

Outcome after Resection of Hepatic and Pulmonary Metastases of Colorectal Cancer

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Abstract

Introduction Multimodal therapies (especially surgery of metastases and “aggressive” chemotherapy) in patients with metastases of colorectal cancers (CRC) are increasingly performed and may provide long-term survival in selected patients with more than one location of metastases. In the current literature, there are only few studies with relatively low patient numbers reporting on the outcome after resection of both hepatic and pulmonary metastases of CRC. We therefore evaluated survival of patients who underwent sequential resection of hepatic and pulmonary metastases under potentially curative intention.

Material and Methods From 1987 until 2006, 44 patients (32% female; median age, 58 years) with hepatic and pulmonary CRC metastases underwent resections at both metastatic sites. The primary CRCs were in 50% rectal and in 50% colonic carcinomas (61% node positive, all with free resection margins). Metastases occurred synchronously (regarding primary CRC) in 32% of the patients. In 86%, liver resection was performed prior to pulmonary resection. The first resection of metastases was performed a median of 16 months after resection of the primary CRC; the median interval between the first and the second resection of metastases was 7 months. Forty-seven percent of the patients also underwent at least a third metastasectomy. During resection of the first and second site of metastases, free margins were achieved in 98% and 95%, respectively. Survival analysis was performed using Kaplan–Meier and Cox regression methods.

Results The 5-year survival rates (SV) were 64% after initial surgery of CRC, 42% after the first resection of metastases, and 27% after the last metastasectomy. Patients with synchronous metastases had a 5-year SV after first metastasectomy of 43% and in patients with metachronous metastases of 41% (n.s.). The location of the primary tumor (20% 5-year SV in rectal vs. 57% in colonic cancer; $p < 0.02$) and the lung as primary site of metastatic disease (5-year SV 0% vs. 60% in patients with primarily hepatic metastases only; $p < 0.001$) significantly influenced survival in univariate analysis. Patients with rectal cancer had a significantly higher frequency of the lung as first metastatic site (46%) compared to patients with colonic cancer (14%; $p < 0.03$). Multivariate survival analysis revealed the lung as first metastatic site and as the sole significant independent factor for the outcome ($p < 0.001$; relative risk vs. liver first metastases 4.7).

Dedicated to Eva Fischer (died 2008).

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Conclusion In selected patients with metastasized CRC resection of both hepatic and pulmonary metastases may improve survival rates or even provide long-term survival. Patients with lung as the first site of metastatic disease (either lung only or in combination with hepatic metastases) have a significantly worse outcome than patients with metastases primarily confined to the liver.

Keywords Colorectal cancer · Liver metastases · Pulmonary metastases · Surgery · Survival

Introduction

The liver and the lung are the most frequent sites of metastases of colorectal cancer (CRC). During the last two decades, liver surgery for CRC metastases evolved in many centers with several of them reporting more than 400 resections.^{1–6} Perioperative mortality has been reported to be clearly below 5%.^{6–9} Most important, however, is the fact that curative resection of isolated liver metastases may achieve long-term survival in many of those patients, with current 5-year survival rates of up to 58%. As for isolated liver metastases, resection may also be beneficial in selected patients with pulmonary metastases. Since the early 1990s, several larger series have reported 5-year survival rates of higher than 50% after resection of isolated lung metastasis.¹⁰ In patients eventually presenting with both hepatic and pulmonary metastases, the role of surgery is less well defined as in patients with a single metastatic site. Regarding the literature, there are only five articles reporting the outcome of more than 30 patients,^{11–14} including only one with more than 100 patients.¹⁵

The aim of this study was to analyze the experience with 44 patients who underwent both hepatic and pulmonary resection for CRC metastases at our institution during a 20-year period.

Material and Methods

Patients undergoing resection of both hepatic and pulmonary metastases at our institution between 1987 and 2006 were identified in the hospital information system using the International Classification of Disease and procedure codes. The detailed information required for our analyses was then mainly gained by retrospective chart reviews. In addition, further data were retrieved from our prospective hepatic surgery database (data included since 1996). Data principally assessed were patient demographics, time point of treatment, type of surgical treatment, tumor characteristics, neo-/adjuvant therapy, and survival. Survival information was obtained from the tumor registry at the Comprehensive Cancer Center at the University Hospital Freiburg. Our analysis included 44 patients whose primary colorectal tumor had been resected at our as well as other institutions

(who were then referred to our center for the treatment of metastatic disease). In all patients, complete information regarding the primary CRC and further surgical treatment were available. Synchronous metastatic disease in this series was defined as the presence of metastases at the time of resection of the primary CRC. The patient demographics and tumor characteristics at the time of first CRC resection are shown in Table 1.

Patient selection for resectional treatment was done individually. There were not always predefined criteria or algorithms applied in our institutions. Until 2004, no strict internal protocol of staging procedures and or neoadjuvant/adjuvant therapy was followed. Patients were, in general, treated according to the current guidelines of the German Cancer Society. Since 2004, patients with CRC (including metastatic disease) are treated according to internal guidelines of our Comprehensive Cancer Center after case presentation and discussion in the interdisciplinary tumor board. In general, the indication for metastasectomy was

Table 1 Patient Demographics and Tumor Characteristics in 44 Patients at the Time of First Colorectal Cancer (CRC) Resection

	Number of patients	Percent
Gender		
Male	30	68
Female	14	32
Location of primary CRC		
Colon	22	50
Rectum	22	50
Nodal status of primary CRC		
Node-positive	28	63
Node-negative	16	37
Grading primary CRC		
G1	–	–
G2	34	77
G3	5	11
G4	–	–
Unknown	5	11
Free margins CRC resection	44	100
T stage		
T 1	–	–
T 2	6	14
T 3	34	77
T 4	4	9
Median age; years (range)	58 (38–71)	

given when preoperative staging indicated that margin-negative resections were achievable in patients otherwise fit to undergo (major) surgery. In the presence of simultaneous hepatic and pulmonary metastases, hepatic resection was done prior to pulmonary resection at our institution.

The extent of liver resection was defined as wedge or segmental resection, hemihepatectomy, or extended hemihepatectomy. Hemihepatectomy was referred to as resection of Couinaud's segments 5–8 (right) or 2–4 (left). Extended hemihepatectomy was referred to as resection of segments 4–8 (extended right hemihepatectomy) or 2–5 plus 8 (extended left hemihepatectomy).¹⁶ The extent of pulmonary resection was defined as wedge resection (including segmentectomy), lobectomy or pneumonectomy. Actuarial survival was calculated for the whole patient group after resection of the primary CRC, after the first metastasectomy and after the last resection of a metastatic lesion. Various parameters like the site of primary colorectal disease, primary nodal disease, synchronous vs. metachronous metastatic disease, site of first metastases, and others were assessed regarding their influence on survival after first metastasectomy.

Actuarial survival was estimated by the Kaplan–Meier method using SPSS® for Windows™ (version 15.0, Chicago, IL, USA). In subgroup analyses differences between groups were assessed by a log-rank test. Multivariate survival analysis was performed using the Cox proportional hazard model.

Results

In 31 of the 44 patients (70%), the liver was the first site of metastatic CRC (without lung metastases); six patients (14%) presented with lung first metastases and seven patients (16%) had both lung and liver disease at first diagnosis of metastatic disease. The site of first metastases correlated significantly with the location of primary CRC: Of the 22 patients with rectal cancer, ten (46%) presented with lung first metastases (lung or lung plus liver), whereas only three of the 22 patients (14%) with colonic cancer had lung first metastases ($p < 0.03$).

In the 44 patients of our study, a total of 155 resectional procedures (including resection of the primary CRC; mean, 3.5 per patient) ranging from two (initially simultaneous colonic resection plus metastasectomy) to six per patient were performed (Table 2). In five cases, a resection of liver metastases was performed simultaneously with the resection of the colonic primary tumor. In all other 39 patients, the first metastasectomies were performed as either staged procedures (synchronous metastases) after resection of the primary or after later detection of the metastases (metachronous metastases). In 86%, liver resection was the first metastasectomy. Four of the 111 resectional procedures after

Table 2 One Hundred Seventeen Resections Performed During 112 Metastasectomies (Five Patients Simultaneously had Resection of Hepatic and Pulmonary Metastases During One Operation)

	Number of patients
Hepatic resections	60
Wedge resection	18
Resection of one segment	13
Resection 2–3 segments	4
Hemihpatectomy	16
Extended hemihpatectomy	9
Pulmonary resections	57
Wedge resection	48
Lobectomy	6
Resection of 2 lobes (bilobectomy)	2
Pneumonectomy	1

the initial operation were colorectal re-resections (without metastasectomy) for recurrent locoregional disease. During five metastasectomies (three times at first metastasectomy and twice at second metastasectomy), resection was simultaneously performed at both sites (liver and lung). The other 107 metastasectomies were undertaken at “only” one site for either hepatic or pulmonary metastases. After their initial metastasectomy in the liver and lung, 21 of the 44 patients (48%) underwent at least one further metastasectomy. Median follow-up after resection of the primary CRC was 4.9 years (range, 1.2–14.8) and 3.3 (0.5–14.2) years after first metastasectomy.

Surgical Treatment

The procedures performed during the 112 metastasectomies are given in Table 2. For liver metastases, “larger” resections (multiple segments, hemihepatectomy, and extended hemihepatectomy) were performed in about half of the patients, whereas the vast majority of pulmonary metastasectomies consisted of wedge resections. Three patients had simultaneous (one stage) bilateral procedures of the liver, and seven patients underwent simultaneous bilateral pulmonary resections.

During the initial removal of metastases, free resection margins were achieved in 43 of 44 patients (98%) at the first site and in 42 of 44 (95%) patients at the second site of metastases. The median number of resected metastases during first metastasectomy was one (range, 1–5). Twenty-six patients had one metastasis, ten patients had two, five patients had three, one patient had four, and one five metastases removed initially (number unknown in one patient). Two patients underwent local ablation (one cryotherapy and one thermoablation) of a liver metastasis in addition to resection.

Additional Treatment

A total of 35 of the 44 patients (80%) received chemotherapy between the time of initial diagnosis of CRC and last surgery. Five patients received 5-FU-based chemotherapy as a part of neoadjuvant or adjuvant chemoradiation of rectal cancers. Twenty patients received 5-FU-based adjuvant chemotherapy after resection of their primary CRC, but the exact type and number of cycles was not available in all of those. Before the first metastasectomy, four further patients received oxaliplatin-based ($n=3$) or irinotecan-based ($n=1$) chemotherapy under initially palliative or neoadjuvant intention. The remaining six patients received an irinotecan-based ($n=3$) or oxaliplatin-based ($n=3$) chemotherapy after their first metastasectomy. After their last metastasectomy, most patients were followed and treated by external oncologists. We, therefore, could not obtain reliable data on chemotherapeutic regimens administered after last metastasectomy (most of those eventually under palliative intention) by our retrospective analysis.

Survival

During the median follow-up of almost 5 years after initial surgery for CRC, 25 of the 44 patients died. Up to now, three patients are alive for more than 10 years after their first metastasectomy (10, 11, and 14 years, respectively). Cumulative five-year survival rates were 64% after initial surgery for CRC (Fig. 1), 42% after first metastasectomy (Fig. 2), and 27% after the last metastasectomy. The detailed univariate subgroup survival analyses after first metastasectomy are given in Table 3. Patients with colonic cancer had a significant better survival after their first metastasectomy than patients with rectal cancer ($p<0.02$; Fig. 3). In patients with lung as the first metastatic site

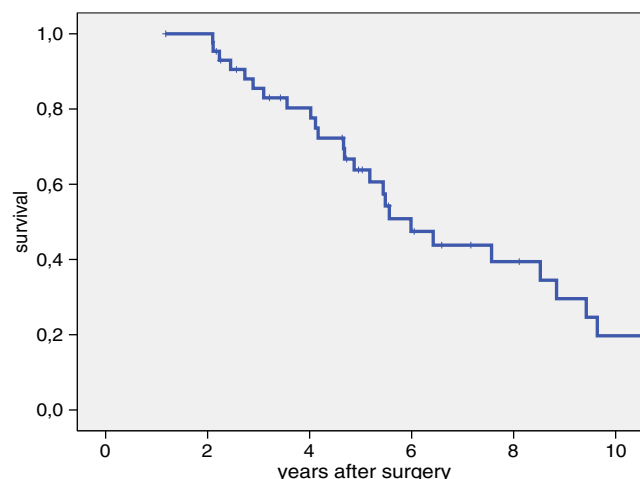


Figure 1 Actuarial survival after resection of the colorectal primary ($n=44$).

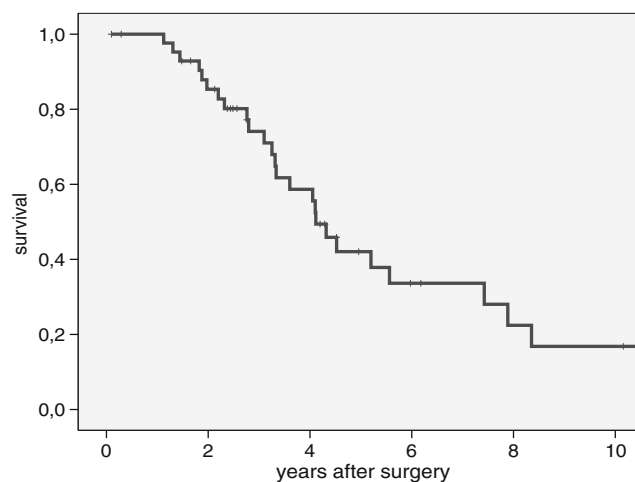


Figure 2 Actuarial survival after resection of the first metastasis ($n=44$).

($n=13$, including seven patients with synchronous lung and liver metastases), actuarial 5-year survival was 0%, whereas 5-year survival was 60% in the 31 patients with liver metastases only as the first metastatic site ($p<0.001$; Table 3 and Fig. 4). In the subgroup of patients with lung first metastases, survival was not influenced by the presence of additional liver metastases. In both the group of patients with lung first ($n=6$) and the group of patients with synchronous lung and liver first metastases ($n=7$), the last patient at risk died in the fifth year after first metastasectomy (Table 3). The nodal status of the primary CRC did not significantly influence survival after first metastasectomy. Further factors like gender, age, time interval (synchronous vs. metachronous), number of metastases initially resected, and chemotherapy administered also did not correlate with survival (Table 3). Survival in the subgroup of patients with only one metastasectomy per site (i.e., one liver and one lung resection; $n=23$) and in the subgroup of patients with more than two metastasectomies ($n=21$) was comparable (5-year survival 40% and 42%, respectively; $p=0.34$).

The lung as the site of first metastasis (lung or lung and liver) was the sole and very strong prognostic factor influencing survival in multivariate analysis ($p<0.001$; relative risk compared to liver first metastases, 4.7; 95% confidence interval, 1.9–11.8).

Discussion

Published series reporting the outcome after resection of both hepatic and pulmonary colorectal metastases including relevant numbers of patients are rare.^{11–15} In addition, the results of most studies (including our series) are somewhat limited by the retrospective nature and a long inclusion period (with evolving diagnostic and treatment modalities).

Table 3 Univariate Actuarial Survival Analysis in 44 Patients After First Metastasectomy of Hepatic or Pulmonary Colorectal Metastases

Parameter	Number of patients	3 years (%)	5 years (%)	10 years (%)	<i>p</i> value
Gender					
Male	30	84	49	16	0.37
Female	14	56	32	24	
Age (first operation)					
<60 years	26	69	40	17	0.85
≥60 years	18	83	46	17	
Site of first metastases					
Liver only	31	82	60	24	0.001
Lung only	6	80	0	0	
Liver and lung	7	43	0	0	
Site of first metastases					
Liver only	31	82	60	24	0.001
Lung/liver and lung	13	54	0	0	
Site of primary tumor					
Rectum	22	61	20	0	0.01
Colon	22	85	57	30	
Time of first metastasis					
Synchronous	14	76	43	–	0.93
Metachronous	30	73	41	18	
Nodal status primary tumor					
Positive	28	67	37	7	0.14
Negative	16	87	52	35	
Number of metastases ^{a,b}					
1	26	74	37	20	0.52
>1	17	72	54	14	
Chemotherapy ^b					
Yes	34	77	42	13	0.74
No	9	63	47	47	
All patients	44	74	42	17	

The numbers of patients at risk was 24 (3 years), ten (5 years), and three (10 years)

^a At time of first metastasectomy

^b Unknown in one patient

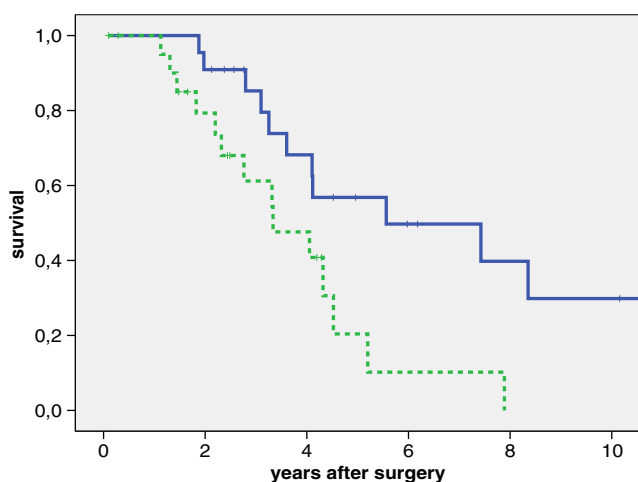


Figure 3 Subgroup survival analysis after resection of the first metastasis by location of the primary CRC. *Continuous line* colon cancer, *dotted line* rectal cancer (*p*=0.013; log-rank test).

The study by Miller et al.¹⁵ from the Memorial Sloan Kettering Cancer Center reporting the results of 131 patients is the only one including more than 60 patients. Our study is the first from our country assessing the results of more than 30 patients after resection of hepatic and pulmonary metastases. The fact that “only” 44 patients were resected at both sites during a period of almost 20 years demonstrates the relative rare indication for these procedures, at least during the past.

Five-year survival after the first metastasectomy was 42% in our patients. Ten-year survival was “only” 17%. However, the fact that we already observed three patients surviving more than 10 years after metastasectomy underlines the possibility of definitive cure by these procedures in selected patients.

Published survival rates of larger studies (Table 4) show large variations of 5-year survival after metastasectomy ranging between 11% and 74%. However, these results are difficult to compare due to different patient selection and

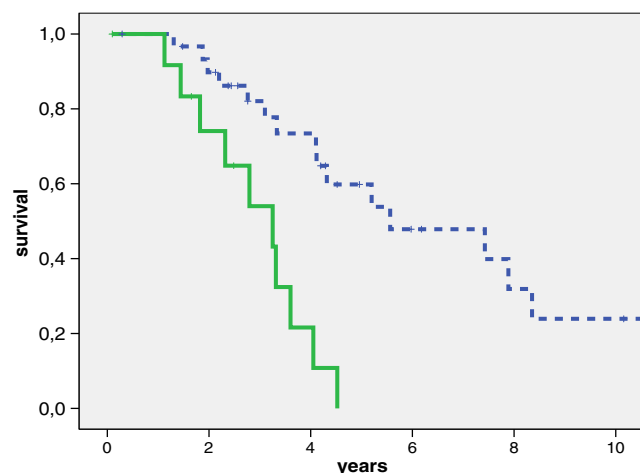


Figure 4 Subgroup survival analysis after resection of the first metastasis by site of the first metastases. *Continuous line* lung first metastases ($n=13$, including seven patients with additional hepatic metastases), *dotted line* liver first metastases ($n=31$; $p<0.001$; log-rank test).

different time points of the calculation of survival (some studies calculated after first metastasectomy, others after first pulmonary resection, see footnotes of Table 4). The reported survival rates after resection of hepatic and pulmonary metastases are in the range of current outcomes after resection of hepatic metastases alone.^{2,3,5,17} Current 5-year survival after resection of CRC liver metastases since 1998 was 46% in our own institution ($n=214$; data not shown).

In contrast to the outcomes after resection of primary CRC, of isolated liver metastases,^{2,3,5,17} or of isolated pulmonary metastases,^{18–21} only few data are known to predict prognosis after resection of both hepatic and pulmonary metastases. The main reason for this is clearly the low number of evaluated patients. In the (only) larger series from the Memorial Sloan Kettering Cancer Center, Miller et al.¹⁵ could demonstrate that a longer disease-free interval after first metastasectomy, the presence of only one liver metastasis, and a younger age were associated with a

better outcome. In the second largest series reporting 58 patients, by contrast, Headrick et al.¹¹ from the Mayo Clinic identified the carcinoembryonic antigen level before metastasectomy as the sole prognostic factor. In our evaluations, we found that patients with lung first metastases (including patients with concomitant liver metastases) had a significantly worse outcome than patients presenting with liver metastases only as the first metastatic site. This clear prognostic difference might partially be explained by a higher rate of lung first metastases in patients with rectal cancer. A possible explanation for this prognostic finding, which has not been described as in the other series, is the route of venous tumor cell dissemination from the primary CRC (possible systemic venous drainage in lower rectal cancers vs. portal venous drainage in colonic cancers). It is of note that the groups of patients with rectal or colonic cancer were comparable regarding other potential risk factors like the time interval of the occurrence of metastasis (synchronous vs. metachronous) or the frequency of primary nodal disease.

Metastatic involvement of more than one organ is often believed to represent disseminated disease, which contributes to the reluctance in proposing metastasectomy. Since data are still scarce, it is difficult to define whether metastasectomy should be offered in the presence of multiple sites of metastatic disease. In the presence of isolated hepatic metastases, in contrast, prognostic factors and scores have been derived from large series.^{2,3,17} There are arguments, however, that may favor a more aggressive approach with current treatment modalities in patients with more than one metastatic site: Very low mortality rates after hepatic and pulmonary resections in experienced centers have made those resections safe during the last two decades.^{6–9,18–21} It has also been shown that selected patients with hepatic and extrahepatic disease²² or even with peritoneal carcinosis²³ may benefit from surgical resection. More importantly modern chemotherapeutic regimens (including oxaliplatin, irinotecan, and targeted

Table 4 Outcome Results of Selected Published Series After Resection of Hepatic and Pulmonary Colorectal Metastases

Author	Year	Number of patient	5-year survival after primary CRC	5-year survival after 1st metastasectomy
Miller et al. ¹⁵	2007	131	65%	49%
Shah et al. ¹⁴	2006	39	84%	74%
Headrick et al. ¹¹	2001	58	–	30% ^a
Kobayashi et al. ¹²	1999	47	–	22%/50% ^b
Regnard et al. ¹³	1998	43	64%	11% ^c
Own results	2009	44		42%

^a After first lung resection

^b Twenty-two percent in synchronous hepatic and pulmonary metastases, 50% in sequential (hepatic followed by pulmonary) metastases

^c After first lung resection (=second metastasectomy)

therapy with antibodies such as bevacizumab/cetuximab) have been shown to better control or even downstage metastatic disease to render a subset of patients resectable.^{24–26} In addition to possible effective downstaging or downsizing, the early response evaluation after intensive chemotherapy given for metastatic disease may further delineate the potential biological behavior of the disease and may help select patients for metastasectomy. In this context, it might also be helpful to study the role of newer imaging modalities like positron emission tomography (PET) in disease and response assessment in patients with multiple site CRC metastases.²⁷

As already outlined above, the indication for metastasectomy was potentially given in our experience when preoperative staging indicated that margin-negative resections were achievable in patients otherwise fit to undergo surgery. Although prognosis is worse in subgroups (e.g., patients with lung first or synchronous hepatopulmonary metastases, with multiple metastases or a short disease-free interval after first metastasectomy), surgery should still be offered to those patients with good biology (e.g., response to systemic chemotherapy, younger age, and low perioperative risk) when an R0 resection can be obtained.

Conclusion

We conclude that resection of both hepatic and pulmonary metastases may prolong survival in selected patients with CRC. However, patients with lung as the first site of metastatic disease (more frequent in rectal cancer) clearly have a poorer outcome than patients with metastases primarily confined to the liver. Further studies should be performed to define the exact role of combined metastasectomy in the context of modern chemotherapeutic (e.g., targeted therapy) and staging (e.g., PET) modalities.

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