Paper IV

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Presumed Radically Treated Renal Cell Carcinoma

Recurrence of the Disease and Prognostic Factors for Subsequent Survival

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Objective: To gain knowledge about when, where and how metastases after presumed radical treatment for renal cell carcinoma (RCC) are detected, and to use this information to establish a follow-up programme for radically treated RCC. Further aims were to establish survival rates, together with identifying prognostic factors influencing survival for different groups of patients after recurrence of the disease.
Material and Methods: A retrospective study of 305 pT1-4N0M0/pT1-4NxM0 (clinically N0) tumours treated with nephrectomy was performed.
Results: A total of 89 patients (29.2%) developed metastases, with a median time to recurrence of 25.1 months. Within 5 years, 80% of the metastases had been detected. The lungs were the commonest metastatic site. A total of 34.8% of the recurrences were diagnosed as a result of routine follow-up. Median cancer-specific survival (CSS) after recurrence was 9.8 months. For patients with a disease-free interval (DFI) $\geq$24 months the median CSS was 35 months. In a univariate analysis, performance status, DFI $\geq$24 months, metastases in a single organ, primary tumour size $\leq$70 mm, primary tumour stage pT1-2 and age $<$65 years were all associated with better survival. In a multivariate analysis, performance status, DFI and number of organs affected were independent predictors of survival.
Conclusion: The information from this material is used to suggest a simple, but adequate, follow-up protocol. Easily accessible information can be used to identify groups with different prognoses regarding survival after recurrence of the disease.

Key words: follow-up, metastatic disease, renal cell carcinoma, survival.

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According to older literature, ≈50% of presumed radically treated patients with renal cell carcinoma (RCC) will develop metachronous metastases (1). During the last 5–7 years there have been several studies published on this topic. Most authors have used their data to establish guidelines for routine follow-up, and several different protocols have been suggested (2–4). There is a tendency towards more and more complicated protocols, and the first aim of this study was to investigate the possibility of simplifying the follow-up protocols. On searching the available medical databases, we found relatively few up-to-date reports on survival after detection of metastases. Hence another aim of this study was to investigate survival after detection of metastases. Finally, we tried to identify prognostic factors that influence the prospects for survival within this population of patients.

MATERIAL AND METHODS

The material consisted of 305 consecutive patients (181 males, 124 females; mean age 64.9 ± 11.7 years; range 15–91 years) treated with nephrectomy for RCC at Innlandet Hospital—Lillehammer (n = 146) between 1978 and 2000 and Aker University Hospital (n = 159) during the 20-year period 1978–97. The patients were pT1-4NxM0 (clinically N0)/pT1-4N0M0 at operation. Any pN+ or M+ patients were excluded.

The study was retrospective and all patient records were reviewed. Information about causes of death was collected from the patient records or from the national death certificates held by Statistics Norway.

Preoperatively, all patients were examined using chest X-ray or CT of the abdomen. However, for the older part of the material (20%), CT technology was not available and most tumours were detected using i.v. pyelography and the final preoperative diagnosis was made by means of selective renal angiography. Preoperative bone scans, cavagraphy, CT of the thorax and MRI were performed only where indicated.

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The type of surgical approach used was based on the surgeon's preference. However, the kidneys were removed together with perirenal fat and Gerota's fascia. Clinical N-staging was performed using a combination of the preoperative CT images of the abdomen and the peroperative findings. However, before CT became available, clinical N-status was determined using the peroperative findings alone. Throughout the entire study period, only enlarged regional lymph nodes were removed, i.e. no type of extensive lymph node dissection was performed.

The tumours were staged according to the TNM classification system (1997 revision of the International Union Against Cancer guidelines) (5). Tumour size was measured in the removed kidney specimens. In only a minority of the cases were a sufficient number of negative nodes (four to eight) to establish pN0 reported. Hence, >90% of the patients were pNx (clinically N0).

At both hospitals, most of the patients were followed according to the routine follow-up programme, which consisted of 6-monthly chest X-rays, physical examinations and blood tests at the hospital for a total of 5 years. A decision regarding further follow-up was based on the urologist's preference. Many patients have been followed for substantially more than 5 years. In addition, probably due to the very stable settlement patterns in the older age groups in Norway, only one patient was lost to follow-up (due to emigration), and most of the patients have been in contact with the hospital at some later date. Therefore, from the information in the patient records, the median follow-up time as of 1 April, 2003 for the surviving patients was 99 months (range 28–296 months).

In most cases, radiological investigations (chest X-ray, CT, ultrasound) were the tools with which metastatic lesions were diagnosed. However, some were found by means of clinical examination (i.e. local recurrence in the wound or skin metastases) or due to elevated blood test values (i.e. erythrocyte sedimentation rate, liver function tests). Biopsy for histopathological verification was performed when there was doubt concerning the diagnosis of metastasis.

The performance status (PS) at the time of detection of metastases was established retrospectively. This was possible due to specific information in the records (i.e. "the patient is fully bedridden", "the patient is not physically capable of self-care" or "the patient is still working full hours without any symptoms of the disease"). However, classification was limited to good or poor PS. In the following analysis, good PS corresponds to Eastern Cooperative Oncology Group (ECOG) groups 0 and 1, and poor PS to ECOG groups 2–4. For 9/89 patients with recurrence of the disease, PS could not be established.

Statistical analysis

For survival analysis the Kaplan–Meier survival estimates were used, and for comparison of survival between groups we used the log-rank test. For statistical analysis the Mann–Whitney U-test and χ^2 test were used. For multivariate analysis, Cox's proportional hazard model was used. $p \leq 0.05$ was considered statistically significant. The SPSS software package (version 11.0) was used to perform the calculations.

RESULTS

Recurrence

Of the 305 pT1-4N0M0/pT1-4NxM0 (clinically N0) patients, 89 (29.2%) were subsequently diagnosed with metastases. The median (range) time from nephrectomy to diagnosis of metastatic disease was 25.1 (1–203) months for the whole group. Table I shows these figures according to the respective primary stages.

A total of 23/89 patients (26%) were diagnosed with metastases within the first year after nephrectomy. The cumulative percentages were 48% within 2 years, 63% within 3 years, 80% within 5 years and 93% within 10 years. The risk of metachronous metastases was significantly higher for pT3 tumours than for pT1 and pT2 tumours combined ($p \leq 0.001$). The time to diagnosis of recurrence was significantly longer for pT2 than for pT3 tumours ($p = 0.005$) but there was no significant difference between pT1 and pT2 tumours. Of 66 patients with a disease-free interval (DFI) ≥10 years, six (9.1%) have so far been diagnosed with subsequent recurrences. Regarding pT2 tumours, 3/12 patients at risk (25%) developed metastases after 10 years.

Among the 89 patients, a total of 111 metastatic sites were located primarily. Pulmonary metastases were found in 38.2% of the patients, and the lungs were the commonest metastatic site. Table II shows the distribution of the metastatic locations according to the primary tumour stage. Recurrences >10 years post-

Table I. *Number of patients and interval to recurrence for the different stages after presumed radical treatment for pN0(X)M0 RCC*

Primary stage	*n*	No. (%) with metastases	Median (mean) [range] time to occurrence of metastases (months)
pT1N0(x)M0	108	14 (13.0)	40 (48) [8–149]
pT2N0(x)M0	45	13 (28.9)	47 (72) [9–203]
pT3aN0(x)M0	94	34 (36.2)	24 (33) [1–98]
pT3bN0(x)M0	54	25 (46.3)	19 (26) [1–156]
pT4N0(x)M0	4	3 (75)	55 (55) [43–67]
Total	305	89 (29.2)	25 (39) [1–203]

Table II. *Distribution of first and second metastases in 89 patients diagnosed with recurrence after presumed radical treatment for pN0(X)M0 RCC*

Site	T1 ($n = 14$)	T2 ($n = 13$)	T3A ($n = 34$)	T3B ($n = 25$)	T4 ($n = 3$)	Total ($n = 89$) (%)
Pulmonary	5	5	12	12	0	34 (38.2)
Liver	1	0	8	3	1	13 (14.6)
Bone	3	1	6	8	0	18 (20.2)
Intra-abdominal	0	2	1	0	0	3 (3.4)
Local recurrence	3	2	5	4	2	16 (18.0)
Brain	1	2	3	1	1	8 (9.0)
Others[a]	4	3	4	8	0	19 (21.3)
Total	17	15	39	36	4	111 (124.7)

[a] Includes vagina, testis, contralateral suprarenal gland or kidney, lymphatic system, skin.

Table III. *Reason for detection and interval to recurrence for the different stages after presumed radical treatment for pN0(X)M0 RCC*

Metastatic site	No. of patients			Median (mean) [range] time to diagnosis (months)	Reason for detection/suspicion of metastases at follow-up
	Symptoms	Follow-up	Total		
pT1-2					
Pulmonary	2	8	10	22 (52) [9–149]	Chest X-ray, $n = 8$
Bone	4		4	40 (40) [8–74]	
Liver	1		1	60 (60) [60]	
Intra-abdominal	1		1	203 (203) [203]	
Local recurrence	2		2	115 (115) [52–179]	
Brain	3		3	33 (27) [17–33]	
Other	4	2	6	48 (59) [16–122]	Phys. ex, $n = 1$; lab tests, $n = 1$
pT3-4					
Pulmonary	9	9	18	33 (42) [4–156]	Chest X-ray, $n = 9$
Bone	9	1	10	6 (14) [1–61]	Chest X-ray, $n = 1$
Liver	9	3	12	25 (33) [5–78]	Lab tests, $n = 2$; NIA, $n = 1$
Intra-abdominal	1		1	90 (90) [90]	
Local recurrence	5	3	8	7 (15) [1–43]	Phys. ex, $n = 1$; lab tests, $n = 1$; NIA, $n = 1$
Brain	2	1	3	28 (34) [6–67]	Phys. ex, $n = 1$
Other	6	4	3	24 (34) [1–90]	Phys. ex, $n = 2$; lab tests, $n = 1$

Phys. ex = physical examination; NIA = no information available.

nephrectomy had a similar distribution to earlier recurrences.

Metastatic lesions were diagnosed as a result of routine follow-up in 31 patients (34.8%), and due to symptoms in 58 (65.2%). Table III shows the location of the first metastasis, and the reason for detection. When the first metastasis was located in the lungs, 61% of metastases were found at routine follow-up. In contrast, of the patients who had their first metastasis in the bone, liver or brain, only 15% of metastases were found as a result of routine follow-up.

Of 37 patients with pT1 tumours <4.0 cm in diameter, 3 (8.1%) later developed distant metastases, all within 5 years post-nephrectomy.

More than 50% of patients only received palliative care after the progression of the disease. Table IV shows the number of patients who received different modalities of treatment after the diagnosis of recurrence.

Survival after detection of metastases

The survival rates for all the patients with metachronous metastases are shown in Fig. 1. The 1-, 3- and 5-year cancer-specific survival (CSS) rates were 46%, 30% and 14%, respectively. Overall survival (OS) rates were 44%, 28% and 11%, respectively (Fig. 1a).

Patients with metachronous metastases diagnosed ≥ 2 years after the primary operation (Group B) had significantly ($p < 0.001$) better CSS than those diagnosed within the first 2 years (Group A) (Fig. 1b). The 1-, 3- and 5-year CSS rates were 68%, 48% and 26% for Group B and 22%, 11% and 0 for Group A, respectively. The difference in OS between these groups was also highly significant ($p < 0.001$).

Patients with good PS had significantly better survival than those with poor PS ($p < 0.001$) (Fig. 1c).

Patients with metastases confined to a single organ system (i.e. the lungs, liver or skeletal system) had significantly better CSS than those with metastases in two or more organ systems ($p = 0.003$) (Fig. 1d).

Patients with primary tumour confined to the kidney (pT1-2) had better 1- and 3-year CSS after metastasis detection than patients with primary tumours not confined to the kidney (pT3-4) ($p = 0.03$).

Table IV. *Type of treatment after recurrence after presumed radical treatment for pN0(X)M0 RCC. The values shown represent numbers of patients*

Modality	Primary metastases	Secondary metastases
Surgery	17	
Pulmonary resection	6	
Liver resection	2	
Orthopaedic reconstruction	3	
Other resections[a]	6	
Radiation	8	2
Alone	8	
After orthopaedic reconstruction		2
Immunotherapy	2	3
Primary	2	
After surgery for metastases		3
Palliative care only	48	
Lack of data	14	
Total	89	5

[a] Includes pancreatoduodenectomy, orchiectomy and resection of a metachronous metastatic lesion in the remaining kidney.

Patients in whom the maximum size of the primary tumour did not exceed 70 mm had better CSS than those with larger tumours ($p = 0.044$). Patients aged <65 years at the time of metastasis detection had better CSS than older patients ($p = 0.014$).

There was a tendency towards poorer CSS if the metastases were situated in the liver, brain or bone, although the difference was not significant ($p = 0.11$).

Regarding parameters such as gender, detection of metastases in connection with routine follow-up ($n = 31$) or whether the primary tumour had been diagnosed incidentally ($n = 21$), no differences in CSS could be demonstrated.

Six patients were operated on for pulmonary metastases with surgical resections. Five patients were alive 36 months after metastasis detection, and three have so far survived for ≥ 60 months.

Multivariate analysis

PS, DFI and the number of organs with metastases were found to be independent prognostic factors for survival after progression. The results are listed in Table V.

DISCUSSION

A retrospective study will always have its disadvantages, and in this study the accuracy of the N- and M-staging might be questioned. However, the probability of finding lymph node metastasis when there is no pre- or peroperative suspicion is low (2–3%) (6, 7), even if extensive lymph node dissection is carried out. The removal of only enlarged or suspicious nodes seems to be in line with recommendations (6). Routine scintigraphy in patients without symptoms from the skeletal system is probably not worthwhile. Henriksson et al. (8) investigated 70 consecutive non-symptomatic RCC patients and did not reveal a single bone metastasis. Chest X-ray and CT will identify pulmonary and liver metastases, which together with the skeleton represent the commonest metastatic sites (1–4, 9). Hence, the accuracy of our primary N- and M-staging would seem to be trustworthy.

Metachronous metastases after radical surgery for RCC are reported to occur in 24–50% of cases. The 29.2% recurrence rate found in this study is in line with those reported earlier. The more widespread use of CT and ultrasound results in the detection of tumours which are asymptomatic, smaller and in a lower stage at the time of diagnosis. This phenomenon, described as "stage migration", and which is reported to occur worldwide (10–12), will probably decrease the overall number of RCC recurrences in the years to come.

Our study showed a longer median time to recurrence of the disease and a lower percentage of patients with recurrence before 3 years than others (63% and 72–85%, respectively) (2–4). The probable reason for this is the longer observation period in our study (median 99 months versus median 37–66 months) (2, 3).

The significant difference in DFI between pT2 and pT3 tumours is in line with a report by Levy et al. (2), who reported median times to metastasis of 32 and 17 months, respectively. Sandock et al. (4) reported the same tendency. However, their data are not directly comparable because they used the old (1992) TNM classification. Ljungberg et al. (3) and Levy et al. (2) reported the longest median DFI among pT1 tumours, in contrast to our study. However, the numbers of patients with pT1 tumours involved were small (five, eight and 14, respectively), so conclusions should be drawn with care. The time to recurrence among the patients with pT4 tumours was remarkably high. None of them were given adjuvant treatment, so no explanation has been found for this finding.

The proportions of recurrences in the pT1 (13%) and pT2 (29%) groups may be regarded as high. However, Levy et al. (2) reported a 27% recurrence rate in their pT2 group. We reported previously (13) 5-, 10- and 15-year CSS rates for these groups, which were comparable to those of other reports. However, the CSS for pT1 tumours tended to drop more with time in our material than in other reports. In addition, we also reported previously (14) lower 5- and 10-year CSS rates in the first decade of the study period. These findings might be due to the longer observation periods for the whole study and for the first decade, but could also be the result of understaging of these tumours due to the retrospective nature of the study and the

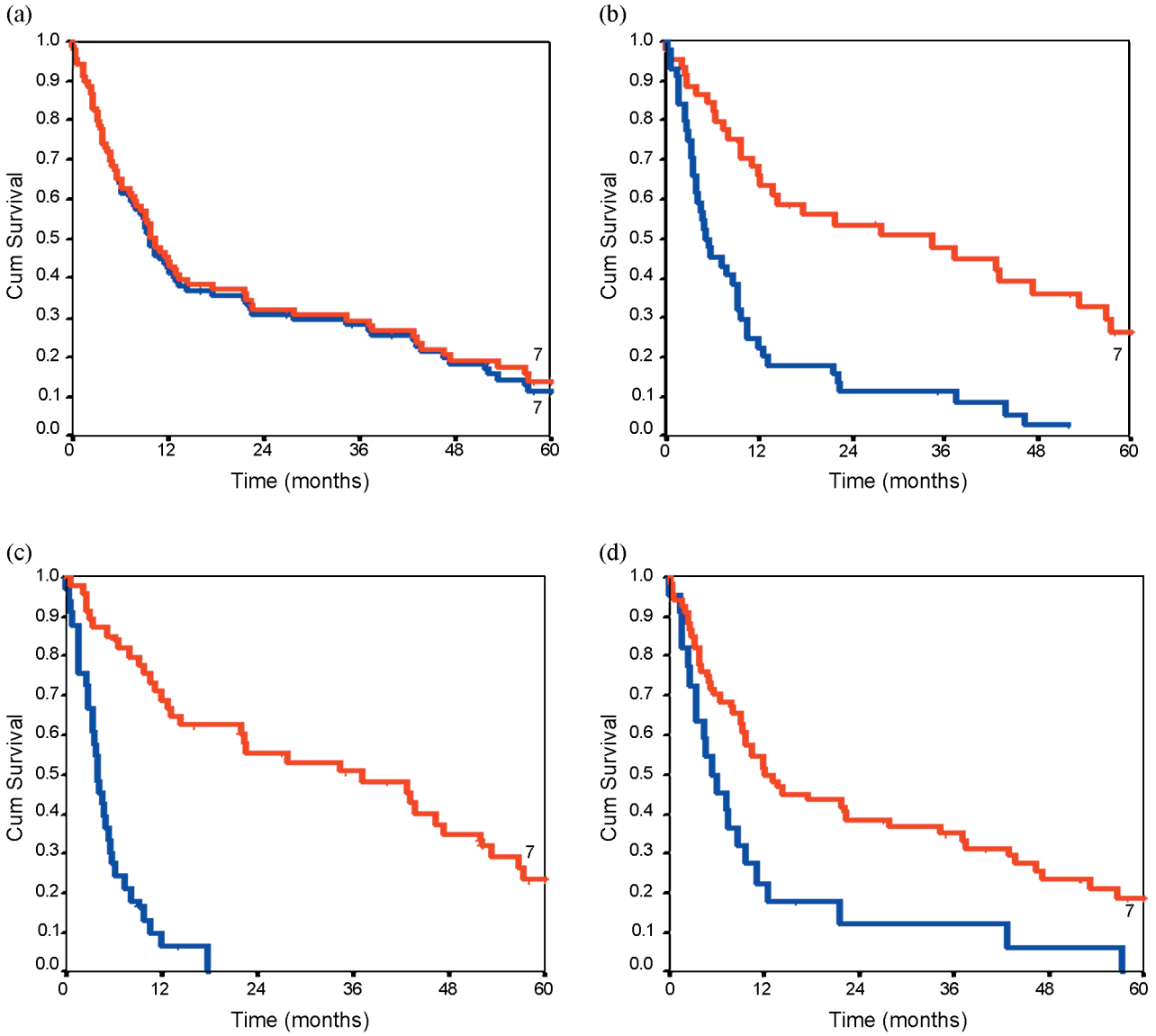

Fig. 1. (a) Kaplan–Meier survival curves for patients ($n = 89$) after detection of metastases (*red*, CSS; *blue*, OS). (b) Kaplan–Meier survival curves for patients with DFI ≥24 months (*red*; $n = 46$) and <24 months (*blue*; $n = 43$) ($p < 0.001$). (c) Kaplan–Meier survival curves for patients with good (*red*; $n = 47$) and poor (*blue*; $n = 33$) PS ($p < 0.001$). (d) Kaplan–Meier survival curves for patients with metastases to a single organ system (*red*; $n = 67$) and to two or more organ systems (*blue*; $n = 22$) ($p = 0.003$). All values shown represent patients still at risk.

Table V. *Results of Cox's proportional hazard model in 89 patients with metachronous metastases after presumed radical treatment for pN0(X)M0 RCC*

Factor	*p*	Exp (B)	95% CI for Exp (B)
DFI (cont. in months)	0.024	0.988	0.978–0.999
PS (good vs poor)	>0.001	0.167	0.078–0.355
Organs with metastases (single vs multiple)	0.01	0.407	0.206–0.805

improving preoperative radiological workup in this material.

The 9.1% risk of developing metastases >10 years after the primary operation found in our study is similar to results reported by McNichols et al. (15). No time-point has been established after which RCC patients may be considered free from the risk of recurrence.

The distribution of metastatic lesions in our study does not differ substantially from that reported elsewhere (1–4).

The median CSS of 9.8 months after detection of metastases in this study is in line with that given in previous reports (15). The DFI has been recognized as a prognostic factor by other authors (16, 17), but this view was opposed by Citterio et al. (18). Within the first years after nephrectomy, there seems to be better prognosis the longer the DFI. This aspect should be

Table VI. *Follow-up protocol for pN0(X)M0 RCC treated with radical nephrectomy*

Group	RCC stage (T1-4N0M0)	Follow-up recommendation after nephrectomy
1	pT1a	No routine follow-up
2	pT1b-pT2	Physical examination, chest X-ray and blood tests every 6 months for 3 years, thereafter yearly for 2 years
3	pT3-pT4	Same as Group 2, with additional abdominal CT at 6 and 12 months

taken into account when there is question of a possible metastasectomy.

The number of organs affected by metastases is prognostic regarding survival. This has also been shown in earlier reports, and probably reflects the total tumour burden on the patient. Solitary metastases are relatively uncommon in metastatic RCC. In a review by Kozlowski in 1994 (1), the incidence of solitary metastases was reported to be in the range 1.6–3.6%. Although solitary pulmonary metastases have better 5-year survival rates than multiple metastases, when treated with pulmonary resection, 5-year survival rates as high as 19% after resection for multiple pulmonary metastases have been reported (19). Patients with multiple metastases in one organ, in combination with other favourable prognostic factors, should therefore at least be considered for metastasectomy.

In our study, 34.8% of metastases were found as a result of follow-up procedures. In previous reports this proportion varied between 28% and 68% (2–4, 20).

Ljungberg et al. (3) diagnosed almost every pulmonary metastasis on routine chest X-ray, compared to only 26% in the case of Sandock et al. (4). In our study, 61% of metastases were diagnosed in this way, highlighting the value of chest X-ray in routine follow-up. The prolonged survival following metastasectomy for pulmonary metastases makes it the main follow-up procedure for RCC.

In our study, 85% of metastases to the liver, brain or bone were found as a result of symptoms; Ljungberg et al. (3) found a corresponding value of 100%. Therefore, routine follow-up investigations intending to reveal metastatic lesions in these organs do not seem to be indicated.

Local recurrence was the first metastasis found in 10 patients. In three patients with a primary pT3 tumour, local recurrence was found as a result of routine follow-up. Including CT in routine follow-up would seem to be indicated in high-risk patients (pT3), because long-term survival after radical resections of local recurrence can be achieved (21). In our study, the median time to local recurrence for pT3 tumours was 6.5 months. Routine CT at 6 and 12 months, as suggested by Ljungberg et al. (3), seems justified for the pT3 group.

In our study, 3 (8.1%) patients with pT1 tumours <4.0 cm in diameter developed distant metastases. Hafez et al. (20) demonstrated similar results after nephron-sparing surgery for pT1 tumours <2.5 cm in diameter. Ljungberg et al. (3) found no patients with subsequent metastases when pT1 tumours were <5.0 cm in diameter. Consequently, for pT1 tumours <4 cm in diameter (pT1a) treated with nephrectomy, routine follow-up is not cost-effective and should not be indicated.

A follow-up programme should be kept simple and should focus on those common metastatic sites where additional surgical or other treatment modalities can be offered to the patient. Furthermore, it should be cost-effective, both with regard to the amount of money spent and the time used for routine follow-up. Based on our study and earlier studies, we present our suggestion for a follow-up protocol in Table VI.

The overall risk of recurrence >5 years after nephrectomy was 11.5% in this study (18 recurrences after 5 years in 156 patients at risk). Using our figures for patients, recurrences and the percentage metastasis detection as a result of follow-up, a simple model was constructed to calculate how many follow-up visits were necessary to diagnose one patient with metastases. We found that with one yearly routine follow-up visit 5–10 years post-nephrectomy, 100–125 patients had to be examined in order to diagnose one with metastases. In addition, our study showed no survival benefit due to recurrence detection at routine follow-up. Hence, in our opinion, routine follow-up after 5 years is not indicated. However, patients should be informed of their approximately 1/10 chance of developing a subsequent recurrence.

CONCLUSIONS

Based on the information presented in this retrospective study, a simple, but adequate, follow-up protocol is suggested for routine use in everyday urological practice. Survival rates after recurrence of RCC have been established. Furthermore, we conclude that, on the basis on easily accessible information, patients with different prognoses for survival after the detection of metastases can be identified.

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