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ORIGINAL ARTICLE

# Recurrence pattern in patients with locally advanced renal cell carcinoma: The implications of clinicopathological variables

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**KEYWORDS**

Kidney;
Mass;
Failure;
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RCC

**ABBREVIATIONS**

LA, locally advanced; mRCC, metastatic RCC; RFS, recurrence-free survival; CSS, cancer-specific survival; AJCC, American Joint Cancer Committee

**Abstract** ***Objectives:*** Recurrence rates for patients with locally advanced renal cell carcinoma (LARCC) remain high. To date the predictors of recurrence in those patients remain controversial. The aim of the present study was to assess the relapse pattern in those patients and identify predictors for recurrence.

***Patients and methods:*** We evaluated retrospectively 112 consecutive patients who underwent surgery for LARCC (T3–T4N0M0) between January 2000 and December 2010. Clinical and pathological data were collected from hospital medical records and compiled into a computerized database. Studied variables were age, mode of presentation, Tumour-Node-Metastasis (TNM) stage, Fuhrman nuclear grade, histological subtype, tumour size, venous thrombus level, collecting-system invasion and sarcomatoid differentiation. Recurrence-free survival (RFS) was estimated using the Kaplan–Meier method. Univariate and multivariate analyses were conducted.

***Results:*** Patients were followed for a mean and median follow-up of 33 and 24 months, respectively, after surgery. During the follow-up, recurrences (distant and/or local) were recorded in 58 patients, representing 52% of the cohort. The mean and median times to recurrence were 25 and 13 months, respectively. Sites of recurrence were multiple in 36 patients (62%), lung only in 14 (24%), and local

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in eight (14%). RFS rates at 1, 2, and 5 years were 50%, 43% and 34%, respectively, while the median RFS was 23.7 months. Using univariate analysis, RFS after nephrectomy was significantly shorter in patients aged $<70$ years, symptomatic at presentation, with larger tumours, higher nuclear grade, collecting-system invasion, and/or sarcomatoid differentiation. After multivariate analysis, T-stage, nuclear grade and sarcomatoid differentiation retained their power as independent predictors of RFS ($P = 0.032$, $<0.001$ and 0.003, respectively).

***Conclusions:*** For patients with LARCC, T-stage, grade and sarcomatoid differentiation independently dictate the risk of tumour recurrence. Considering these variables in the postoperative surveillance protocols and in the need for a multimodal therapeutic approach is highly recommended.



## Introduction

Advanced RCC can be metastatic (mRCC) or locally advanced (LARCC). Of patients with RCC, 25% present with LA or disseminated disease, and 20–30% of those with localized disease at presentation will develop systemic recurrence [1].

The prognosis for patients with RCC primarily depends on disease stage. The American Joint Cancer Committee (AJCC) TNM staging system for RCC was last modified in 2009 and recently validated [2–4]. Organ-confined disease (pathological stage pT1–2) is associated with the best prognosis, with 5-year cancer-specific survival (CSS) rates after nephrectomy of 71–97%. However, mRCC has a 5-year CSS rate of $<10\%$ [5–7]. Locally, once RCC has reached the perinephric fat space or the venous system, it changes from organ-confined to LA, and the 5-year CSS rate after nephrectomy decreases to 53% [5].

In LARCC there is controversy about the prognostic role of different factors, e.g. the cranial level of tumour thrombus, the location of perinephric extension, and adrenal gland involvement [8–12]. The objectives of the present study were to assess the relapse pattern of these patients and identify predictors of recurrence.

## Patients and methods

Included in the study were all surgically treated patients with RCC, pathological evidence of being LARCC, and with full clinical and pathological data. Patients with metastatic or nodal disease at initial presentation were excluded from the study. Of 848 patients who underwent nephrectomy for RCC from 2000 to 2010, full clinical and pathological data were only available in 659. After reviewing the available pathological data, 157 patients had a pathological T-stage of either T3 or T4; of these, 45 at the time of nephrectomy had confirmed N+ or M1 disease, and were excluded from the study. The net result was a study population of 112 patients with the stage of T3a–T4N0M0 disease LARCC, operated on at Alexandria University Main Hospital between 2000 and 2010. Clinical and pathological data were collected from hospital medical records and gathered into a computerized database. Patients were initially treated mainly with radical nephrectomy. For each patient the following variables were included; age at nephrectomy, gender, symptoms at presentation, pathological tumour size, histological subtype, nuclear grade, peripheral perinephric fat invasion, vascular invasion, collecting-system invasion and sarcomatoid differentiation.

Pathological staging was readjusted according to the 2009 AJCC TNM system [4]. Tumour size was based on pathological specimens and taken as the greater diameter. Histological type and grade were classified according to the Heidelberg classification of RCC and the Fuhrman grading system, respectively [13,14]. Both histological subtype and nuclear grade were available for all tumours. Other pathological data, e.g. tumour size, collecting-system violation and sarcomatoid differentiation, were retrieved.

The duration of follow-up was calculated from the date of nephrectomy to the date of death or last follow-up. The study endpoint was the incidence of documented recurrence, whether radiological or pathological, distant or local. Recurrence-free survival (RFS) was defined as the duration in months from the time of nephrectomy to the incidence of documented recurrence. The RFS was estimated using the Kaplan–Meier method and differences were analysed using the log-rank test (univariate analysis) [15]. To identify factors that independently affected RFS, we used the Cox proportional-hazards model. A minimum significance level of 0.05 on univariate analysis was used as the criterion for determining variable entry.

## Results

The mean (range) age of the 112 patients in the study was 59 (22–87) years; 77 (69%) were men. Most patients were symptomatic at presentation (64%); Table 1 summarizes the demographic and clinical characteristics of

**Table 1** The clinical and pathological characteristics of the 112 patients with LARCC.

| Variable | Value |
|---|---|
| *Age (years)* | |
| Mean (SD) | 59 (12) |
| Median (range) | 59 (29–87) |
| *n (%)* | |
| Male | 77 (69) |
| Female | 35 (31) |
| *Mode of presentation* | |
| Asymptomatic, S1 | 40 (36) |
| Local symptoms, S2 | 56 (50) |
| Systemic symptoms, S3 | 16 (14) |
| *Side* | |
| Right | 62 (55) |
| Left | 50 (45) |
| *Pathological tumour size (cm)* | |
| Mean (median, range) | 8.7 (8.1, 4–16) |
| *n (%)* | |
| *Histological type* | |
| Clear cell | 96 (86) |
| Chromophobe | 8 (7) |
| Papillary | 8 (7) |
| *Fuhrman nuclear grades (for 96 tumours with clear-cell histology)* | |
| Grade I | 5 (5) |
| Grade II | 40 (42) |
| Grade III | 33 (34) |
| Grade IV | 18 (19) |
| *Pathological T-stage* | |
| pT3a | 57 (51) |
| pT3b | 33 (30) |
| pT3c | 7 (6) |
| pT4 | 15 (13) |
| Perinephric fat invasion | 77 (69) |
| Adrenal gland invasion | 5 (5) |
| Venous tumour thrombus | 64 (57) |
| Collecting system invasion | 10 (9) |
| Sarcomatoid differentiation | 9 (8) |

the cohort. Surgery was the primary management in all patients, and none received neoadjuvant or adjuvant systemic therapy.

The pathological data of the 112 patients are also shown in Table 1; 97 (87%) had T3 RCC, and 15 (13%) had pT4 RCC. According to the Heidelberg classification, most patients (86%) had clear-cell RCC.

Perinephric fat invasion was documented in 77 patients (69%), among whom 35, 23, four and 15 were pT3a, pT3b, pT3c and T4, respectively. Overall there were 64 cases (57%) with venous tumour thrombus; this reached the main renal vein in 34 (30%). In the 30 patients with caval tumour thrombus, seven were suprahepatic and 23 were infrahepatic.

At the time of nephrectomy, none of the patients had radiological evidence of either metastatic or nodal extension. A lymphadenectomy was performed in 32 patients (29%), and all submitted lymph nodes were free of disease.

Of the 70 patients (63%) who had a concomitant ipsilateral adrenalectomy, five had direct adrenal invasion. According to the new 2009 TNM staging system, these are considered as T4 disease. Surgical margins were involved (positive) in eight patients.

The mean (median, range) follow-up for the entire cohort was 33.3 (24, 3–125) months. At the last follow-up, of the 112 patients, 27 (24%) died from disease, two (2%) died from other causes, and one had metastatic disease and died from another cause. Patients who died had been followed for mean and median of 25 and 23 months, respectively (range 4–71).

At the last follow-up 27 (24%) patients were alive with disease, and 55 (49%) were alive with no evidence of disease recurrence. The mean (median, range) follow-up of these survivors was 36 (24, 3–125) months. The 1-, 2- and 5-year CSS probabilities for all patients were 75%, 73% and 52%, respectively (Fig. 1).

During the study period there were recurrences in 58 patients (52%); the final outcome was death from disease in 27, alive with disease in 27, one with metastases who died from another cause, and three patients were cured with no evidence of disease on resection of their solitary metastatic lesions.

The mean and median disease-free duration was 25 and 13 months, respectively. Sites of recurrence were multiple in 36 patients (32%), lung only in 14 (13%) and local in eight (7%).

Surgical metastasectomy was carried out in 23 patients and yielded three with no evidence of disease. Thirty-two patients received systemic treatment. The 1-, 2- and 5-year RFS probabilities were 50%, 43% and 34%, with a median RFS of 23.7 months.

On univariate analysis, the following variables were statistically significant: age $<$ and $>70$ years, mode of presentation, pathological tumour size, nuclear grade, collecting-system invasion, and sarcomatoid differentiation. By contrast, perinephric fat invasion, presence of thrombus, and histological subtype were not statistically significant (Table 2). On multivariate analysis, only pathological T-stage, nuclear grade and sarcomatoid differentiation remained statistically significant (Table 2).

Pathological T-stage maintained its prognostic power on multivariate analysis ($P = 0.032$). Detailed analysis of the subgroups showed that the 2-year RFS was 68% for pT3a, 42% for pT3b, 17% for pT3c and 10% for pT4 tumours. There was a significantly better RFS in patients with pT3a disease than pT3b ($P = 0.047$) and pT3c ($P = 0.013$), and T4 disease ($P < 0.001$). Also, the RFS in patients with T3b disease was significantly better than in those with T4 ($P = 0.002$). However, there was a comparable RFS between T3b and T3c disease ($P = 0.227$), and between the pT3c and pT4 subgroups ($P = 0.353$) (Fig. 2).

Patients with thrombus limited to the renal vein (level 0) had a significantly longer RFS than those with caval

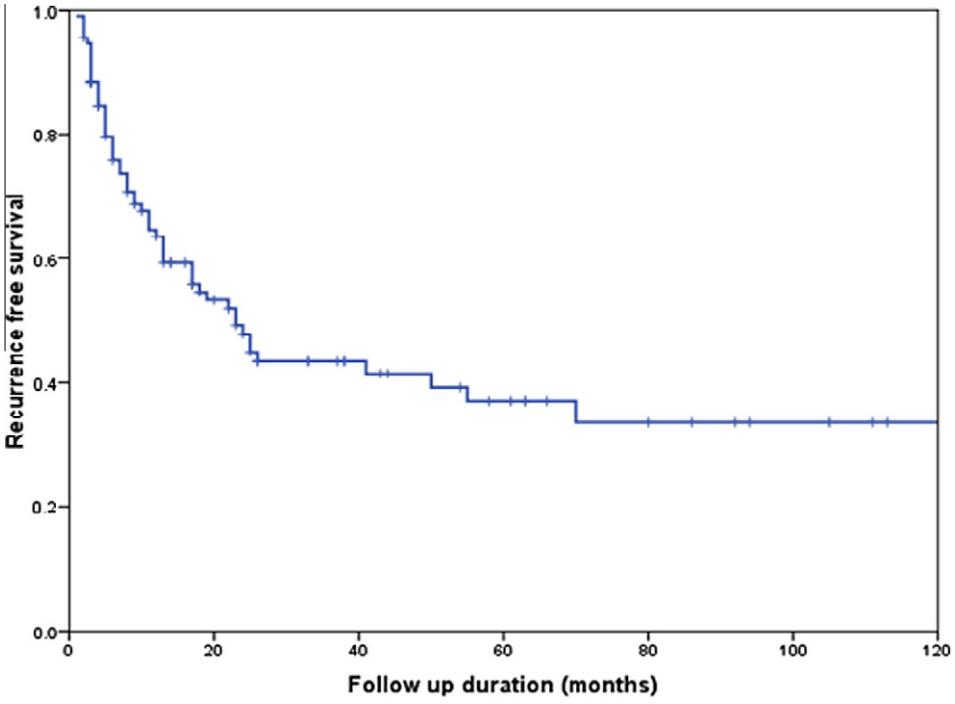


**Figure 1** The RFS curve for patients with LARCC.

**Table 2** Univariate and multivariate analyses of different variables with RFS in patients with LARCC.

| Variable | Hazard ratio (95% CI) | *P* |
|---|---|---|
| *Univariate (log-rank for P)* | | |
| Age in years (< and >70) | 0.325 (0.139–0.763) | 0.006 |
| Presence of symptoms | 0.443 (0.242–0.810) | 0.007 |
| Presence of thrombus | 0.998 (0.527–1.889) | 0.248 |
| Tumour size (by 10 cm) | 1.105 (1.038–1.177) | 0.014 |
| Histological type (clear cell vs. others) | 0.907 (0.322–2.554) | 0.820 |
| Fuhrman nuclear grades (1 and 2 vs. 3 and 4) | 4.330 (1.788–10.40) | <0.001 |
| Pathological T-stage | 1.700 (1.231–2.349) | <0.001 |
| Perinephric fat invasion | 1.157 (0.605–2.209) | 0.508 |
| Collecting system invasion | 4.331 (1.797–10.44) | 0.004 |
| Sarcomatoid differentiation | 1.700 (1.231–2.349) | <0.001 |
| *Multivariate* | | |
| Age in years (< and >70) | 0.993 (0.970–1.016) | 0.554 |
| Presence of symptoms | 0.641 (0.316–1.300) | 0.218 |
| Tumour size | 0.721 (0.380–1.365) | 0.315 |
| Pathological T-stage | 3.577 (1.119–11.43) | 0.032 |
| Nuclear grade (high and low) | 3.302 (1.707–6.387) | <0.001 |
| Collecting system invasion | 1.551 (0.583–4.125) | 0.379 |
| Sarcomatoid differentiation | 4.677 (1.664–13.14) | 0.003 |

thrombus (levels I–IV). The 5-year RFS for patients with caval thrombus was 16%, compared with 53% for those with renal vein thrombus ($P = 0.028$, log-rank; Fig. 3). Patients with caval thrombus of different levels had a comparable RFS.

Of the 34 patients with level 0 (renal vein) thrombus, 12 had perinephric fat extension and in 22 the tumour did not reach the renal capsule. Patients with venous thrombus limited to the renal vein had a similar RFS when stratified by the presence of perinephric fat invasion ($P = 0.075$).

## Discussion

Local extension of RCC beyond the renal parenchyma through either the renal capsule or venous system had been categorized as T3 or T4. Patients with that kind of tumour had a much worse disease course than those with intraparenchymal tumour (T1–T2). LARCC carries a mixture of pathological features, such as perinephric fat invasion, adrenal gland involvement and venous system thrombosis. These features, as well as other clinicopathological features, were assessed

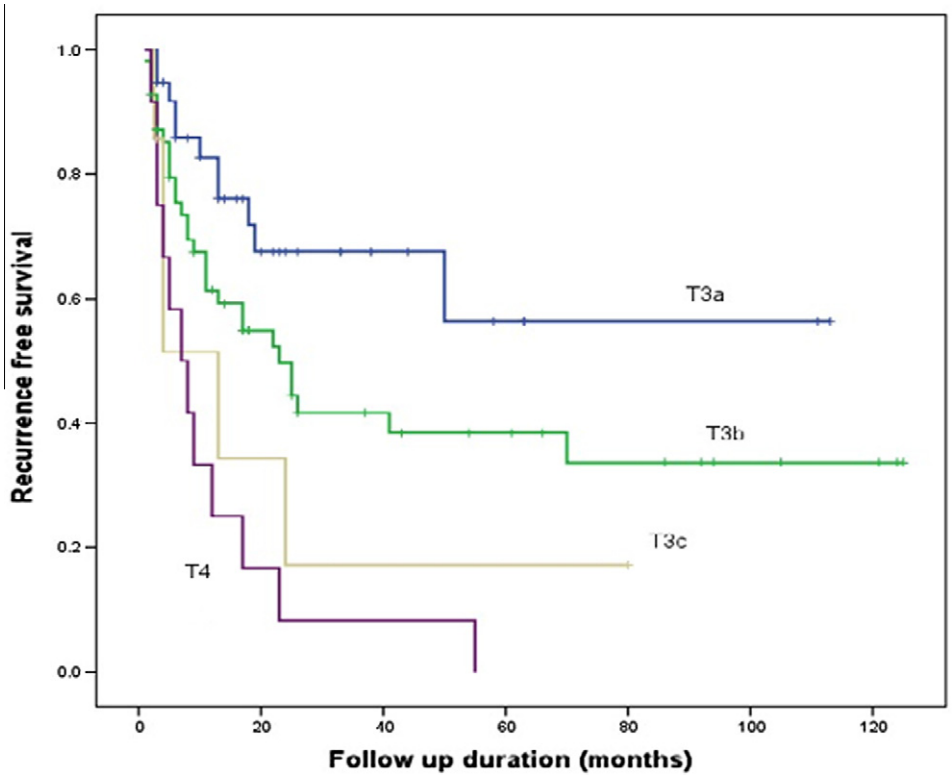


**Figure 2** The RFS curve for patients with LARCC stratified by T-stage.

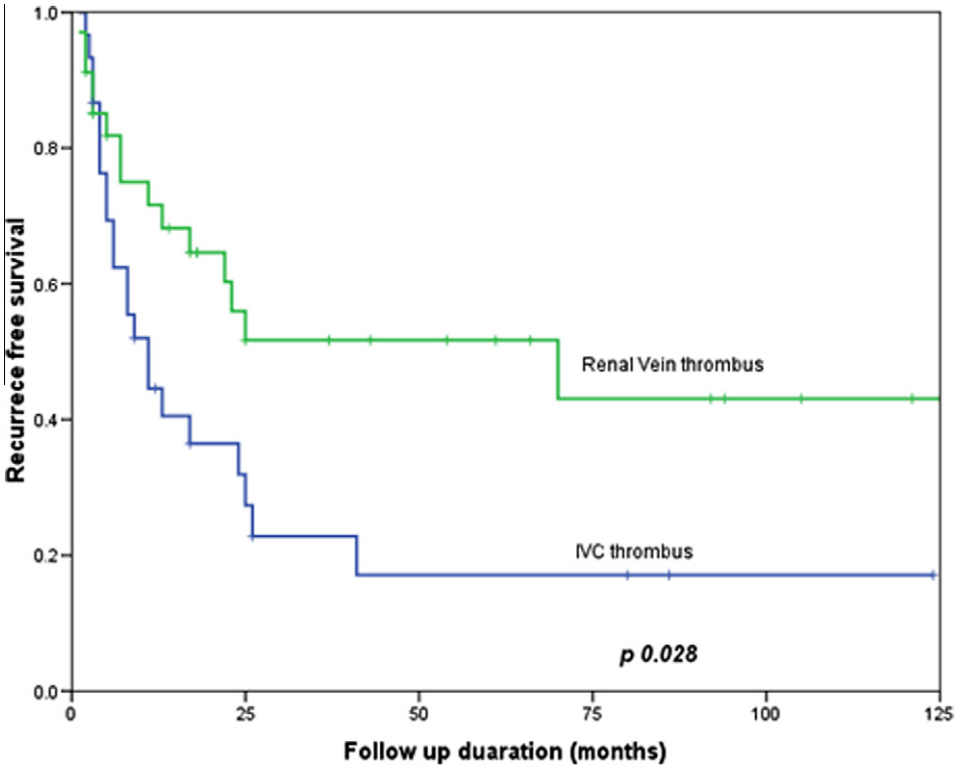


**Figure 3** The CSS probability curve after thrombectomy, stratified by the level of thrombus.

to identify prognostic factors within this subset of patients.

Tumour extension to the regional lymph nodes cannot be labelled as LA disease, as the survival of patients

with regional lymph node involvement only was identical to that of patients with distant metastatic disease only [16–18]. Based on this we excluded patients with radiological or pathological evidence of nodal extension.

In the present study there was a significant difference in RFS between patients with pT3a and pT3b disease ($P = 0.047$), while the RFS for patients with T3b and T3c was similar ($P = 0.227$). Based on the older TNM staging system, Kim et al. [19] found that the CSS was similar for patients with pT3a and T3b ($P = 0.536$). CSS rates for inferior vena caval thrombus below the diaphragm (T3b) and venous thrombus above the diaphragm (T3c) were significantly different ($P = 0.009$). The present patients with T4 disease had a significantly worse RFS than those with both T3a and T3b disease ($P < 0.001$ and $= 0.002$, respectively). We also noted that patients with T3c had a similar RFS to those with T4 disease ($P = 0.353$; Fig. 2). Likewise, Ficarra et al. [20] reported a similar CSS between patients with pT3c, pT4, and those with adrenal gland invasion.

A critical issue in the RCC staging system is the level of tumour thrombus, i.e. within the renal vein and in the vena cava. Reviewing previous reports showed that the CSS rate was significantly higher in cases of renal vein thrombus than for vena cava thrombosis [8,21]. The present patients with thrombus limited to renal vein (level 0) had a significantly longer RFS than those with caval thrombus (levels I–IV; $P = 0.028$) and that agreed with the recent TNM staging system, in which renal vein thrombus was downstaged from T3b to T3a [4]. Recently, the International Renal Cell Carcinoma–Venous Thrombus Consortium published its multicentric study on 1122 patients with venous thrombus, showing a significantly longer CSS in patients with tumour thrombus limited to the renal vein than in those with level 1 thrombus ($P = 0.002$) [2]. By contrast, Kim et al. [19] reported similar disease-specific survival probabilities for patients with thrombosis within the renal vein and the inferior vena cava below the diaphragm (3-year disease-specific survival, 36% and 35%, respectively).

Nuclear grade is one of the most powerful prognostic factors in patients with RCC. Many prognostic systems have integrated nuclear grade as the most important pathological variable [22–24]. There is a tendency to suggest that the four Fuhrman categories should be collapsed into two grades; low grade (grades I and II) and high grade (grades III and IV), as this appears to decrease the intra- and inter-observer variability without interfering with the discrimination of outcome [25]. In the present study, nuclear grading was categorized as low and high grades, and was the strongest independent predictor of RFS in patients with LARCC.

On review, the prognostic significance of perinephric fat involvement in LARCC was controversial. Fujita et al. [10] found that the mean (SD) disease-specific survival time in those with pT3b only was significantly longer, at 70.9 (9.1) months, than the 25.0 (4.4) months in those with pT3b with perinephric fat invasion and/or adrenal invasion ($P = 0.003$). However, Thompson et al. [26] reported that the CSS in localized disease was similar for patients with and without perinephric fat involvement ($P = 0.058$), regardless of the thrombus level. In the present cohort, perinephric fat invasion had no statistical significance in patients with T3–T4 disease ($P = 0.508$). The presence of perinephric fat invasion was assessed in patients with renal vein thrombus separately and there was an insignificant difference in RFS ($P = 0.370$).

The significance of collecting-system invasion was apparent in patients with localized tumour [27–29]. For LARCC, Palapattu et al. [29] reported that the 3-year overall survival for patients with or without collecting-system invasion by stage was 31% vs. 46% for T3, and 29% vs. 12% for T4 disease. The present study did not support this observation in patients with LARCC, with a comparable effect on time to recurrence.

Sarcomatoid features are found in $< 5\%$ of RCCs and are associated with a poor outcome with, many of these tumours already LA or metastatic at diagnosis [30,31]. In a review of 2381 RCC cases at the Mayo Clinic, sarcomatoid differentiation was present in 5% of the patients. Sarcomatoid differentiation was an independent predictor of CSS regardless of histological subtype, stage, size, and necrosis. Even among patients with grade IV clear-cell RCC, and after adjusting for TNM stage, tumour size and histological tumour necrosis, the presence of a sarcomatoid component retained its significant association with a poor outcome [31]. Similarly, in LARCC, sarcomatoid differentiation was an independent predictor of RFS in the present study.

A limitation of the present study is the size of the series, with only 112 patients, treated over a limited period. The limited sample size made some variables difficult to analyse, as occurrences were infrequent, e.g. adrenal gland invasion and surgical margin involvement. Moreover, the retrospective nature of the study did not allow an assessment of the prognostic role of important variables like performance status, tumour necrosis, and sinus fat invasion.

In conclusion, in LARCC, T-stage, nuclear grade and sarcomatoid differentiation independently determine the risk of relapse after surgical resection. Considering these variables in the postoperative surveillance protocols and in the need for a multimodal therapeutic approach is highly recommended. The current TNM staging system can provide an appropriate stratification of the patients' cancer-related outcomes. Thrombus advancement from renal vein to inferior vena cava has prognostic significance for RFS, providing further support of the current staging for pT3 RCC.

## Conflict of interest

The authors have no conflict of interest to declare.

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