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Prognostic role of tumour multifocality in renal cell carcinoma

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What's known on the subject? and What does the study add?
In RCC about 5% of the patients presented multifocal disease. Prevalence of tumour multifocality was associated with a higher percentage of symptomatic RCC, higher pathological TNM stages, higher tumour grade and higher prevalence of tumour necrosis.

Although in univariable analysis multifocal tumours had lower probability of CSS, tumour multifocality did not retain an independent predictive role in multivariable analysis. Patient age at surgery, gender, mode of presentation, pathological N stage and presence of metastases were independent predictors of CSS in multivariable analyses.

OBJECTIVE

- To evaluate the prevalence and the prognostic role of multifocality in a large multi-institutional series of patients who underwent radical or partial nephrectomy for renal cell carcinoma (RCC).

METHODS

- We retrospectively collected the data of 5378 patients who were surgically treated for RCC in 16 academic centres involved in the Surveillance and Treatment Update Renal Neoplasms (SATURN) project.
- Univariable and multivariable Cox regression models addressed time to cancer-specific survival (CSS) after surgery.

RESULTS

- Tumour multifocality was identified in 249 patients (5%). The median follow-up of the whole cohort was 42 months. At last follow-up, 786 (14.6%) were dead of cancer and 336 (6.2%) had experienced non-cancer-related death.
- The 5- and 10-year CSS estimates were 84.1% and 77.3%, respectively, in patients with monofocal RCC, compared with 71.1% and 63.6%, respectively, in patients with multifocal disease ($P < 0.001$).
- In univariable Cox regression analysis, tumour multifocality was significantly associated with CSS (hazard ratio [HR] = 1.83; $P < 0.001$).
- On multivariate Cox regression analysis adjusted for the effects of other covariates, tumour multifocality did not retain an independent predictive value (HR = 1.24; $P = 0.291$).

CONCLUSIONS

- In the present multi-institutional collaboration, about 5% of the patients presented multifocal RCC.
- The presence of multifocal cancer was associated with some unfavourable clinical and pathological features.
- Although in univariable analysis multifocal tumours had lower CSS probabilities, tumour multifocality did not retain an independent predictive role in multivariable analysis, once adjusted for the effect of the other clinical and pathological covariates.

KEYWORDS

renal cell carcinoma, multifocality, prognostic factor, cancer-specific survival

INTRODUCTION

Multifocal RCC continues to be an unresolved clinical problem from diagnostic, prognostic and therapeutic perspectives. Currently, there are conflicting reports on the clinical and pathological aspects in patients with multifocal RCC as well as on the therapeutic strategy for these patients [1,2]. The contemporary urological literature offers only limited data on these neoplastic lesions, even if they have been well described in von Hippel–Lindau disease, hereditary papillary RCC, familial oncocytoma, and Birt–Hugg–Dubè syndrome. According to the standard pathological features, tumour multifocality is often associated with large, high-stage or papillary tumours in sporadic RCC [3]. The real clinical impact of tumour multifocality on cancer-specific survival (CSS) is not completely understood, probably due to the low prevalence of multifocal RCC. Specifically, some authors have reported that multifocal RCC was often associated with metastasis and poor survival, whereas others stated that it had no impact on patient outcome [4,5].

The purpose of the present study was to evaluate the prevalence and the prognostic role of multifocality in a large multi-institutional series of patients who underwent radical or partial nephrectomy for RCC.

MATERIALS AND METHODS

The retrospective study was planned in the Surveillance and Treatment Update Renal Neoplasms (SATURN) project, promoted by the Leading Urological No-Profit Foundation for Advanced Research (LUNA) of the Società Italiana di Urologia (Italian Society of Urology). A total of 16 academic centres in Italy provided data. A computerized databank was generated for data transfer. The database comprised 5463 patients who underwent radical or partial nephrectomy between 1995 and 2007 for suspicion of kidney cancer. After exclusion of those patients for whom histological tumour subtype was unavailable ($n = 85$) and hereditary RCC was diagnosed, the remaining 5378 patients with clear-cell ($n = 4.371$), papillary ($n = 579$), chromophobe ($n = 291$), collecting duct ($n = 47$) or unclassified RCC ($n = 90$) were the subjects of the present analysis.

The mode of presentation was distinguished according to the Patard classification [6]. Clinical staging included abdominal CT scans and chest X-rays. Bone scans and brain CT scans were obtained only when indicated by signs and symptoms.

Surgery was performed by several surgeons according to the standard criteria for radical nephrectomy (i.e. extrafascial dissection of the kidney). The hilar and regional lymph nodes adjacent to the ipsilateral great vessel generally were resected, along with enlarged lymph nodes if abnormal on preoperative CT scans or if palpable intraoperatively. Extended lymphadenectomy was routinely performed in a few centres. In patients with contralateral normal kidney, elective nephron-sparing surgery (NSS) was routinely indicated in the presence of single, peripheral tumours ≤4 cm in size, although some referral centres also performed elective NSS for larger tumours. Imperative NSS was performed in patients with bilateral tumours or with neoplasia involving anatomically or functionally solitary kidneys. NSS was performed as enucleoresection, simple enucleation or polar nephrectomy, according to the clinical indications and the surgeon's preference. Patients with metastatic disease were treated with radical nephrectomy followed by immunotherapy in accordance with the guidelines of care at that time.

All surgical specimens were processed according to standard pathological procedures at each institution. Multifocality was defined as the existence of at least one other tumoral localization macroscopically and microscopically diagnosed as RCC in the same kidney. Tumours were staged according to the American Joint Committee on Cancer–Union Internationale Contre le Cancer TNM classification [7]. The Heidelberg and Fuhrman classifications were used to assign the histological type and nuclear grade, respectively [8,9]. Moreover, presence of microscopic tumour necrosis, sarcomatoid differentiation and margin status were evaluated in most cases. No central pathological slide review was performed.

For follow-up, patients were generally observed every 3–4 months for the first year after surgery, every 6 months from the second through the fifth years, and annually thereafter. Follow-up consisted of a history, physical examination, routine blood work and serum chemistry studies, chest radiography and radiographic evaluation of the contralateral or remnant kidney. Elective bone scan, chest CT, and MRI were performed when clinically indicated.

Cause of death was determined by the treating physicians, by chart review corroborated by death certificates or by death certificates alone. Most patients who were identified as having died of kidney cancer had progressive, widely disseminated metastases at the time of death.

For the statistical analysis, continuous variables were reported as mean value ± SD or as median value and interquartile range (IQR), as appropriate. Student's *t*-test and the Mann–Whitney *U*-test were used to compare the locations of continuous variables, as appropriate. Pearson's chi-squared test was used to compare variables. The Kaplan–Meier method was used to calculate survival functions, and differences were assessed with the log-rank statistic. Univariable and multivariable Cox regression models addressed time to cancer-specific mortality after surgery. $P \leq 0.05$ was considered to indicate statistical significance. All reported *P* values are two-sided. Analyses were performed with SPSS v.17.0 (SPSS Inc., Chicago, IL, USA) by one of the authors.

RESULTS

Table 1 shows the association between tumour focality and clinical and pathological features of the 5378 patients in this cohort. Tumour multifocality was identified in 249 patients (5%). The prevalence of tumour multifocality was associated with a higher percentage of symptomatic RCC; higher pathological T, N and M stages; higher tumour grade; and higher prevalence of tumour necrosis (all $P < 0.001$). Moreover, type of surgery, histological subtypes and pathological tumour size were significantly different when comparing unifocal and multifocal RCC (all $P < 0.01$).

The median (IQR) follow-up of the whole cohort was 42 (24–75) months. At last follow-up, 786 patients (14.6%) had died of cancer and 336 (6.2%) had experienced non-cancer-related death.

The median (IQR) follow-up for 3987 patients (74.1%) who were alive and

TABLE 1 Association of tumour multifocality with clinical and pathological characteristics of 5378 patients treated with radical or partial nephrectomy for RCC

	Overall	Unifocal (n = 5129, 95%)	Multifocal (n = 249, 5%)	P value
Mean age, years	61.9 ± 12	61.8 ± 12	62 ± 12	0.754
Gender				0.157
Men	3557 (66%)	3382 (95%)	175 (5%)	
Women	1821 (34%)	1747 (96%)	74 (4%)	
Mode of presentation*				<0.001
Incidental	3356 (62%)	3214 (96%)	142 (4%)	
Local symptom	1455 (27%)	1382 (95%)	73 (5%)	
Systemic symptoms	261 (5%)	235 (90%)	26 (10%)	
Type of surgery				<0.001
Radical nephrectomy	3838 (72%)	3672 (96%)	166 (4%)	
Elective NSS	1311 (24%)	1275 (97%)	36 (3%)	
Imperative NSS	229 (4%)	182 (80%)	47 (20%)	
Histological subtype				<0.001
Clear cell	4371 (81%)	4199 (96%)	172 (4%)	
Papillary	579 (11%)	520 (90%)	59 (10%)	
Chromophobe	291 (5%)	282 (97%)	9 (3%)	
Collecting duct	47 (1%)	45 (96%)	2 (4%)	
Unclassified	90 (2%)	83 (92%)	7 (8%)	
Median pathological tumour size	5 (3.5–7)	5 (3.5–7)	4.5 (3–7)	0.01
Pathological T stage				<0.001
pT1a	1991 (37%)	1889 (95%)	102 (5%)	
pT1b	1473 (27%)	1433 (97%)	40 (3%)	
pT2	602 (11%)	585 (97%)	17(3%)	
pT3a	662 (12%)	617 (93%)	45 (7%)	
pT3b–c	531 (10%)	494 (93%)	37 (7%)	
pT4	119 (2%)	111 (93%)	8 (7%)	
Pathological N stage				<0.001
pN0	2040 (38%)	1981 (97%)	59 (3%)	
pNx	3094 (58%)	2924 (95%)	170 (5%)	
pN1	117 (2%)	112 (96%)	5 (4%)	
pN2	127 (2%)	112 (88%)	15 (12%)	
M stage				<0.001
M0	5055 (94%)	4836 (96%)	219 (4%)	
M1	230 (4%)	209 (91%)	21 (9%)	
M2	93 (2%)	84 (90%)	9 (10%)	
Tumour grade†				<0.001
G1	621 (11%)	606 (98%)	15 (2%)	
G2	2789 (52%)	2672 (96%)	117 (4%)	
G3	1418 (26%)	1354 (96%)	64 (4%)	
G4	422 (8%)	385 (91%)	37 (9%)	
Microscopic tumour necrosis‡				<0.001
Absent	2533 (47%)	2470 (98%)	63 (2%)	
Present	762 (14%)	718 (94%)	44 (6%)	

**Mode of presentation was missing in 306 patients. †Tumour grade was missing in 128 patients. ‡Microscopic tumour necrosis was missing in 2083 patients.*

disease-free at last follow-up was 48 (24.7–83.5) months; the overall 5- and 10-year CSS (standard error [SE]) estimates were 83.5% (0.6%) and 76.7% (0.9%). The 5- and 10-year CSS estimates were 84.1% (0.6%) and 77.3% (0.9%), respectively, for patients with monofocal RCC, compared with 71.1% (3.6%) and 63.6% (4.9%), respectively, in patients with multifocal disease (Fig. 1; $P < 0.001$).

Stratifying by histological subtype, tumour multifocality was significantly associated with CSS only in clear-cell and unclassified RCC (log-rank P values <0.001; Fig. 2).

Table 2 summarizes univariable and multivariable Cox regression analyses. On univariable Cox regression analysis, tumour multifocality was significantly associated with CSS (HR = 1.83; $P < 0.001$) as well as year of surgery, age, gender, mode of presentation, type of surgery, histological subtype, pathological T, N and M stages, Fuhrman grade, tumour size and coagulative tumour necrosis (Table 2). In multivariate Cox regression analysis adjusted for the effects of all of the above-mentioned variables, tumour multifocality did not retain an independent predictive value (HR = 1.24; $P = 0.291$), whereas gender, mode of presentation, pathological T, N, and M stages, histological subtype, nuclear grade and tumour necrosis turned out to be independent predictors of CSS (Table 2). Multiple subgroup analyses were run and resulted in consistent statistical patterns and P values for tumour multifocality in patients with pathologically localized, locally advanced, pN0, pN+, M0 or M+ RCC, stratifying by tumour histological subtypes or excluding patients with collecting duct RCC (data not extensively shown).

We evaluated the predictors of CSS in the 249 patients with multifocal RCC. Age, gender, mode of presentation, type of surgery, histological subtype, pathological tumour size, pathological stage of both primary tumour and lymph nodes, presence of metastases, Fuhrman nuclear grade and presence of tumour necrosis were all significantly associated with patient outcome in univariable analyses (all $P <$ 0.01). In multivariable analyses, only patient year of surgery (HR = 1.4; $P = 0.005$), gender (HR = 6.1; $P = 0.007$), pathological T stage ($P = 0.032$) and presence of metastases ($P = 0.001$) were independent predictors of CSS (data not extensively shown).

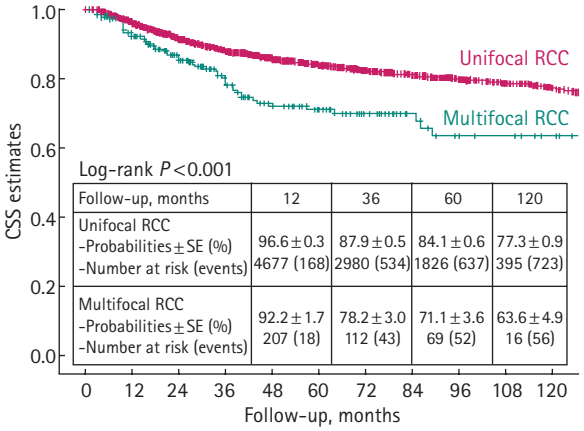
DISCUSSION

To our knowledge, the present series is the largest one evaluating the prognostic

relevance of multifocality in RCC. We found that about 5% of the tumours included in the SATURN data set were multifocal. Multifocal RCC was associated with several other unfavourable clinical and pathological features, including symptoms at presentation and higher tumour stage and grade. Although patients with multifocal tumours had lower CSS estimates in univariable analysis, multifocality was not shown to have any impact on patient outcome, once adjusted for the effects of the other clinical and pathological covariates. Finally, year of surgery, pathological T stage and presence of synchronous metastases were independent predictors of CSS in those patients with multifocal RCC.

Our figures regarding prevalence of multifocality seem to be lower than the previous data reported in the literature, in which multifocality was reported in 5–25% of the cases [1,3,10,11]. This latter aspect could be explained by different radiological or intraoperative procedures that were probably used to define tumour multifocality and/or by the different prevalence of the histological subtypes. In the present study, papillary RCC was the most frequent histological pattern in multifocal RCC, with an incidence of 10%, followed by unclassified histotypes (7.7%), Bellini duct carcinoma (4.2%), clear-cell RCC (3.9%) and the chromophobe variant (3%). These pathological findings confirm that multifocal RCC occurs at a higher frequency in papillary RCC than in the conventional clear-cell variant [12–16].

With regard to the association of tumour multifocality with other clinicopathological variables, we found a higher prevalence of unfavourable features, including symptoms at presentation and higher stage and grade. Similar data have been reported previously [1,10,11,14,17,18], although our finding of



Follow-up, months	12	36	60	120
Unifocal RCC -Probabilities±SE (%) -Number at risk (events)	96.6±0.3 4677 (168)	87.9±0.5 2980 (534)	84.1±0.6 1826 (637)	77.3±0.9 395 (723)
Multifocal RCC -Probabilities±SE (%) -Number at risk (events)	92.2±1.7 207 (18)	78.2±3.0 112 (43)	71.1±3.6 69 (52)	63.6±4.9 16 (56)

FIG. 1.
CSS according to tumour multifocality in 5378 patients with RCC.

FIG. 2. CSS according to tumour multifocality stratified by tumour histological subtype. Red, unifocal RCC; green, multifocal RCC.

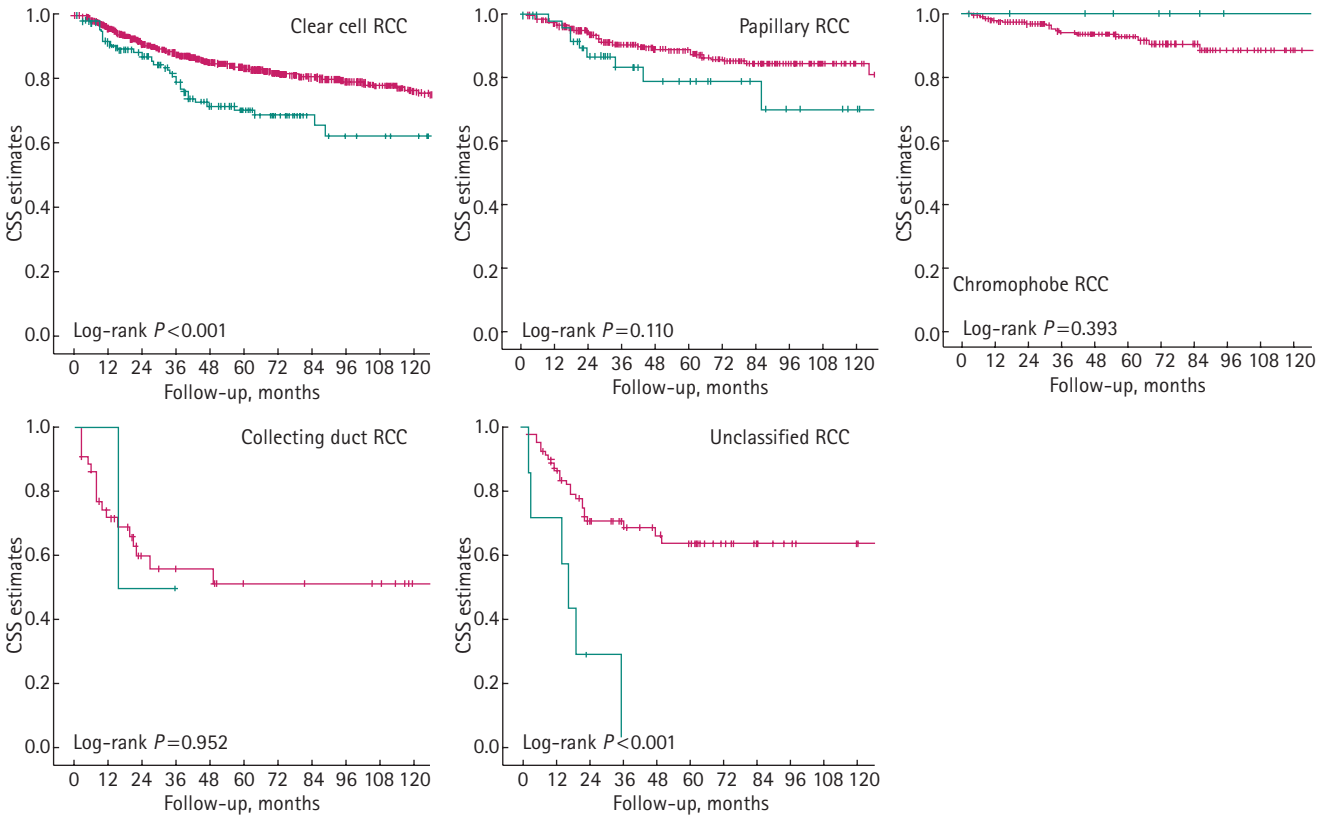


TABLE 2 Univariable and multivariable Cox regression analyses of tumour multifocality for prediction of cancer-specific mortality in 5378 patients treated with radical or partial nephrectomy for RCC (786 cancer-specific deaths)

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Year of surgery	0.97 (0.95–0.99)	0.003	0.98 (0.95–1.01)	0.143
Age	1.02 (1.01–1.02)	<0.001	1.01 (1.00–1.02)	0.060
Gender (male vs female)	0.82 (0.71–0.96)	0.012	0.81 (0.66–1.00)	0.050
Mode of presentation		<0.001		0.001
Incidental	1 (reference)	–	1 (reference)	–
Local symptom	2.64 (2.25–3.09)	<0.001	1.4 (1.12–1.72)	0.003
Systemic symptoms	7.02 (5.67–8.69)	<0.001	1.7 (1.23–2.33)	0.001
Type of surgery		<0.001		0.271
Radical nephrectomy	1 (reference)	–	1 (reference)	
Elective NSS	0.20 (0.15–0.27)	<0.001	0.66 (0.40–1.1)	0.115
Imperative NSS	0.59 (0.39–0.88)	0.01	1.07 (0.55–2.1)	0.849
Histological subtype		<0.001		0.043
Clear cell	1 (reference)	–	1 (reference)	
Papillary	0.76 (0.59–0.98)	0.036	1.01 (0.71–1.43)	0.976
Chromophobe	0.42 (0.26–0.66)	<0.001	0.70 (0.41–1.20)	0.196
Collecting duct	4.17 (2.64–6.58)	<0.001	2.36 (1.15–4.90)	0.020
Unclassified	2.94 (2.05–4.22)	<0.001	1.60 (0.91–2.82)	0.106
Median pathological tumour size	1.17 (1.16–1.18)	<0.001	1.02 (0.98–1.05)	0.368
Pathological T stage		<0.001		<0.001
pT1a	1 (reference)	–	1 (reference)	–
pT1b	1.63 (1.21–2.20)	0.001	1.11 (0.70–1.75)	0.648
pT2	4.77 (3.56–6.37)	<0.001	2.37 (1.46–3.87)	0.001
pT3a	8.46 (6.50–11.0)	<0.001	3.38 (2.16–5.29)	<0.001
pT3b–c	16.7 (12.9–21.6)	<0.001	5.15 (3.26–8.11)	<0.001
pT4	29.2 (21.2–40.2)	<0.001	2.92 (1.64–5.18)	<0.001
Pathological N stage		<0.001		<0.001
pN0	1 (reference)	–	1 (reference)	–
pNx	0.62 (0.53–0.72)	<0.001	0.89 (0.69–1.16)	0.410
pN1	6.92 (5.34–8.95)	<0.001	1.90 (1.38–2.62)	<0.001
pN2	8.70 (6.92–11.0)	<0.001	2.19 (1.49–3.21)	<0.001
M stage		<0.001		<0.001
M0	1 (reference)	–	1 (reference)	–
M1	11.5 (9.66–13.8)	<0.001	4.68 (3.61–6.10)	<0.001
M2	17.4 (13.6–22.3)	<0.001	6.61 (4.56–9.60)	<0.001
Tumour grade		<0.001		0.024
G1	1 (reference)	–	1 (reference)	–
G2	2.03 (1.36–3.03)	<0.001	0.99 (0.61–1.63)	0.981
G3	6.33 (4.27–9.38)	<0.001	1.30 (0.78–2.18)	0.314
G4	17.2 (11.5–25.8)	<0.001	1.65 (0.94–2.88)	0.081
Microscopic tumour necrosis	4.71 (3.93–5.64)	<0.001	1.56 (1.25–1.95)	<0.001
Tumour multifocality	1.83 (1.40–2.41)	<0.001	1.24 (0.83–1.87)	0.291

the association of multifocality with a higher prevalence of tumour necrosis was original.

The available literature evaluating the prognostic relevance of tumour multifocality for CSS is quite limited, and the findings are controversial [14,17,19]. In the largest published series, Klatte *et al.* [17] evaluated more than 10 000 patients treated in 12 academic centres and showed with univariable analyses that those patients with multifocal tumours had CSS estimates that overlapped with patients with unifocal RCC. Other single-centre series, including very limited numbers of patients with multifocal RCC, also failed to show any prognostic relevance [14,19]. In the present study, we found that tumour multifocality was associated with CSS in univariable analyses, although the covariate did not retain an independent predictive value in multivariable analysis, once adjusted for the effect of the other clinical and pathological covariates.

The present study has several limitations. First and foremost are the limitations inherent in any retrospective analysis. In addition, the population in the present study underwent surgery in multiple centres, specimens were evaluated by multiple pathologists without slide review, some heterogeneity in outcome assessment might be present and some data were not available in all the cases (e.g. Eastern Cooperative Oncology Group performance status, patient comorbidity, surgical margin status). All surgeons, however, operated at selected centres with significant experience in RCC management, which might increase the external validity of the data compared with the single-centre, single-surgeon setting. Similarly, although it might be preferable for a single pathologist specialized in genitourinary pathology to review each specimen, the present study reflects a 'real world' scenario. Moreover, preoperative data regarding radiological imaging were not available in our dataset. Finally, most of the patients who recurred in the present cohort did not have access to targeted therapies because they were treated before the development of tyrosine kinase and mammalian target of rapamycin inhibitors.

In conclusion, in the present multi-institutional collaboration, about 5% of patients presented multifocal RCC. The presence of multifocal cancer was associated with some unfavourable clinical and pathological features such as symptoms at presentation and higher tumour stage and grade. Although in univariable analysis multifocal tumours had lower probability of CSS, tumour multifocality did not retain an independent predictive role in multivariable analysis, once adjusted for the effect of the other covariates. Finally, patient age at surgery, gender, mode of presentation, pathological N stage and presence of metastases were independent predictors of CSS in multivariable analyses.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **CSS**, cancer-specific survival; **HR**, hazard ratio; **NSS**, nephron-sparing surgery.

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