

Survival, disease-free interval, and associated tumor features in patients with colon/rectal carcinomas and their resected intra-pulmonary metastases

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Abstract

Objective: Colon/rectum cancer often presents with intrapulmonary metastases. Surgical resection can be performed in a selected group of patients. In this study, the search for possible prognostic factors of patients with primary colon/rectum cancer and lung metastases was performed. **Methods:** Medical records of 110 patients operated on pulmonary metastases of primary colon/rectum cancer were reviewed. The clinical parameters include age, sex, pTNM/UICC stage, grading, localization, surgical and adjuvant therapy of the primary cancer. The number, maximum diameter and total intra-thoracic resected tumor-mass ('load'), the pre-thoracotomy serum carcinoembryonic antigen (CEA) levels, localization of the metastases (uni- vs. bilateral), the presence of hilar/mediastinal tumor-infiltrated lymph nodes, the surgical procedure and performed therapy schemes of lung metastases were recorded. **Results:** The cumulated 5- and 10-year total survival after diagnosis of the primary carcinomas was estimated to 71 and 33.7%, respectively. After resection of the pulmonary metastases, the 3- and 5-year post-thoracotomy survival measured 57 and 32.6%, respectively. The median time interval between diagnosis of the primary cancer and thoracotomy (disease free interval (DFI)) was found to be 35 months. A non-negligible percentage of patients (15.4%) displayed limited tumor stages of the primary cancer (pT1/2, pN0). The median diameter of the largest metastasis measured 28 mm, and the median resected intrathoracic tumor-load was calculated to 11.4 cm³. In only 8 patients hilar or mediastinal tumor-involved lymph nodes were found. A potentially curative resection of lung metastases was recorded in 96 patients. The overall survival was significantly correlated with the DFI and the number of intrapulmonary metastases. The DFI correlated significantly with the tumor load and the number of metastases; the post-thoracotomy survival with the number of metastases, tumor-load and pre-thoracotomy serum CEA level. Treatment, stage and grade of the primary cancer, occurrence of liver metastases and local recurrences, mode of treatment of metastases and postoperative residual stage had no significant correlation with either total nor post-thoracotomy survival. **Conclusions:** Pulmonary metastases occur even in patients with limited tumor-stages of primary colon/rectum cancer. DFI is the major parameter to estimate the total survival of patients with lung metastases. The survival after thoracotomy depends on the number of metastases, the intrapulmonary tumor load and the presence of elevated serum CEA level prior to thoracotomy. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Colon/rectum cancer; Lung metastasis; Tumorload; Serum carcinoembryonic antigen level; Survival

1. Introduction

Second to lung cancer in men and breast cancer in women, colon/rectum cancer is an important cause of death with increasing incidence over the past 20 years [1,2]. After potential curative resection of the primary tumor, dedicated surveillance in order to detect distant metastases or local recurrence in early stage is recommended [3]. The measurement of the serum carcinoembryo-

nic antigen (CEA) level can be used in patients potentially being candidates for resection of liver and lung metastases [4]. The lungs are the most common extra-abdominal site of metastases in patients affected by cancer of the large bowel [5]. The treatment of metastases is controversially discussed; however, non-surgical treatment still is of only limited benefit to the patients [6–8], and surgical intervention currently is the therapy of choice if a metastatic intrapulmonary process is confined [9,10]. About 10% of patients with primary colon/rectum cancer will develop lung metastases [11]. The majority of patients additionally have recurrent extra-pulmonary disease. Only 2–4% of

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patients with recurrent colon/rectum cancer display metastases limited to the lungs, and surgical treatment of lung metastases may be indicated [10]. The 5-year post-thoracotomy survival of this selected group of patients is reported to range between 9 and 40.5%. The overall 5-year survival rate of potentially curative resected cancer of the large bowel has been estimated to 71% [12]. Several reports report a median time interval between the resection of the primary tumor and the pulmonary metastases (disease free interval, DFI) between 29 and 41 months [11–15].

The aim of this study is to evaluate parameters of the primary cancer and the pulmonary metastases which might be of prognostic value for patients with potentially curative resected colon/rectum carcinomas and solitary pulmonary metastases treated surgically.

2. Material and methods

The medical records of 110 patients with potentially curative resected (R0) colon/rectum carcinomas and surgically treated lung metastases operated on at the Thoraxklinik Heidelberg between 1.1.1988 and 1.3.1999 were reviewed. All patients who underwent a potentially curative resection of colon/rectum metastases were included in this study. The surgical approach was based upon routinely tumor follow-up after resection of the primary colon/rectum carcinoma, and specifically upon findings in CT scans. Bronchoscopy prior to operation was a routine procedure, whereas a bilateral surgical approach was not systematically performed. In case of bilateral abnormal findings a sequential operation of left and right lung (or vice versa) was the normal procedure. The patients underwent a chemotherapy of the colon/rectum carcinoma in case of extended tumor stage. The analyzed tumor features include age, sex of patients, maximum diameter of primary tumor, localization, pTNM/UICC stage, development of local recurrent disease and distant metastasis in the liver, number and maximum diameter of metastases, tumor load of metastases (calculated from the number and maximum diameter of occurring lung metastases), presence of mediastinal or hilar lymph node involvement, serum CEA levels prior to resection of the lung metastases, post-operative treatment, and surgical procedures of primary and secondary tumors. The statistical tests include parametric and non-parametric correlation tests, log-rank and COX regression tests including Kaplan–Meier analysis [16], and multivariate discriminant analysis (number cruncher statistical system, NCSS60 program package, Utah, USA).

3. Results

The median age of patients at time of the diagnosis of the colon/rectum cancer was 58 years (range: 34–78 years). Patients with primary tumors located in the rectum (55 years) were significantly younger compared to those with

colon carcinomas (59 years) ($P < 0.01$). Sixty-eight patients were men and 42 were women. In 104 cases (94.5%) the primary tumor stage was accessible, which was not documented in six cases (5.5%). The distribution of pTNM stages of 104 patients with lung metastases is demonstrated in Table 1. Although the majority of patients was operated on in advanced tumor stages, and 15% of patients displayed limited tumor stages (pT1/2, pN0). The majority (53.6%) of tumors arose from the colon ($n = 59$) and in only 51 patients from the rectum. The rectum carcinomas were located in the lower region in 10 patients, in the middle part in 26 patients and in the upper part in 12 patients. Colon cancer was found in the sigmoid in 32 patients and in the descend colon in seven patients. Right-sided cancer was detected in the transverse colon in one patient only, in the ascending part in 11 patients, and in the caecum in five patients. All patients underwent a radical resection of the primary tumor. In the majority of cases an anterior resection was performed ($n = 47$) followed by a hemicolectomy ($n = 36$), abdominosacral resection (ASR, $n = 15$), abdominoperineal resection (APR, $n = 11$), and transanal disc-excision (one patient). The median follow-up time after resection of the primary tumor was calculated to 70 months (range: 14–252 months). No significant association of tumor localization with the DFI or total survival could be obtained. 39 patients (35.5%) underwent a course of postoperative adjuvant therapy. Seventeen patients received a postoperative chemotherapy, seven patients radiotherapy, and 15 patients a combined radio-chemotherapy. Local recurrence of the primary cancer occurred in 15 patients (13.6%). Fourteen patients could be potentially curative resected, residual tumor mass after resection was found in only one patient. The presence of local recurrences had no statistically significant correlation neither with (DFI) nor the total survival. Liver metastases were found in 20 patients (18.2%), in ten cases metastatic hepatic spread was detected at time of primary diagnosis. All liver metastases, detected at primary diagnosis, could be resected with clean

Table 1
Postsurgical tumor stages of primary colon/rectum carcinomas (number of cases)

pTNM stage distribution	Stage	Colon	Rectum	Total
pT	pT1	3	3	6
	pT2	7	11	18
	pT3	42	33	75
	pT4	4	1	5
pN	pN0	28	21	49
	pN1	21	17	38
	pN2	5	6	11
	pN3	2	4	6
pM	pM0	43	43	86
	pM1	13	5	18

Table 2

Pre-thoracotomy CEA serum levels and intrapulmonary tumor load, number of metastases, and maximum diameter of pulmonary metastases (largest metastasis in case of multiple tumors)

Preoperative Serum CEA level \geq or $<$ 5 ng/ml	<i>P</i>
Pulmonary metastatic tumorload	0.046
number of metastases	0.092
Maximum diameter of pulmonary metastases	0.334

tumor boundaries. The presence of liver metastases was not associated with the DFI or the total survival at a statistically significant level ($P > 0.05$). The median DFI was calculated to 35 months (range: 2–216 months) and the follow-up after resection of pulmonary metastases to 31 months (range: 4–142 months). The intra-pulmonary tumor load was correlated with the pre-thoracotomy CEA serum levels at a significant level (Table 2). In the majority of cases only one metastasis was detected ($n = 56$). Twenty-one patients had two, 10 patients three, seven patients four, one had five, three had six, and four patients had seven metastases. Two patients had eight and nine metastases, respectively. The maximum number of lung metastases accounted to 18 tumor nodules (one patient). The mean number was computed to 2.6 intrapulmonary metastases per patient. The median of the maximum diameter defined in the largest metastasis measured 28 mm (range: 6–110 mm) and the median total intrapulmonary tumor load was calculated to 11.4 cm³ (range: 0.11–342 cm³). The thoracic intervention was performed most frequently (83 patients) through lateral thoracotomy (76%). Median sternotomy was documented in 21 patients (19%), transverse thoracotomy in four patients (3.6%), anterior thoracotomy in one patient, and thoracoscopic guided intervention in one case. The mode of the

pulmonary resection is presented in Fig. 1. The pulmonary resection was potentially curative in 96 patients. Residual tumor were documented in 14 patients (R1: 10 patients, R2: 4 patients). The presence of residual tumor and/or the presence of mediastinal or hilar lymph node involvement (eight patients) was not statistically significantly associated with the post-surgical survival. After thoracotomy 15 patients underwent adjuvant therapy. Fourteen patients had chemotherapy and a single patient had combined radio-chemotherapy. Twenty-nine patients developed recurrent lung metastases, and 23 patients underwent a secondary operation. The surgically treated patients had a statistically significant longer post-thoracotomy survival ($P = 0.03$). A third lung operation was undertaken in eight patients, and one patient underwent four intrapulmonary resections of metastases. The pre-thoracotomy serum CEA level was documented in 101 cases (92%) and found to be elevated (≥ 5 ng/ml) in 42 patients. The DFI is statistically significantly associated with the intra-pulmonary tumor load and the maximum diameter of metastases (Table 3). The post-thoracotomy survival was statistically significantly correlated with the number of metastases (Fig. 2), the tumor load (Fig. 3), and the pre-thoracotomy CEA serum level (Fig. 4), whereas the total survival only displayed a correlation with the number of intra-pulmonary metastases and the length of the DFI (Table 4).

4. Discussion

Patients with colon/rectum carcinomas are subject to develop lung metastases even at early tumor stages of the primary cancer. The cumulated 2-, 3-, 5-, and 10-year overall survival rates were calculated to 98, 92, 71 and 34%, respectively. In contrast to the prognosis of non-selected

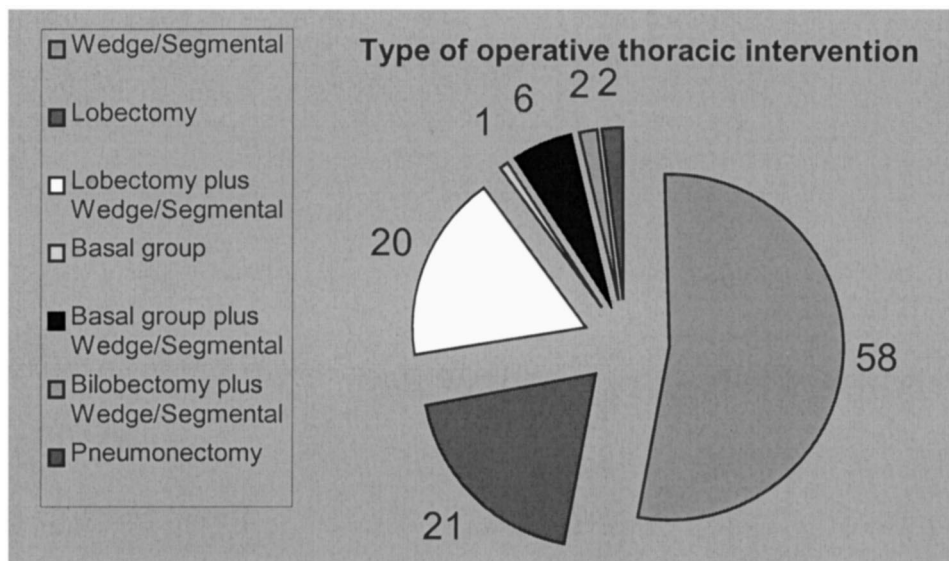


Fig. 1. Mode of resection of intrapulmonary metastases.

Table 3

Relationship of the disease-free interval (DFI) and tumor features of primary and secondary tumors (log rank test)

Tumor feature	Cut-off	DFI (months)			Significance <i>P</i>
		Median	Mean	Range	
Pulmonary metastatic tumorload (cm ³)	< 11.4	32	34.5	4–120	0.029
	≥ 11.4	41	47.6	2–216	
Maximum diameter of pulmonary metastases (mm)	< 28	31	34.7	4–120	0.029
	≥ 28	42	47.2	2–216	
pT1/pT2		36.5	44.2	8–103	0.09
pT3/pT4		32	35.4	2–114	
pN0		35	40.2	2–103	0.19
pN +		29	34.9	3–114	
pM0		36	40.7	5–114	0.0004
pM1		16	21.6	2–78	

patients developing colon/rectum carcinomas [3,17], the total survival of this selected cohort has not been found to be significantly associated with the stage (pTNM, UICC [18]) ($P = 0.2$) or grade of the primary tumor. However, the DFI, which is significantly correlated with the total survival ($P < 0.001$), measured 48.5 months in stage I ($n = 14$ patients), 35 months in Stage II ($n = 28$ patients), and 36 months in Stage III ($n = 40$ patients) disease. The 22 patients at stage IV (18.5 months) had a significantly ($P < 0.002$) shorter DFI. The patients' age and sex, or mode of primary resection, postoperative adjuvant therapy, development of liver metastases or local recurrence of the primary tumor, no significant correlation to the overall survival could be observed. Calculated by multivariate analysis, the DFI, the number of lung metastases, the pulmonary metastatic tumor-mass and the occurrence of lymphonodal tumor-infiltration of the primary tumor (pN) was found to significantly correlate with the total survival of patients. After thoracotomy the 3-year survival was calculated to 57% and the 5-year survival to 32.6%, postoperatively. The median length of the DFI measures about 3 years, i.e. an intensive control of operated tumor patients should be performed at least within this period. The median

survival after post-thoracotomy amounts to 41 months, i.e. is comparable or even in favor to that of patients suffering from primary bronchial carcinomas with comparable tumor mass (tumor load) [19]. This statement is important as the cohort with lung metastases including patients with multiple tumors is comparable to patients with primary lung tumors [19]. In this study only 51% ($n = 56$) of patients had a singular metastasis and 49% multiple intrapulmonary tumors. In studies with comparable number of patients Okamura et al. [20] report 67.3% and McAfee et al. [21] report 70.5% of patients with singular metastasis at the time of operation. In other studies [22–25] singular metastasis was present in 62.9–78.9% of patients. In the study of Okamura et al. [20] the 5-year survival rate was calculated to 40.5% and McAfee et al. [21] reported 30.5% of patients survived 5 years. Other studies [11,13,14,22–25] calculated 5 year survival rates between 9% [5] and 38.7% [15]. In contrast to the data of Okamura et al. [20], we could not find, that cancer patients had different survival rates between patients with/without liver metastases or with/without developed local recurrences at the site of the primary cancer. Furthermore, none of the clinical parameters (age at time of diagnosis of lung metastases, sex, type and extent

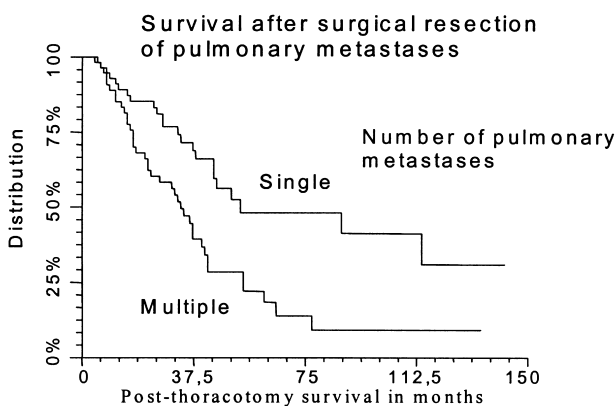


Fig. 2. Post-thoracotomy survival and number of metastases.

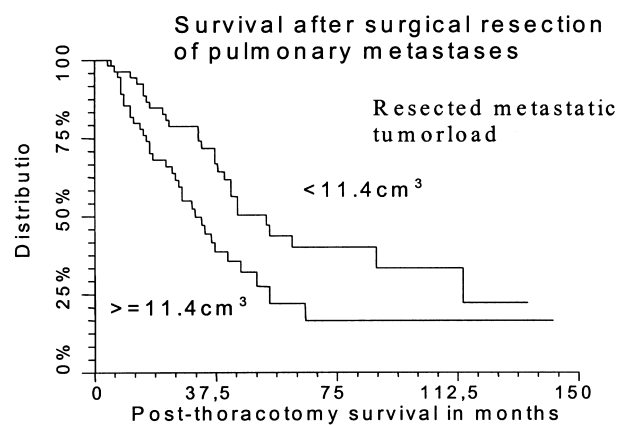


Fig. 3. Post-thoracotomy survival and tumor load.

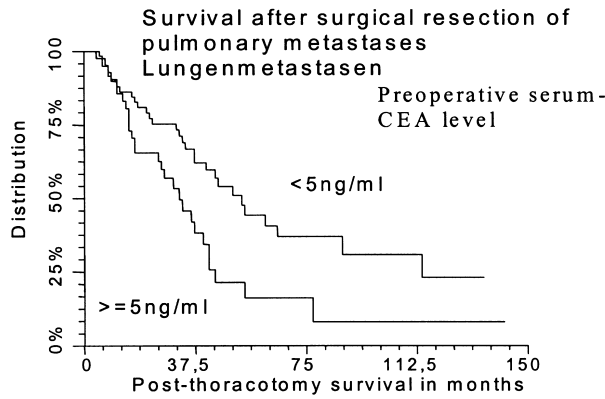


Fig. 4. Post-thoracotomy survival and pre-surgical CEA serum level.

of surgical intervention on lung metastases) had a potential prognostic value in predicting the post-thoracotomy survival. Additionally, in agreement with data of other studies [5,11,14,15,21,23], the tumor stage of the colon/rectal cancer had no influence on the survival after resection of metastases at a statistically significant level. Reviewing the literature, only Okamura et al. [20] and McCormack et al. [25] reported a significantly improved post-thoracotomy survival of patients whose large bowel cancer was staged to Duke's A. Although the DFI was statistically significantly correlated with the total survival of patients, a statistically significant correlation between the DFI and the post-thoracotomy survival could not be found. These findings are in agreement to most of the other studies [5,13,15,20–23,25]; however, in contrast to the results of Briester et al. [14]. Interestingly, the patients with an elevated serum CEA level prior to thoracotomy had a significantly reduced survival after pulmonary metastasectomy. These findings have also been reported by McAfee et al. [21] in their study

Table 4
Multivariate analysis of parameters associated with total survival and post-thoracotomy survival (Cox-regression)

Parameter	Rank	Relative hazard	Z-value	P
Total survival				
Disease-free interval	1	0.970866	-4.03	0.001
Number of pulmonary metastases	2	1.075493	2.49	0.013
Pulmonary tumor load	3	1.004071	2.18	0.029
Infiltration of lymph nodes by the primary tumor	4	2.276568	2.01	0.045
Stage (UICC) of primary tumor	5	0.750827	-1.29	0.198
Post-thoracotomy survival				
Number of metastases	1	1.0885	2.51	0.012
Maximum diameter of metastasis	2	1.0133	2.22	0.026
Pre-operative serum CEA level	3	1.7336	1.09	0.055

comprising 52 patients with recorded serum CEA level. Patients with mediastinal or hilar lymph node involvement ($n = 8$) displayed no major differences in survival after thoracotomy in comparison to their normal counterparts. Goya et al. [23] reported similar results whereas Okamura et al. [20] found a statistically significant negative association of hilar or mediastinal lymph node metastases with the post-thoracotomy survival.

In aggregate, the total 5-year survival rate of patients with potentially curatively operated colon/rectum carcinomas and subsequent excised lung metastases measures 71% which is in the range of the total survival of large bowel cancer patients treated surgically in a potentially curative manner [12].

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