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ORIGINAL ARTICLE

Liver resection for metastatic disease prolongs survival in renal cell carcinoma: 12-year results from a retrospective comparative analysis

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Abstract The value of surgical resection of renal cell carcinoma (RCC) liver metastases still remains unclear.
Objective Of our study was to evaluate the efficacy of liver resection by comparing patients who could have undergone metastasectomy due to limited disease, but refused surgery.
Materials and methods Eighty-eight patients were identified with liver metastases and indication of surgery between 1995 and 2006. In 68 patients, liver resection was performed, 20 patients denied surgery and served as comparison group. Patients were followed for survival.
Results Median age was 58. Median amount of liver metastases was 2 (range 1–30). Median follow-up was 26 months (range 1–187). In both groups, 79% received systemic therapy. The 5-year overall survival rate (OSR-5) after metastasectomy was 62.2% ± 11.4% (SEM) with a median survival (MS) of 142 (95% confidence interval (CI) 115–169) months. OSR-5 in the control group was 29.3% ± 22.0% (SEM) with a MS of 27 (95% CI 16–38) months ($P = 0.003$). MS was 155 (95% CI 133–175) months with metachronous metastases compared to 29 (95% CI 25–33) months in the comparison group ($P = 0.001$). Low-grade primary RCC had a MS of 155 (95% CI 123–187) months compared to 29 (95% CI 8–50) months without resection ($P = 0.0036$). High-grade RCC as well as patients with synchronous metastases did not benefit from surgery.
Conclusions Liver metastasectomy is an independent valuable tool in the treatment of metastatic RCC and significantly prolongs patient's survival, even if further systemic treatment is necessary. With the evidence given, patients may benefit from liver metastasis resection if technically feasible.

Keywords Renal cell carcinoma · Surgery · Metastasectomy · Liver metastases · Resection · Survival

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Introduction

Renal cell cancer (RCC) has a rising incidence with an estimated 51,190 patients to be diagnosed with and 12,890 patients to die of cancer of the kidney and renal pelvis in 2007 in the United States. RCC is the most deadly urological malignancy with only 62% of the patients surviving 5 years in all stages [1]. Approximately 20–30% of patients present with synchronous metastatic disease at initial diagnosis, and 20–40% undergoing nephrectomy for clinically localized RCC will develop metastases [2]. Metastatic RCC has a poor prognosis as conventional therapy strategies such as chemotherapy, radiation or hormonal treatment have almost no influence on progression of this disease. Better results are achieved with anti-angiogenetic therapies, but the cure rate still is very low, with a median 5-year overall survival of approximately 20% [3]. Autopsy studies have shown hepatic involvement in metastatic RCC in 41% of the patients [4]. Treatment of liver metastases by surgery so far is uncommon, although survival could significantly be improved by surgery in lung metastasis [5, 6]. Despite

the great number of hepatectomies for metastatic disease, there are only four retrospective uncontrolled series of more than 10 patients reporting on RCC. Although some authors claimed prospective multicenter trials with matched controls without surgery, the value of liver metastasectomy in metastatic RCC still remained unclear [7, 8]. We evaluated the importance of partial liver resection in patients with technically resectable RCC liver metastases by comparing patients who could have undergone surgery, but refused the surgical approach.

Materials and methods

We retrospectively analyzed data from $n = 240$ patients in an institutional database of metastatic RCC patients who underwent resection of RCC metastases. We identified $n = 88$ patients with liver metastases as the only site of metastasis at our institution with the indication of liver surgery at administration between 1995 and 2006. In $n = 68$ patients, liver resection was performed, 20 patients declined surgery and served as comparative group. All 88 patients were offered surgery but 20 refused or declined surgery due to several reasons, not related with the underlying disease or the surgeon's decision. Surgery usually was performed as partial or wedge liver resection. Depending on the localization and the amount of the metastases, a left- or right-sided hemihepatectomy was performed if indicated. Prior to liver surgery, bone scintigraphy and computed tomography (CT) of thorax and abdomen as well as magnetic resonance imaging of the liver were performed.

Statistical analysis was carried out using the SPSS 17.0 statistics software. Survival analysis was done using the Kaplan–Meier estimation and the log rank test. Descriptive statistics were performed using the Pearson correlation coefficient and log rank testing. Multivariate analysis was performed according to the cox proportional hazard model.

Results

Median age at presentation was 58 (range 17–78). Of the patients, 65% ($n = 57$) were men and 35% ($n = 30$) were women. Oncological baseline parameters (Fuhrman, Grading, ECOG, Memorial Sloan Kettering Risk Score (MSKCC), synchronous/metachronous metastases, subsequent therapy) were not significantly different between the two patient groups (see Table 1). Median amount of liver metastases was 2 (range 1–30) with 36% of the patients having only one metastasis, 30% having two or three, 19% having between 4 and 10 and 14% having more than 10 liver metastases (see Table 1). Median follow-up was 26 months (range 1–187). Of the patients who underwent surgery, 79% ($n = 54$) received systemic therapy in the later course of their underlying disease. In the comparative group, this rate did not differ significantly from 79% of the patients getting systemic treatment. Systemic treatment was based on interferon-alpha s.c. and/or interleukin-2 s.c. Only few patients ($n = 5$) received multi-kinase inhibitors.

Liver resection was performed as wedge resetion ($n = 52$), segementectomy ($n = 26$), hemihepatectomy ($n = 15$) and extended hemihepatectomy ($n = 3$). In $n = 42$ patients, a regional lymphadenectomy (hepatoduodenal ligament) was performed. No patient died within 30 days after surgery. Morbidity of surgery was 20.1% ($n = 15$) caused by non-fatal secondary bleeding, bilary leackage, abcess formation, pleural effusion and paralytic ileus.

The overall survival rate at 5 years after metastasectomy was 62.2% $\pm$ 11.4% (SEM) with a median survival of 142 (95% confidence interval (CI) 115–169) months. The 5-year overall survival rate of the comparative group was significantly reduced to 29.3% $\pm$ 22.0% (SEM) with a median of 27 (95% CI 16–38) months ($P = 0.003$; Fig. 1).

Grading was a predictive factor of survival. Patients with low-grade (grade 1 and grade 2) primary RCC showed a significantly improved median survival following surgery with 155 (95% CI 123–187) months compared to 29 (95% CI 8–50) months in patients without resection ($P = 0.0036$). Interestingly, patients with high-grade (grade 3 and 4) primaries did not benefit from surgery with a median survival of 24 (95% CI 1–47) months versus 27 (95% CI 16–39) months in the comparative group ($P = 0.593$; Fig. 2).

Synchronous liver metastases at initial diagnosis were associated with a significantly lower survival than metachronous metastases. Median survival was 155 (95% CI 133–175) months with metachronous metastases and significantly longer after surgery compared to 29 (95% CI 25–33) months in the control group ($P = 0.001$). However, surgical resection of synchronous metastases did not significantly improve the median survival with 29 (95% CI 14–44) months when compared to 15 (95% CI 0–34) months ($P = 0.593$) in the comparative group.

Patients were divided into subgroups according to Eastern Cooperative Oncology Group Performance Status (ECOG) at initial diagnosis. An ECOG of 0 led to a significant better prognosis with a median survival of 155 (95% CI 126–184) months in patients after metastasectomy when compared to 31 (95% CI 20–42) months in the comparative group. With higher ECOG status, the median survival did not differ between the groups.

Multivariate analysis based on the cox proportional hazard model revealed that grading, lymph node status at initial diagnosis, metachronous vs. synchronous metastasis and ECOG performance status were statistically significant parameters for overall survival, as well as liver metastasectomy itself. Details are given in Table 2.

Table 1 Patients characteristics

	Metastasectomy (n = 68)		No Metastasectomy (n = 20)		Statistical difference
	Number	%	Number	%	P
Sex					
Male	44	65	11	55	0.43
Female	24	35	9	45	
MSKCC score					
Low	4	7	2	10	0.92
Intermediate	59	87	17	85	
High	4	6	1	5	
Histology					
Clear cell RCC	60	88	11	55	0.004
Papillary RCC	4	6	4	20	
Other	4	6	5	25	
Systemic therapy					
Yes	55	81	16	80	0.93
No	13	19	4	20	
Metastasis at initial diagnosis					
M1	19	28	8	40	0.08
M0	33	49	5	25	
Mx	16	24	7	35	
Grading of RCC					
G1	3	4	0	50	0.08
G2	45	66	10	50	
G3/4	19	28	10		
No of metastastic lesions in liver					
1	26	38	6	30	0.07
2 + 3	21	31	5	25	
4–10	15	22	6	30	
>10	6	9	3	15	

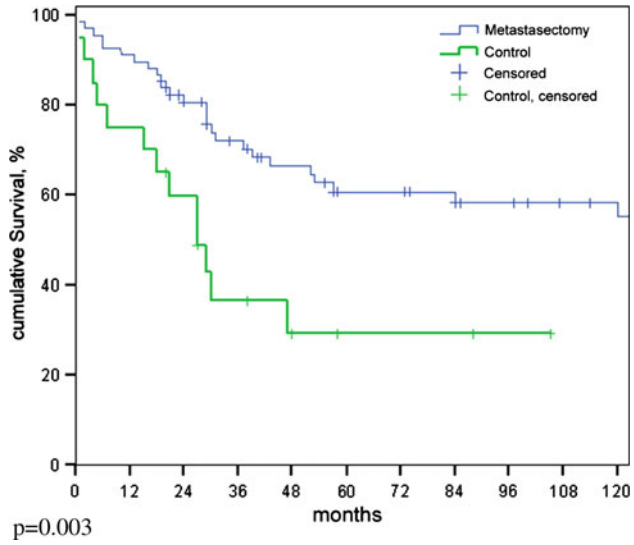

Fig. 1 Kaplan–Meier survival curves for patients with liver metastases

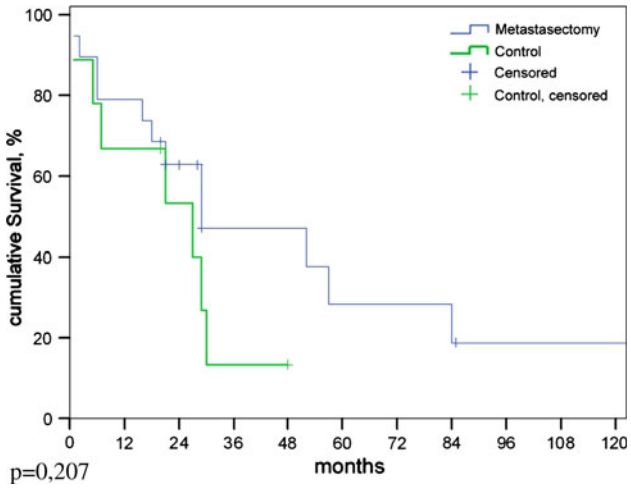

Fig. 2 Kaplan–Meier survival curves according to high-grade primary RCC (G3 and G4)

Table 2 Multivariate Cox proportional hazard for predicting overall survival

	Hazard ratio	95% Confidence interval	Significance (*P*)
Fuhrman Grading	2.568	1.238–5.329	0.011
Initial *T*-stage	3.712	1.44–9.552	0.007
Meta- vs. synchronous metastases	1.967	0.907–4.244	0.087
ECOG performance status 0 vs. ≥1	3.763	1.777–7.972	0.001
Metastasectomy yes vs. no	2.23	1.054–4.719	0.036

Discussion

Modern surgical techniques have rendered liver resection, a procedure with a low mortality of 0–2% and reasonable morbidity of no more than 33% with, in some series, experience of up to 1,452 patients [8–12]. In older series, mortality was up to 30% of the patients, proofing that resection of liver metastases from solid tumors should be limited to centers of excellence [7].

In historic series of liver resection, the median survival for patients with mRCC was 16–48 months with a 5-year overall survival rate between 8% and 38.9%. Follow-up in these series was up to 29 months [9, 13–15]. Of course, these data are based on relatively small numbers of patients with 13–31 individuals without relevant control groups.

In contrast, our comparative data proof a median survival of 142 months with a median 5-year overall survival rate of 62.6% and a median follow-up of 26 months. The comparative group had a significantly lower survival with 27 months and 29.3%, respectively. As the only comparative series published, our achieved data indeed resemble the best historical results for those patients with mRCC who underwent partial liver resection. The long median survival could be influenced by the high proportion of patients receiving systemic therapy in the later course of the disease, but with the same proportion of patients treated systemically in the comparative group, the difference in the survival rate in the two groups is clearly an expression of the efficacy of liver resection.

Prognostic factors so far were determined to be negative surgical margins with complete resection of all masses, a long disease-free interval (DFI) from initial diagnosis of RCC, extrahepatic metastases, major hepatectomy and a left sided primary [8, 9, 11, 12, 14–17]. The same prognostic factors seem to be applicable for RCCs with direct hepatic involvement [18, 19]. We identified grading and performance status as further prognostic factors and a trend toward clear cell histology being related to a longer survival than other subtypes of RCC.

Indication for resection of liver metastases so far was seen, if complete resection seemed to be achievable, and DFI was longer than 6 months or 2 years, respectively [11, 16]. Selection criteria for patients were not clearly defined, with some authors supporting a very wide indication in RCC and others restricting it to those patients, who initially tend to have a better prognosis as discussed above [8, 10, 11]. A French cohort of 41 centers developed a prognostic model based on age >60, histology (non-breast, melanoma, squamous cancer versus others), extrahepatic metastases, major hepatectomy and resection status to stratify patients [12] (Table 3). However, especially in RCC even older patients and patients who had extrahepatic metastases will surely benefit from resection. Thus, surgical feasibility seems to be the only restricting parameter for patient selection in metastatic RCC.

The present study represents the only series in the literature that compares two groups of patients with liver metastases to estimate the effect of metastasectomy. Our survival rates of the patients with mRCC following surgery are the most favorable results reported so far. The long-term results are not inferior to survival rates achieved with liver resection in patients with metastases from colorectal cancer.

Our series of patients adds fundamental new aspects. As the largest comparative series, it surely proofs surgery to be an independent factor for patient's survival. With a similar rate of patients who underwent systemic therapy in the further course of disease, the effects of this medical regimen

Table 3 Comparison of results after liver metastasectomy in RCC

Author	*n*	Median survival (months)	5-year overall survival rate	Prognostic factors	Limitations
Thelen [14]	31	48	38.9%	Resection margin, disease-free interval, left- vs. right-sided primary	
Alves [15]	14	26	26% (3 years)	Disease-free interval	4 patients without RCC
Lang [9]	13	25	8%	Resection margin	
Stief [7]	17	16	–		4 patients no surgery
This series	68	142	62.2%	ECOG, disease-free interval, grading	

are eliminated in the analysis of the data. Metastasectomy bares a high potential for long-term curative treatment. Our series therefore proofs the value of surgery in the treatment of hepatic metastases of RCC.

Conclusions

With this first comparative analysis of the efficacy of liver resection for metastases, we could demonstrate surgery to be an independent valuable tool in the treatment of metastatic RCC. Resection of liver metastases significantly prolongs patient's survival in patients with low or intermediate Fuhrman grading, even if further systemic treatment is necessary. Therefore, it might be regarded first-line treatment in singular metastases and should similarly be considered in cases of multiple lesions as long as complete resection is achievable. Even in patients with more than one organ manifestation of metastases, liver metastasectomy should be performed.

Conflict of interest statement None.

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