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Survival after Lung Metastasectomy in Colorectal Cancer Patients with Previously Resected Liver Metastases

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Abstract
Background Resection of hepatic metastases is indicated in selected stage IV colorectal cancer (CRC) patients. A minority will eventually develop pulmonary metastases and may undergo lung surgery with curative intent. The aims of the present study were to assess clinical outcome and identify parameters predicting survival after pulmonary metastasectomy in patients who underwent prior resection of hepatic CRC metastases.
Methods We performed a retrospective analysis of 27 consecutive patients (median age 62 years; range: 33–75 years) who underwent resection of pulmonary metastases after previous hepatic metastasectomy from CRC in two institutions from 1996 to 2009. All patients underwent complete resection (R0) for both colorectal and hepatic metastases.
Results Median follow-up was 32 months (range: 3–69 months) after resection of lung metastases and 65 months (range: 19–146 months) after resection of primary CRC. Three- and 5-year overall survival rates after lung surgery were 56 and 39%, respectively, and median survival was 46 months (95% CI 35–57). Median disease-free survival after pulmonary metastasectomy was 13 months (95% CI 5–21). At the time of last follow-up, seven patients (26%) had no evidence of recurrent disease and 6 of these 7 patients presented initially with a single lung metastasis.
Conclusions Resection of lung metastases from CRC patients may result in prolonged survival, even after previous hepatic metastasectomy. Yet, prolonged disease-free survival remains the exception, and seems to occur only in patients with a single lung lesion.

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Introduction

Liver and lung are the most frequent sites of metastases from colorectal cancer (CRC). Up to 25% of colorectal cancer (CRC) patients initially present with metastatic disease, usually confined to the liver, and another 25% of patients will develop metachronous liver metastases after primary tumor resection [1, 2]. Pulmonary metastases develop in 8–10% of CRC patients, and may occur after previous liver metastases [3, 4]. Although several novel chemotherapeutic and biological agents have been developed, surgery is considered the most effective therapy for selected patients with liver metastases [5]. Specialized

centers have reported 5-year survival rates up to 50% after liver resection for CRC metastases [6, 7]. Similarly, surgical resection of synchronous or metachronous pulmonary metastases has gained increased acceptance. Since 2000, multiple series have investigated the outcome of CRC patients who underwent resection of lung metastasis, with 5-year survival rates ranging from 24 to 68% [8–11].

However, the role of surgery is controversial for patients presenting with both hepatic and pulmonary metastases. In the literature, there are few series reporting the outcome of more than 30 patients with resection of both hepatic and pulmonary metastases [12–18]. In addition, these studies were conducted at a time when hepatectomy was rarely considered in patients with extensive liver metastasis and before the modern era of chemotherapeutic and biological agents. The aim of the present study was to assess the clinical outcome after pulmonary metastasectomy in patients who underwent prior resection of hepatic CRC metastases and to identify predictors for survival.

Patients and methods

We performed a retrospective analysis of all CRC patients who underwent pulmonary surgical resection with a curative intent in two different institutions (Geneva University Hospital and Lausanne University Hospital) in Switzerland. Among 70 patients with pulmonary metastases who underwent pulmonary metastasis resection, 27 patients had previously undergone resection of hepatic metastases. All of these patients were operated on since 1996 and they constitute the subject of this retrospective study. Lung surgery and liver metastases surgery were performed in the Thoracic Surgery Unit and in the Visceral Surgery Unit of both institutions. We included all patients with a histopathological diagnosis of colorectal adenocarcinoma metastatic to the lung who had undergone prior liver surgery.

The following parameters were recorded and considered for statistical analysis: (1) patient characteristics; (2) primary tumor characteristics (TNM stage, location, preoperative radiation therapy, adjuvant chemo-and/or chemotherapy); (3) characteristics of liver metastases (number and location, size of largest metastases, adjuvant chemotherapy, and extent of liver resection); (4) characteristics of lung metastases (number and size of the largest metastasis, type of resection [wedge, lobectomy or pneumonectomy], involvement of mediastinal lymph nodes, adjuvant chemotherapy, disease-free interval between primary tumor resection and development of lung metastases, and unilateral or bilateral distribution). The study was conducted in accordance with institutional guidelines of the Ethics Committee for Clinical Research of Geneva University Hospital and Lausanne University Hospital.

Eligibility for surgical resection of lung metastases from CRC after previous liver surgery was based on four criteria: (1) control of primary tumor considered as achieved; (2) absence of extrathoracic lesions at the time of lung surgery; (3) possibility to perform a complete resection (R0) of pulmonary metastases; and (4) adequate pulmonary reserve to tolerate the planned resection. Follow-up was performed in the Surgical Oncology Unit of both institutions, with repeated clinical examination and thoracoabdominal CT scan imaging once a year for 5 years to detect local or systemic tumor recurrence. In addition all patients underwent colonoscopy surveillance at 1, 3, and 5 years postcolectomy.

All patients received two to six cycles of chemotherapy before liver resection, using a combination of oxaliplatin [O], irinotecan (CPT-11[C]), 5-fluorouracil (5-FU) [F], and leucovorin [L], according to the following doses and schedule: oxaliplatin 70 mg/m^2 on days 1 and 15, irinotecan (CPT-11) 100 mg/m^2 on days 8 and 22, 5-FU 2 g/m^2/24 h and leucovorin (LV) 30 mg on days 1, 8, 15, and 22, repeated every 5 weeks. Seven patients had a similar regimen, but with 5-FU/LV replaced with capecitabine (the oral prodrug of 5-FU) 800 mg/m^2 per day from day 1 to day 28. One patient received a standard treatment with capecitabine and oxaliplatin (capecitabine 2 g/m^2, oxaliplatin 130 mg/m^2 day 1, days 1–14, repeated every 3 weeks). The response to chemotherapy was assessed after two to three cycles. Further evaluations were obtained according to the clinical response and surgical pattern of disease. More recently, patients were treated with the addition of bevacizumab (Avastin) and cetuximab (Erbitux) to complement the OCFL regimen.

Statistical analysis

The follow-up was complete for all patients. Frequency distributions were obtained for descriptive patient variables. Kaplan–Meier methods were used to examine relapse-free survival and overall survival. The association between tumor relapse and death was explored in a Cox proportional hazards model where relapse was a time-dependent covariate: a patient switched from low-risk status to high-risk status at the time of the relapse (not at baseline). Simple Cox models were used to examine associations between patient characteristics and risk of death. Because of the low number of patients, no multivariate model was constructed. The analyses were performed with SPSS version 17 (SPSS, Chicago, IL). A P value <0.05 was considered statistically significant.

Results

The study sample included 27 patients (14 men, 13 women) initially diagnosed with CRC who first underwent resection

of liver metastases and then surgery for lung metastases. The median age at the time of lung surgery was 62 years (range: 33–75 years). Primary tumor location was predominantly the left colon (14 patients) and the rectum (11 patients). Using the TNM classification, most patients presented initially with an advanced local tumor stage (stages III/IV: 18 patients). Less than half of patients presented initially with synchronous metastatic disease (M0: 17 patients, M1: 10 patients). The clinical stage at diagnosis was advanced for most patients (stage I: 2 patients; stage II: 7 patients; stage III: 8 patients and stage IV: 10 patients). The clinical, pathological, and surgical characteristics of the study population are summarized in Table 1.

The mode of development and the sequence of metastatic spread are summarized in Fig. 1. Interval between resection of primary tumor and that of liver metastases ranged from 0 to 50 months (median: 11 months). Liver locations were in the right lobe in 17 patients, in the left lobe in four patients and in both lobes in six patients. The median delay between primary tumor resection and surgery for lung metastasis was 32 months (range: 0–100 months). Twenty patients had a single lung metastasis; the others had between 2 and 7 metastases. The median size of the largest metastasis was 25 mm (range: 6–75 mm). The vast majority of patients (74%) underwent pulmonary wedge resections as a major lung resection. No patient had simultaneous liver and pulmonary resection.

Table 1 Clinicopathological characteristics of 27 colorectal cancer (CRC) patients with resection of both hepatic and pulmonary metastases

Parameters	Number of patients	Percent
Gender		
Male	14	52
Female	13	48
Age		
<60 years	11	41
>60 years	16	59
Location of primary CRC		
Colon	16	59
Rectum	11	41
T stage		
T1/T2	5	18
T3/T4	22	82
Nodal status		
N0	12	44
N1	8	30
N2	7	26
Metachronous metastasis	10	37
Number of pulmonary metastases		
1	20	74
>1	7	26
Number of liver metastases		
<3	19	70
>3	8	30
Type of liver resection		
Wedge	7	26
Segmentectomy	11	41
Left hepatectomy	2	7
Right hepatectomy	7	26

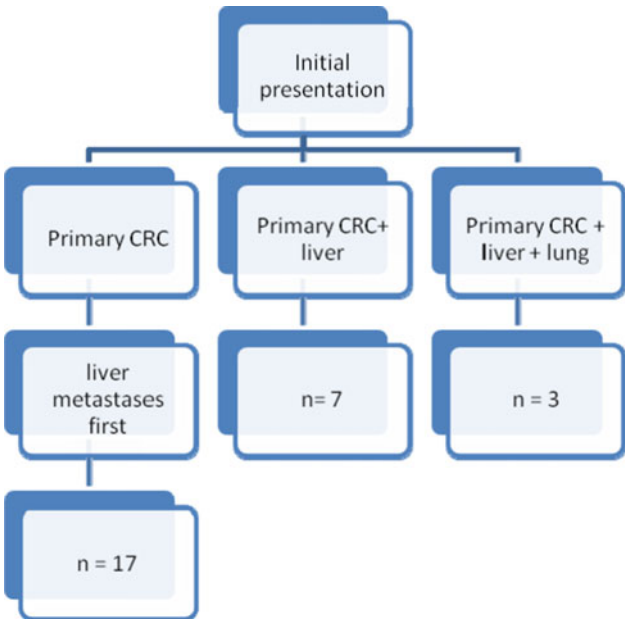

Fig. 1 Sequence of hepatic and pulmonary metastases after the diagnosis of colorectal cancer

Follow-up was obtained for all patients until death (11 patients) or last visit (16 patients). The median duration of follow-up was 32 months (range: 3–69 months) after lung surgery. During this period, 20 patients had a relapse of the primary tumor, in the liver (5), lung (5), bone (4), brain (1), or multiple sites (5). Ten of the 20 patients who relapsed died, versus 1 of the 7 relapse-free patients. Occurrence of relapse was a strong predictor of death. In a proportional hazards model in which relapse was a time-dependent covariate (i.e., the patient moved to the high risk group only at the time of the relapse), tumor relapse was associated with an almost nine-fold increase in the risk of death (relative hazard 8.9, 95% CI 1.1–71.7). Three- and 5-year overall survival rates after lung surgery were 56 and 39%, respectively, and median survival was 46 (95% CI 35–57) months (Fig. 2). Median disease-free survival after pulmonary metastasectomy was 13 (95% CI 5–21) months (Fig. 3).

As an exploratory analysis, because of the small sample size, we examined patient characteristics that may be

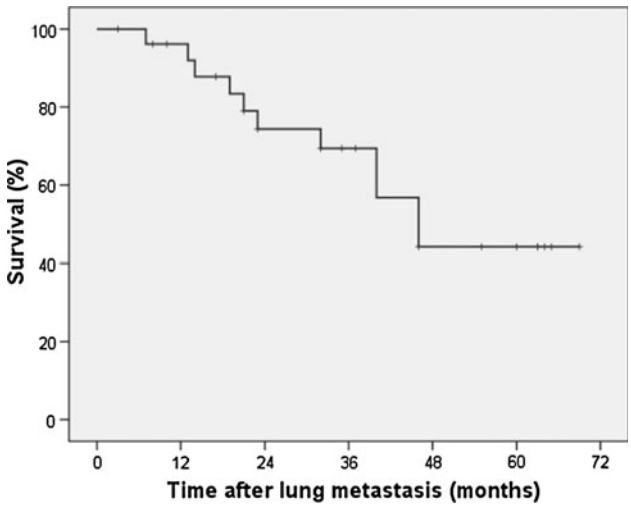

Fig. 2 Overall survival after lung metastasectomy

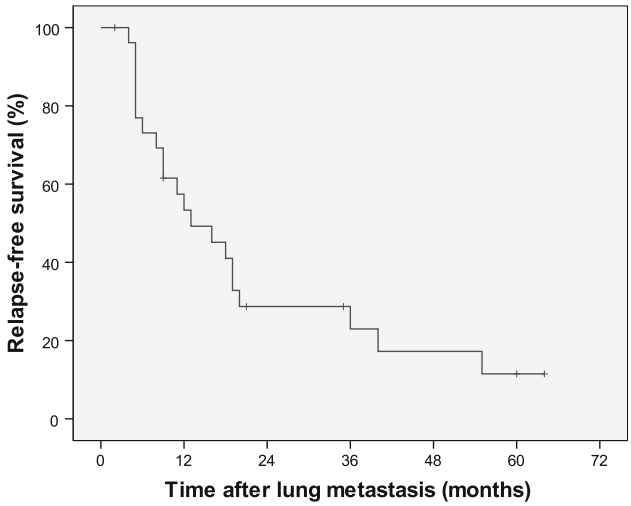

Fig. 3 Relapse-free survival of patients with lung metastases

associated with mortality (Table 2). Three parameters were associated with an average twofold increase in mortality: (1) age >60 years; (2) primary tumor stage III/IV; and (3) presence of multiple lung metastases, as opposed to a single metastasis (Fig. 4). None of these associations appeared, however, statistically significant.

Discussion

We report a series of 27 CRC patients treated with modern chemotherapy (oxaliplatin, irinotecan, and biologic agents), who underwent liver surgery after 1999, and then subsequent lung metastasectomy. Our data indicate that these patients may experience prolonged (median 46 months) survival. However, a majority (74%) of

Table 2 Association between patient characteristics and risk of death

Patient characteristics	Deaths/ patients	Relative hazard (95% CI)	*P* value
Gender			0.83
Male	6/14	1.0 (reference)	
Female	5/13	1.1 (0.3–3.8)	
Age			0.27
<60 years	3/11	1.0 (reference)	
≥60 years	8/16	2.1 (0.6–8.0)	
Primary location			0.78
Colon	6/16	1.0 (reference)	
Rectum	5/11	1.2 (0.4–3.9)	
Tumor stage			0.40
1–2	2/9	1.0 (reference)	
3–4	9/18	1.9 (0.4–9.0)	
Time to first metastasis			0.44
0–6 months	7/14	1.6 (0.5–5.5)	
>6 months	4/13	1.0 (reference)	
Time from liver metastasis to lung metastasis			0.49
0–24 months	5/16	0.7 (0.2–2.2)	
>24 months	5/11	1.0 (reference)	
Number of lung metastases			0.38
1	8/20	1.0 (reference)	
2 or more	3/7	1.8 (0.5–7.1)	
Size of largest lung metastases			0.94
≤25 mm	7/16	1.0 (reference)	
>25 mm	4/11	1.0 (0.3–3.6)	

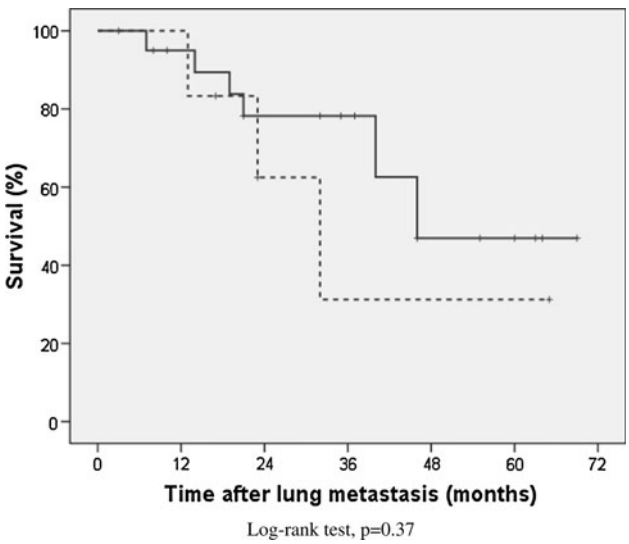

Fig. 4 Survival in patients with single (*solid line*) or multiple (*dashed line*) lung metastases

patients developed tumor recurrence with short median relapse-free survival (13 months). Six of seven patients who were alive with no evidence of disease at last follow-up had a single isolated lung metastasis. This group of patients with limited CRC spread to the lung (a single lesion less than 2 cm in size) may benefit the most from pulmonary metastasectomy.

Surgical resection is rarely curative in CRC patients who subsequently develop both hepatic and pulmonary metastases: most clinicians rightfully consider that metastatic spread to more than one organ reflects the systemic nature of the disease. Yet, in selected cases, resections of pulmonary and hepatic metastases of CRC are increasingly considered as a curative option. In our series, as in others [12], this approach is now associated with median survival up to 4 years, even though long-term relapse-free survivals remain exceptional. The challenge is now to identify the group of patients which will benefit from this aggressive sequential surgical approach. Unfortunately, predictive factors for prolonged disease-free survival in these patients are yet to be defined.

Various parameters have been associated with prolonged survival in isolated pulmonary metastasectomy from CRC including: (1) a long disease-free interval [19–22]; (2) prethoracotomy carcinoembryonic antigen (CEA) level <5 ng/ml [23]; (3) a single isolated metastasis <3 cm in size [24]; and (4) the absence of thoracic lymph node invasion [25, 26]. In contrast, predictive prognostic factors after both liver and lung metastases resection of CRC have not been clearly defined in the literature. Miller et al. [12] reported in 2007 the largest series of patients and identified prognostic factors for improved survival: (1) disease-free interval in-between metastases greater than 1 year, (2) single liver metastasis, and (3) age less than 55. Others reported that lung first metastases [15] and high CEA level before metastasectomy [13] were prognostic factors of worse outcome. In our series, mortality was increased by twofold in patients with primary tumor stages III or IV and presence of multiple lung metastases, but due to the small sample size, results were not statistically significant.

Five-year survival rates after first metastasectomy reported in various series ranged from 11 to 50% [12–18]. These different results are difficult to compare due to probably better patient selection in a long inclusion period and different tumor biology. Liver resection was generally performed before 2000 in selected patients before the improvement of perioperative care and surgical techniques. Our results did not differ from the literature with 5-year survival rate of 39% after lung metastasectomy. Interestingly, a recent series indicates that patients who underwent resection of both liver and lung colorectal metastases may experience longer survival than patients who underwent resection of liver metastases alone (5-year overall survival rates 50% vs. 40%) [18].

In conclusion we report a series of highly selected CRC patients with both liver and lung metastases and who benefited from a modern chemotherapy regimen in addition to surgery with a curative intent in both metastatic locations. While resection of lung metastases from CRC may be compatible with prolonged survival (even when patients have undergone prior resection of liver metastases), it is clear that the majority of patients will experience a recurrence within 2 years after lung surgery and ultimately will die from colorectal cancer. We observed that 6 of 7 patients who were disease-free at the time of last follow-up presented with a single, small (<2 cm) lung metastasis. Clearly, CRC patients with this type of disease extension are good candidates for pulmonary resection, even when they have previously undergone resection of liver metastases.

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