

## A Cohort Study Evaluating the Role of Surgery for Lung Metastases from Colorectal Cancer

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**Abstract.** *Background/Aim:* Surgery may be curative in some patients with metastatic colorectal cancer (mCRC). We analyzed the role of lung metastatectomy in this population. *Patients and Methods:* In this retrospective cohort study, cases were defined as mCRC patients with lung metastases (LM's) who underwent metastatectomy. Controls had LM's but did not undergo resection. *Results:* There were 28 cases and 46 controls. The median overall survival (OS) was 53 months among the cases and 26.3 months for the controls. The cases were more likely to have 1 or 2 lung metastases, unilateral versus bilateral LM's, metachronous versus synchronous presentation of LM's and more likely to have a carcinoembryonic antigen (CEA) level less than 10 ng/ml at diagnosis. The interval from diagnosis to the development of lung metastases was significantly longer in cases versus controls (22.9 versus 8.5 months). *Conclusion:* Patients selected using these criteria may have prolonged survival with therapy that includes lung metastatectomy.

Colorectal cancer (CRC) is one of the most common malignancies and the second leading cause of cancer-related deaths in the United States (1). There were an estimated 142,820 new cases diagnosed in the United States in 2014 and 50,830 deaths due to this disease (2). More than half of the

patients who undergo resection for localized CRC eventually have a recurrence, with the most frequent sites of metastases being the liver and the lungs (3, 4). Isolated lung metastases occur in approximately 5% of patients following curative resection of colon cancer and 11-15% of rectal cancer (5).

Systemic chemotherapy and targeted-therapy are the mainstay of treatment for patients with metastatic colorectal cancer (mCRC). Improvements in systemic therapy have led to prolongation of survival for patients with stage IV disease; the median overall survival (OS) seen with historical trials of fluorouracil and leucovorin was 14 months (6), compared to more contemporary trials with median OS times exceeding 2 years (7). As systemic therapies have gotten better, patients with oligo-metastatic disease are increasingly being referred for surgery. The role of surgery is well-established in patients with liver metastases with 5-year survival rates of 20 to 80% by the use of combination chemotherapy and liver resection (8-13).

The typical pattern of lung metastasis from CRC is single or multiple nodules rather than miliary tumors or lymphangitic spread. Therefore, metastatectomy is commonly performed, especially in patients where the primary colonic tumor is controlled, there are no other metastatic sites, the surgery is technically feasible and there is adequate cardiopulmonary reserve (14, 15). Using these criteria, patients undergoing lung metastatectomy can achieve 5-year survival rates of 40%-61% (8, 16-20). The data supporting the role of lung metastatectomy are all retrospective. Therefore, we designed a retrospective cohort study comparing patients who underwent resection *versus* a non-surgical group of controls. Our specific objectives were to determine the survival of CRC patients with lung metastases who underwent lung resection compared to a matched group of CRC patients with lung metastases that did

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Table I. Baseline characteristics.

	Non-resection (N=46)	Resection (N=28)	p-Value
Age			
Median (years)	58.6	59.5	0.719
Range	40-85	40-82	
Gender			
Male	22 (48%)	8 (29%)	
Female	24 (52%)	20 (71%)	
Stage at diagnosis			
Stage II	6 (13%)	5 (18%)	0.514
Stage III	21 (46%)	12 (43%)	
Stage IV	18 (39%)	9 (32%)	
Histological grade			
Well differentiated	3 (7%)	5 (19%)	0.184
Moderately differentiated	32 (75%)	20 (74%)	
Poorly differentiated	8 (18%)	2 (7%)	
Number of lung metastases			
1	6 (13%)	19 (68%)	<0.01
2	2 (4%)	6 (21%)	
≥3	38 (83%)	3 (11%)	
Lung metastases distribution			
Unilateral	5 (11%)	26 (93%)	<0.01
Bilateral	40 (89%)	2 (7%)	
Lung metastases presentation			
Synchronous with primary	15 (33%)	3 (11%)	<0.049
Metachronous with primary	31 (67%)	25 (89%)	
Time from primary tumor to lung mets diagnosis	8.5 months	22.9 months	0.02
Carcinoembryonic antigen (CEA) level			
Median at initial diagnosis	253.4	7.4	0.065
Median at lung metastases diagnosis	568.4	9.91	0.125
No. with CEA >10 at lung metastases diagnosis	20 (59%)	3 (15%)	0.02
No. with CEA <10 at lung metastases diagnosis	14 (41%)	17 (85%)	

not undergo lung resection and to determine predictors of better survival after lung resection for CRC metastases.

### Patients and Methods

We conducted an Institutional Review Board-approved retrospective cohort study with two groups - cases (resection group) were patients with mCRC who underwent lung resection and controls (non-resection group) were patients with mCRC who had lung metastases but did not undergo lung resection. The cases were first identified by searching the surgical database at our institutions for all patients with lung metastases who underwent thoracotomy or thoracoscopy for resection. The search range was limited to January 2000 to December 2012. Only patients with a colon or rectal primary were included. Next, controls were selected by searching the Florida Cancer Data System (FCDS). This registry was queried for patients treated between January 2000 to December 2012 with colon or rectal cancer and lung metastases. A random selection of these patients was used to make up the control group.

A chart review was performed to extract demographic and clinical baseline characteristics of each patient, as well as treatment administered. Specific variables included age at diagnosis, gender,

stage at diagnosis, histological grade, number of lung metastasis, performance status, synchronous vs. metachronous disease, carcinoembryonic antigen (CEA) level at the time of primary tumor and lung metastasis diagnosis, type of chemotherapy received, number of lines of chemotherapy, liver resection, type of thoracotomy, subsequent thoracotomies, size and number of lung metastases. Survival was calculated using the date of death or last follow-up and the vital status was obtained for all patients from the FCDS.

Statistical analysis was performed using the SPSS software, version 21 (IBM, New York, NY, USA). The cases *versus* control groups were compared for differences in baseline characteristics using the student's *t*-test for continuous data and the chi-squared test (or Fisher's exact test) for categorical data. The Kaplan-Meier method was used for survival analysis and the Cox proportional hazards model was used to identify variables associated with differences in survival.

### Results

We identified 28 cases with mCRC who underwent lung metastatectomy and 46 controls with mCRC to the lung who did not have resection of their lung metastases. Table I shows

Table II. *Chemotherapy administration.*

Chemotherapy	Non-resection (N=46)	Resection (N=28)
Perioperative chemotherapy		8 (29%)
Anti-EGFR monoclonal antibody	12 (26%)	6 (21%)
Bevacizumab*	31 (67%)	12 (43%)
Median number of lines of chemotherapy	2	3

EGFR, Epidermal growth factor receptor. \* $p=0.03$

the baseline characteristics of the cases and the controls. The treatments administered are shown in Table II.

After a median follow-up of 39 months (range=11-105), the median overall survival (OS) from the time of diagnosis with lung metastases for the cases undergoing resection was 53 months (95% confidence interval (CI)=43.8-62.2) *versus* 26.3 months (95% CI=11.8-40.8) for the controls (log-rank  $p=0.009$ ), as shown in Figure 1. The median disease-free interval, defined as the time from initial colorectal cancer diagnosis until lung metastasis, was 22.9 months (95% CI=18.6-27.2) in the cases undergoing resection *versus* 8.5 months (95% CI=2 -15) for the controls (log-rank  $p=0.02$ ).

Among the patients who underwent resection, various characteristics were tested for prognostic importance as depicted in Table III. In univariate testing, none of these characteristics were associated with better survival – grade of differentiation, timing of lung metastases (synchronous *versus* metachronous), number and distribution of metastases, any history of liver metastatectomy, subsequent lung metastatectomy, type/extent of resection, CEA level at initial diagnosis and CEA level at the time of diagnosis with lung metastases.

## Discussion

Resection of lung metastases from colon cancer is a commonly performed surgery and the literature supports prolonged survival in some of these patients. Some consistent factors that have been reported to be associated with better survival in surgical case series are a longer interval from diagnosis to the development of lung metastases, fewer metastases and a lower CEA level at diagnosis with lung metastases (21). The main factor associated with worse survival is involvement of the hilar or mediastinal lymph nodes (21). Patients selected, according to these criteria, can achieve 5-year survival rates of 27-68% (22).

In this retrospective study, patients with mCRC to the lung who were referred for lung resection were more likely to have features of favorable disease biology: longer disease-free interval, solitary and unilateral tumors, metachronous disease and CEA levels at the time of lung metastasis less than 10. We found that patients selected using these criteria,

Table III. *Analysis of prognostic factors among patients undergoing resection.*

Prognostic factors	Resection group	<i>p</i> -Value
Tumor grade		
Well differentiated	5 (19%)	0.559
Moderately differentiated	20 (74%)	
Poorly differentiated	2 (7%)	
Presentation of lung metastases		
Metachronous with primary	25 (89%)	0.573
Synchronous with primary	3 (11%)	
Number of lung metastases		
1	19 (68%)	0.40
2	6 (21%)	
≥3	3 (11%)	
Lung metastasis distribution		
Unilateral	26 (93%)	0.717
Bilateral	2 (7%)	
Liver resection performed		
No	21 (75%)	0.109
Yes	7 (25%)	
Subsequent thoracotomies		
No	23 (82%)	0.09
Yes	5 (18%)	
Type of surgery		
Wedge resection	21 (75%)	0.484
Lobectomy	5 (18%)	
Pneumonectomy	2 (7%)	
Carcinoembryonic antigen level		
<10 at diagnosis	17 (85%)	0.984
≥10 at diagnosis	3 (15%)	
<10 at diagnosis with lung metastases	19 (83%)	0.865
≥10 at diagnosis with lung metastases	4 (17%)	

who had surgical resection of their lung metastasis, had a median survival time of 53 months. This figure is in the range of what has been reported in the literature (8-13).

To date, all the published evidence in support of lung metastatectomy consists of case series of patients undergoing surgery with analyses of prognostic factors among these patients. However, prospective randomized trials have not been performed to delineate which patients are more likely to benefit from this procedure. In the absence of a randomized trial, it is difficult to know if the prolonged survival seen is due to selection of patients with favorable biology who were destined to live longer even if they did not undergo surgery. With the improvement in systemic therapies, it is possible that the combination of effective chemotherapy with good disease biology may be responsible for prolonged survival times. However, given the experience with curative resections for patients with “oligo-metastatic” liver-only disease, it is likely that surgery may be adding some survival advantage for a subset of these patients with lung metastases as well, possibly by removing resistant tumor clones or cancer stem cells, which may have led to faster disease progression if not removed.

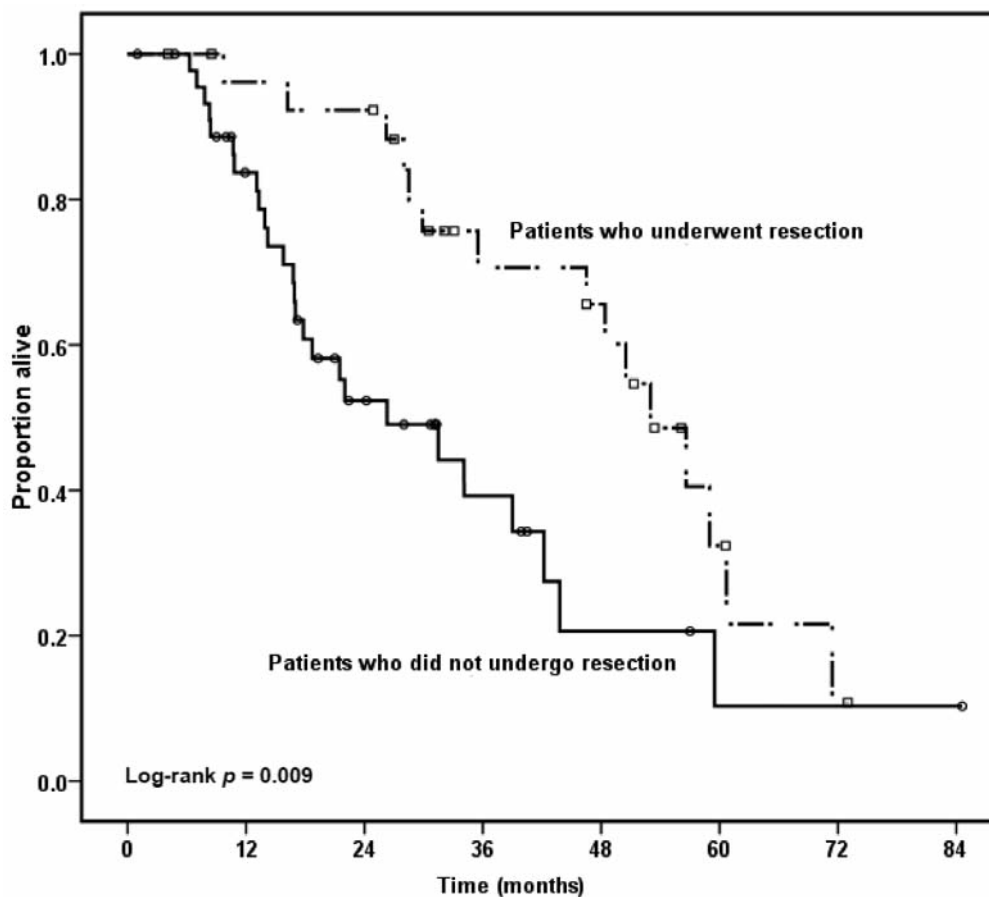


Figure 1. Overall survival from the time of diagnosis with lung metastases.

The ongoing PulmiCC trial (23) will add some valuable information to our knowledge in this area. This trial was initiated in 2010 in Europe and is being offered to patients with resectable lung metastases from colorectal cancer who have their primary tumors controlled, have no other sites of metastatic disease that cannot be removed surgically or by some other local/ablative modality and do not have any contraindications to surgery. Until these results are reported, it seems reasonable to continue the current practice of offering lung metastatectomies to patients with low volume disease with otherwise favorable characteristics as described above and who are relatively low-risk for surgical intervention.

### Conflicts of Interest

None.

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