INTERNATIONAL JOURNAL OF UROLOGY
International Journal of Urology (2016) 23, 36–40 doi: 10.1111/iju.12962

Original Article: Clinical Investigation

Features, risk factors and clinical outcome of "very late" recurrences after surgery for localized renal carcinoma: A retrospective evaluation of a cohort with a minimum of 10 years of follow up

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Abbreviations & Acronyms
CT = computed tomography
RR = relative risk

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Received 29 June 2015; accepted 8 September 2015. Online publication 14 November 2015

Objective: To evaluate the features and the predictors of "very late" recurrences after surgery for localized renal cell carcinoma.
Methods: Since 1983, an institutional database with data of more than 2300 consecutive patients treated for renal cancer has been prospectively maintained. Patients N_0/N_xM_0 followed for a minimum of 10 years without recurrences were retrieved. The site, time and treatment of recurrences observed afterwards were recorded, and the predictors were investigated by Cox regression analysis.
Results: A total of 554 patients (231 women, 323 men; age 59.3 ± 11.6 years) followed for a mean/median time of 15.1/13.6 years (range 10.0–34.1 years) were analyzed. A recurrence was observed in 26 patients (4.6%) after a mean/median interval of 13.3/12.3 years (range 10.5–30.2 years). The pathological stage 2/3 was the only independent predictor of recurrence ($P = 0.003$), and it was related also to the latency of recurrence (mean/median latency 15.4/14.0, 11.4/10.8 and 12.5/12.0 years, respectively, for stage 1, 2 and 3; $P < 0.005$ for stage 1 *vs* stage 2 or 3). The contralateral kidney was the most frequent site of relapse in patients with stage pT1, whereas multiple sites were more frequent for stage pT2 and pT3.
Conclusions: The risk of a "very late" recurrence of renal cancer is approximately 5%, and it depends on the pathological stage. For stage pT1, the kidney/s should be surveilled for indefinite time, preferably by ultrasound to reduce the X-ray exposition; for stage pT2 and pT3, the abdomen and the lungs should be monitored, by computed tomography scan during the first years, and then by abdominal ultrasound and chest X-ray.

Key words: follow up, oncological outcome, recurrence, renal cell carcinoma, stage.

Introduction

Relapses after surgery for renal cancer account for 20–40% of cases without metastasis at diagnosis.[1,2] For patients who experienced relapse, curative options are very limited, even after the introduction of targeted therapies, which are effective in 20–40% of cases, but able to reach a complete and durable response in a minimal (2%) proportion.[3] Therefore, the early detection of a recurrence is crucial, because surgical removal can lead to the regression of the disease in a significant proportion of patients and in a minority of them be truly curative.[4] The advantages of intensive follow up must be balanced by the economic costs of instrumentation and operators, as well as the biological burden related to the exposure to ionizing radiation. Recurrences can occur in multiple sites, mainly in the lungs, adrenal glands, bones and kidneys, but also in various atypical sites,[5,6] making the extent and the frequency of a CT scan very difficult to define.[7,8]

Thus, the duration of follow up is a matter of interest, especially for the patients who remain free from recurrences for many years, as they benefit from a long-term life expectancy.

Many retrospective studies defined some risk groups based on post operative or preoperative features to rationalize follow-up schedules.[9,10] However, these studies provided mean/median follow-up duration of approximately 5 years, and their results should be applied exclusively for the prediction of recurrences during this time range. Also, the European Asso-

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ciation of Urology and American Urological Association guidelines suggest well-defined strategies only for the first 5 years after surgery, but afterwards recommendations are generic or not reported at all.[11,12]

Nevertheless, recurrences could also occur after a very long latency, up to more than 40 years,[13,14] and therefore clinicians are generally reluctant to suspend controls. Contemporary data on late recurrences have been reported by very few studies and from tertiary institutions or collaborative databases, which investigated follow up after the first 5 years of negative controls,[15–18] but, to our knowledge, only one multicenter Japanese study assessed the outcome of "very late" recurrences; that is, those that occurred after 10 years of negative controls.[19] Therefore, the evidence to trigger follow up after 10 years without relapses is very weak or empiric.

The aim of the present study was to evaluate the features, risk factors and clinical outcome of "very late" recurrences observed in a single-center large cohort followed for a minimum of 10 years of negative controls.

Methods

Since 1983, the clinical, surgical, pathological and follow-up data of more than 2300 patients submitted to surgery for a renal mass at our institution have been stored in a prospectively maintained database. For the present study, in lieu of a formal approval from the ethical committee, the principles of the Declaration of Helsinki were followed.

The data of patients operated up to the year 2004 for a non-metastatic (N_0/N_x M_0) renal carcinoma were retrieved from this database, so that a minimum follow-up time of 10 years could be warranted; in particular, the cases in which no recurrences were observed during their first 10 years were recruited.

During the study period, both partial and radical nephrectomy were carried out by open surgery according to current guidelines.

A single expert uropathologist (RT) reviewed all the histological specimens. TNM staging was updated to the 2009 version; histological subtype and grading were assigned according to the recommendations of the World Health Organization 2004 classification and International Society of Uropathologists.[20,21]

All the patients were followed at a dedicated office, for an unrestricted timespan, applying a single schedule of controls regardless of the clinical and pathological baseline features of each case. In particular, at each visit patients were submitted to a physical examination, and provided blood and urine tests, and a chest and abdominal study at an interval of 6 months for the first 2 years, then yearly; chest X-ray along with abdominal ultrasonography were alternated to thorax and abdominal computer tomography, unless the use of medium contrast was contraindicated. Periodically, the records of patients who missed their planned control were updated by telephone interview or hospital database consultation.

The site, time and treatment of recurrences were recorded. At the diagnosis of a recurrence, a whole body restaging was carried out. A histological diagnosis of the metastasis was carried out in all cases; surgical treatment of the relapse was indicated in all the cases with an isolated recurrence, when technically feasible, whereas a medical therapy was carried out in cases with diffuse metastasis, with interleukin-2 or interferon before the year 2005, with target therapy afterwards.

Statistical analysis

Categorical variables were compared by Fisher's exact test or χ^2-test, and continuous variables by *t*-test or *U*-test, as appropriate.

A Cox regression model was applied to investigate disease-free survival and to find predictors of recurrence; the Kaplan–Meier method was used to estimate differences in survival among groups of patients; disease-free survival was considered as the interval from the date of surgery to relapse or the last follow up available. All *P*-values were two-tailed and considered as significant if <0.05 (Software SPSS v.13.0; IBM, Armonk, NY, USA).

Results

The study recruited 554 patients with a non-metastatic renal carcinoma (231 women, 323 men, mean age 59.3 ± 11.6 years) followed for a mean/median time of 15.1/13.6 years (range 10.0–34.1 years). The baseline features of the cohort are summarized in Table 1. At the last available follow up, 453 patients (81.7%) were alive without evidence of recurrence, nine (1.6%) with a progression, 15 (2.7%) died as a result of renal cancer and 77 (13.9%) died as a result of causes unrelated to the renal cancer. Cancer-specific survival was 98.2% and 96.0% at 15 and 20 years, respectively, whereas other-cause survival was 88.4% and 75.8%.

An event of progression was observed in 26 patients (4.6%) after a mean and median interval of 13.3 and 12.3 years (range 10.5–30.2 years) from surgery.

At univariate analysis, tumor diameter and pathological T were related to the risk of recurrence; whereas at multivariable analysis, only the pathological T retained this relationship ($P = 0.003$, Table 2). Patients with stage pT1, pT2 and pT3 were followed for a mean/median time of 15.0/13.9 years, 15.4/15.0 years and 15.3/13.4 years (*P* not significant); the estimation of disease-free survival with the Kaplan–Meier equation (Fig. 1) confirmed a significant difference between pT1 versus pT2 and pT3 grouped (log–rank test, $P = 0.002$). The mean/median latency of recurrence was 15.4/14.0 years, 11.4/10.8 years and 12.5/12.0 years (stage 1 *vs* stage 2, $P < 0.001$; stage 1 *vs* stage 3, $P = 0.047$).

In Table 3, the site, latency and treatment of recurrences, and the survival from the time of recurrence are reported. The contralateral kidney was the most frequent site of relapse in pT1 patients (55.6% of the relapses); whereas for patients with pT3, relapses in multiple sites were more frequently observed (45.5% of the relapses *vs* 16.5% and 22.2% in stage 2 and 1, respectively).

Discussion

The present study investigated the issue of "very late" relapses of renal carcinoma; that is, the relapses that occurred

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Table 1 Baseline features of the cohort

Feature	Value
Type of surgery, no. patients (%)	
Partial nephrectomy	131 (23.7)
Radical nephrectomy	423 (76.3)
Charlson Comorbidity Index, no. patients (%)	
0	409 (73.8)
1	56 (10.1)
2	56 (10.1)
>2	33 (5.9)
Symptoms, no. patients (%)	
None	306 (55.2)
Local	200 (36.1)
Systemic	38 (6.8)
Laterality, no. patients (%)	
Right	274 (49.4)
Left	257 (46.3)
Bilateral	23 (4.1)
Tumor diameter, clinical (cm)	
Mean	5.2
Median	4.5
Range	1.0–17.0
Clinical stage, no. patients (%)	
1–2	422/554
3–4	132/554
Tumor diameter, pathological (cm)	
Mean	5.1
Median	4.5
Range	1.0–20.0
Pathological stage, no. patients (%)	
1	393 (70.9)
1a	249 (44.9)
1b	144 (26.0)
2	54 (9.7)
2a	35 (6.3)
2b	19 (3.4)
3	107 (19.3)
3a	65 (11.8)
3b	41 (7.4)
3c	1 (0.2)
4	–
Lymphonodal status, no. patients (%)	
N_x	389 (71.5)
N_0	155 (27.5)
Grading, no. patients (%)	
1	85 (15.3)
2	306 (55.2)
3	118 (21.3)
4	35 (6.3)
Histological subtype, no. patients (%)	
Clear cell	477 (86.1)
Papillary	40 (7.2)
Chromophobe	27 (4.9)
Other	9 (1.6)

after at least 10 years of uneventful follow up. With this aim, a large cohort of surgical patients was analyzed, treated at a tertiary academic institution and followed through a homogeneous schedule of control that was not tailored to the baseline features of the patients.

There are several important findings to remark on.

First, the risk that a renal carcinoma N_0/N_xM_0 at diagnosis further develops a very late progression is not negligible, being approximately 5%, and depends on the stage of the tumor. In particular, for patients with larger – pT2 – and more advanced tumors – pT3 – the risk is similar, 11% and 9%, whereas for patients with pT1 it is significantly lower, close to 2%.

Second, the patients with a stage pT1 frequently showed an isolated recurrence in the contralateral kidney, occurring after a very long interval. Given this latency from the first operation and the good prognosis after salvage surgery, it should be questioned if these are true relapses or newborn tumors: histological subtype was concordant in all the cases and grading in six out of eight, supporting the hypothesis of a recurrence, but only a comparison of the chromosomal or genetic pattern of alterations of the two tumors could ascertain this hypothesis. Also, the patients with a stage pT2 experienced more frequently isolated recurrences, not in the kidney, but interestingly in sites that are not usually colonized by renal cancer, such as the thyroid and pancreas, confirming that these late recurrences are typical of a disease with a particular biological behavior.[22,23] Finally, patients with stage pT3 had more frequent relapses in multiple sites, generally diagnosed during the years 10–13.

Third, it can be stated that a schedule with a yearly check of the abdomen and chest allows an early diagnosis of the recurrence – that is, a recurrence still amenable with surgical therapy – in two thirds of cases. At the same time, controls were not intense enough for pT3 patients, as they had a multiple recurrence in approximately 50% of cases. It is noteworthy that the median survival from the recurrence of the patients of this study amenable to metastasectomy was 5.1 years versus 1.3 years for the cases in which surgery was not feasible. Such a difference in survival supports the use of an extended and tailored follow up. Indeed, as these patients have renal cancer without an aggressive behavior, and given that 10 years passed without recurrences, it is reasonable to point out that the differences in survival can be attributed to the punctuality of diagnosis and treatment.

The literature that specifically investigates the issue of relapses beyond 10 years is very poor, probably because an accurate collection of data on late outcomes is possible only with a dedicated institutional office, which was established at our center in the 1980s. Otherwise, at that time patients are poorly motivated, and tend to shift from a systematic follow up to a regimen more similar to observation.

Miyao *et al*. published the only study, to our knowledge, on very late recurrences: it analyzed the data of 470 patients followed for at least 10 years, finding that only lymphnodal invasion – and not the pathological stage – was a predictor of recurrence.[19] Some comments should be made to compare the two studies. First, we did not include N+ cases, because it is quite extraordinary that such patients have not experienced any relapse in the first years of controls – in our cohort, there were just six patients N+ followed for more than 10 years with no relapses. Thus, the clinical utility of a stratification on the lymphnodal status to determine if long-term follow up is necessary is quite debatable. Furthermore, the source of data is completely different: in Miyao's study, 13 centers with heterogeneous follow-up regimens were involved, but in the present study there was a

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Table 2 Univariate and multivariable Cox regression analysis of progression-free survival (only statistically significant results are reported)

Feature	Univariate analysis RR (95% CI)	*P*	Multivariable analysis RR (95% CI)	*P*
Age (continuous, years)	1.003 (0.998–1.015)	0.459		
Male	1.287 (0.971–1.341)	0.132		
Symptoms	1.416 (0.891–2.321)	0.324		
Laterality (uni- *vs* bilateral)	1.121 (0.732–3.123)	0.519		
Clinical stage (intra *vs* extracapsular)	1.988 (0.873–2.512)	0.731		
Type of surgery (partial *vs* radical nephrectomy)	2.221 (0.912–4.320)	0.115		
Histological subtype (clear cell *vs* others)	1.561 (0.787–3.123)	0.667		
Tumor diameter (continuous, cm)	1.198 (1.077–1.333)	0.001	1.231 (0.997–1.455)	0.216
Pathological stage		0.003		0.003
1	Referent		Referent	
2	3.544 (1.182–10.626)	0.008	6.423 (1.414–29.183)	0.016
3	3.580 (1.478–8.674)	0.002	6.967 (2.146–22.618)	0.001
Grading (1–2 *vs* 3–4)	2.419 (0.992–3.129)	0.538		

single institution that applied the same schedule of controls to all the patients. Third, the features of patients in Miyao's study were largely different from the present patients and the contemporary scenario of renal cancer in Western countries, as <2% were submitted to partial nephrectomy and 55% received some adjuvant therapy.

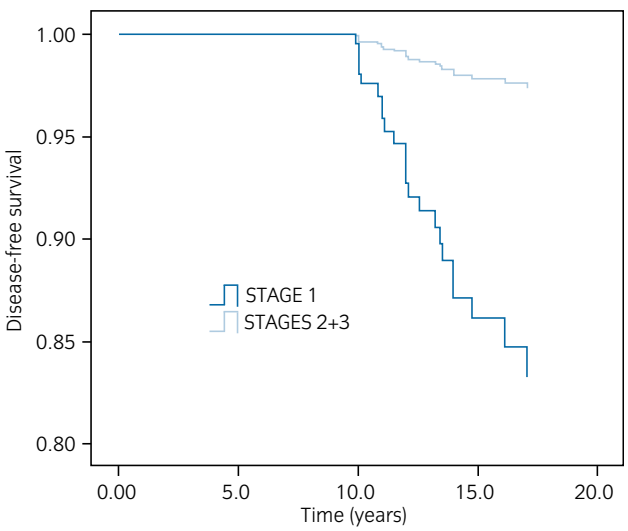

Fig. 1 Curves of estimated disease-free survival of patients with renal cancer pT1 versus pT2/pT3 showing a statistically significant difference (log–rank test, $P = 0.002$; the scale of the *y*-axis starts from 0.80 to render the difference between curves more evident).

A few more studies focused their attention on the recurrences that occurred after 5 years of controls and, even within given limits, their results might be compared with ours. Uchida *et al.* on a cohort of 239 cases did not find any factor related to late recurrence.[15] Brookman-May *et al*., from a very large (>5000 patients) international multicenter dataset, concluded that the risk of late recurrence is related to grading, lymphovascular invasion and pT stage >1, confirming the present findings.[16] Also, Kim *et al*. in a single center study, on a large cohort (>1400 patients), confirmed that the stage is a strong predictor of late recurrence.[18]

In conclusion, the risk of a "very late" recurrence in non-metastatic renal cancer patients is approximately 5%, and the pathological stage is the main predictor, being related also to the latency from surgery. On the basis of the patterns of recurrence observed after 10 years of uneventful follow up, it is possible to give the following suggestions: for stage pT1, the kidney/s should be surveilled for an indefinite time-span, preferably by ultrasound to reduce the X-ray exposition; for stage pT2 and pT3, the whole abdomen and the lung should be monitored, by CT scan in the first years when the risk is higher, afterwards by abdominal ultrasound and chest X-ray.

Table 3 Latency, treatment, outcome and distribution in each pathological stage of the sites of relapses

Site of relapse	*n*	Median latency (years)	Treatment	Median survival from recurrence (years)	Pathological stage (%) 1	2	3
Contralateral kidney	8	12.9	Surgery 8	6.7	5/8 (62.5)	–	3/8 (37.5)
Lung	5	11.1	Surgery 3, medical therapy 2	4.8	1/5 (20.0)	2/5 (40.0)	2/5 (40.0)
Pancreas	4	12.0	Surgery 4	2.7	1/4 (25.0)	2/4 (50.0)	1/4 (25.0)
Thyroid	1	13.5	Surgery 1	3.2	–	1/1 (100.0)	–
Multiple†	8	12.0	Medical therapy 8	1.5	2/8 (25.0)	1/8 (12.5)	5/8 (62.5)

†Kidney, lung and bone – 2 patients; lung and bone – 3 patients; lung and renal fossa – 2 patients; lung, liver and bone – 1 patient.

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Conflict of interest

None declared.

References

1 Ljungberg B, Campbell SC, Choi HI *et al.* The epidemiology of renal cell carcinoma. *Eur. Urol.* 2011; **60**: 615–21.
2 Nguyen MM, Gill IS, Ellison LM. The evolving presentation of renal carcinoma in the United States: trends from the Surveillance, Epidemiology, and End Results program. *J. Urol.* 2006; **176**: 2397–400.
3 Iacovelli R, Alesini D, Palazzo A *et al.* Targeted therapies and complete responses in first line treatment of metastatic renal cell carcinoma. A meta-analysis of published trials. *Cancer Treat. Rev.* 2014; **40**: 271–5.
4 Kim DY, Karam JA, Wood CG. Role of metastasectomy for metastatic renal cell carcinoma in the era of targeted therapy. *World J. Urol.* 2014; **32**: 631–42.
5 Antonelli A, Arrighi N, Corti S *et al.* Surgical treatment of atypical metastasis from renal cell carcinoma (RCC). *BJU Int.* 2012; **110**(11 Pt B): E559-63.
6 Sountoulides P, Metaxa L, Cindolo L. Atypical presentations and rare metastatic sites of renal cell carcinoma: a review of case reports. *J. Med. Case Rep.* 2011; **2**: 429.
7 Doornweerd BH, de Jong IJ, Bergman LM *et al.* Chest X-ray in the follow-up of renal cell carcinoma. *World J. Urol.* 2014; **32**: 1015–9.
8 Patel U, Sokhi H. Imaging in the follow-up of renal cell carcinoma. *Am. J. Roentgenol.* 2012; **198**: 1266–76.
9 Antonelli A, Cozzoli A, Zani D *et al.* The follow-up management of non-metastatic renal cell carcinoma: definition of a surveillance protocol. *BJU Int.* 2007; **99**: 296–300.
10 Sun M, Shariat SF, Cheng C *et al.* Prognostic factors and predictive models in renal cell carcinoma: a contemporary review. *Eur. Urol.* 2011; **60**: 644–61.
11 Ljungberg B, Bensalah K, Canfield S *et al.* EAU guidelines on renal cell carcinoma: 2014 update. *Eur. Urol.* 2015; **pii**: S0302-2838(15)00019-6. doi: 10.1016/j.eururo.2015.01.005.
12 Donat SM, Diaz M, Bishoff JT *et al.* Follow up for clinically localized neoplasms: AUA guideline. *J. Urol.* 2013; **190**: 407–16.
13 Featherstone JM, Bass P, Cumming J *et al.* Solitary, late metastatic recurrence of renal cell carcinoma: two extraordinary cases. *Int. J. Urol.* 2006; **13**: 1525.
14 Tapper H, Klein H, Rubenstein W *et al.* Recurrent renal cell carcinoma after 45 years. *Clin. Imaging* 1997; **21**: 273–5.
15 Uchida K, Miyao N, Masumori N *et al.* Recurrence of renal cell carcinoma more than 5 years after nephrectomy. *Int. J. Urol.* 2002; **9**: 19–23.
16 Brookman-May S, May M, Shariat SF *et al.* Features associated with recurrence beyond 5 years after nephrectomy and nephron-sparing surgery for renal cell carcinoma: development and internal validation of a risk model (PRELANE score) to predict late recurrence based on a large multicenter database (CORONA/SATURN project). *Eur. Urol.* 2013; **64**: 472–7.
17 Kroeger N, Choueiri TK, Lee JL *et al.* Survival outcome and treatment response of patients with late relapse from renal cell carcinoma in the era of targeted therapy. *Eur. Urol.* 2014; **65**: 1086–92.
18 Kim SP, Weight CJ, Leibovich BC *et al.* Outcomes and clinicopathologic variables associated with late recurrence after nephrectomy for localized renal cell carcinoma. *Urology* 2011; **78**: 1101–6.
19 Miyao N, Naito S, Ozono S *et al.* Late recurrence of renal cell carcinoma: retrospective and collaborative study of the Japanese Society of Renal Cancer. *Urology* 2011; **77**: 379–84.
20 Trpkov K, Grignon DJ, Bonsib SM *et al.* Handling and staging of renal cell carcinoma: the International Society of Urological Pathology Consensus (ISUP) conference recommendations. *Am. J. Surg. Pathol.* 2013; **37**: 1505–17.
21 Delahunt B, Cheville JC, Martignoni G *et al.* The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. *Am. J. Surg. Pathol.* 2013; **37**: 1490–504.
22 Ballarin R, Spaggiari M, Cautero N *et al.* Pancreatic metastases from renal cell carcinoma: the state of the art. *World J. Gastroenterol.* 2011; **17**: 4747–56.
23 Beutner U, Leowardi C, Bork U *et al.* Survival after renal cell carcinoma metastasis to the thyroid: single center experience and systematic review of the literature. *Thyroid* 2015; **25**: 314–24.

Editorial Comment

Editorial Comment to Features, risk factors and clinical outcome of "very late" recurrences after surgery for localized renal carcinoma: A retrospective evaluation of a cohort with a minimum of 10 years of follow up

Late recurrence has been considered to be one of the unique behaviors of renal cell carcinoma (RCC). The present study was carried out to evaluate the features and risk factors of "very late" recurrences in RCC patients followed for a minimum 10 years of negative controls after curative surgery.[1] Of 554 patients treated in an Italian single center, "very late" recurrence was observed in 26 patients, and the pathological stage was shown to be the main predictor for late recurrence. Although the contralateral kidney was the most frequent site of recurrence in pT1 patients, multiple sites were more frequently observed in pT3 patients. The authors recommended a longer follow-up schedule for RCC patients based on the initial pathological stage of primary tumor.

As mentioned by the authors, the articles on "very late" recurrence of curatively resected RCC are rare. However, "very late" recurrences have been well-known in Japan, and are considered to be unremarkable events in RCC patients. Onishi *et al.* evaluated the clinical outcomes of 50 patients who survived for more than 10 years after nephrectomy carried out at the Jikei University Hospital and affiliated institutions.[2] Of these, recurrences were detected in four patients (8%) 10 years postoperatively. Miyao *et al.* also evaluated clinical features and outcomes of late recurrences observed in the Japanese multicenter collaborative database.[3] The frequency of "very late" recurrences was 6.4%, almost equal to the rate observed in the present study (4.6%).[1,3] Thus, "very late" recurrences might be relatively rare events, but have been shown to occur regardless of race. Furthermore, recurrences were detected as a solitary metastasis in 69% of 26 patients with "very late" recurrences in the present study (contralateral kidney in eight, lung in five, pancreas in four and thyroid in one).[1] Miyao's study reported similar results (87% of all recurrent patients; lung in 16, contralateral kidney in 11 etc.).[3] To these patients, metastasectomy is frequently recommended. When the lesion is relatively localized, metastasectomy might also contribute to an improved prognosis.[4] Naito *et al.* analyzed the prognosis of 559 Japanese metastatic RCC patients who had undergone metastasectomy, and reported that their prognosis was excellent, with a median overall survival of approximately 8 years.[5] In contrast, if early detection could not be carried out, disease progression occurs even in patients followed for a minimum 10 years of negative controls after curative surgery, and a chance of curative metastatectomy would be missed in these patients. There-

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