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Pulmonary resection for metastases from colorectal cancer: factors influencing prognosis. Twenty-year experience

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Abstract

Objective: We reviewed our experience in the surgical management of 80 patients with colorectal pulmonary metastases and investigated factors affecting survival. **Material and methods**: From January 1980 to December 2000, 80 patients, 43 women and 37 men with median age 63 years (range 38–79 years) underwent 98 open surgical procedure (96 muscle-sparing thoracotomy, one clamshell and one median sternotomy) for pulmonary metastases from colorectal cancer (three pneumonectomy, 17 lobectomy, seven lobectomy plus wedge resection, six segmentectomy, three segmentectomy plus wedge resection and 62 wedge resection). Pulmonary metastases were identified at a median interval of 37.5 months (range 0–167) from primary colorectal resection. Second and third resections for recurrent metastases were done in seven and in four patients, respectively. **Results**: Operative mortality rate was 2%. Overall, 5-year survival was 41.1%. Five-year survival was 43.6% for patients submitted to single metastasectomy and 34% for those submitted to multiple ones. Five-year survival was 55% for patients with disease-free interval (DFI) of 36 months or more, 38% for those with DFI of 0–11 months and 22.6% for those with DFI of 12–35 months ($P = 0.04$). Five-year survival was 58.2% for patients with normal preoperative carcino-embryonic antigen (CEA) levels and 0% for those with pathologic ones ($P = 0.0001$). Patients submitted to second-stage operation for recurrent local disease had 5-year survival rate of 50 vs. 41.1% of those submitted to single resection ($P = 0.326$). **Conclusions**: Pulmonary resection for metastases from colorectal cancer may help survival in selected patients. Single metastasis, DFI > 36 months, normal preoperative CEA levels are important prognostic factors. When feasible, re-operation is a safe procedure with satisfactory long-term results.

Keywords: Pulmonary metastases; Colorectal carcinoma; Lung resection; Carcinoembryonic antigen

1. Introduction

Since no effective chemotherapy regimen has been proposed for pulmonary metastases from colorectal cancer, surgery is the only potentially curative treatment. In 1965, Thomford et al. reported the principles for resection of metastatic lung tumours, and these have been accepted by most surgeons [1]. Over a few decades, the indications for metastatic lung tumours have been extended.

Resection of a solitary lung metastasis has been accepted by physicians, while pulmonary resection for multiple or bilateral lesions remains controversial. In addition, the role of repeated thoracotomy for recurrent cancer has not been well defined.

We review our experience in the surgical management and investigate factors affecting survival of 80 patients with colorectal pulmonary metastases, 69 from the Thoracic Surgery Department of the University of Torino and 11 from the Thoracic Surgery Unit of the University of Eastern Piedmont of Novara.

2. Materials and methods

From January 1980 to December 2000, 80 patients underwent 98 operations for the resection of lung metastases from colorectal cancer. There were 37 men and 43 women. Their age at surgery ranged from 38 to 79 years, and median age was 63 years. The primary tumour site was the colon in 59 patients and the rectum in 21 patients. The median interval between the colorectal resection and the diagnosis of the pulmonary metastases was 37.5 months (range 0–167).

Six of the 80 patients were identified with pulmonary nodules at the time of the work-up of their primary colorectal carcinoma. In these patients, surgical resection of the

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pulmonary nodule followed recovery of the primary malignancy from the patient's surgical management.

Pulmonary lesions were identified at least 6 months beyond the time of the primary resection colorectal surgery in the remaining 74 patients.

Selection criteria for resection were as follows: controlled primary tumour, controlled or controllable extrathoracic lesions, and computed tomography (CT) scan demonstrating that radical resection could be performed regardless of the number of the lesions. Tumours in the bilateral thorax were not considered as a contraindication.

A full metastatic work-up was undertaken prior to therapeutic surgical resection of colorectal metastases in all patients. Colonoscopic examination was routinely performed, as was CT scanning of the chest, abdomen and pelvis. Since 1990, thin cut (0.5–1.0 cm) high-resolution CT images were obtained of the entire lung fields and preoperative carcino-embryonic antigen (CEA) levels were obtained in 68 of the patients immediately before their surgical resection. Physiological assessments, including pulmonary function studies, were undertaken on all 80 patients and all patients were felt to be at low preoperative risk for pulmonary resection.

Among the 98 operations, 96 were carried out through muscle-sparing thoracotomy, one through bilateral thoracotomy associated with transverse sternotomy (clam-shell incision) and one through median sternotomy.

Principally, wedge resection was the procedure of choice, and we tried to preserve normal pulmonary parenchyma as much as possible. Lymph node dissection was not undertaken unless macroscopically positive findings were seen during operation.

Surgical procedures were wedge resection in 62 patients, segmentectomy in six patients, segmentectomy plus wedge resection in three patients, lobectomy in 17 patients (three middle lobe resections), lobectomy plus wedge resection in seven patients (three middle lobe resections) and pneumonectomy in three patients. Therefore, 71 operations (72.5%) involved less than a lobectomy. Six out of 24 lobectomies were resections of the middle lobe which could be carried out with small parenchymal amputation.

Survival was estimated by the method of Kaplan and Meier, using the date of pulmonary resection as the starting point. The influence of variables on survival was analysed using the log-rank test for discrete variables. Multivariate analysis was performed by the Cox proportional hazards model.

3. Results

There was one postoperative death due to pulmonary embolism 4 days after a wedge resection and one due to pneumonia 6 days after a lobectomy (operative mortality rate: 2.02%).

The follow-up was complete on August 31, 2001 or to death for 73 out of 80 patients (91.2%). Overall, 3-, 5- and 10-year survival rates were 54.4, 41.1 and 18%, respectively, and mean survival was 26.8 ± 20.4 months (range 6–89) (Fig. 1).

Pulmonary resection followed colorectal resection in all patients. The disease-free interval (DFI) was defined as the interval between colon resection and detection of lung deposits. The DFI ranged from 0 to 167 months, and the median DFI was 37.5 months; 17 patients had a DFI of 0–11 months, 23 patients had a DFI of 12–35 months and 40

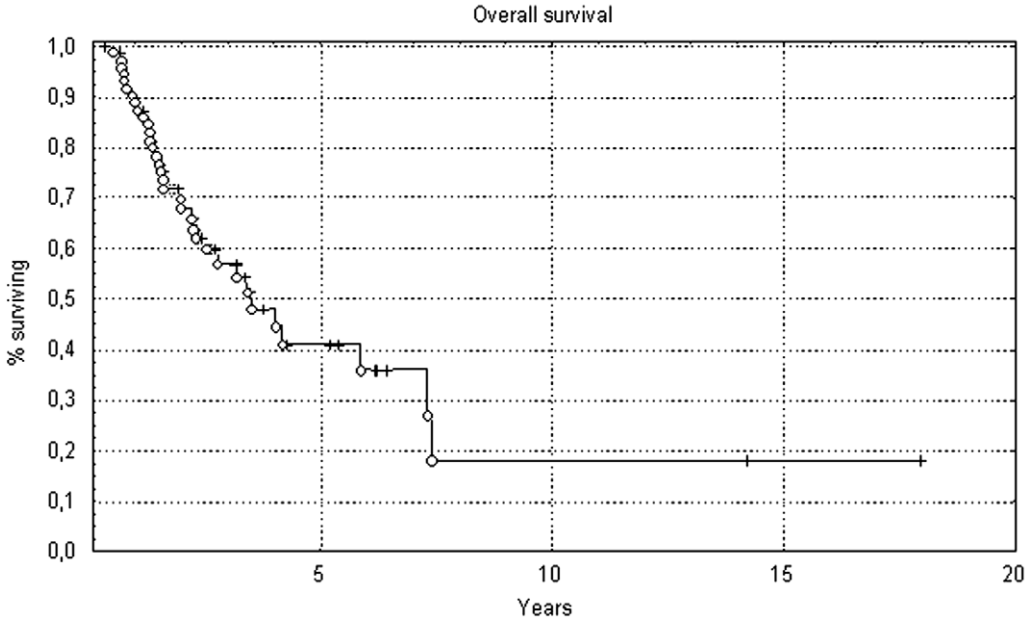

Fig. 1. Kaplan–Meier overall survival curve (patients at risk: at 3 years, 18; at 5 years, 9).

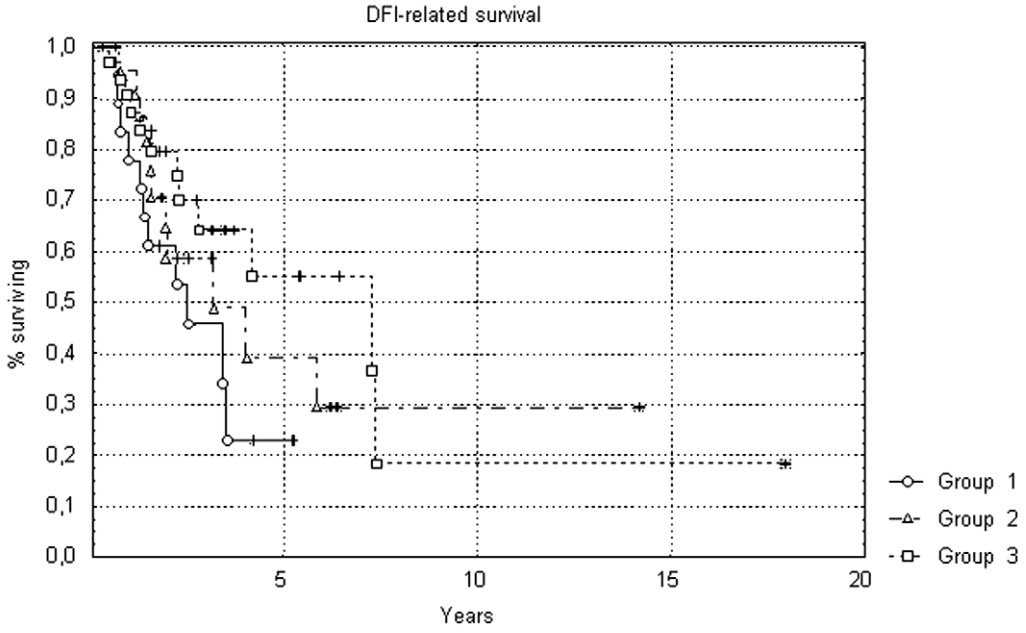

Fig. 2. Kaplan–Meier survival curve related to the DFI. Group 1: DFI of 0–11 months; Group 2: DFI of 12–35 months; Group 3: DFI of 36 months or more; log-rank test: $P = 0.04$ (patients at risk at 3 years: group 1, four, group 2, six, group 3, nine; patients at risk at 5 years: group 1, one, group 2, four, group 3, five).

patients had DFI of 36 months or more. Five-year DFI-related survival rates were 22.6, 38.6 and 55%, respectively, and this observation was significant ($P = 0.04$; Fig. 2). Fifty-nine patients had a solitary lesion, and 21 had multiple ones. The number of resected nodules through a single thoracotomy was one in 59 cases, two in nine cases, three in five cases; and four or more in six cases. The mean number of resected deposits was 1.59 ± 1.36 (range 1–8). Three- and 5-year survival rates were 60 and 42.2% for patients with solitary metastasis, 49 and 36% for those with two or three metastases and 34 and 0% for those with three or more metastases; there were no significant difference ($P = 0.265$) (Fig. 3). Patients were divided into two groups: the first constituted by patients affected by single metastasis

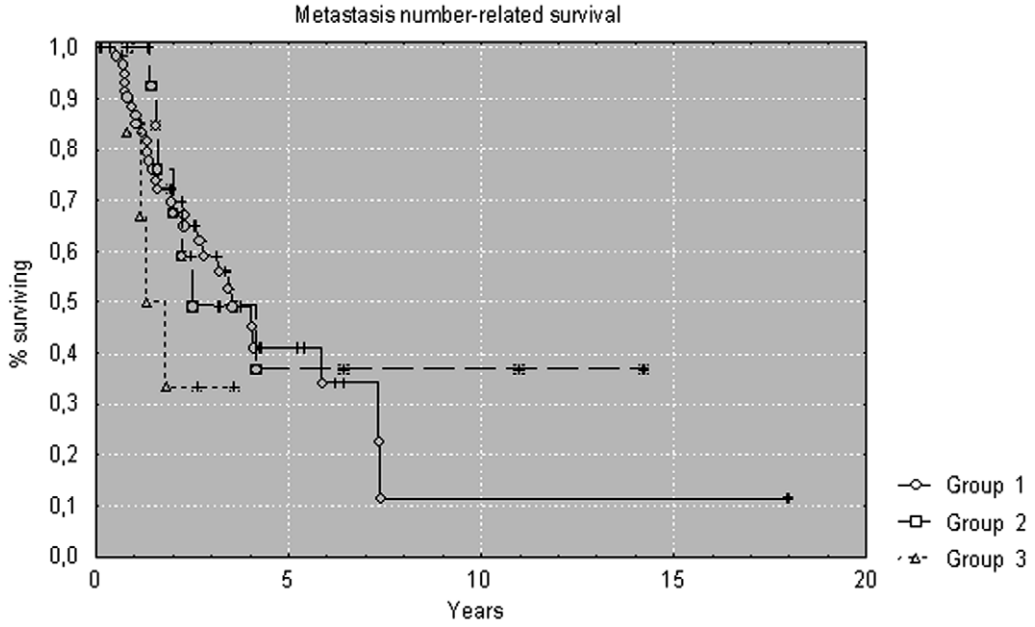

Fig. 3. Kaplan–Meier survival curve related to the number of the metastases resected. Group 1: single metastasis; Group 2: two or three metastases; Group 3: four or more metastases; log-rank test: $P = 0.217$ (patients at risk at 3 years: group 1, 16; group 2, five; group 3, one; patients at risk at 5 years: group 1, eight, group 2, three, group 3, none).

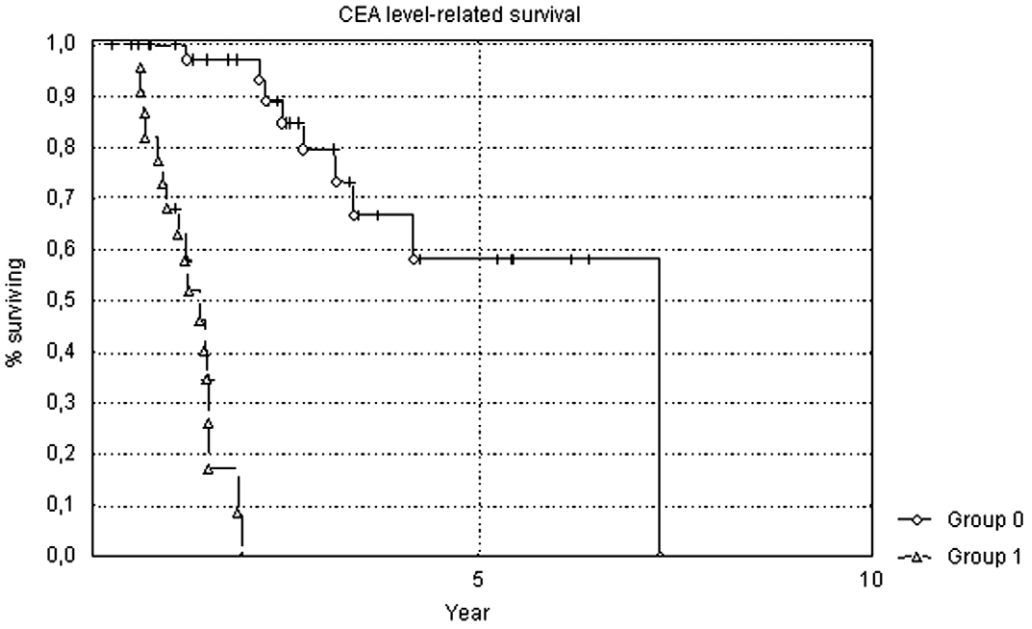

Fig. 4. Kaplan–Meier survival curve related to the preoperative CEA serum level. Group 0: CEA <5 ng/mL; Group 1: CEA > 5 ng/mL; log-rank test: $P = 0.0001$ (patients at risk at 3 years: group 0, 12, group 1, none; patients at risk at 5 years: group 0, 5, group 1, none).

($n = 59$) and the second by multiple ones ($n = 21$). Three- and 5-year survival rates were 60 and 43.6% for the first group and 44 and 34% for the second one ($P = 0.77$).

Prethoracotomy CEA levels were measured in 68 patients. Five-year survival rate was 58.2% for 39 patients with normal prethoracotomy CEA levels and 0% for 29 patients with elevated prethoracotomy CEA levels (>5 ng/mL) (Fig. 4). Patients with normal prethoracotomy CEA levels had better prognosis than those with elevated prethoracotomy levels ($P = 0.0001$).

Among the 80 patients, nine received incomplete resection: the survival rates at 3 and 5 years were 57 and 41% for patients submitted to complete resection, and 43 and 21% for those submitted to incomplete one: the difference was not significant ($P = 0.661$).

Data resulting from the analysis suggested that three factors, excluding the complete resection of the disease, should be related with better postoperative prognosis: single metastasis, DFI of 36 months or more and preoperative CEA levels of 5 ng/mL or less. Multivariate analysis using the Cox proportional hazards model was used to define the prognostic significance of the following variables: DFI, CEA levels and number of resected deposits (Table 1). For multivariate analysis, DFI and CEA levels were found to be significant in survival prediction.

Patients were then divided into three groups according to the presence or absence of the above mentioned risk factors: group I, patients with single metastasis, DFI > 36 months, CEA levels of 5 ng/mL or less; group II, patients with single metastasis and DFI < 36 months or CEA levels >5 ng/mL; group III, patients with single metastasis, DFI < 36 months and CEA levels >5 ng/mL. The survival rates at 3 and 5 years were: 76 and 76% for the first group, 73 and 38% for the second one and null for the third one. High significant difference was recorded between the groups ($P = 0.0001$) (Fig. 5).

A second resection for recurrent metastases was done in seven patients (8.7%) (in one case, the re-operation was bilateral), and a third resection was done in four out of seven patients (in one case, the re-operation was bilateral).

The mean DFI after the first metastasectomy was 23.4 ± 20.3 months (range 6–72). The survival rates at 3 and 5 years were 66 and 50% for patients submitted to the second metastasectomy; the mean survival was 42.5 ± 36.69 months, range 1–218; even if higher than that of patients submitted to single metastasectomy, the difference was not significant ($P = 0.329$).

Table 1
Prognostic significance of variables related to patients 5-year survival tested using multivariate (Cox proportional hazards) analysis

Variables	*N*	5-Year survival (%)	*P* value
Disease-free interval	80		0.0317
<12 months	17	22.6	
12 < DFI < 35	23	38.6	
>36 months	40	55	
CEA levels	68		0.0001
<5 ng/mL	39	58.2	
>5 ng/mL	29	0	
Metastases number	80		0.234
Single	59	42.2	
Two or three	15	36	
Four or more	6	0	

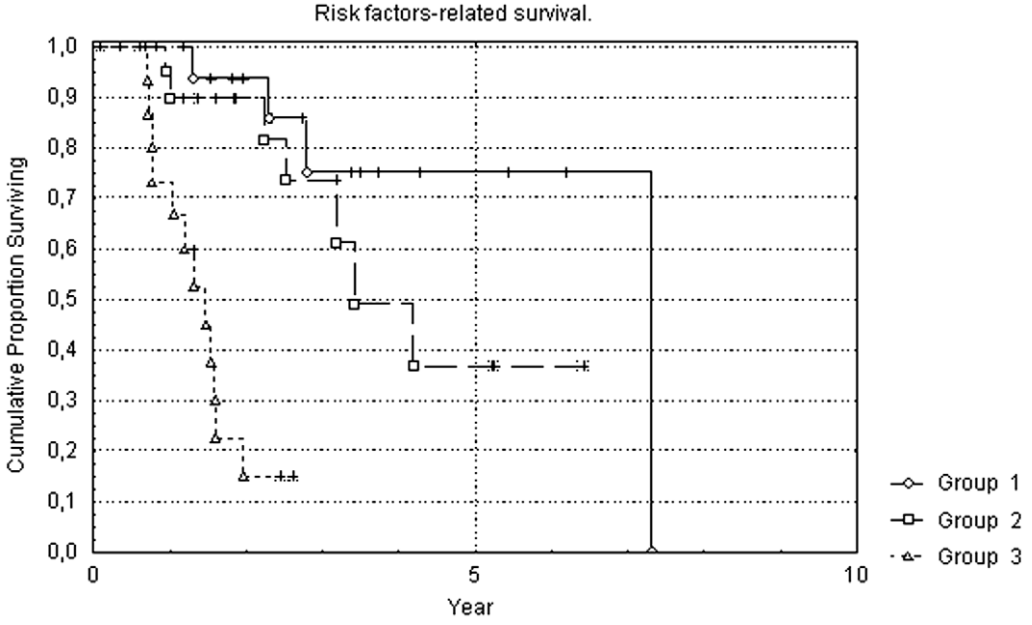

Fig. 5. Kaplan–Meier survival curve related to the presence of risk factors for single complete metastasectomy. Group 1: DFI > 36 months or more and CEA <5 ng/mL; Group 2: DFI <36 months or CEA >5 ng/mL; Group 3: DFI <36 months and CEA >5 ng/mL; log-rank test: $P = 0.0001$ (patients at risk at 3 years: group 1, seven; group 2, six; group 3, none; patients at risk 5 years: group 1, three; group 2, two; group 3, none).

On August 31, 2001, 30 patients had experienced recurrent systemic disease or local recurrent disease with multiple nodules which were considered not to benefit re-operation and they died with a median survival of 18 months (range 6–51); 11 patients had experienced recurrent local disease and were re-operated, among these patients four died with median survival of 30 months (range 16–71) and five are alive with median survival of 31 months (range 19–133); 29 patients are alive and disease-free with median survival of 24 months (range 2–218), 12 patients are alive with recurrent disease considered not surgically manageable with median survival of 29 months (range 7–78).

4. Discussion

We retrospectively analysed the data relative to pulmonary resection for colorectal matastases in order to identify the factors eventually influencing prognosis in these patients.

As referred by others, sex, age and gender such as the site of the primary malignancy (colon or rectum) were not factors influencing prognosis. On the other hand, and according to other authors, DFI (considered as the period between the surgical resection of the primary tumour and the detection of the pulmonary deposit) was identified as an important prognostic factor [2–4]. We decided to group patients following the same methods described by the International Registry of Lung Metastases (IRLM): patients were divided into three groups according to the DFI of 0–11 months, DFI of 12–35 months, and DFI of 36 months or more [5]. Patients with DFI > 36 months had better prognosis than the others and the difference was significant.

Many authors reported that patients with solitary metastasis had a better prognosis than those affected by multiple ones [5–11]. Our data indicate the same result but in our studies, the difference did not reach significance. Patients were divided into three groups on the basis of the number of metastases, following the same criteria of the IRLM [5], but differences in survival rates were not significant too.

In our studies, nine patients out of 80, received incomplete resection of the metastatic disease: their survival rate was lower than that of patients submitted to complete resection of the pulmonary deposits, but the difference was not significant. This is probably due to the great difference in the composition of the two groups.

During the last 10 years, prethoracotomy CEA serum levels were evaluated in all patients: we collected 68 data, in 39 patients, the CEA level, under 5 ng/mL, was considered normal and in 29 patients, it was higher than 5 ng/mL and so it was considered pathologic. Survival rates for these two groups of patients revealed the significant prognostic value of the normal preoperative CEA level. Patients with pathologic preoperative CEA level had worse prognosis. A few authors reported similar results: elevation of CEA implies a worse prognosis [6,9,10,12]. CEA itself participates in intracellular recognition and attachment and may promote adhesions of tumour cells to each other or to host cells [13]. Therefore, preintervention CEA levels can be taken into account in selecting patients for pulmonary resection, especially if tumours are multiple or bilateral [11,14].

From the above-mentioned analyses, DFI of 36 months or more, normal preoperative CEA level, single metastasis and

complete resection (even if the last two not significant) were identified as important prognostic factors. DFI <36 months and pathologic CEA levels were considered as important risk factors. Patients affected by single pulmonary metastases completely resected were divided into three subgroups: group I, patients with DFI > 36 months and normal CEA level; group II, patients with DFI < 36 months or pathologic CEA level; group III, patients with DFI < 36 months and pathologic CEA level. This classification was tested by the Kaplan–Meier method in evaluating survival and the survival rates for the three groups were significantly different ($P = 0.0001$).

From the above cited analyses, we can conclude that patients with single metastasis completely resectable, with DFI > 36 months and normal preoperative CEA levels are the better candidates for lung resection for colorectal metastases [14].

Local recurrence after pulmonary metastasectomy is a crucial problem during follow-up, and the indication for operation is controversial. In our studies, 19 patients experienced recurrent local disease, but only 11 were eligible for re-operation (the other 10 were affected by multiple bilateral pulmonary nodules (range 12–18) or by multiple pulmonary nodules associated with mediastinal lymph nodes enlargements). McAfee et al. reported that 5-year survival for 19 patients who underwent a second thoracotomy was 30.2% from the date of the second thoracotomy [6]. Kandioler et al. reported similar results [15]. In our studies, the 5-year survival rate for 11 patients submitted to re-operation was 50%. This is probably related to the fact that patients with recurrent operable disease probably belong to a group of patients with less aggressive disease.

We consider wedge resection as the procedure of choice, and resection greater than a lobectomy should be avoided whenever possible. In our studies, we reported three pneumonectomies, all carried out during the first decade of our experience, in patients with high DFI (DFI > 90 months) and with misleading preoperative diagnosis. Twenty-four lobectomy, nine associated with wedge resection, were carried out for nodules ranging the lobar hilum; in six cases they were middle lobe resection, associated with small parenchyma sacrifice. We think that open procedures such as muscle-sparing thoracotomy are to be recommended in each case of pulmonary metastases, even if the progress in imaging techniques (such as high-resolution CT scan and spiral CT) have ameliorated the possibility in detecting and localising all the pulmonary lesions of smaller diameter too. Landreneau et al., during the previous years, referred about series of patients submitted to the resection of pulmonary metastases by endoscopic procedures such as video-assisted thoracoscopy [12]. They referred that the use of this technique is strictly subordinated to the preoperative evaluation of the patient by high-resolution imaging devices such as high-resolution CT scan of the chest, which allow the prompt recognition and localisation of the smallest pulmonary deposits. Since it will not be disposable, any comparative study in the management of metastatic lung disease by open and endoscopic procedures, we will reserve the surgical treatment of these patients by video-assisted thoracoscopy only for single little nodes in contact with the lung surface, palpable with a finger. In our studies, the more frequent surgical access was represented by thoracotomy ($n = 96$; 98%): improvement in the diagnostic accuracy of high-resolution CT scan in detecting smallest pulmonary nodules has reduced the necessity to palpate and inspect both lungs at the same surgical time, which was allowed only by bilateral procedures or sternotomy.

5. Conclusions

Single deposit, DFI > 36 months and normal preoperative CEA levels are indicators of better prognosis in the surgical management of colorectal lung metastases. Re-operation, when feasible, is a safe procedure which allows satisfactory long-term results, probably related to a less aggressive disease.

Resections should be carried out taking maximum care of the residual normal parenchyma, which could allow safer re-operation when necessary. Even if the preoperative detection of the smallest deposits has been improved by high-resolution imaging techniques increasing the role of the endoscopic procedures, we consider the muscle-sparing open procedures as the gold standard in the management of pulmonary metastases; when a superficial node cannot be palpated with a finger introduced in one of the surgical ports, we prefer a conversion to a thoracotomy as small as possible.

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