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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Repeated Resection of Colorectal Cancer Pulmonary Oligometastases: Pooled Analysis and Prognostic Assessment

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ABSTRACT

Background. Repeated resection of colorectal cancer pulmonary metastasis is associated with long-term survival. Nevertheless, very limited data addressing the best candidates for repeated pulmonary resection is available.

Patients and Methods. We searched the PubMed database for retrospective studies evaluating lung metastasectomy for metastatic colorectal cancer (CRC). We included studies with available data about repeated pulmonary metastasectomy. Potential prognostic factors were analyzed for possible impact on survival following the second metastasectomy through univariate and multivariate analysis.

Results. Between 1983 and 2008, 944 lung metastasectomies were carried out on 759 patients. Of those, 148 patients had a second metastasectomy. The 5-year survival rate was 52 % for patients who had 1 metastasectomy and 57.9 % from the second metastasectomy for patients who had repeated resection. More than 2 metastatic pulmonary nodules and maximum diameter of largest pulmonary nodule $\geq$3 cm were the only independent factors associated with inferior survival following repeated pulmonary resection.

Conclusions. In selected patients with metastatic CRC, repeated pulmonary metastasectomy offers an excellent chance for long-term survival and is associated with a quite low operative mortality. Patients with more than 2 metastatic nodules and a maximum diameter of the largest metastatic lung nodule of $\geq$3 cm have a significantly inferior survival.

Many retrospective studies suggest improved survival following resecting lung metastasis from colorectal cancer (CRC).[1–7] The principles and prerequisites for pulmonary metastasectomy (PM) include the absence of extrapulmonary metastases and a controlled primary site.[8,9] Because no randomized data comparing metastasectomy with systemic therapy are yet available, the main focus of these studies was to identify prognostic factors following metastasectomy that could serve as a selection tool for surgery. Limited but encouraging data suggest the feasibility and safety of repeated PM following lung recurrences after the first PM for metastatic CRC and showed encouraging 5-year survival rates of 33–79 % from the second lung resection.[10–13] The small number of patients included, however, remained a major limitation.

In a previous report of pooled individual patient data, we identified 3 independent poor prognostic factors that could be helpful in predicting survival following the first PM for those who were rendered disease-free following metastasectomy, and a prognostic model, which could be used as a

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tool for selecting patients for the first metastasectomy, was constructed.[14]

In this paper, we analyze factors that can be prognostic for the second resection in an attempt to identify the best candidates for repeated metastasectomy.

METHODS

Search Strategy and Patients

We underwent a PubMed search using the terms: lung metastasis, colon cancer, surgery, and metastasectomy. Studies published before the year 2000, and/or including fewer than 20 patients were excluded.

Included patients were those 18 year or older, with CRC and pulmonary metastases, who had undergone surgical resection of their CRC and the lung metastases and who were free of other organ metastases at the time when their lung metastases were first detected. Previous resection of other organ metastasis (e.g., previous resection of liver metastasis) was allowed if it was carried out with negative margins and the patient was free of other organ metastases at the time of detection of lung metastases.

Patients with any of the following were excluded: gross residual disease (R2 resection) or positive margins (R1 resection) following PM, uncertain follow-up data, or they were excluded if other metastatic sites could not be excluded with certainty.

Statistical Analysis

Survival curves for patients were plotted using the Kaplan-Meier's method and were calculated from the first as well as the second PM, until death or last follow-up. Assessment of heterogeneity among patients included from the different studies was carried out using a fixed-effect model, which tests variation using the χ^2 test.

We performed the analysis on crude individual patients' data. The following factors were evaluated using the log-rank test for their influence on survival for patients who had a second pulmonary metastasectomy: age, gender, whether the metastasis was associated with elevated carcinoembryonic antigen (CEA) level of $\geq$5 ng/ml, disease-free interval (DFI) (defined as the time from the first lung metastasectomy until the detection of recurrent lung metastasis), mode of surgical resection (sublobar resection, lobar resection, or pneumonectomy), laterality of pulmonary metastases, number of metastatic lung nodules, maximum diameter of the largest lung metastatic nodule, status of lymph nodes (LN) involvement in the primary resected CRC, status of LN involvement in the thorax, and whether the patient had a previous curative hepatic resection. A p value of $<.05$ was considered statistically significant.

Variables with p values of <0.1 were entered into multivariate analysis using the Cox regression model. All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Search Results and Patients

A total of 83 retrospective studies were identified. Of these, 42 were excluded: 18 studies for being published before the year 2000, 14 studies because each included <20 patients, and 10 studies for both reasons. Of the remaining 41 studies, we were able to get crude data from the authors for only 7 retrospective studies that contained information about repeated PM.[12,15–20] The 7 studies included 820 patients, for whom we got individual data for every patient. Excluded were 61 patients: 24 for synchronous lung and liver metastases, 36 for R1 or R2 resection, and 1 for uncertain survival data. After excluding the 61 patients, 759 patients were eligible. Of those patients, 148 had repeated metastasectomy.

Patients' Characteristics

The characteristics of the patients who had repeated resection are illustrated (Table1). Median follow-up time from the first resection was 36.01 months. Patients with 1 resection had a median follow-up time of 32.14 months from metastasectomy, while patients with a second resection had a median follow-up time of 50.72 months from the first resection. The median DFI from the second resection was 13.35 months.

Assessment of heterogeneity among patients included from the different studies did not demonstrate significant differences regarding age, number of metastatic lung nodules, mode of surgical resection, prethoracotomy CEA level, DFI, or maximum diameter of the largest metastatic lung lesion, $\chi^2 < .0001$.

Surgical Outcomes

Between 1983 and 2008, 944 lung metastasectomies were carried out on 759 patients. A total of 148 patients (19.5 %) had repeated metastasectomy. Of patients with repeated metastasectomy, a third metastasectomy was carried out on 32 patients (22 %) and a fourth metastasectomy on 5 patients (3.4 %). The modes of surgical resection during the 185 repeated metastasectomies were: a sublobar resection in 105 (57 %), a lobectomy in 52

TABLE 1 Characteristics of the 148 CRC patients with repeated pulmonary metastasectomy

Clinical variable	No. of patients (%)
Gender	
Male	87 (59)
Female	61 (41)
Age (years)	
≤ 60	70 (47)
> 60	78 (53)
DFI (months)	
≤ 12	59 (40)
> 12	89 (60)
CEA (ng/ml)	
< 5	94 (64)
≥ 5	21 (14)
Missing	33 (22)
Previous liver metastases	
No	114 (77)
Yes	34 (23)
No. of metastases	
< 3	104 (70)
≥ 3	19 (13)
Missing	25 (17)
Size (cm)[a]	
< 3	85 (57)
≥ 3	31 (21)
Missing	32 (22)
Mode of surgery	
Sublobar resection	88 (59)
Lobectomy	39 (26)
Pneumonectomy	1 (< 1)
Missing	20 (14)
LN thorax[b]	
Not involved	35 (24)
Involved	6 (4)
Not performed	83 (56)
Missing	24 (16)
LN primary[c]	
Not involved	47 (32)
Involved	85 (57)
Missing	16 (11)

[a] Maximum diameter of the largest metastatic lung nodule

[b] Status of LN involvement in the thorax at the time of repeated metastasectomy, not involved vs involved. Not performed: LN sampling or dissection was not carried out

[c] Status of regional LN involvement at the time of CRC surgery

(28 %), and a pneumonectomy in 2 (1 %), while data were not available for 26 metastasectomies (14 %). Of the 148 patients with repeated metastasectomy, 1 patient (0.7 %) died within 2 months of surgery, and 1 patient died within 2 months of the 37 subsequent (third and fourth) metastasectomies, corresponding to a 0.7 % surgical mortality rate following the second metastasectomy and 2.7 % surgical mortality rate following subsequent metastasectomies.

Survival Outcomes

The 5-year OS rate for the entire cohort of patients was 58.03 % calculated from first PM. Patients who had only 1 metastasectomy had a 5-year OS of 52 %; the 148 patients with repeated metastasectomy had a 5-year OS rate of 71.7 % from the first metastasectomy and 57.9 % from the second metastasectomy (Fig. 1).

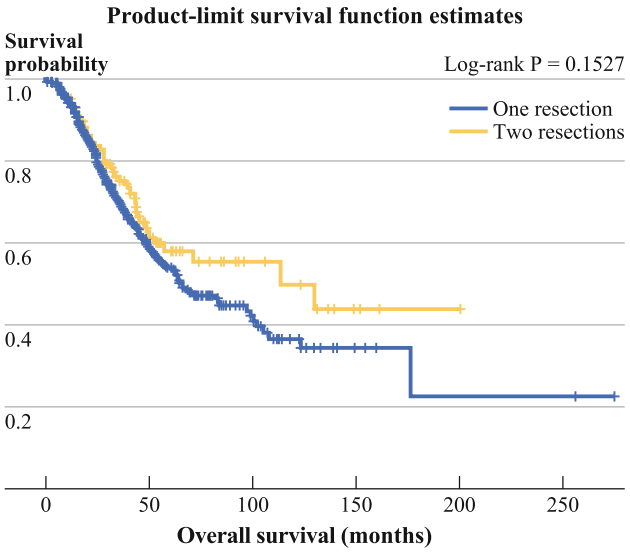
A total of 9 patients are alive more than 10 years following the second metastasectomy; 5 of these patients had 3 metastasectomies, and 3 of them had had previous curative hepatic resection before the first thoracotomy. The patient with the longest survival in our cohort was still alive at 201 months following the second metastasectomy and at 184 months following the third metastasectomy.

We explored in univariate analysis the influence of patient- and disease-related factors on survival following the second PM. Significant differences in survival were detected based on the number of metastatic lung nodules (Fig. 2) and the maximum diameter of the largest metastatic lesion (Fig. 3). The 5-year OS was significantly higher for patients with less than 3 metastatic lung nodules at the time of second metastasectomy, as opposed to 3 or more (5-year survival of 62.5 % and 37.6 %, respectively, $p = .0136$). Similarly, patients with maximum diameter of the largest metastatic lung nodule of less than 3 cm had a favorable 5-year OS rate compared with patients with a larger nodule size (5-year survival of 70.9 % vs 27.0 %, respectively, $p = .0011$). The other factors had no influence on survival.

Finally, we performed a multivariate analysis, taking into account all the potentially significant survival predictors in the univariate analyses. The 2 poor prognostic factors identified in the univariate analysis retained their significance and were thus confirmed to be independent (Table 2).

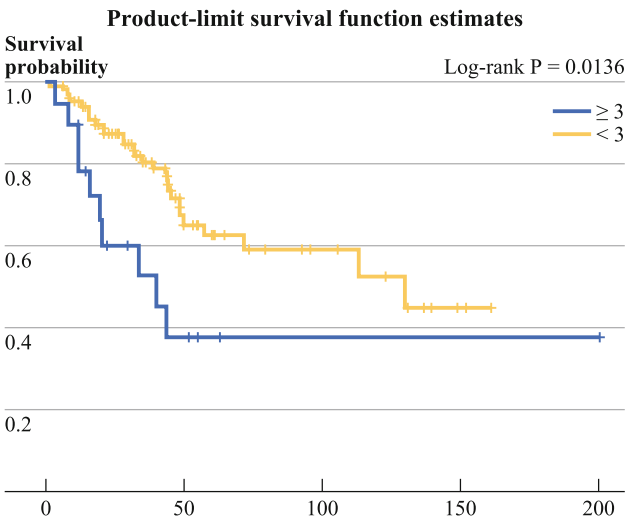
DISCUSSION

Colon cancer remains one of the leading causes of cancer death. Following an initial primary curative resection, around 50–60 % of CRC patients will develop metastases.[21,22] Metastases most commonly develop in the liver, while the lungs remain the second most common metastatic site, with isolated lung metastases occurring in around 5 % of patients following curative resection of colon cancer and in around 11–15 % following curative resection for rectal cancer.[23–26]



	Number of subjects	Event	Censored	5-year survival
One resection	610	228 (37%)	382 (63%)	52.0%
Two resections	148	48 (32%)	100 (68%)	57.9%

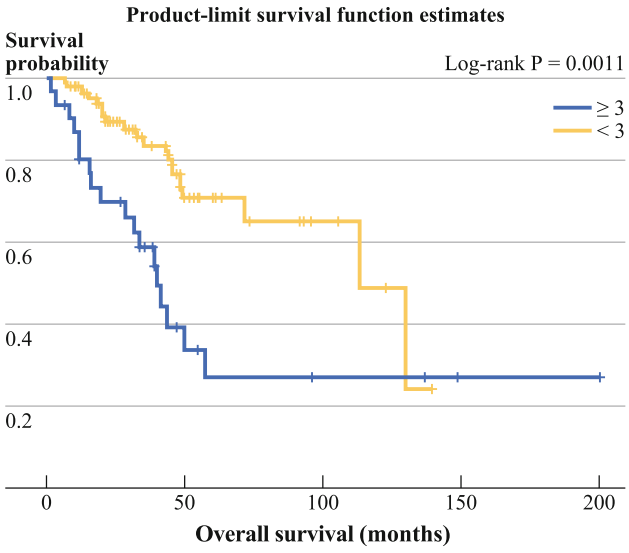
FIG. 1 Kaplan-Meier survival estimation for patients with one pulmonary metastasectomy versus patients with repeated pulmonary metastasectomy (survival was calculated from second metastasectomy for the latter group). 91 × 98mm (300 × 300 DPI)



	Number of subjects	Event	Censored	5-year survival
≥ 3	19	10 (53%)	9 (47%)	37.6%
< 3	104	29 (28%)	75 (72%)	62.5%

FIG. 2 Kaplan-Meier overall survival estimation according to number of metastatic lung nodules at the second pulmonary metastasectomy. 91 × 97mm (300 × 300 DPI)

Pulmonary metastasectomy in the setting of metastatic CRC was a common practice supported by data from non-randomized retrospective studies demonstrating encouraging



	Number of subjects	Event	Censored	5-year survival
≥ 3	31	18 (58%)	13 (42%)	27.0%
< 3	85	19 (22%)	66 (78%)	70.1%

FIG. 3 Kaplan-Meier overall survival estimation according to maximum diameter of the largest metastatic lung nodule (cm) at the second pulmonary metastasectomy. 91 × 97mm (300 × 300 DPI)

5-year survival rates of 30–60 %, which compared favorably to the poor 5-year survival rate of <10 % when patients with metastatic CRC were managed with systemic chemotherapy alone.[4–7,17,27–29]

Several studies assessed the feasibility and safety of repeated PM in patients who develop recurrent pulmonary metastases following an initial PM. However, given the small number of included patients, prognostic factors were not consistently reproduced, and debate continues to exist regarding the best surgical candidates. Park et al. assessed 48 CRC patients who had a second PM; although preoperative CEA level was a significant factor for survival in univariate analysis; multivariate analysis did not identify any independent prognostic factor.[12] Chen et al. reported in a study that included 22 CRC patients who had repeated PM that less than 1 year of DFI from the first metastasectomy until detection of the second isolated lung recurrence was a significant predictor of inferior survival following the second PM.[10] Welter et al. found that the number of metastases was an important prognostic factor for the second metastasectomy in a series that included 33 CRC patients with repeated lung metastasectomies.[13] In a study by Kanzaki et al.,[30] repeat pulmonary resections for CRC lung metastases were performed in 25 patients; patients with hilar and mediastinal LN involvement had inferior survival following the second metastasectomy. Most other studies, however, did not disclose any significant prognostic factor.

TABLE 2 Results of multivariate analysis

Clinical variable	Odds ratio	95 % CI	*p* value
Size (cm)[a]			
< 3	1	1.494–9.287	.0048
≥ 3	3.724		
Number of metastases			
< 3	1	1.194–10.761	.0229
≥ 3	3.584		
LN involvement[b]			
Not involved	1.658	0.618–4.446	.3152
Involved	1		
CEA (ng/ml)			
< 5	1.185	0.365–3.848	.7776
≥ 5	1		

[a] Maximum diameter of the largest metastatic lung nodule

[b] Status of regional LN at the time of the primary CRC surgery

The 5-year OS rate of 58 % from the second metastasectomy suggests that the biology of metastatic cancer in these patients is favorable, as it has a tendency to be limited at subsequent recurrences, which might serve as a rationale for repeated resection with curative intent, and highlights the fact that these minority of patients are salvageable and probably curable, with a strategy of repeated PM.

Comprehensive restaging to rule out extrapulmonary metastases is an essential step before proceeding with metastasectomy, and positron emission tomography (PET) scan is a valuable and sensitive staging modality that can save some patients unnecessary surgery.[31–33] Pastorino et al. investigated the utility of PET scan as a preoperative staging modality in 86 patients with isolated lung metastases from a variety of cancers.[31] Although the preoperative CT scans did not show extrathoracic metastases in any of these patients, PET scan identified extrapulmonary metastases in 11 patients (13 %) and resulted in the avoidance of surgery.

The extent of resection is a balance between complete removal of all metastatic nodules and preserving as much lung parenchyma as possible. We emphasize a lung parenchyma saving approach during the PM; 69 % of our patients with known data about the mode of surgical resection during the second metastasectomy had undergone sublobar resection. This approach will save lung parenchyma that will allow for further resection of future recurrences.

Our findings support findings from other studies that previous liver metastases that had been completely resected do not adversely impact survival of CRC patients with PM.[1,13,34–36] Consequently, repeated PM should not be denied for patients with previously resected CRC liver metastases.

An important limitation in our study is that it did not contain information about disease-free survival (DFS) and only assessed OS as an outcome measure. This occurred because information about DFS was not available in the studies included. In fact, most of studies that assessed the role of PM in CRC did not consider the DFS as an outcome measure because the aim was to identify subgroups who may survive longer with the surgical approach as OS difference would serve as a justification for a potentially morbid surgery in the setting of metastatic disease as opposed to a difference in DFS.

Our data identify a subgroup of patients who are expected to derive the best benefit of repeated PM, namely those with fewer than 3 metastatic lung nodules and a maximum diameter of the largest metastatic lesion of less than 3 cm. We believe that surgery should be considered for this subset of patients after restaging workup rules out other metastatic sites. On the other hand, patients with any of the 2 poor prognostic factors mentioned previously have more than a threefold increase in the risk of death following the second metastasectomy. For such patients, the benefit of surgery as opposed to systemic therapy is questionable and warrants further evaluation.

We did not find a prognostic significance of LN involvement in our study, although some studies and a recent meta-analysis showed an influence in the first or the repeated metastasectomy setting.[7,30,37] The small proportion of patients with proven LN involvement (4 %) is a possible factor that the status of LN in our study was not shown to be significant. Our practice is not to perform routine LN dissection as the likelihood of microscopically positive LN in those patients whose clinical staging do not suggest nodal involvement is quite low and because such a strategy was not shown to be associated with therapeutic or survival advantage. For that reason, thoracic LN sampling/dissection was not performed for majority of patients included in our pooled analysis. On the other hand, for patients whose preoperative studies, including PET/ CT scan, suggest thoracic LN involvement, mediastinoscopy should be performed and if the LN involvement is confirmed, systemic chemotherapy as opposed to pulmonary metastasectomy is a more reasonable option.

The low postoperative mortality of less than 1 % following the second metastasectomy is in accordance with what was previously reported.[10,12,13] This low postoperative mortality is likely secondary to improved selection of patients who can tolerate repeated lung resection, and the fact that we excluded publications before the year of 2000, which would exclude patients treated in an era of less advanced approaches in surgery and intensive care medicine.

Given the retrospective nature of our analysis, we could not avoid some of the important limitations, such as

missing potentially important factors. These may include the contribution of any administered perioperative chemotherapy to survival, the quality of life for the patients following repeated resection, their ability to tolerate exercise, and the requirement for home oxygen therapy. Additionally, the patients included are highly selected, with presumed good performance status and minimal comorbidities, which could at least contribute to the demonstrated long-term survival. We emphasize the importance of addressing these limitations in future studies if feasible.

In conclusion, in a carefully selected subset of patients who develop a resectable recurrence in the lungs following an initial metastasectomy of CRC lung metastasis, repeated resection is feasible and is associated with long-term survival and a quite low operative mortality. Patients with less than 3 metastatic nodules and a maximum diameter of metastatic lesion of less than 3 cm are the best candidates for repeated metastasectomy.

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