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Evaluation of the Prognostic Significance of Perirenal Fat Invasion and Tumor Size in Patients with pT1–pT3a Localized Renal Cell Carcinoma in a Comprehensive Multicenter Study of the CORONA project. Can We Improve Prognostic Discrimination for Patients with Stage pT3a tumors?

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Abstract

Background: The current TNM system for renal cell carcinoma (RCC) merges perirenal fat invasion (PFI) and renal vein invasion (RVI) as stage pT3a despite limited evidence concerning their prognostic equivalence. In addition, the prognostic value of PFI compared to pT1–pT2 tumors remains controversial.
Objective: To analyze the prognostic significance of PFI, RVI, and tumor size in pT1–pT3a RCC.
Design, setting, and participants: Data for 7384 pT1a–pT3a RCC patients were pooled from 12 centers. Patients were grouped according to stages and PFI/RVI presence as

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Tumor size
Cancer-specific survival

follows: pT1–2N0M0 (n = 6137; 83.1%), pT3aN0M0 + PFI (n = 1036; 14%), and pT3aN0M0 (RVI ± PFI; n = 211; 2.9%).
Intervention: Radical nephrectomy or nephron-sparing surgery (NSS) (1992–2010).
Outcome measurements and statistical analysis: Cancer-specific survival was estimated using the Kaplan-Meier method. Univariate and multivariate Cox proportional-hazards regression models, as well as sensitivity and discrimination analyses, were used to evaluate the impact of clinicopathologic parameters on cancer-specific mortality (CSM).
Results and limitations: Compared to stage pT1–2, patients with stage pT3a RCC were significantly more often male (59.4% vs 53.1%) and older (64.9 vs 62.1 yr), more often had clear cell RCC (85.2% vs 77.7%), Fuhrman grade 3–4 (29.4% vs 13.4%), and tumor size >7 cm (39.1% vs 13%), and underwent NSS less often (7.5% vs 36.6%; all $p < 0.001$). According to multivariate analysis, CSM was significantly higher for the PFI and RVI ± PFI groups compared to pT1–2 patients (hazard ratio [HR] 1.94 and 2.12, respectively; $p < 0.001$), whereas patients with PFI only and RVI ± PFI did not differ (HR 1.17; $p = 0.316$). Tumor size instead enhanced CSM by 7% per cm in stage pT3a (HR 1.07; $p < 0.001$) with a 7 cm cutoff yielding the highest prediction accuracy.
Conclusions: Since the prognostic impact of PFI and RVI on CSM seems to be comparable, merging both as stage pT3a RCC might be justified. Enhanced prognostic discrimination of stage pT3a RCC appears to be possible by applying a tumor size cutoff of 7 cm within an alternative staging system.
Patient summary: Prognosis prediction for patients with localized renal cell carcinoma up to stage pT3a can be enhanced by including tumor size with a cutoff of 7 cm as an additional parameter in the TNM classification system.

1. Introduction

According to the current TNM classification system for renal cell carcinoma (RCC), pT stage is defined by tumor size and local tumor extension. Prognostic discrimination between different staging categories poses a major challenge for classification systems in general, and improvements in discriminative power represent an important reason for modifications of such systems. However, refinements of the TNM system for RCC conducted in the past have been partly targeted at classifying tumors from the perspective of potential surgical approaches and feasibility rather than addressing the optimization of prognostic discrimination alone. The recent seventh edition of the TNM system was the first to merge tumors with perirenal fat invasion (PFI) and renal vein invasion (RVI) as stage pT3a [1]. However, only limited data are available on whether PFI and RVI are equivalent from a prognostic perspective [2,3]. Furthermore, the questionable difference in prognostic implications attributable to PFI in comparison to pT1–2 tumors remains controversial [2–16].

To the best of our knowledge, the present multicenter study, comprising more than 7300 surgically treated RCC patients with stage pT1–3aN0M0, represents the largest investigation to date evaluating and comparing the specific prognostic significance of PFI and RVI regarding cancer-specific mortality (CSM). In addition, the prognostic role of tumor size in pT1–pT3a RCC is analyzed.

2. Patients and methods

2.1. Patient selection, data collection, and pathologic evaluation

After institutional review board approval, clinical and histopathologic data for patients who had undergone unilateral radical nephrectomy or nephron-sparing surgery (NSS) for RCC between 1992 and 2010 were pooled from 12 centers of the CORONA (Collaborative Research on Renal Neoplasms Association) collaboration. The data assessment has been described elsewhere [17].

All patients had pT1–pT3aN0M0 RCC according to the 2009 TNM staging system [1]. Histopathologically confirmed and clinically uninvolved nodes (pN0/cN0) were merged as stage N0. Tumors staged pT3b–pT4, N+/M1 disease, and histology different from clear cell (cc), papillary, or chromophobe RCC were excluded [18]. The final study group comprised 7384 patients grouped according to stages and the presence of PFI and RVI as follows: organ-confined RCC (pT1–2N0M0; n = 6137; 83.1%), stage pT3a RCC with PFI only (pT3a/PFI,N0M0; n = 1036; 14%), and stage pT3a RCC with RVI ± PFI (pT3a/RVI,N0M0; n = 211; 2.9%).

Abdominal computed tomography (CT) or magnetic resonance imaging (MRI), chest imaging (CT or chest x-ray), and a serum metabolic panel were used for clinical staging. When indicated by symptoms, a bone scan and/or brain imaging were performed. None of the patients received (neo)-adjuvant therapy. Histopathologic processing of tumor specimens differed only slightly between the centers and closely followed standardized AUP guidelines. Histopathologic classification of all tumors, including measurement of maximum tumor diameter and Fuhrman grade (FG), was performed by experienced genitourinary pathologists at each institution [1,19]. All tumors were restaged according to the 2009 TNM system.

2.2. Follow-up

Patients were regularly followed up according to protocols established at each institution in line with current guidelines. The cause of death was documented according to medical records, using either chart review corroborated by the death certificate or the death certificate alone, and was categorized as cancer-related or not. To minimize bias in attributing the cause of death, only patients with RCC listed on the death certificate and with documented evidence of premortem disease progression were considered to have died from cancer. Patterns of recurrence and metastasis during follow-up were not uniquely assessed for all patients, and hence were not analyzed. We previously published data on recurrence patterns in a subset of CORONA patients [17]. The database was frozen in June 2012. The follow-up duration was from the date of surgery until the last follow-up. The study endpoint was CSM.

2.3. Statistical analysis

Continuous variables are reported as the median and interquartile range. The Mann-Whitney *U* test was applied for variables with a non-normal distribution. The Fisher exact test was used for comparison of categorical variables and a χ^2 test for comparison of more than two groups or nondichotomized variables. For sensitivity analyses, subgroups representing <5% of the entire study group were avoided.

Cancer-specific survival (CSS) was estimated using the Kaplan-Meier method, and the log-rank test was applied to compare survival curves. Univariate and multivariate Cox proportional hazards regression models were fitted to assess the effect of age (continuous), gender (female/male), surgical approach (NSS/radical nephrectomy), histologic subtype (non-ccRCC/ccRCC), tumor size (continuous), FG (3–4/1–2), nodal status (pNx/pN0), and staging (pT1–2/pT3a + PFI/pT3a + RVI ± PFI) on CSM. To identify an ideal tumor size cutoff for prognostic discrimination of RCC patients, Martingale residuals were calculated from the proportional hazards regression model and plotted as a function of tumor size to identify the cutoff yielding the highest c-index [20]. Sensitivity analyses were conducted to reduce any potential effect of unmeasured confounding due to relationships between tumor stage and invasion pattern (pT1–2 vs PFI vs RVI ± PFI) and CSM by restricting the study group to patients with (1) tumor size up to the optimal cutoff, (2) tumor size above this cutoff, and (3) the ccRCC subtype only. The clinical impact of modified pT classification in comparison to the current system was analyzed by assessing c-index values to evaluate the degree to which predictability was changed by incorporation of specific parameters [21].

Data were evaluated using the R statistical package (v.2.12.2) and SPSS 19.0 (SPSS Inc. Chicago, IL, USA). Reported *p* values are two-sided with the statistical significance level set at $p \leq 0.05$.

3. Results

Patient and tumor characteristics are listed in Table 1. In summary, compared with stage pT1–2, patients with pT3a RCC (PFI and/or RVI) were significantly more frequently male (59.4% vs 53.1%), less frequently underwent NSS (7.5% vs 36.6%), and more commonly had ccRCC (85.2% vs. 77.7%) and FG 3–4 (29.4% vs 13.4%; all $p < 0.001$). Some 13% of pT1–2 RCC patients (795/6137) compared to 39.1% of pT3a patients (487/1247) had a maximum tumor diameter >7 cm ($p < 0.001$). Patients at stage pT3a were significantly older than patients with pT1–2 RCC (64.9 vs 62.1 yr, $p < 0.001$). The proportion of stage pT3a patients was comparable among the participating centers (range 14.2–19.8%, mean 16.9%).

For patients staged pT1–2N0M0 versus pT3aN0M0, CSS rates at 3, 5, and 10 yr after surgery were 97% versus 90%, 95% versus 85%, and 91% versus 73%, respectively ($p < 0.001$). For stage pT3a, the 5- and 10-yr CSS rates differed significantly between patients with PFI alone (86% and 75%) and those with RVI ± PFI (81% and 66%, $p = 0.026$; Fig. 1).

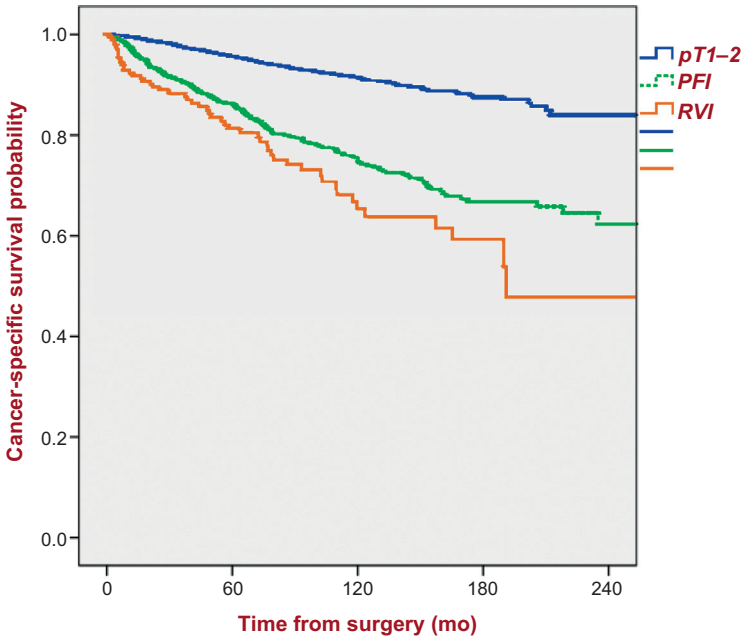
According to multivariate analysis adjusted for age ($p < 0.001$), gender ($p < 0.001$), surgical approach ($p < 0.001$), histopathologic subtype ($p = 0.003$), tumor size ($p < 0.001$), FG ($p < 0.001$), and nodal status (pNx vs pN0, $p = 0.46$), RCC patients with PFI only and with RVI ± PFI had a significant difference in CSM compared to pT1–2 patients (hazard ratio [HR] 1.94 and 2.12, respectively; both $p < 0.001$; Table 2). However, CSM did not differ between the PFI and RVI ± PFI groups (HR 1.17, 95% confidence interval [CI] 0.86–1.61; $p = 0.316$).

Prognostic differentiation of patients with pT3a tumors was not possible using PFI and RVI, so we assessed whether tumor size instead could support prognostic differentiability. According to multivariate analysis restricted to pT3a tumors, tumor size significantly influenced CSM: an increase of 1 cm was associated with a 7% increase in CSM (HR 1.07, 95% CI 1.03–1.12; $p < 0.001$). Discrimination analysis using Martingale residuals suggested that a cutoff of 7 cm provides the highest c-index for patient discrimination. Applying this cutoff, 5 and 10 yr after surgery, CSS rates for patients with pT3a tumors ≤7 cm versus >7 cm

Table 1 – Clinicopathological characteristics for 7384 RCC patients with tumor stages pT1a–pT3aN0M0

Characteristics	pT1–3a (*n* = 7384, 100%)	pT1–2 (*n* = 6137, 83.1%)	PFI (*n* = 1036, 14%)	RVI ± PFI (*n* = 211, 2.9%)
Median age, yr (IQR)	62.7 (54.0–70.1)	62.1 (53.3–69.9)	64.9 (55.8–72.0)	65.0 (57.0–72.0)
Male gender, *n* (%)	3998 (54)	3257 (53)	623 (60)	118 (56)
Type of surgery, *n* (%)				
Radical nephrectomy	5046 (68)	3892 (63)	953 (92)	201 (95)
Partial nephrectomy	2338 (32)	2245 (37)	83 (8)	10 (5)
Histological subtype, n (%)				
Clear cell	5831 (79)	4768 (78)	871 (84)	192 (91)
Papillary	1070 (14.5)	944 (15)	113 (11)	13 (6)
Chromophobe	483 (6.5)	425 (7)	52 (5)	6 (3)
Mean tumor size, cm (IQR)	4.3 (3.0–6.0)	4.0 (2.8–5.8)	6.5 (4.5–8.2)	7.0 (5.0–9.0)
Tumor size, *n* (%)				
≤7 cm	6102 (83)	5342 (87)	640 (62)	120 (57)
>7 cm	1282 (17)	795 (13)	396 (38)	91 (43)
Fuhrman grade, *n* (%)				
Grade 1–2	6193 (84)	5312 (87)	749 (72)	132 (63)
Grade 3–4	1191 (16)	825 (13)	287 (28)	79 (37)
pN stage, *n* (%)				
pN0	3174 (43)	2644 (43)	451 (43.5)	158 (37)
pNx (cN0)	4210 (57)	3493 (57)	585 (56.5)	264 (63)
Median follow-up, mo (IQR)	57.3 (25.7–102.0)	56.7 (25.2–102.0)	62.2 (28.8–128.0)	65.3 (24.4–118.1)

RCC = renal cell carcinoma; PFI = perirenal fat invasion; RVI = renal vein involvement; IQR = interquartile range.



No. of patients at risk / no. of cumulative events	0 mo	60 mo	120 mo	180 mo	240 mo
pT1–2	6137/0	2879/186	1121/272	256/300	39/305
PFI	1036/0	512/113	261/165	108/186	23/189
RVI	211/0	104/32	45/47	14/50	2/152

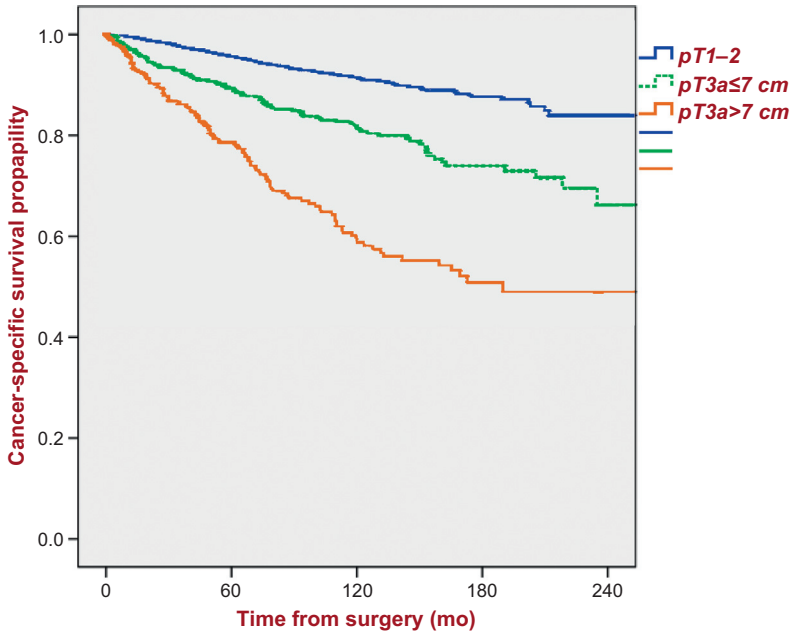
Fig. 1 – Kaplan-Meier cancer-specific survival estimates for 7384 renal cell carcinoma patients (all N0M0) with tumor stage pT1–2 ($n = 6137$), tumor stage pT3a with perirenal fat invasion only (PFI, $n = 1036$), and tumor stage pT3a with renal vein involvement with or without PFI (RVI, $n = 211$). pT1–2 versus PFI, $p < 0.001$; pT1–2 versus RVI, $p < 0.001$; PFI versus RVI, $p = 0.026$.

Table 2 – Univariate and multivariate Cox proportional hazards regression analyses for prediction of cancer-specific mortality in 7384 RCC patients with tumor stages pT1a–pT3aN0M0

Variable	Univariate analysis		Multivariate analysis			
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, continuous per year	1.03 (1.02–1.04)	<0.001	1.03 (1.02–1.04)	<0.001	1.03 (1.02–1.03)	<0.001
Female gender (ref. male)	0.65 (0.55–0.77)	<0.001	0.69 (0.58–0.82)	<0.001	0.70 (0.59–0.83)	<0.001
Partial nephrectomy (ref. radical)	0.27 (0.20–0.36)	<0.001	0.54 (0.39–0.74)	<0.001	0.42 (0.31–0.58)	<0.001
Non-cc RCC (ref. ccRCC)	0.63 (0.49–0.80)	<0.001	0.70 (0.54–0.89)	0.004	0.72 (0.56–0.92)	0.007
Tumor size, continuous per cm	1.19 (1.17–1.21)	<0.001	1.10 (1.08–1.13)	<0.001		
FG 3–4 (ref. FG 1–2)	5.64 (4.76–6.68)	<0.001	3.74 (3.13–4.47)	<0.001	4.16 (3.48–4.96)	<0.001
pNx (ref. pN0)	0.99 (0.97–1.01)	0.13	0.99 (0.97–1.01)	0.35	0.98 (0.97–1.01)	0.103
Tumor stage groups						
pT1a–pT2b (ref.)	1		1			
pT3a-PFI	3.27 (2.72–3.92)	<0.001	1.94 (1.60–2.34)	<0.001		
pT3a-RVI	4.74 (3.54–6.35)	<0.001	2.12 (1.57–2.88)	<0.001		
Tumor stage groups						
pT1a–pT2b (ref.)	1				1	
pT3a and ≤7 cm	2.48 (2.00–3.08)	<0.001			1.86 (1.49–2.31)	<0.001
pT3a and >7 cm	5.48 (4.46–6.74)	<0.001			2.89 (2.33–3.59)	<0.001

RCC = renal cell carcinoma; HR = hazard ratio; CI = confidence interval; ref. = reference; cc = clear cell; FG = Fuhrman grade; PFI = perirenal fat invasion; RVI = renal vein involvement.

were 89% and 81% versus 78% and 59%, respectively ($p < 0.001$; Fig. 2). In addition, according to multivariate analysis, the CSM HRs for patients with pT3a tumors ≤7 cm and >7 cm were 1.86 and 2.89, respectively, compared to pT1–2 RCC patients (both $p < 0.001$; Table 2). This model also revealed significant differences in CSM between tumor sizes of ≤7 cm and >7 cm in pT3a RCC (HR 1.71, 95% CI 1.31–2.24; $p < 0.001$).



No. of patients at risk / no. of cumulative events	0 mo	60 mo	120 mo	180 mo	240 mo
pT1–2	6137/0	2879/186	1121/272	256/300	39/305
pT3a and ≤7 cm	760/0	415/66	214/94	87/108	17/112
pT3a and >7 cm	487/0	201/79	91/119	35/128	8/129

Fig. 2 – Kaplan-Meier cancer-specific survival estimates for 7384 patients with pT1–2N0M0 (n = 6137), pT3aN0M0 ≤7 cm (n = 880), and pT3aN0M0 >7 cm (n = 578) renal cell carcinoma. pT1–2 versus pT3 ≤7 cm, pT1–2 versus pT3 >7 cm, and pT3 ≤7 cm versus pT3 >7 cm all p < 0.001.

Table 3 – Multivariate Cox proportional hazards regression analyses for prediction of cancer-specific mortality in RCC patients with tumor stages pT1a–pT3aN0M0 categorized using a tumor diameter cutoff of 7 cm (sensitivity analyses)

Variable	Tumor size ≤7 cm (n = 6102)		Tumor size >7 cm (n = 1282)		ccRCC subtype only (n = 5831)	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age, continuous per year	1.03 (1.02–1.04)	<0.001	1.03 (1.01–1.04)	<0.001	1.03 (1.02–1.03)	<0.001
Female gender (ref. male)	0.63 (0.50–0.80)	<0.001	0.74 (0.56–0.96)	0.023	0.75 (0.62–0.90)	0.002
Partial nephrectomy (ref. radical)	0.81 (0.56–1.16)	0.24	0.63 (0.20–2.00)	0.43	0.42 (0.30–0.60)	<0.001
Non-cc RCC (ref. ccRCC)	0.70 (0.50–0.98)	0.04	0.78 (0.55–1.12)	0.18		
Tumor size, continuous per cm	1.31 (1.21–1.44)	<0.001	0.99 (0.94–1.04)	0.69		
FG 3–4 (ref. FG 1–2)	4.61 (3.64–5.84)	<0.001	2.47 (1.90–3.20)	<0.001	3.58 (2.94–4.33)	<0.001
pNx (ref. pN0)	1.01 (0.98–1.04)	0.58	0.97 (0.95–1.00)	0.08	0.98 (0.96–1.01)	0.13
Tumor stage groups						
pT1 or pT2 (ref.)	1 (pT1)		1 (pT2)			
pT3a-PFI	1.75 (1.34–2.28)	<0.001	1.67 (1.26–2.20)	<0.001		
pT3a-RVI	2.26 (1.46–3.50)	<0.001	1.74 (1.13–2.66)	0.011		
Tumor stage groups						
pT1a–pT2b (ref.)					1	
pT3a and ≤7 cm					1.93 (1.53–2.44)	<0.001
pT3a and >7 cm					3.18 (2.52–4.00)	<0.001

RCC = renal cell carcinoma; HR = hazard ratio; CI = confidence interval; ref. = reference; cc = clear cell; FG = Fuhrman grade; PFI = perirenal fat invasion; RVI = renal vein involvement.

Table 3 lists the results for additional sensitivity analyses for data validation. Two separate multivariate Cox models that included patients with tumors ≤7 cm and >7 cm yielded 1.75-fold and 1.67-fold increases in the CSM HR in comparison of pT3a patients with PFI alone and pT1–2 patients, respectively (both $p < 0.001$; Table 3). Nonetheless, no significant difference in CSM between patients with PFI alone and those with RVI ± PFI could be confirmed for

Table 4 – Comparison of the prognostic discrimination of the original pT staging system (2009) and two modified pT classification systems

	2009 pT staging system [1] (pT1a, pT1b, pT2a, pT2b, pT3a)	Alternative pT staging system 1 (pT1a, pT1b, pT2 any size, pT3a ≤7 cm, pT3a >7 cm)	Alternative pT staging system 2 (pT1a, pT1b, pT2 any size/pT3a ≤7 cm, pT3a >7 cm)
CSS after 5 and 10 yr	pT1a: 98% and 96% pT1b: 95% and 89% pT2a: 89% and 78% pT2b: 83% and 80% pT3a: 85% and 73%	pT1a: 98% and 96% pT1b: 95% and 89% pT2: 88% and 79% pT3a ≤7 cm: 89% and 81% pT3a >7 cm: 78% and 59%	pT1a: 98% and 96% pT1b: 95% and 89% pT2 any size/pT3a ≤7 cm: 88% and 80% pT3a >7 cm: 78% and 59%
CSM, univariate HR (95%CI)	pT1a: 1 (reference) pT1b: 2.60 (1.95–3.48)* pT2a: 6.08 (4.42–8.35)* pT2b: 6.35 (4.10–9.83)* pT3a: 7.81 (6.00–10.17)*	pT1a: n1 (reference) pT1b: 2.60 (1.95–3.48)* pT2: 6.14 (4.56–8.27)* pT3a ≤7 cm: 5.52 (4.11–7.43)* pT3a >7 cm: 12.20 (9.14–16.28)*	pT1a: 1 (reference) pT1b: 2.60 (1.95–3.48)* pT2 any size/pT3a ≤7 cm: 5.81 (4.45–7.59)* pT3a >7 cm: 12.20 (9.14–16.28)*
PA, % (95% CI)	74.5 (72.4–76.6)	74.9 (72.8–77.0)	75.0 (72.8–77.1)

CSS = cancer-specific survival; CSM = cancer-specific mortality; HR = hazard ratio; CI = confidence interval; PA = predictive accuracy.
* $p < 0.001$.

either pT3a tumors ≤7 cm or tumors >7 cm. Notably, in an analysis of patients with pT1–pT3a tumors >7 cm alone, tumor size made no further contribution to prognostic ability (HR 0.99; $p = 0.685$; Table 3). In addition, a further Cox model designed for ccRCC patients alone (n = 6023) confirmed the significant difference in CSM between pT3a ≤7 cm and pT3a >7 cm (HR 1.774, 95% CI 1.34–2.35; $p < 0.001$).

Table 4 compares staging categories between the current 2009 TNM system and two alternative staging systems modified according to our study results. Besides an increase in c-index from 74.5% (2009 TNM classification) to 75.0% according to alternative staging system 2, a considerable improvement in discrimination of substages compared to the current T system is evident from the lack of overlap of the corresponding 95% CIs.

4. Discussion

The results of this multicenter study allow five major conclusions regarding prognostic discrimination for patients with pT1a–pT3a RCC. First, our data confirm that PFI is a prognostic parameter that independently enhances CSM (HR 1.94; $p < 0.001$). Second, merging PFI and RVI in the same T stage category is justified because both parameters impact CSM similarly and their separation does not convey additional prognostic information. Third, in pT3a RCC, tumor size has independent prognostic signature and a 7 cm cut-off provides the best possible prognostic discrimination. Patients with stage pT3aN0M0 tumors with a diameter >7 cm exhibited a high-risk profile: more than 40% of these patients had experienced recurrent disease during 10-yr follow-up. The proposed 7-cm cutoff for stage pT3a avoids unnecessary complication of the TNM system because it is already commonly used for organ-confined RCC staging. Fourth, for pT2–pT3a tumors >7 cm, tumor size does not add any further prognostic information. This supports the recommendation that the current subdivision of stage pT2 with a tumor size cutoff of 10 cm could possibly be waived, a notion previously suggested by study results from our own group and others [22,23]. Fifth, prognosis is very similar for patients with pT2 RCC and patients with pT3a tumors ≤7 cm exhibiting PFI and/or RVI, which possibly justifies merger into one staging category. Our data are in line with the findings by Lam et al [9], who reported no significant difference in CSS between pT2 and pT3a tumors ≤7 cm. Interestingly, in their study on 623 RCC patients (all N and all M stages [$N_{all}M_{all}$]) with PFI, the authors also determined 7 cm as the best prognostic cutoff [9]. However, before further modifications of the pT staging system, the primary question to be answered is what we actually expect from RCC staging, either the best possible prognostic discrimination or merging of anatomically related invasion patterns owing to their close relation to surgical amenability.

Table 5 summarizes data from relevant studies on the prognostic role of PFI [2–16]. The data generated by these studies are inconsistent and partly conflicting, which may be attributable to cohort inhomogeneity ($N_{all}M_{all}$), a limited number of patients, or use of univariate outcome analysis alone [6,9,10,15]. In the second largest investigation, by Lam et al [9], 623 $N_{all}M_{all}$ RCC patients with PFI were compared to 639 $pT2N_{all}M_{all}$ RCC patients. After adjusting for tumor size, the authors found that PFI increased CSM by 36% [9]. Bedke et al [11] evaluated 106 RCC patients and reported that PFI independently influenced CSM when renal sinus fat was simultaneously invaded. By contrast, Poon et al [12] found that PFI and invasion of renal sinus fatty tissue did not differ in their prognostic impact [12]. Furthermore, two studies on 24 and 63 patients found an increase in CSM for patients with simultaneous PFI and RVI [2,3]. It is clear that larger multicenter studies are needed to validate the prognostic role of combined invasion patterns in the future.

In keeping with other relevant studies, our data suggest that a maximum tumor diameter of 7 cm represents the optimal cutoff for prognostic discrimination of patients with pT3 RCC [4,9,14,16]. Thus, the data confirm the prognostic significance of the 4- and 7-cm cutoffs applied in the current TNM classification for pT1–2 tumors (data not shown). By contrast, our data do not support the 5.5-cm cutoff for organ-confined RCC proposed by Ficarra et al [24].

According to the results of the present study, we suggest two possible modifications of the recent RCC staging classification, as shown in Table 4. The first alternative staging model separates pT1a, pT1b, pT2, pT3a ≤7 cm, and pT3a >7 cm by considering anatomically related invasion

Table 5 – Overview of current literature on the prognostic significance of perirenal fat invasion in surgically treated RCC patients

Study	PFI group (*n*)	Control group(s)	Study design	Results
Siemer et al [4]	237	pT1–2, *n* = 1077	1. Retrospective unicenter study 2. RCC patients $N_{all}M_{all}$ 3. Multivariate analysis of CSM predictors	1. PFI is not an independent predictor of higher CSM in comparison to pT1–2 stages 2. Stratification of PFI according to tumor size (7 cm cutoff) is useful
Thompson et al [5]	205	–	1. Retrospective multicenter study 2. ccRCC patients $N_{all}M_{all}$ 3. Multivariate analysis of CSM predictors	Renal sinus fat invasion is an independent predictor of higher CSM in comparison to PFI
Gilbert et al [6]	82	pT1–2, *n* = 150	1. Retrospective unicenter study 2. All ccRCC patients in stage N0M0 3. Univariate analysis of DFS predictors	PFI is not a predictor of worse DFS in comparison to pT1–2 stages
Siddiqui et al [7]	163	pT1–2, *n* = 2002	1. Retrospective unicenter study 2. All RCC patients in stage N0M0 3. Multivariate analysis of CSM predictors	PFI is an independent predictor of higher CSM irrespective of tumor size
Gofrit et al [8]	46	pT1–2, *n* = 182	1. Retrospective unicenter study 2. All RCC patients in stage N0M0 3. Multivariate analysis of DFS predictors	1. PFI is an independent predictor of higher DFS in comparison to pT1a stage 2. PFI is an independent predictor of higher DFS in comparison to pT2 stage 2. Stratification of PFI according to tumor size (7 cm cutoff) is useful
Lam et al [9]	623	pT2, *n* = 639	1. Retrospective multicenter study 2. RCC patients $N_{all}M_{all}$ 3. Multivariate analysis of CSM predictors	1. PFI in RCC with tumor size $\leq$7 cm is an independent predictor of higher CSM in comparison to pT2 stage 2. PFI in RCC with a tumor size >7 cm is an independent predictor of higher CSM in comparison to pT2 stage
Margulis et al [10]	365	–	1. Retrospective multicenter study 2. RCC patients $N_{all}M_{all}$ 3. Multivariate analysis of CSM predictors	Renal sinus fat invasion is not an independent predictor of higher CSM in comparison to PFI
Bedke et al [11]	106	–	1. Retrospective unicenter study 2. RCC patients $N_{all}M_{all}$ 3. Multivariate analysis of CSM predictors	Combined PFI + renal sinus fat invasion is an independent predictor of higher CSM compared to PFI alone
Poon et al [12]	230	–	1. Retrospective unicenter study 2. RCC patients $N_{all}M_{all}$ 3. Multivariate analysis of CSM predictors	Renal sinus fat invasion with or without PFI is not an independent predictor of higher CSM in comparison to PFI alone
Terrone et al [13]	235 (PFI or sinus fat invasion alone, "low-risk pT3")	pT3 with other histopathologic invasion patterns (eg, adrenal gland invasion or RVI), *n* = 278	1. Retrospective multicenter study 2. RCC patients $N_{all}M_{all}$ 3. Multivariate analysis of CSM predictors	1. Risk stratification based on different histopathologic subtypes of pT3 can independently predict CSM 2. RCC with tumor size >7 cm is an independent predictor of higher CSM in "low-risk" pT3 patients
Yoo et al [14]	77	pT1–2, *n* = 783	1. Retrospective unicenter study 2. All RCC patients in stage N0M0 3. Multivariate analysis of CSM and DFS predictors	1. PFI is an independent predictor of worse DFS in comparison to pT1–2 stages 2. PFI in RCC with tumor size >7 cm is an independent predictor of higher CSM in comparison to pT2 stage 3. PFI in RCC with tumor size $\leq$7 cm is not an independent predictor of higher CSM in comparison to pT1 stage
da Costa et al [2]	24	RVI, *n* = 22	1. Retrospective unicenter study 2. RCC patients $N_{all}M_{all}$ 3. Multivariate analysis of CSM and DFS predictors	PFI + RVI is an independent predictor of higher CSM and worse DFS in comparison to PFI or RVI alone
Oh et al [15]	33	pT1, *n* = 131	1. Retrospective unicenter study 2. All RCC patients in stage N0M0 and tumor size $\leq$7 cm 3. Univariate analysis of CSM and DFS predictors	1. PFI is a predictor of worse DFS in comparison to pT1 stage 2. PFI is not a predictor of higher CSM in comparison to pT1 stage
Süer et al [16]	63	pT1–2, *n* = 275	1. Retrospective unicenter study 2. All RCC patients in stage N0M0 3. Multivariate analysis of CSM predictors	1. PFI is an independent predictor of higher CSM in comparison to pT1–2 stages 2. PFI in RCC with tumor size >7 cm is an independent predictor of higher CSM in comparison to pT2 stage 3. PFI in RCC with tumor size $\leq$4 cm is not an independent predictor of higher CSM in comparison to pT1a stage

Table 5 (*Continued*)

Study	PFI group (*n*)	Control group(s)	Study design	Results
Baccos et al [3]	63	RVI, *n* = 59	1. Retrospective unicenter study 2. RCC patients $N_{all}M_{all}$ 3. Multivariate analysis of CSM predictors	PFI + RVI is an independent predictor of higher CSM in comparison to PFI or RVI alone
Present series	1036	pT1–2, *n* = 6137; pT3a RVI, *n* = 211	1. Retrospective multicenter study 2. All RCC patients in stage N0M0 3. Multivariate analysis of CSM predictors	1. PFI is an independent predictor of higher CSM in comparison to pT12 stages 2. PFI and RVI have no significant prognostic difference 3. Stratification of pT3a RCC according to tumor size (7 cm cutoff) is useful

RCC = renal cell carcinoma; cc = clear cell; PFI = perirenal fat invasion; RVI = renal vein involvement; CSM = cancer-specific mortality; DFS = disease-free survival; N_{all} = all N stages; M_{all} = all M stages.

patterns, which increases the predictive ability of the model compared to the current TNM system by 0.4%. However, this model lacks prognostic segregation between stages pT2 and pT3a $\leq$7 cm, which represents a clear limitation. By contrast, the second alternative model, in which pT2 tumors of any size and pT3a $\leq$7 cm are combined, raises Harrell's *c* by 0.5% and shows no overlap of CIs between all stages and sub-stages which indicates certain prognostic discrimination (Table 4). As already outlined above, the current T-staging system does not allow for significant prognostic segregation of all stages and substages and shows overlapping CIs, which highlights the clinical need for an improved T-staging system [4,9,14,16,22–24].

Excluding population-based studies, the present investigation used the largest database reported to date to validate the prognostic role of PFI in RCC. However, our study is limited by its retrospective nature and the lack of standardization for diagnostic procedures, therapy, and follow-up, despite the application of current guidelines. Details regarding symptoms at diagnosis, comorbidity, smoking status, laboratory and histopathologic parameters (such as lymphovascular invasion, tumor necrosis, and sarcomatoid dedifferentiation), metastatic patterns, and treatment of recurrent disease were not available for all patients, and hence were not analyzed. No central pathology review was performed because this would have been virtually impossible for more than 7000 patients. One further limitation is the lack of delineation between perirenal and renal sinus fat invasion, which was not assessed for the entire study cohort. Moreover, molecular markers and anatomic scoring systems should ideally be incorporated into multivariate models in future studies to possibly boost prognostic discrimination, which was not done in the present study or in any previous studies on this topic. Although the modified staging classifications we propose yield improved prognostic discrimination of all stages and substages in contrast to the current T system, external and if possible prospective validation of these models is clearly required before considering further amendments of the TNM system.

5. Conclusions

PFI represents an independent adverse prognostic parameter comparable to RVI for postsurgical CSM in RCC patients. Hence, merging these criteria as stage pT3a seems justified. In addition, the results of this comprehensive study show that further prognostic differentiation of pT3a tumors by tumor size is feasible, and that pT2 and smaller pT3a tumors have close prognostic similarity.

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