may potentially benefit from abdominal cross-sectional imaging surveillance in the first 2 yr after surgery at intervals that are more frequent than advised by the European Association of Urology guidelines. Cross-sectional imaging examinations are more accurate than ultrasound, which can currently be used according to the American Urological Association (AUA) and the National Comprehensive Cancer Network 2014 guidelines for intermediate- and high-risk disease, at 6 monthly intervals [27,28]. Additionally, this distinctive pattern raises the question about the role of lymphadenectomy in high-risk pRCC patients. Should these patients undergo “routine” lymphadenectomy during nephrectomy? Owing to the low percentage of pRCC patients, randomised studies to investigate a potential survival benefit will not be feasible. Nevertheless, we were able to demonstrate that the lymphatic spread is more common among high-risk patients, as defined by the UISS, than among low-risk patients. These results are supported by a recent study by Narayan et al [29], a post hoc retrospective analysis of patients with non-ccRCC enrolled in a large randomised trial of adjuvant antiangiogenic

therapy for high-risk (≥T1b grade 3–4 N0) RCC (phase III ASSURE trial). Results showed that 39% of non-ccRCC patients in this cohort developed the first recurrence within the retroperitoneal lymph nodes, indicating that patients with high-risk non-ccRCC indeed appear to demonstrate this distinct pattern of recurrence.

Interestingly, in 2008, Siddiqui et al [30] attempted to create a subtype and risk-specific surveillance protocol, based on the patterns of RCC recurrence. In their study, they mapped the sites of recurrence according to risk factors, in an attempt to evaluate the cost effectiveness of existing protocols. Similar to our study, the rate of recurrences in the thoracic region among chRCC patients was negligible, allowing them to recommend a different follow-up protocol from ccRCC or pRCC. However, the authors based their protocol and analysis on a cohort of patients dating back to 1970. The nephrectomy techniques, quality of imaging, and follow-up scheme have developed over time, creating an inevitable bias in data interpretation. Still, Siddiqui et al's [30] protocol, in support of the current data, may lead to a more refined surveillance protocol, tailored specifically by different cancer characteristics.

We acknowledge the limitations associated with the retrospective nature of the study, as well as the low rate of recurrence at some sites, confounding the interpretation of data, especially in the less frequent subtypes (ie, pRCC and chRCC). Moreover, we recognise the potential clinical heterogeneity across centres regarding different follow-up strategies, including the type of imaging (eg, CT, ultrasound, chest x-ray, etc.), timing of first and subsequent imaging after treatment, and imaging frequency. Moreover, no central review of radiological imaging was performed. Lastly, we do not have information regarding the distinction between pRCC types 1 and 2. To avoid loss of power for statistical analyses, all risk groups of each subtype were analysed together. Nevertheless, most of the recurrences occurred in the intermediate- to high-risk groups, which reflect clinical reality. In addition, this study owes its uniqueness to its size as well as to the contemporary data included (2011–2016), which are relevant to current clinical practice.

The current results emphasise the need for evidence-based standards for risk assessment to counsel patients and tailor subtype-specific follow-up, to avoid overuse or to increase the frequency of imaging modalities where necessary.

Conclusions

The findings from this study suggest that patients with intermediate- to high-risk pRCC may benefit from cross-sectional abdominal imaging every 6 mo until 2 yr after surgery, while routine imaging can potentially be avoided for the majority of patients with chRCC, except for those with advanced tumour stage or positive margins. While the study presents novel data, due to the retrospective approach, clinical heterogeneity, and small sample bias, the evidence derived is subject to some uncertainty. We recommend that the findings are corroborated in prospective studies such as control arms of adjuvant trials.

Author contributions: Yasmin Abu-Ghanem had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Abu-Ghanem.
Acquisition of data: Dabestani.
Analysis and interpretation of data: Abu-Ghanem, Bex, Lam.
Drafting of the manuscript: Abu-Ghanem, Bex.
Critical revision of the manuscript for important intellectual content: Powles, Capitanio, Beisland, Järvinen, Stewart, Gudmundsson, Lam, Marconi, Fernandéz-Pello, Nisen, Meijer, Volpe, Ljungberg, Klatte, Dabestani, Bex.
Statistical analysis: Abu-Ghanem.
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Supervision: Bex.
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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euo.2020.09.005.

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