Prognostic Factors Associated With Resectable Pulmonary Metastases From Colorectal Cancer

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OBJECTIVE: To analyze prognostic factors associated with survival in a group of patients who underwent resection of pulmonary metastases from colorectal cancer.

PATIENTS AND METHODS: A retrospective review was performed for 55 consecutive patients who had undergone resection of pulmonary metastases from colorectal adenocarcinoma between January 1993 and June 2004. Univariate and multivariate analyses were performed to assess the effect of the recorded variables on overall survival.

RESULTS: Median overall survival was 32.9 months and the probability of survival at 1, 3, and 5 years was 79%, 44%, and 22%, respectively. Survival was lower in patients in whom the largest metastasis was at least 4 cm (8.6 vs 34.5 months, *P*=.0085) and in patients with elevated levels of carcinoembryonic antigen (24.5 vs 41.4 months, *P*=.05). Significantly longer survival was observed in patients who received adjuvant chemotherapy after surgery (49.8 vs 30.9 months, *P*=.0058). Preoperative positron emission tomography (PET) and the absence of previous or synchronous liver metastases were associated with a nonsignificant trend toward increased survival. In the multivariate analysis, only size of the largest pulmonary metastasis influenced overall survival (*P*=.036).

CONCLUSIONS: The preoperative variables that best predicted survival in our patients were size of the largest pulmonary metastasis and the level of carcinoembryonic antigen. Prospective studies are needed to determine the usefulness of PET for tumor staging prior to resection of pulmonary metastases.

Key words: *Colorectal cancer. Pulmonary metastases. Surgical resection. Adjuvant chemotherapy.*

Factores pronósticos en metástasis pulmonares resecables de carcinoma colorrectal

OBJETIVO: Estudiar los factores pronósticos de supervivencia en una serie de pacientes con metástasis pulmonares resecadas de cáncer colorrectal.

PACIENTES Y MÉTODOS: Se revisaron retrospectivamente los casos de 55 pacientes consecutivos a quienes entre enero de 1993 y junio de 2004 se había practicado una metastasectomía pulmonar de adenocarcinoma colorrectal. Se realizó un análisis univariante y multivariante para la supervivencia global con las variables recogidas.

RESULTADOS: La mediana de la supervivencia global fue de 32,9 meses, con una probabilidad de supervivencia a 1, 3 y 5 años del 79, el 44 y el 22%, respectivamente. La supervivencia fue inferior (p = 0,0085) en los pacientes en que la metástasis mayor era de 4 cm o más respecto a aquellos en que era menor de 4 cm (8,6 frente a 34,5 meses), y en los pacientes con títulos elevados de antígeno carcinoembrionario frente a aquéllos con valores normales (24,5 frente a 41,4 meses; p = 0,05). Quienes recibieron quimioterapia adyuvante tras la cirugía vivieron significativamente más (49,8 frente a 30,9 meses; p = 0,0058). La realización de una tomografía por emisión de positrones preoperatoria y la ausencia de metástasis hepáticas previas o sincrónicas se asociaron a una tendencia no significativa hacia una mejor supervivencia. En el análisis multivariante sólo el tamaño de la metástasis pulmonar mayor influyó en la supervivencia global (p = 0,036).

CONCLUSIONES: El tamaño de la metástasis mayor y el valor del antígeno carcinoembrionario fueron las variables preoperatorias que mejor predijeron la supervivencia de nuestros pacientes. Se necesitan estudios prospectivos que valoren el papel de la tomografía por emisión de positrones como estudio de extensión previo a metastasectomías pulmonares.

Palabras clave: *Cáncer colorrectal. Metástasis pulmonares. Resección quirúrgica. Quimioterapia adyuvante.*

Introduction

Colorectal cancer is one of the most common forms of cancer in developed countries. It has been estimated that in the USA alone more than 148 000 new cases would have been diagnosed in 2006 and that more than 55 000 patients would have died as a result of the disease in that year.[1] Approximately 10% of patients with colorectal cancer develop pulmonary metastases, although only 2%

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to 4% of all patients have metastases limited exclusively to the lung.[2] Although chemotherapy for treatment of metastases from colorectal cancer has advanced a great deal in the last decade, achieving a median survival of 20 to 22 months, 5-year survival of patients not eligible for rescue surgery is still less than 5%.[3]

Various retrospective case series of patients with pulmonary metastases of colorectal cancer have been published in the last 20 years. The overall 5-year survival reported in those studies ranges from 21% to 56%,[4-18] probably due to the heterogeneity of the selection criteria and the variation in the multimodality treatment provided. Unlike the situation in liver metastases of colorectal cancer,[19] universally accepted prognostic factors are still lacking because of conflicting results from different studies. In addition, the large majority of studies omitted from their analysis prognostic factors with known relevance in colorectal cancer, such as adjuvant chemotherapy (following resection) or pathologic factors relating to the primary tumor.

In this study, we assessed prognostic factors and overall survival in a series of patients with pulmonary metastases from colorectal cancer. The study included patients from a single hospital in whom resection was performed over a 10-year period and treatment of all patients was based on consistent surgical and oncologic criteria.

Patients and Methods

A retrospective cohort study was performed to include patients who had undergone resection of pulmonary metastases of colorectal cancer in our hospital between January 1993 and June 2004. Cases were identified using the hospital's computerized database. The criteria for indication of pulmonary metastasis resection were as follows: *a)* the pulmonary metastases identified by radiography could be feasibly resected, irrespective of their number or location; *b)* estimated respiratory function following resection was sufficient to rule out impairment of day-to-day activities; *c)* the primary tumor had been successfully treated; *d)* there was no evidence of nonpulmonary disease, and if there was, involvement was limited to a single organ and resection was also feasible; and *e)* functional status and comorbidity did not contraindicate thoracic surgery.

The following analyses were performed in a period of no more than 6 weeks before surgery: chest radiograph, electrocardiogram, general biochemical analysis, complete blood count, determination of carcinoembryonic antigen (CEA) titer, spirometry, intravenous contrast-enhanced computed tomography (CT) of the chest and abdomen (and pelvis in the case of primary rectosigmoid carcinoma) with CT slices separated by no more than 1 cm, preanesthetic assessment, and complete colonoscopy (unless a normal result had been obtained with this procedure within the last 6 months). According to the symptoms of each patient and the findings of other examinations, head CT, bone scintigraphy, and magnetic resonance imaging of the pelvis and/or liver may also have been performed. Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose was performed according to availability and clinical judgment. Prior to surgery, the patients were jointly evaluated by a member of the thoracic surgery, radiology, and medical oncology departments of the hospital to assess the indication and to confirm that all the established criteria were met.

In general, the surgical procedure of choice was atypical resection, attempting to preserve as much lung parenchyma as possible, although larger anatomical resections were not ruled out if they were necessary to completely eradicate the tumor. Systematic lymph node dissection was not employed, and excision was only performed when there was visual evidence of lymph node involvement during the intervention.

If there was no early progression of the disease, the patients received adjuvant chemotherapy within 10 weeks of surgery, as long as they had recovered from possible surgical complications, had no formal contraindications, and active drugs were available with which they had not been unsuccessfully treated previously. Periodic follow-up was initiated following surgery at intervals of no more than 3 months during the first 2 years and every 6 months from the third year. At each follow-up visit, a history was taken and a physical examination performed along with general laboratory workup to include analysis of CEA titer; CT was also performed at least every 6 months.

Data were collected on the following clinical variables for analysis of prognostic factors: age; sex; respiratory and cardiac comorbidity; site (rectum, sigmoid colon, colon) and TNM staging of the primary tumor[20]; degree of differentiation and histologic subtype of adenocarcinoma; adjuvant treatment administered after resection of the primary tumor; resection of prior or synchronous nonthoracic metastases; use of PET; preoperative CEA titer; pulmonary resection technique used; size, number, and site of the extirpated pulmonary metastases; presence of pleural invasion or involvement of the margins in pathology examination; postsurgical complications; and adjuvant treatment administered.

Statistical Analysis

Overall survival was calculated from the date of surgery for pulmonary metastasis until death or last contact. The disease-free interval at the time of surgery for pulmonary metastasis was calculated from the date of the last surgery performed with the aim of curing the cancer (the primary tumor or previous liver metastases) to the date of diagnosis of pulmonary metastasis. Continuous quantitative variables relating to analytical parameters were categorized according to the reference limits in our laboratory. For other continuous variables, the cut point that achieved the best discrimination was chosen. Statistical significance was established a priori at a value of $P<.05$. Median and actuarial survival were calculated using the Kaplan-Meier method. The Cox–Mantel log-rank test was used to compare the survival curves. A Cox proportional hazards model including those variables with a value of $P\leq.20$ in the univariate analysis was used to analyze the effect of covariates on survival. Variables were introduced using a backward stepwise approach based on the likelihood ratio test. Statistical analysis was performed using version 12.0 of the Statistical Package for Social Sciences (SPSS, Chicago, Illinois, USA) for Windows.

Results

The study included 55 patients (36 men [65.5%] and 19 women [34.5%]) in whom resection of pulmonary metastases of colorectal cancer was performed in our hospital. The mean (SD) age was 64.5 (10.2) years (range, 41-80 years). In 7 patients (12.7%), liver metastases had been resected prior to diagnosis of pulmonary metastasis. At the time of diagnosis of pulmonary metastasis, 10 patients (18.2%) had

TABLE 1
Characteristics of the Patients (n=55) Prior to Resection of Pulmonary Metastases*

	No.	%
Site of the primary tumor		
Rectum	32	58.2
Sigmoid colon	13	23.6
Colon	10	18.2
pT of the primary tumor		
pT2	3	5.5
pT3	48	87.3
pT4	4	7.2
pN of the primary tumor		
pN0	20	36.3
pN1-2	32	58.2
pNx	3	5.5
Degree of differentiation		
1	21	38.2
2	18	32.7
3	5	9.1
Unknown	11	20
Adjuvant chemotherapy after primary tumor resection		
Yes (5-fluorouracil)	35	63.7
No	20	36.3
Carcinoembryonic antigen		
Normal (≤6 U/mL)	38	69.1
Elevated (>6 U/mL)	13	23.6
Unknown	4	7.3
Other previously resected metastases		
Liver	7	12.7
Other simultaneously resected metastases		
Liver	9	16.4
Brain	1	1.8
Preoperative staging		
CT	38	69.1
CT + PET	17	30.9
Cardiac comorbidity		
Ischemic heart disease	3	5.4
Myocardial hypertrophy	3	5.4
Atrial fibrillation	2	3.6
Atrioventricular block	1	1.8
Respiratory comorbidity		
COPD	4	7.3
Asthma	3	5.4
Pneumoconiosis	1	1.8
Pulmonary restrictive syndrome	1	1.8
IRLM groups†		
I	8	14.7
II	34	61.8
III	11	20
IV	2	3.6

*COPD indicates chronic obstructive pulmonary disease; IRLM, International Registry of Lung Metastases; PET, positron emission tomography; CT, computed tomography.
†Group I, resectable, unique, disease-free interval ≥36 months; group II, resectable, unique or disease-free interval <36 months; group III, resectable, multiple, and disease-free interval <36 months; group IV, unresectable.

nonpulmonary metastases, which were also resected, 1 in the brain and 9 in the liver (1 of whom had previously undergone resection of liver metastases). The median disease-free interval at the time of surgery for pulmonary metastasis was 21.2 months (range, 1.9-62.7 months). The characteristics of the patients and primary tumors are shown in Table 1.

TABLE 2
Characteristics of Surgery and Treatment Administered in the Study Patients (n=55)

	No.	%
No. of pulmonary metastases		
1	35	63.6
2	8	14.5
3	8	14.5
≥4	4	7.3
Site of the pulmonary metastases		
Unilateral	45	81.8
Bilateral	10	18.2
Type of thoracotomy		
Unilateral	43	78.2
Unilateral + subcostal laparotomy*	2	3.6
Bilateral during the same session	5	9.1
Bilateral in 2 sessions	5	9.1
Type of pulmonary resection		
Atypical	46	83.6
Segmentectomy	2	3.6
Atypical + segmentectomy	1	1.8
Lobectomy	4	7.3
Lobectomy + atypical	2	3.6
Quality of resection		
R0 (tumor-free margins)	53	96.4
R1 (positive microscopic margins)	2	3.6
Negative histopathologic factors		
Pleural invasion	7	12.7
Vascular or lymphatic permeation	3	5.4
Morbidity†		
Wound bleeding	3	5
Hemoptysis	2	3.3
Paralytic ileum	2	3.3
Infection of surgical wound	1	1.7
Intense pain (catheter placement)	1	1.7
Pneumonia	1	1.7
Adjuvant chemotherapy		
Yes	26	47.3
No, due to early progression or death	9	16.4
No, due to other causes	20	36.3
Chemotherapy protocol		
5-fluorouracil + leucovorin	21	38.2
Irinotecan	4	7.3
Oxaliplatin + capecitabine	1	1.8

*Subcostal laparotomy was performed for resection of liver metastases at the same time as thoracotomy. †Percentage calculated based on 60 interventions.

A total of 60 procedures were performed in 55 patients: 43 unilateral thoracotomies, 2 unilateral thoracotomies with simultaneous subcostal laparotomy for resection of synchronous liver metastases, 5 bilateral thoracotomies performed in the same session, and 5 bilateral thoracotomies performed in 2 sessions. A posterolateral approach was used in all thoracotomies. One patient died 3 days after surgery due to nosocomial pneumonia following unilateral thoracotomy for a single pulmonary metastasis and was excluded from the analysis of prognostic factors. The rate of postoperative mortality (30 days) was 1.7%. The mean number of resected pulmonary metastases was 1.8 (range, 1-9) and the mean size of the largest metastasis was 2.42 (1.58) cm (range, 0.6-10 cm). Atypical resection was used in 46 patients (83.6%) and tumor-free surgical margins were obtained in 53 (96.4%). In 81.8% of cases (n=45),

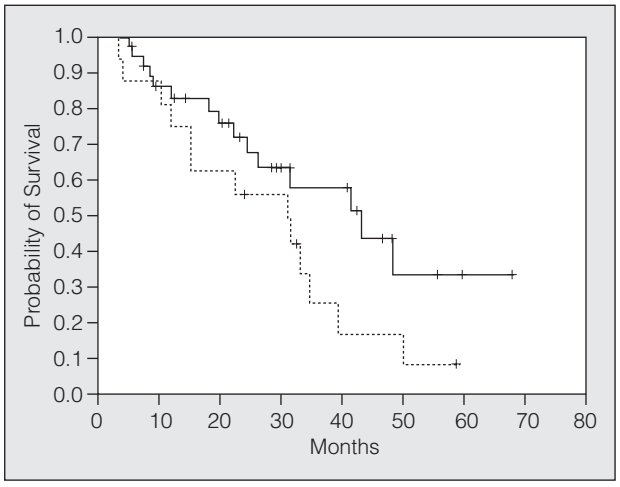

Figure 1. Overall survival in patients with nonpulmonary metastases resected previously or simultaneously (dotted line) and patients with only pulmonary metastases as the onset of disease spread (continuous line) (*P*=.08).

no negative pathologic factors (pleural invasion, vascular or lymphatic permeation) were encountered in pathology of the resected tissue. Following resection of the pulmonary metastases, 26 patients (47%) received adjuvant chemotherapy with various drugs according to the date of surgery and the drugs they had received previously. Twenty-nine patients did not receive chemotherapy—8 because of early progression, 1 because of postoperative death, and the remainder because of patient refusal or because no drugs with proven effectiveness were available at that time. Table 2 shows the characteristics of the surgery and treatment administered.

The median overall survival for the patient group was 32.9 months (95% confidence interval [CI], 28.6-37.3 months), with estimated actuarial survival at 1, 3, and 5 years of 79%, 44%, and 22%, respectively. Survival was significantly shorter in those patients in whom the size of the largest pulmonary metastasis was 4 cm or more: median overall survival was 8.6 months (95% CI, 5.4-11.9 months) compared with 34.5 months (95% CI, 23.1-45.9 months) (*P*=.0085). Likewise, survival was significantly shorter in the 13 patients (23.6%) who had a CEA titer above the normal limit (6 U/mL) than in those patients in whom the titer was normal: 24.5 months (95% CI, 14.8-34.2 months) compared with 41.4 months (95% CI, 26.1-56.8 months) (*P*=.05). Patients with previous or synchronous resected liver metastases displayed a nonsignificant trend (*P*=.08) towards poorer survival than those with exclusively lung disease: 30.9 months (95% CI, 15.2-46.6 months) and 43.1 months (95% CI, 24.2-62 months), respectively (Figure 1). The same occurred in the patients in whom CT alone had been performed to assess extension prior to surgery (31.5 months; 95% CI, 22.9-40.1 months) compared with those in whom PET had also been performed (41.3 months; 95% CI, 8.8-74.1 months) (*P*=.14). The remaining preoperative clinical variables showed no association with the probability of survival (Table 3).

In terms of the postoperative variables, it was observed that the patients who received adjuvant chemotherapy following surgery for pulmonary metastases lived significantly longer than those in whom no adjuvant treatment was administered (49.8 months [95% CI, 28.5-71.2 months] vs 30.9 months [95% CI, 17.1-44.7 months], *P*=.0058) (Figure 2). That difference remained statistically significant (*P*=.027) after exclusion of patients who did not receive adjuvant chemotherapy due to early progression. In contrast, none of the variables analyzed relating to pathology of the pulmonary metastases or the primary tumor had any effect on survival in our patients.

The following dichotomized variables were included in the multivariate analysis, according to the established method: CEA titer, size of the largest pulmonary metastasis, previous or simultaneous liver resection, and use of PET. The only variable that remained statistically significant in the regression model was the size of the pulmonary

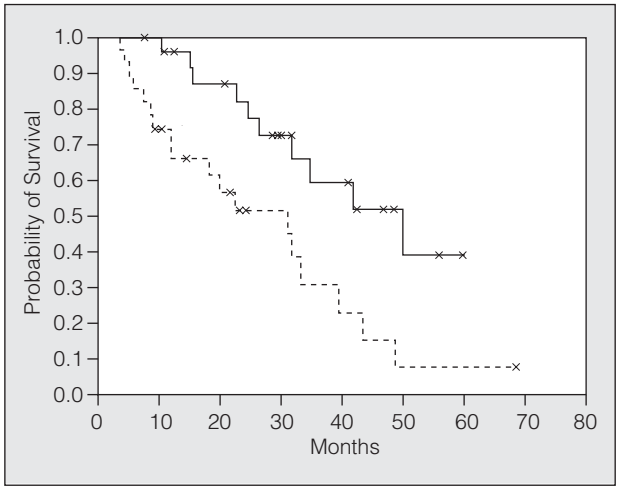

Figure 2. Overall survival in patients who received adjuvant chemotherapy (continuous line) and those who did not (dotted line) (*P*=.0058).

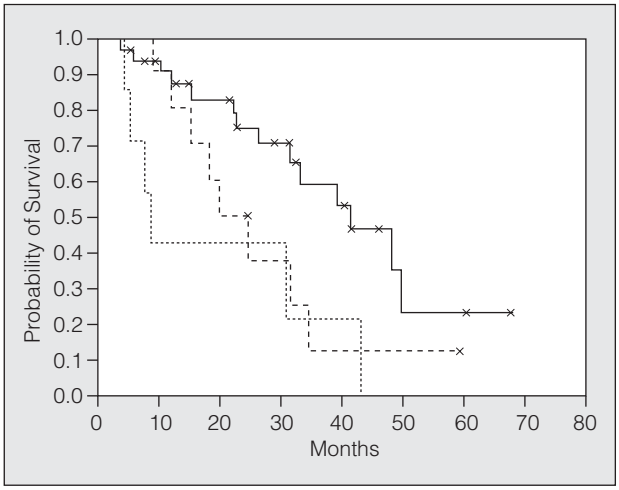

Figure 3. Overall survival in subsets of patients. Continuous line indicates patients in whom the largest pulmonary metastasis was less than 4 cm and CEA titer was normal; dashed line, patients with the largest pulmonary metastasis less than 4 cm and elevated CEA titer; dotted line, patients with pulmonary metastasis greater than 4 cm (*P*=.012).

TABLE 3
Univariate Analysis of Potential Prognostic Factors in Terms of Overall Survival*

	No.	Median Survival, Months	95% CI	*P*
All	55	32.9	28.6-37.3	
Age				.60
<70 years	35	34.5	22.4-46.6	
≥70 years	19	30.9	20.9-40.9	
Sex				.55
Male	36	32.9	29.2-36.7	
Female	18	49.8	0-104.8	
Site of the primary tumor				.25
Rectum	31	41.4	36.2-46.7	
Colon	23	30.9	20.2-41.7	
pN of the primary tumor				.88
pN0	19	41.4	17.1-65.7	
pN1-2	32	32.9	21.7-44.1	
Degree of differentiation				.45
1-2	39	32.9	28.9-36.9	
3	5	48.4	0-119.8	
Adjuvant chemotherapy after primary tumor resection				.87
No	19	39.3	27.2-51.4	
Yes	35	32.9	22.5-43.8	
Carcinoembryonic antigen				.050
Normal (≤6 U/mL)	37	41.3	26.1-56.7	
Elevated (>6 U/mL)	13	24.5	14.8-34.2	
Previous or synchronous resected metastases				.080
No	38	43.1	24.2-62.0	
Yes	16	30.9	15.2-46.7	
Preoperative staging				.14
CT	38	31.5	22.9-40.1	
CT + PET	16	41.4	8.7-74.1	
Cardiac comorbidity				.98
No	45	34.5	23.3-45.7	
Yes	9	32.9	19.4-46.4	
Respiratory comorbidity				.78
No	45	32.9	18.9-46.9	
Yes	9	31.5	19.7-43.4	
Disease-free interval				.25
<24 months	27	32.9	12.5-53.3	
≥24 Months	27	24.5	10.2-38.9	
No. of pulmonary metastases				.61
1	34	39.3	26.1-52.5	
>1	20	32.9	21.1-44.8	
Size of the largest metastasis				.0085
<4 cm	47	34.5	23.1-45.9	
≥4 cm	7	8.6	5.4-11.9	
Site				.91
Unilateral	44	32.9	28.9-36.9	
Bilateral	10	26.2	21.3-31.1	
Pleural invasion				.52
No	47	32.9	28.4-37.4	
Yes	7	41.4	20.8-62.0	
Adjuvant chemotherapy				.0058
No	28	30.9	17.1-44.7	
Yes	26	49.8	28.5-71.2	

*CI indicates confidence interval; PET, positron emission tomography; CT, computed tomography.

metastasis (*P*=.036), with an odds ratio (OR) of 0.279 (95% CI, 0.084-0.921). On multivariate analysis taking into account not only the preoperative variables, it was confirmed that the size of the largest pulmonary metastasis influenced survival (OR, 0.11; 95% CI, 0.021-0.577; *P*=.009), while administration of adjuvant chemotherapy was close to the cutoff for statistical significance (OR, 2.44; 95% CI, 0.96-6.206; *P*=.06).

Three groups of patients (Figure 3) with differing median survival (*P*=.012) could be distinguished based on the 2 preoperative variables that were confirmed as prognostic factors in the univariate analysis: *a)* size of the largest pulmonary metastasis of 4 cm or more (8.6 months; 95% CI, 5.4-11.9 months); *b)* size of the pulmonary metastasis less than 4 cm and elevated CEA titer (24.5 months; 95% CI, 15.8-33.2 months); and *c)* size of the largest pulmonary

TABLE 4
Summary of the Main Findings of Other Published Studies*

Authors	No.	5-Year Overall Survival	Worse Prognosis		Adjuvant Chemotherapy
			Univariate Analysis	Multivariate Analysis	
Goya et al[4]	62	42%	Number (>1) Size (>3 cm)	Not performed	Not analyzed
McAfee et al[5]	139	30.5%	Number (>1) CEA (>5 U/mL)	Not performed	Not analyzed
Regnard et al[6]	101	21%	Number (>1) CEA (>5 U/mL)	Not performed	Not analyzed
McCormack et al[7]	144	40%	Node involvement†	Not performed	Not analyzed
Girard et al[8]	86	24%	CEA (>5 U/mL) Incomplete resection	CEA (>5 U/mL) Incomplete resection	Not analyzed
Okumura et al[9]	159	40.5%	Liver metastases Number (>1) Dukes stage C‡ Node involvement†	Not performed	Not analyzed
Zink et al[10]	110	32.6%	Number (>1) Size (>2.8 cm) CEA (>5 U/mL)	Number (>1) Size (>2.8 cm)	Not analyzed
Irshad et al[11]	49	55%	Number (>1) Bilateral Disease-free interval (<24 months)	Not performed	NS
Sakamoto et al[12]	47	48%	CEA (>5 U/mL) Liver metastases	Not performed	Not analyzed
Rena et al[13]	80	41.1%	CEA (>5 U/mL) Disease-free interval (<36 months)	CEA (>5 U/mL) Disease-free interval (>36 months)	Not analyzed
Saito et al[14]	165	39.6%	Number (>1) Bilateral CEA (>10 U/mL) Node involvement†	CEA (>10 U/mL) Node involvement†	.3376
Pfannschmidt et al[15]	167	32.4%	Number (>1) CEA (>5 U/mL) Node involvement†	CEA (>5 U/mL) Node involvement†	Not analyzed
Watanabe et al[16]	49	56%	Number (>1)	Not performed	Not analyzed
Pop et al[17]	42	29.5%	Incomplete resection Disease-free interval (<24 months)	Not performed	Not analyzed
Vogelsang et al[18]	75	27%	Size (>3.75 cm) Nonanatomical resection Stage III-IV (TNM)	Size (>3.75 cm) Nonanatomical resection	NS
Our study	55	22%	Size (≥4 cm) CEA (>6 U/mL)	Size (≥4 cm)	.006

*CEA indicates carcinoembryonic antigen; NS, not significant.
†Tumor invasion of hilar or mediastinal lymph nodes. ‡Invasion of at least 1 regional lymph node in the primary tumor.

metastasis less then 4 cm and normal CEA titer (41.4 months; 95% CI, 27.1-55.8 months).

At the time of analysis, 41 patients (74.5%) had relapsed: 17 with recurrence only in the lung, 6 in the lung and liver, and 5 in the lung and another site. Of those 41 patients, 13 (31.7%) were treated again with the aim of curing the cancer: 11 for isolated pulmonary metastases, 1 for liver metastasis, and 1 for brain metastasis. The median overall survival, calculated from the date of the second surgical procedure, in patients with isolated recurrence in the lung in whom surgery was repeated was 17.9 months (95% CI, 11.6-24.2 months), with an estimated survival at 2 and 3 years of 33% and 17%, respectively. When overall survival was calculated from the day of the initial thoracotomy, no significant difference was observed between those patients and the remainder of the patients included in the study: 34.5 months (95% CI, 30.6-38.4 months) versus 31.5 months (95% CI, 13.8-49.2 months) (P=.73).

Discussion

Surgical resection of pulmonary metastases is considered a routine technique with relatively low morbidity and mortality.[21,22] The International Registry of Lung Metastases (IRLM) collected data on 5206 patients who underwent surgery over a period of more than 40 years and established 4 groups with differing survival according to the quality of the resection, the disease-free interval, and the number of metastases.[23] The main problem with that study was that it did not analyze the influence of prognostic factors specific to each tumor. Although the model has been validated in other case series involving resection of pulmonary

metastases of differing etiology,[24] its applicability to a case series of patients with pulmonary metastases exclusively from colorectal cancer has never been assessed. The retrospective studies published on surgical treatment of pulmonary metastases of colorectal cancer have used a variety of selection criteria and differing preferences in terms of surgical technique. In addition, many of them did not analyze recognized prognostic factors that relate to the primary tumor and subsequent treatment, and sometimes a multivariate analysis was not performed (Table 4).

In our study, we obtained a median survival of 32.9 months, which represents an intermediate value within the range described in other published studies (19-41 months).[4-18] The estimated 5-year survival of 22% can be considered low in comparison with previous reports (21%-56%), but considering that 26 patients (47.2%) were alive at the time of analysis, some with only a short follow-up period completed, the reliability of this figure is more doubtful (95% CI, 0%-47%). Consistent with previous descriptions, age, sex, and primary tumor site (colon or rectum) were not associated with survival in our study. More importantly, we observed that the size of the largest pulmonary metastasis represented the principal prognostic factor for the survival of our patients and the only factor that was statistically significant in the multivariate analysis. Those patients in whom the largest pulmonary metastasis was 4 cm or more had a 9-fold greater risk of death and a probability of survival at 2 years of 15% and at 5 years of 0%. A greater volume of visible tumor usually indicates a greater likelihood that other undetectable metastases are present. In fact, tumor size is a prognostic factor in most malignant tumors and is accepted as one of the prognostic factors in surgically treated liver metastases of colorectal cancer.[19] Tumor size has also been associated with survival in another 2 recently published studies, with cut points of 2.8 cm[10] and 3.75 cm.[18] One explanation for the failure to observe this association in previous studies could be that as selection criteria have widened over time, the number of surgically treated patients with large metastases has increased. Likewise, other variables associated with tumor volume, the number of metastases, or the CEA titer, may have played a role as confounders.

CEA titer above the normal limit (6 U/mL) also acted as a negative prognostic factor in our study. Although not all tumors express CEA, the serum concentration of the antigen is usually considered an indicator of tumor volume in colorectal cancer. CEA titer was first described by McAffee et al[5] and is the variable that has been most commonly associated with survival of patients following resection of pulmonary metastases,[8,10,12-15] and even appears as an independent prognostic factor.[8,13-15] On the other hand, elevated CEA titer is also associated with worse disease course in patients with metastatic colorectal cancer who receive chemotherapy[25] and in patients who undergo resection of liver metastases.[19]

With these 2 clinical variables (size of the largest pulmonary metastasis and CEA titer), both of which can be easily determined prior to surgery, we were able to define 3 groups of patients with different survival in our case series. The definition of subgroups with worse prognosis may allow studies to be undertaken with new treatment strategies, such as administration of neoadjuvant chemotherapy, as well as the development of follow-up protocols with closer monitoring. In our opinion, however, until universally accepted criteria are established to allow identification of patients with no possibility of long-term survival following surgery, these variables should not be used to exclude patients from potentially curative surgical treatment.

The possible relationship between survival and the use of PET to assess tumor extension is also of interest. Although a statistically significant association was not obtained in our study, we did observe a positive trend. It should be taken into account that the majority of our patients who underwent a PET study had a shorter follow-up, and this could have been a factor in the absence of statistical significance. Use of PET can facilitate recognition of metastatic foci not identified in CT and therefore allow surgery to be ruled out in patients in whom it would not be effective. In a recent prospective study involving 32 patients with pulmonary metastases of colorectal cancer, surgery was ruled out in 4 patients (12.5%) due to evidence of local recurrence or distant metastasis in PET studies.[21] Although more studies are required to confirm these findings, it is our opinion that PET may be indicated for assessment of extension prior to surgery, particularly in patients with factors associated with a poor prognosis.

Number of pulmonary metastases is one of the least well accepted prognostic factors. Most studies have observed better survival in patients with single resected pulmonary metastases,[4-6,9-11,14-16] although occasionally it has been reported as an independent prognostic factor.[10] Similarly, only 1 study has found a relationship between disease-free interval and survival in the multivariate analysis.[13] In our study, we found no relationship between these variables and overall survival. Not even classification into prognostic groups according to IRLM categories, which include both variables, revealed differences in disease course in our patients. In our opinion, the use of those variables as prognostic factors in patients with pulmonary metastases of colorectal cancer is questionable.

In our study, we found that administration of chemotherapy following resection of metastases appeared to influence survival. Although randomized trials have not been published on the efficacy of systemic chemotherapy following resection of metastases of colorectal cancer, its theoretical basis seems reasonable. The indication for chemotherapy in advanced disease has been clearly demonstrated,[3] and furthermore, adjuvant therapy increases overall survival following resection of colon cancer in high-risk stage II patients and stage III patients.[3,26] The large majority of case series involving resected pulmonary metastases have not analyzed the administration of treatment following surgery as a prognostic factor, while in the few that have,[11,14,18] no significant association with survival was observed. Although the assessment of subsequent treatments in retrospective studies is subject to significant selection bias, in our study, even excluding patients who were not treated due to early progression or death, it remained significant in the univariate analysis. The high proportion of patients who received adjuvant therapy and its individualized use according to previous treatment may have influenced the positive result in our patients.

A subject under discussion is the indication for resection of pulmonary metastases in patients with previous or synchronous resectable liver metastases. Although some authors have found that a history of resected liver metastases is a negative prognostic factor,[9] studies that have specifically analyzed the question have concluded that it should not be considered a contraindication for pulmonary surgery.[27-30] In our patients, although the presence of liver metastases was associated with lower median survival, it was not found to be a statistically significant prognostic factor. Furthermore, the median survival of 30.9 months obtained was much higher than the most optimistic predictions for any other treatment modality. Therefore, we believe that resection of pulmonary metastases should not be ruled out on the basis of previous extirpation of liver metastases or concomitant resectable hepatic tumors.

Pulmonary recurrence following resection of metastases is a crucial issue during follow-up and the indication for repeat intervention is the subject of debate. In the study by McAfee et al,[5] patients who underwent repeat intervention for pulmonary progression had a 5-year survival of 30%. In our study, the 11 patients in whom a second resection of pulmonary metastases was performed had a lower survival, but more importantly, that survival did not differ significantly from the survival obtained in the series as a whole.

In conclusion, we believe that all patients with pulmonary metastases of colorectal cancer that are considered potentially resectable according to the criteria employed in this study should be considered candidates for surgery, given the absence of universally accepted prognostic criteria. In patients with various negative prognostic factors, such as elevated CEA titer and increased size of the largest pulmonary metastasis, new therapeutic strategies should be considered, such as the use of neoadjuvant chemotherapy, more exhaustive assessment of extension to include PET, and implementation of follow-up protocols with closer monitoring. Although further studies are required, we believe that adjuvant chemotherapy should also be considered following resection of pulmonary metastases in view of our findings and the proven effectiveness of such therapy in advanced disease and after primary tumor resection.

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