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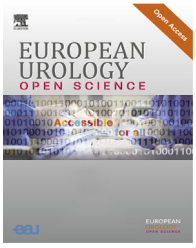

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Kidney Cancer

Defining Tumour Shape Irregularity for Preoperative Risk Stratification of Clinically Localised Renal Cell Carcinoma

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Abstract

Background: Unexpected adverse pathology is a major concern in surgical management of clinically localised renal cell carcinoma (RCC). Further studies are needed to improve preoperative risk stratification.
Objective: To define and classify tumour shape irregularity (TSI) based on preoperative imaging, and to investigate its effect on pathological and oncological outcomes in clinically localised RCC.
Design, setting, and participants: We retrospectively analysed 474 patients with cT1-2N0M0 RCC managed by partial or radical nephrectomy. Preoperative dynamic computed tomography was used to define and classify TSI, graded as 1 (completely elliptical shape), 2 (elliptical shape with minor and focal protrusions), or 3 (nonelliptical shape presenting with major and/or extensive protrusions).
Intervention: Partial or radical nephrectomy.
Outcome measurements and statistical analysis: A logistic regression analysis evaluated the risk factors for pT3a upstaging and Fuhrman grade 3–4. A Cox proportional hazard analysis assessed preoperative variables for recurrence-free survival (RFS).
Results and limitations: The median tumour size was 3.5 cm, and 94 patients (20%) had (R)adius (tumour size as maximal diameter), (E)xophytic/endophytic properties of tumour, (N)earness of tumour deepest portion to collecting system or sinus, (A)nterior (a)/posterior (p) descriptor, and (L)ocation relative to polar lines (RENAL) score $\geq$10. TSI was graded as 1, 2, and 3 in 214 (45%), 151 (32%), and 109 (23%) patients, respectively. Higher TSI was significantly associated with a larger tumour size and a higher RENAL score. Overall, pT3a upstaging and Fuhrman grade 3–4 were observed in 45 (9.5%) and 116 patients (31% in 380 clear cell RCC cases), respectively. The incidence of pT3a upstaging and Fuhrman grade 3–4 was significantly higher in patients with higher TSI (0.5%, 8.6%, and 28% for pT3a upstaging and 12%, 33%, and 60% for

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Fuhrman grade 3–4 in TSI 1, 2, and 3 groups, respectively). In multivariable analyses, higher TSI was independently associated with adverse pathological outcomes. During the median follow-up of 6.0 yr, 49 patients (10%) developed recurrence. Multivariable analyses demonstrated that older age and higher TSI were independent risk factors for worse RFS. The limitations include the retrospective design.

Conclusions: TSI may be a useful adjunct in preoperative risk stratification for adverse pathology and recurrence after surgery in clinically localised RCC.

Patient summary: Tumour shape irregularity is significantly associated with unfavourable pathological outcomes, that is, locally advanced stage or high-grade cancer, and with a higher recurrence rate after surgery in patients with clinically localised renal cell carcinoma. Preoperative evaluation of the tumour shape may help in patient counselling and treatment decisions.

1. Introduction

The mainstay of treatment for clinically localised renal cell carcinoma (RCC) is surgical resection, which provides satisfactory survival outcomes in most patients; however, 20–30% of patients may eventually develop recurrence after surgery [1]. Such variability in clinical outcomes reflects the biological complexity of clinically localised RCC, suggesting the importance of preoperative risk stratification. Partial nephrectomy (PN) has widely been acknowledged as the reference standard for small renal masses [2,3], and recent improvements in surgical techniques have further led to the indication of PN for larger tumours [4,5]. However, previous reports have suggested that, in a few specific cases, imprudent PN can negatively affect the survival outcomes of patients with clinically localised RCC [6,7]. Therefore, further studies are needed to define preoperative features that can predict unfavourable oncological outcomes after surgery in patients with clinically localised RCC.

Adverse pathology has widely been studied as a surrogate endpoint for poor survival outcomes after PN or radical nephrectomy (RN) [8–11]. Previous studies demonstrated that pT3a upstaging from cT1–2 is significantly associated with worse recurrence-free survival (RFS) after surgery, although the potential impact of surgical approaches (PN vs RN) on survival outcomes in such patients remains controversial [8–11]. Fuhrman grade is one of the most important pathological parameters reflecting the aggressiveness of RCC and is incorporated into several postoperative risk stratification models [12,13]. However, it is still challenging to accurately predict such adverse pathological features preoperatively.

In this study, we focused on tumour shape irregularity (TSI) as a potential predictor of high-risk, clinically localised RCC. We defined and classified TSI based on preoperative imaging, and investigated its impact on pathological and oncological outcomes after PN/RN in clinically localised RCC.

2. Patients and methods

2.1. Patient population

This institutional review board–approved study (approval number: M2019-172) included 847 patients with primary, unilateral, non-metastatic, and solid renal tumours managed with PN/RN between 2008 and 2018 (Supplementary Fig. 1). Patients with benign histology, malignancies other than RCC, or inadequate pathological data for analysis; those who received neoadjuvant therapy; and those whose dynamic computed tomography (CT) before surgery was not available were excluded, and preoperative images of the remaining 636 patients were evaluated by an expert radiologist (K.K.) for inclusion in this study. This identified 122 patients (19%) with a maximum tumour size of <2 cm, who were excluded due to the small tumour size preventing a valid evaluation of tumour shape. Forty patients (6.2%) were further excluded due to the diagnosis of ≥cT3a, as an apparent tumour thrombus in the renal vein or an ill-defined tumour contour against the perirenal/sinus fat on CT [14]. Finally, 474 patients with cT1-2N0M0 RCC were included in the analysis of this study. The choice of PN or RN was based on surgeon preference. All PNs and RNs were performed by skilled surgeons at a single institution, using minimum incision endoscopic surgery in the majority of patients [15]. The details of the surgical techniques have been described previously [15,16]. Patient and tumour characteristics and pathological findings were obtained from the medical records. T stage was defined according to the seventh edition of the American Joint Committee on Cancer staging system [17]. Tumour complexity was defined by the (R)adius (tumour size as maximal diameter), (E)xophytic/endophytic properties of tumour, (N)earness of tumour deepest portion to collecting system or sinus, (A)nterior (a)/posterior (p) descriptor, and (L)ocation relative to polar lines (RENAL) score [18].

2.2. Imaging analysis

TSI was stratified based on overall tumour shape and contour (Fig. 1). Two readers (K.K. and H.T., professionally trained in genitourinary radiology for 10 and 15 yr, respectively) retrospectively reviewed the dynamic CT images before PN/RN. Tumour shape was evaluated using all eligible slices on transverse sections of the corticomedullary phase, and TSI was graded as 1–3 in each case. Figures 1D–F show representative CT images for each TSI grade. Adjunctive use of other phases and sections of CT and magnetic resonance imaging was permitted. Two readers, who were blinded to all clinicopathological information, independently reviewed the images, and TSI was finally determined based on their consensus. TSI 1 was defined as a completely elliptical shape with no apparent protrusions along the tumour contour. TSI 2 was defined as an approximately elliptical shape with only focal (<50% of the entire circumference) and minor protrusions. TSI 3 was defined as a nonelliptical shape showing extensive (≥50% of the whole circumference) and/or major protrusions. The presence or absence of tumour protrusions was further assessed separately along the interface with the perirenal or sinus fat.

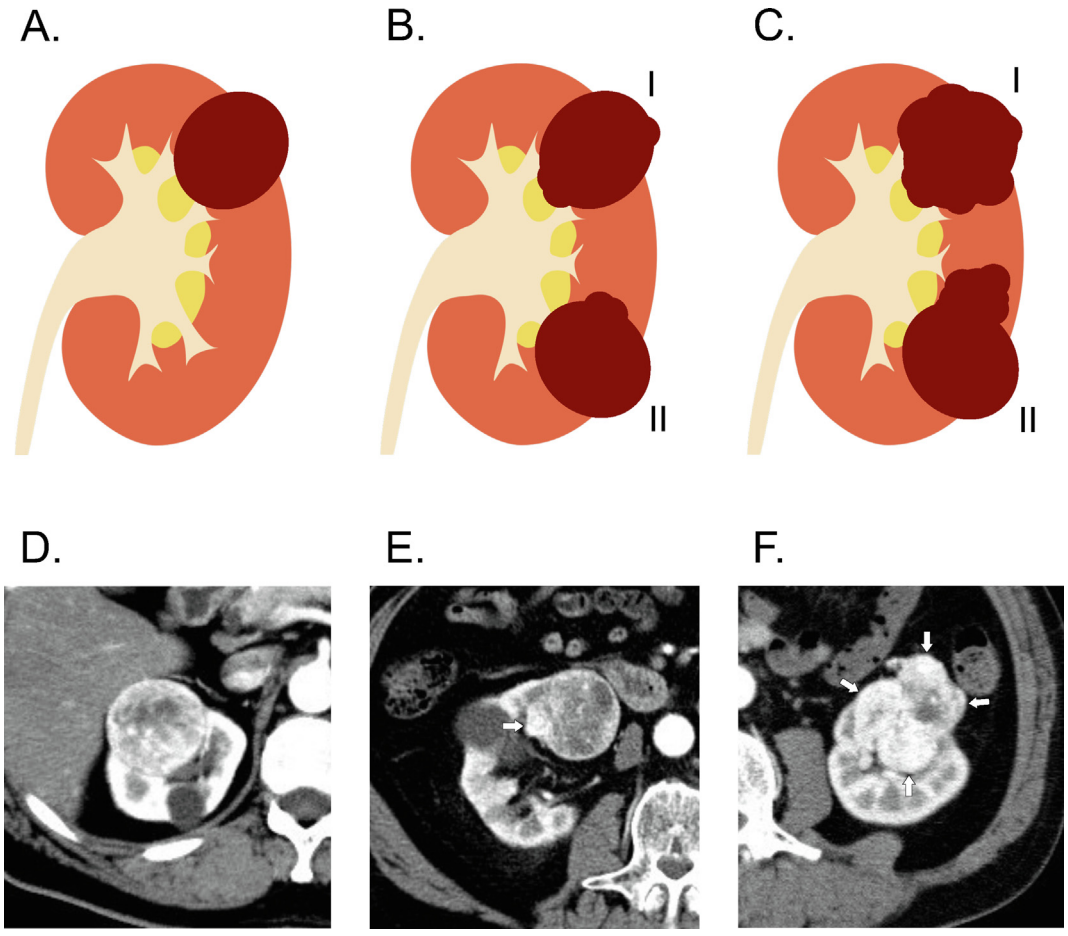

Fig. 1 – (A–C) Schematic of the classification of tumour shape irregularity (TSI) and (D–F) representative images for each TSI grade on transverse section of corticomedullary phase of dynamic computed tomography (CT). TSI was graded as 1–3 based on the overall tumour shape and contour evaluated using imaging. TSI 1: completely elliptical in shape with no apparent protrusions (Fig. 1A and 1D). TSI 2: approximately elliptical shape with minor protrusions focally observed (<50% of the whole circumference) along the tumour interface with perirenal or sinus fat (shown as I) or normal renal parenchyma (shown as II; Fig. 1B and 1E). TSI 3: nonelliptical shape; that is, extensive (≥50% of the whole circumference, shown as I) and/or major (shown as II) protrusions were observed (Fig. 1C and 1F). Arrows on the CT images show protrusions along the tumour contour.

2.3. Statistical analysis

The interobserver agreement of TSI was assessed using the weighted kappa (k) coefficient [18]. Clinical, radiological, and pathological findings were compared among the TSI groups using the Kruskal-Wallis test. A logistic regression analysis was used to evaluate the clinical and radiological risk factors for pT3a upstaging or Fuhrman grade 3–4. The cut-off value of C-reactive protein (CRP) was 5.0 mg/l according to previous reports [19,20]. RFS was defined as the time from the date of PN/RN to the first documented local or distant recurrence of RCC or death due to any cause, whichever occurred first. Overall survival (OS) was defined as the time from the date of PN/RN to death due to any cause. RFS and OS were estimated using the Kaplan-Meier method and compared using the log-rank test. A Cox proportional hazard analysis was used to assess preoperative variables for predicting RFS. Data were analysed using IBM SPSS Statistics, version 25 (IBM Corp., Armonk, NY, USA). All tests were two tailed; $p < 0.05$ was considered significant.

3. Results

3.1. Patient and tumour characteristics

Patient and tumour characteristics are summarised in Table 1. The median age was 60 yr, and 345 patients (73%) were male in the entire cohort. Performance status was 0 in 451 patients (95%). The median preoperative CRP level was 0.6 mg/l. The median tumour size was 3.5 cm; 277 patients (58%) had clinical T1a stage. RENAL score was high (≥10) in 94 patients (20%). Overall, 264 (56%) and 210 (44%) patients underwent PN and RN, respectively; PN was applied for 221 of 277 (80%), 42 of 158 (27%), and one of 39 (2.6%) patients with clinical T1a, T1b, and T2 stage, respectively.

3.2. Interobserver agreement and final consensus of TSI

The independent evaluations of TSI by the two readers yielded a strong interobserver agreement (k = 0.80) [21]. Finally, 214 (45%), 151 (32%), and 109 (23%) patients were classified into TSI 1, 2, and 3 groups, respectively, based on the consensus between the two readers.

3.3. Association of clinical findings and TSI

Clinical findings were compared between patient groups with different TSI grades (Table 1). Higher TSI was significantly associated with older age, larger tumour size, and higher RENAL scores (p = 0.02, <0.001, and <0.001, respec-

Table 1 – Patient and tumour characteristics

	All cases (n = 474)	Tumour shape irregularity (TSI)			p value
		TSI 1 (n = 214)	TSI 2 (n = 151)	TSI 3 (n = 109)	
Age (yr), median (IQR)	60 (51–70)	58 (51–68)	62 (51–73)	64 (55–72)	0.02
Sex: male, n (%)	345 (72.8)	149 (69.6)	110 (72.8)	86 (78.9)	0.21
ECOG performance status, n (%)					0.047
0	451 (95.1)	207 (96.7)	142 (94.0)	102 (93.6)	
1	11 (2.3)	5 (2.3)	3 (2.0)	3 (2.8)	
2–4	5 (1.1)	0 (0)	1 (0.7)	4 (3.7)	
Not available	7 (1.5)	2 (0.9)	5 (3.3)	0 (0)	
Preoperative CRP (mg/l), median (IQR)	0.6 (0.3–1.4)	0.6 (0.3–1.3)	0.6 (0.3–1.3)	0.8 (0.3–2.1)	0.20
Clinical tumour size (cm), median (IQR)	3.5 (2.7–5.0)	2.8 (2.3–3.4)	4.1 (3.0–5.0)	5.6 (4.1–7.3)	<0.001
Clinical T stage, n (%)					<0.001
1a	277 (58.4)	184 (86.0)	68 (45.0)	25 (22.9)	
1b	158 (33.3)	28 (13.1)	74 (49.0)	56 (51.4)	
2a–b	39 (8.2)	2 (0.9)	9 (6.0)	28 (25.7)	
RENAL score, n (%)					<0.001
Low (4–6)	98 (20.7)	65 (30.4)	24 (15.9)	9 (8.3)	
Intermediate (7–9)	282 (59.5)	129 (60.3)	101 (66.9)	52 (47.7)	
High (10–12)	94 (19.8)	20 (9.3)	26 (17.2)	48 (44.0)	
Surgical management, n (%)					<0.001
PN	264 (55.7)	161 (75.2)	80 (53.0)	23 (21.1)	
RN	210 (44.3)	53 (24.8)	71 (47.0)	86 (78.9)	

CRP = C-reactive protein; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; PN = partial nephrectomy; RENAL = (R)adius (tumour size as maximal diameter), (E)xophytic/endophytic properties of tumour, (N)earness of tumour deepest portion to collecting system or sinus, (A)nterior (a)/posterior (p) descriptor, and (L)ocation relative to polar lines; RN = radical nephrectomy; TSI = tumour shape irregularity.

tively). The performance status was marginally worse in patients with higher TSI (p = 0.047). PN was used more often in patients with lower TSI (p < 0.001).

3.4. Association of adverse pathology and TSI

The pathological findings are summarised in Table 2. Overall, pT3a upstaging was observed in 45 patients (9.5%). Among the 380 patients with clear cell RCC, Fuhrman grades 3 and 4 were observed in 106 (28%) and ten (2.6%) patients, respectively. Overall, 15 patients (3.2%), including 13 (4.9%) and two (1.0%) patients managed with PN and RN, respectively, had positive resection margins in the final surgical specimen.

The incidence of pT3a upstaging was significantly higher in patients with higher TSI (0.5%, 8.6%, and 28% in TSI 1, 2, and 3 groups, respectively; p < 0.001; Table 2). An analogous relationship was observed for Fuhrman grade 3–4; in clear cell RCC cases, the incidences of Fuhrman grade 3–4 were 12%, 33%, and 60% in TSI 1, 2, and 3 groups, respectively (p < 0.001; Table 2). Regarding pT3a upstaging, the relationships between the presence of radiological tumour protrusions along the interface with perirenal or sinus fat and the corresponding pathological invasions were further analysed. The positive predictive value of radiological tumour protrusions along the interface with perirenal fat for predicting pathological perirenal fat invasion was 11%. By contrast, the negative predictive value was 98.8% overall, which was particularly high in TSI 1 and 2 groups compared with the TSI 3 group (99.5% and 100% vs 88.9%, p < 0.001; Supplementary Table 1). Analogous findings were also observed for radiological tumour protrusions along the interface with sinus fat to predict pathological sinus fat or renal vein invasion (Supplementary Table 2).

Clinical and radiological parameters including age, sex, preoperative CRP level, clinical T stage, tumour complexity, and TSI were assessed as potential risk factors for pT3a upstaging and Fuhrman grade 3–4 (Table 3). In the multivariable analysis, older age and higher TSI were independently associated with upstaging to pT3a. Moreover, a multivariable analysis identified male sex and higher TSI as independent risk factors using Fuhrman grade 3–4.

3.5. Association of survival outcomes and TSI

In the entire cohort, the median follow-up was 6.0 yr (interquartile range: 4.2–7.9), and 49 patients (10%) developed local (n = 9) or distant (n = 44) recurrence. Overall, six (1.3%) and 30 (6.3%) patients died of RCC and any other causes, respectively. The 5-yr RFS and OS were 84% and 94%, respectively.

Figure 2 shows the RFS and OS according to the TSI grades. RFS was significantly worse in patients with higher TSI (p = 0.002; Fig. 2A). The 5-yr RFS rates were 92%, 84%, and 64% in TSI 1, 2, and 3 groups, respectively. Similar relationships were observed in the subgroup analyses of patients managed with PN or RN (Supplementary Fig. 2A and 2B, respectively). Similarly, OS was significantly worse in patients with higher TSI (p = 0.01; Fig. 2B). In the multivariable analysis incorporating preoperative variables and surgical approaches (PN vs RN), older age and higher TSI were independently associated with RFS (Table 4).

4. Discussion

In clinically localised RCC, the anatomical features of tumours may reflect cancer biology [22,23]. Tumour size and location are incorporated into current staging or scoring systems. However, tumour shape has not been studied well, and its potential impact on pathological and oncological outcomes is unknown. This is the first study to define and classify the radiological tumour shape of RCC, based on the overall tumour shape and contour, and investigate the significance of TSI for pathological and oncological out-

Table 2 – Pathological findings

	All cases (*n* = 474)	Tumour shape irregularity (TSI)			*p* value
		TSI 1 (*n* = 214)	TSI 2 (*n* = 151)	TSI 3 (*n* = 109)	
RCC subtypes, *n* (%)					0.02
Clear cell RCC	380 (80.2)	169 (79.0)	114 (75.5)	97 (89.0)	
Papillary RCC	32 (6.8)	12 (5.6)	16 (10.6)	4 (3.7)	
Chromophobe RCC	48 (10.1)	25 (11.7)	19 (12.6)	4 (3.7)	
Other subtypes	14 (3.0)	8 (3.7)	2 (1.3)	4 (3.7)	
Sarcomatoid/rhabdoid component, *n* (%)	7 (1.5)	1 (0.5)	2 (1.3)	4 (3.7)	0.08
Pathological T stage					<0.001
≤2	429 (90.5)	213 (99.5)	138 (91.4)	78 (71.6)	
3a	45 (9.5)	1 (0.5)	13 (8.6)	31 (28.4)	
Pathological invasions, *n* (%)					
Perirenal fat invasion	20 (4.2)	1 (0.5)	2 (1.3)	17 (15.7)	<0.001
Sinus fat invasion	10 (2.1)	0 (0)	3 (2.0)	7 (6.5)	<0.001
Renal vein invasion	27 (5.7)	0 (0)	8 (5.3)	19 (17.6)	<0.001
Fuhrman grade, *n* (%) [a]					<0.001
1	18 (4.7)	13 (7.7)	5 (4.4)	0 (0)	
2	246 (64.7)	136 (80.5)	71 (62.3)	39 (40.2)	
3	106 (27.9)	19 (11.2)	35 (30.7)	52 (53.6)	
4	10 (2.6)	1 (0.6)	3 (2.6)	6 (6.2)	
Positive surgical margin, *n* (%)	15 (3.2)	8 (3.7)	3 (2.0)	4 (3.7)	0.61

RCC = renal cell carcinoma; TSI = tumour shape irregularity.
[a] The cases of clear cell RCC (*n* = 380) were included only in the analysis of Fuhrman grade.

comes in cT1-2N0M0 RCC. TSI grades were defined by the language and scheme shown in Figure 1, which yielded a strong interobserver agreement. Multivariable analyses, which also incorporated tumour size and complexities, demonstrated that higher TSI was independently associated with pT3a upstaging, Fuhrman grade 3–4, and worse RFS after surgery.

Recent reports have revealed the high feasibility of PN for clinically localised renal masses, and its indication has been expanded to larger tumours [2–5]. Despite technical

Table 3 – Univariable and multivariable logistic regression analyses for adverse pathology

	Category	Univariable	Multivariable	
		p value	OR (95% CI)	*p* value
Upstaging to pT3a				
Age [a]	<60 yr (ref)	–	–	–
	≥60 yr	0.003	2.54 (1.16–5.53)	0.02
Sex	Female (ref)	–	–	–
	Male	0.66	1.15 (0.51–2.61)	0.73
Preoperative CRP	<5.0 mg/l (ref)	–	–	–
	≥5.0 mg/l	0.002	2.12 (0.78–5.82)	0.14
Clinical tumour size	≤4.0 cm (ref)	–	–	–
	>4.0 cm	<0.001	2.34 (0.88–6.21)	0.09
Tumour complexity	RENAL 4–6 (ref)	–	–	–
	RENAL 7–9	0.08	1.82 (0.37–8.99)	0.46
	RENAL 10–12	<0.001	3.05 (0.57–16.5)	0.20
TSI	TSI 1 (ref)	–	–	–
	TSI 2	0.004	11.3 (1.39–91.5)	0.02
	TSI 3	<0.001	33.4 (4.15–268.2)	<0.001
Fuhrman grade 3–4 [b]				
Age [a]	<60 yr (ref)	–	–	–
	≥60 yr	0.43	1.01 (0.61–1.68)	0.96
Sex	Female (ref)	–	–	–
	Male	0.004	2.32 (1.25–4.29)	0.01
Preoperative CRP	<5.0 mg/l (ref)	–	–	–
	≥5.0 mg/l	0.04	1.66 (0.69–4.00)	0.26
Clinical tumour size	≤4.0 cm (ref)	–	–	–
	>4.0 cm	<0.001	1.69 (0.94–3.06)	0.08
Tumour complexity	RENAL 4–6 (ref)	–	–	–
	RENAL 7–9	0.04	1.21 (0.55–2.63)	0.64
	RENAL 10–12	<0.001	1.50 (0.59–3.85)	0.39
TSI	TSI 1 (ref)	–	–	–
	TSI 2	<0.001	2.96 (1.53–5.72)	0.001
	TSI 3	<0.001	6.90 (3.37–14.1)	<0.001

CI = confidence interval; CRP = C-reactive protein; OR = odds ratio; ref: reference; RCC = renal cell carcinoma; ref = reference; RENAL = (R)adius (tumour size as maximal diameter), (E)xophytic/endophytic properties of tumour, (N)earness of tumour deepest portion to collecting system or sinus, (A)nterior (a)/posterior (p) descriptor, and (L)ocation relative to polar lines; TSI = tumour shape irregularity.
[a] The median value of 60 yr was used as the cut-off of age.
[b] The cases of clear cell RCC (*n* = 380) were included only in the analysis of Fuhrman grade.

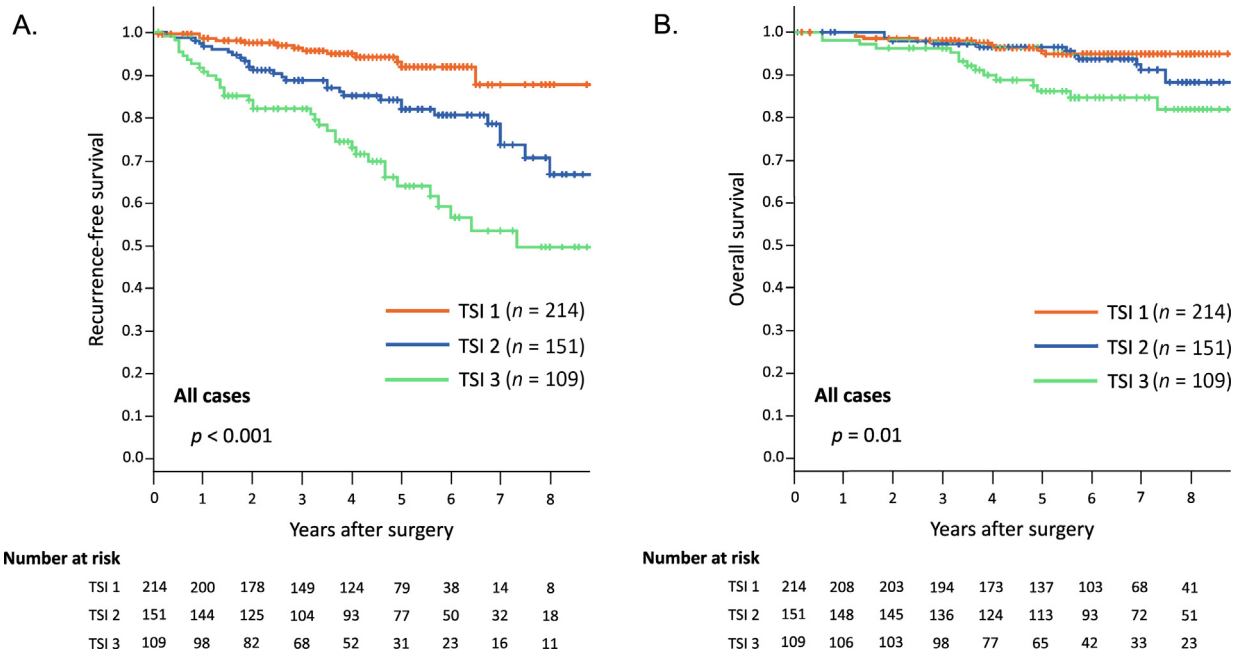

Fig. 2 – Kaplan-Meier curves demonstrating (A) recurrence-free survival and (B) overall survival in all cases according to tumour shape irregularity (TSI) grades.

Table 4 – Univariable and multivariable Cox proportional hazard analysis for recurrence-free survival

	Category	Univariable	Multivariable	
		p value	HR (95% CI)	*p* value
Age [a]	<60 yr (ref)	–	–	–
	≥60 yr	<0.001	3.05 (1.80–5.15)	<0.001
Sex	Female (ref)	–	–	–
	Male	0.13	1.74 (0.99–3.05)	0.054
Preoperative CRP	<5.0 mg/l (ref)	–	–	–
	≥5.0 mg/l	0.10	1.34 (0.68–2.66)	0.40
Clinical tumour size	≤4.0 cm (ref)	–	–	–
	>4.0 cm	<0.001	1.53 (0.81–2.87)	0.19
Tumour complexity	RENAL 4–6 (ref)	–	–	–
	RENAL 7–9	0.70	0.74 (0.35–1.55)	0.42
	RENAL 10–12	0.049	0.78 (0.32–1.91)	0.59
TSI	TSI 1 (ref)	–	–	–
	TSI 2	0.003	1.95 (0.96–3.97)	0.065
	TSI 3	<0.001	3.51 (1.68–7.31)	<0.001
Surgical approach	RN (ref)	–	–	–
	PN	0.001	0.81 (0.42–1.57)	0.53

CI = confidence interval; CRP = C-reactive protein; HR = hazard ratio; PN = partial nephrectomy; ref = reference; RENAL = (R)adius (tumour size as maximal diameter), (E)xophytic/endophytic properties of tumour, (N)earness of tumour deepest portion to collecting system or sinus, (A)nterior (a)/posterior (p) descriptor, and (L)ocation relative to polar lines; RN = radical nephrectomy; TSI = tumour shape irregularity.
[a] The median value of 60 yr was used as the cut-off of age.

improvement, adverse pathology remains a major concern and pT3a upstaging has gained particular attention [8–11]. Hamilton et al [9] analysed a large cohort (*n* = 2573) of patients with cT1–2 RCC managed with PN or RN, and reported that pT3a upstaging was observed in 14% patients overall. Although the diagnostic criteria for cT3a have not been well established [14] and any potential variation in the radiological assessment may introduce a bias into the incidence of pT3a upstaging, the comparable results of previous studies (9–14%) and our study (9.5%) regarding the incidence of pT3a upstaging support the generalisability of clinical T staging in this study [8–11].

The present study suggests that TSI grades could stratify the risks of pT3a upstaging and Fuhrman high-grade tumours in clinically localised RCC, which may facilitate surgeons' decisions regarding surgical approaches. TSI 1 tumours presented with almost no risk of pT3a upstaging and were generally of low grade; accordingly, these were considered the best candidates for PN. Tumours with TSI 2 also showed a relatively low risk of pT3a upstaging. For this population, the absence of tumour protrusions along the interface with perirenal or sinus fat would provide solid evidence for the absence of pathological invasion, as suggested by the high negative predictive values shown in Supple-

mentary Tables 1 and 2. Accordingly, PN can be used based on individualised assessments of preoperative imaging. Further studies are required to assess the feasibility of PN for TSI 3 tumours. The relatively high probability of adverse pathology in this group may drive surgeons to avoid PN, particularly in elective cases.

On the contrary, it is controversial whether RN could improve survival outcomes in patients with clinically localised RCC with adverse pathology compared with PN [8–11]. In this study, higher TSI was significantly associated with worse RFS in both patient groups undergoing PN and RN. This suggests that higher TSI may reflect a high malignant potential in clinically localised RCC, and the prognosis of patients depends more on the cancer biology rather than the surgical approaches. As TSI was strongly related to adverse pathology and recurrence after surgery, histological backgrounds of high TSI tumours should be evaluated further. Recent studies have highlighted the potential importance of radiological and pathological tumour interfaces with the normal renal parenchyma in nonmetastatic RCC [24,25]. Further studies are required to define the implications of irregular tumour shapes and contours in the management of clinically localised RCC.

In our cohort, surgical approaches (PN vs RN) were significantly different according to TSI grade. This suggests that the tumour shape may have affected the surgeons' decisions in our patients. Nevertheless, the development of TSI classification would make surgeons more aware of a potential significance of the tumour shape and further improve the management of renal masses in the same manner as nephrometry scores [18]. Previous studies comparing patient survival after PN and RN almost uniformly suggested that PN yields better outcomes [7,26]. Concerns have been raised about the selection bias; however, even sophisticated statistical approaches appear to have failed to overcome this limitation, possibly due to unrecognised confounders [27]. In future clinical trials, TSI may serve as a potential variable that could provide better statistical adjustment when incorporated in the analysis.

Our multivariable analyses also demonstrated that older age was significantly associated with pT3a upstaging and worse RFS. A potential impact of age on treatment outcomes of RCC has been addressed previously in a few studies [28,29]. Taccoen et al [28] reported that younger adults more often presented with localised stages of RCC and had more favourable cancer-specific survival than older adults. In another study, Feulner et al [29] showed that the gene expression pattern of clear cell RCC varied depending on the patient's age, suggesting that different molecular features may be at least partially related to the disparities of clinical outcomes according to the age of patients with RCC. The impact of age in RCC patients might be more multifactorial, and further investigations are needed. The surgical approach (PN vs RN) was also included in the multivariable analysis for RFS, although it was not independently associated with the endpoint. The percentage of clinical T1b-2 patients who were managed with PN was relatively low in our cohort, which should be noted to discuss the generalisability of the findings in this study.

Our study had some limitations, including its retrospective design. The follow-up period was limited, and a further investigation with a longer follow-up is needed to confirm the present results. Tumours <2 cm were excluded from the analysis, which may have led to a selection bias. Benign renal tumours and other malignant tumours than RCC were also excluded from this study, and the utility of TSI in preoperative evaluation should be examined further using a prospective study design. The potential variance in the assessment of TSI according to readers is another concern, although a strong interobserver agreement was observed between the two investigators in this study. We recently performed a radiomics analysis using dynamic CT of clinically localised RCC, which may also support the significance of radiological tumour shape in the preoperative risk assessment for adverse pathology in an objective manner [30]. Three-dimensional image reconstruction was not used in this study. Although it may help define TSI, the variations of imaging software may affect the evaluations, and further studies will be required to explore potential utility of 3D image reconstructions for defining TSI.

5. Conclusions

To the best of our knowledge, this is the first study to define and classify the radiological tumour shape of RCC for preoperative risk stratification in clinically localised cases. Our classification of TSI stratified the risks of pT3a upstaging, Fuhrman grade 3–4, and recurrence after surgery in patients with cT1-2N0M0 RCC. Higher TSI grades may predict adverse pathological and oncological outcomes preoperatively, although external validation is required for the present results. Future studies are required to assess the potential implications of TSI in decision-making regarding surgical approach, trial design, and surveillance after surgery.

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Acquisition of data: Tanaka, Fukuda, Yasuda.
Analysis and interpretation of data: Tanaka, Fukuda, Kimura, Fukawa, Yamamoto.
Drafting of the manuscript: Tanaka.
Critical revision of the manuscript for important intellectual content: Uehara, Yoshida, Yokoyama, Matsuoka, Saito, Campbell, Fujii.
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Appendix A. Supplementary data

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