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Lung metastases from colorectal cancer: surgical resection and prognostic factors☆

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Abstract

Objective: To analyse our experience with excision of lung metastases from colorectal carcinoma (CRC), and to evaluate clinically relevant prognostic factors, identifying the cluster of patients who would benefit from this procedure. **Methods:** Sixty-one patients, 42 men (69%), with primary CRC who underwent 94 curative resections of pulmonary metastases were retrospectively reviewed. Age was 30—80 years (mean 61.2 ± 15). Population was analysed for age, sex, disease-free interval (DFI), prethoracotomy carcinoembryonic antigen (CEA) level, location and histology of primary tumour, number of lung lesions (and size of largest resected metastasis), type of lung resection, nodal involvement (hilar/mediastinal), use of adjuvant treatment, morbid-mortality and immediate and follow-up survival. **Results:** Mean DFI was 29 ± 22 months (range 5—132 months). There was no hospital mortality and significant morbidity occurred in five patients (8.2%). Mean follow-up was 39 ± 4 months (range 4—173 months). Mean overall survival and disease-free survival were 67 ± 16 months and 52 ± 6 months, respectively. Three-, 5- and 10-year survival rates from date of primary colorectal resection were 83%, 71% and 43%, respectively. Three-, 5- and 10-year survival rates from date of lung resection were 61%, 48% and 11%, respectively. Five-year survival was 57% in patients with normal prethoracotomy CEA levels and 18% for those with high levels (>5 ng/ml) ($p = 0.039$). **Conclusions:** Pulmonary metastasectomy has potential survival benefit for patients with metastatic colorectal carcinoma. Low morbidity and mortality rates, contrasting with lack of any other effective therapy, justify aggressive surgical management. Single deposits, DFI >36 months and normal prethoracotomy serum CEA were significant independent prognostic factors.
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Keywords: Lung metastases; Colorectal cancer; Metastasectomy

1. Introduction

Second only to lung cancer in men and breast cancer in women, colorectal cancer is an important cause of death, with increasing incidence over the past 25 years [1—3]. The lung is one of the most frequent sites of metastatic dissemination of colorectal carcinoma (CRC), which affects 10—25% of all patients [4—6]. Since Blalock reported the first successful removal of a pulmonary metastasis, in 1944, and, later, Thomford reported the principles of surgical resection of lung metastases, the procedure has been gradually accepted as a treatment with proven value if the metastatic process is confined to the lungs [4,6—8].

But while resection of solitary lung metastases has been well accepted by physicians, metastasectomy for multiple or bilateral lesions remained controversial until recently and the role of repeated thoracotomy for recurrent disease has not been well defined [7]. Nonetheless, an increasing number of patients has undergone repeated thoracotomy for recurrent lung metastases [9,10]. Operative indications must be considered from all points of view, as the lung metastasis is a distant lesion and pulmonary resection always causes a decrease in respiratory function. Hence, it is useful to identify the patients who can benefit from surgery [4]. The number of possible candidates for resection of lesions has increased in the last two decades and indications for excision and prognostic factors have been continuously reviewed. Earlier detection of lung metastases as small peripheral densities with spiral or high-resolution computed tomography (CT) favour the increased demand for surgical treatment [10].

We have previously published the results of surgical resection of lung metastases from osteogenic sarcomas and, more recently, from epithelial tumours [8,11]. The aim of the current study was to analyse our experience with excision of lung metastases from colorectal carcinoma and to evaluate clinically relevant prognostic factors, establishing the cluster of patients who may potentially benefit from this procedure.

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2. Material and methods

2.1. Patients

A total of 61 consecutive patients with primary colorectal carcinoma, including 30 colon cancers (49%) and 31 rectal cancers (50%), underwent 94 curative pulmonary resections for suspected lung metastases, at our centre, between January 1988 and December 2005. Forty-two (69%) of the 61 patients were men and the age ranged from 30 to 80 years (mean with standard deviation, 61 ± 14 years).

Only patients in whom all the macroscopic lesions secondary to colorectal carcinoma could be and were excised ('curative' surgery) were included in this study, Patients who had palliative lung metastasectomy from colorectal carcinomas were not considered. Our criteria for curative surgical resection included either unilateral or bilateral excisable lung lesions, as per preoperative chest radiography and CT scan, with no local recurrence of primary lesions and absence of extrapulmonary lesions, except prior resectable hepatic metastases. Patients who had synchronous metastases were operated firstly for the hepatic metastases and 3 weeks later were operated on the lung. We never performed metastasectomy at the same time in liver and lung. Patients with other extrapulmonary metastases should be controlled before any surgical pulmonary procedure. All patients should be able to tolerate the degree of lung parenchyma excision envisaged.

The surgical decision was made jointly by the thoracic surgeon and the medical oncologist and/or general surgeon. The clinical decision about the use of neo-adjuvant or adjuvant therapy was made by the oncologist. A full preoperative metastatic work-up was undertaken in the referring departments. Physiologic assessment, including pulmonary function studies (with arterial blood gases), were carried on all 61 patients. All patients were judged to be at low preoperative risk for the procedure.

Cancer of the colon had occurred in the ascending portion and caecum in 12 cases (20%), in the transverse colon in one patient, in the descending colon in six (10%) and in the sigmoid in 11 cases (18%). Rectal carcinomas were located in the lower third in 11 cases, in the middle portion in 12 patients and in upper third in the remaining 8 cases.

2.2. Surgery

All patients were operated on by lateral thoracotomy. We have routinely conducted a careful palpation of inflated-deflated lung tissue [25], allowing resection of all suspicious lesions, including those not detected by preoperative CT scan. Macroscopically involved lymph nodes were resected. The surgical approach was chosen according to the location and number of pulmonary lesions and the type of lung resection ranged from wedge resection to various types of anatomic lung resection. We attempted to preserve the maximum amount of functioning lung tissue, with 5–10 mm tumour-free margins. Lobectomy or other 'major' procedure was performed when lesser resection did not allow a R0 excision in frozen sections, or when in doubt between primary bronchial adenocarcinoma and metastasis. Lung metastasectomy was considered complete, hence curative, if all known intrathoracic cancer was removed, with histologic-proven tumour-free margin.

2.3. Statistical analysis

All medical records were reviewed and all patients contacted directly or by telephone. For each patient, clinical and pathological features were recorded. Patients were evaluated for location and histology of the primary tumour, disease-free interval (DFI), number of lung lesions, size of largest resected metastases, prethoracotomy carcinoembryonic antigen (CEA) level, type of lung resection, nodal involvement (hilar or mediastinal), use of adjuvant treatment, morbid-mortality and immediate and follow-up survival.

Disease-free interval was calculated from the date of curative surgical treatment of colorectal cancer to the date of diagnosis of lung metastases. Survival was calculated from the time of first lung metastasectomy to the last date of follow-up. All available data were updated in September 2007 (minimum follow-up gap of 12 months). Statistical calculations were carried out with Medcalc® software version 7.6.0.0 (1993–2005, Frank Schoonfans, Belgium). Actuarial survivals were analysed by the Kaplan–Meier method. All variables that by univariate analysis revealed a statistically significant difference were entered into the multivariate analysis. A probability value of 0.05 or less was considered statistically significant.

3. Results

3.1. Clinical and surgical

Data available on the 61 patients are summarised in Table 1. The diagnosis of lung lesions was made by chest radiography in 36 patients (59%), almost two thirds of this before 1995, due to lack of availability of CT scan in the hospital. In the remaining 25 patients (41%), it was made by CT scan, now regularly used in the follow-up of patients with colorectal cancer.

Histology of the primary tumour included 51 well-differentiated neoplasms (83%) and 10 moderately to poorly differentiated tumours. In 55 cases, the primary tumour stage was accessible (91%). Only two patients displayed limited tumour stages (stage I of TNM/UICC; pT1–2, pN0). The majority were operated on in advanced stages.

Among the study patients, the mean DFI was 29.1 months (SD, 22,4) and ranged from 5.2 to 132 months. Almost three fourths of the cases were asymptomatic, and the remaining 15 cases showed cough in 6, dyspnoea in 5, haemoptysis in 3 and pain in 2.

At the operation for metastasectomy, the right lung and the lower lobes were affected in the majority of cases (59% – 36 patients, in both situations). Thirty-seven cases (61%) had a single metastasis, and the mean number of lesions was 1.6 ± 0.8. Forty-four patients (72%) had metastases with diameter smaller than 3 cm. Hilar or mediastinal nodal involvement was macroscopically and histologically confirmed in seven cases (11%).

In total, 94 thoracic procedures were performed in the 61 patients. The surgical approach was chosen according to the

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Table 1
Clinical data.

Variable	*N*	%
Age (years, mean and age limits)	61.2 (30–80)	
Sex		
Male	42	68
Female	19	32
Primary tumour location		
Colon	30	59
Rectum	31	61
DFI		
≤36 months	41	67
>36 months	15	33
Lung nodules (*N*)		
1	37	61
2	13	21
≥3	11	18
Affected lung		
Right	36	60
Left	23	37
Bilateral	2	3
Diameter of lung nodules		
≤3 cm	44	72
>3 cm	17	28
Approach		
Thoracotomy		
Unilateral	79	84
Bilateral	14	15
Sternotomy	1	1
Resection		
Wedge	73	78
Lobe	16	17
Others	5	5
Chemotherapy		
Preoperative	2	3
Postoperative	42	69
None	17	28

location and number of lung lesions. Most frequently (79 cases; 88%), the procedure was performed through standard unilateral posterolateral thoracotomy. A median sternotomy was used in one patient and staged bilateral thoracotomy in the remainder (12%). Wedge resection was the procedure of choice, trying to preserve normal lung parenchyma as much as possible. This surgical procedure was done in 73 cases (78%). Other surgical procedures were lobectomy in 16 patients, enucleation plus lobectomy, or enucleation alone in two patients each, and pneumectomy in one patient.

Chemotherapy was administrated in 44 patients (72%) with metastases, as adjuvant (42 patients) or neo-adjuvant (2 patients) treatment.

3.2. Perioperative results and survival

There was no hospital mortality in this series. Significant perioperative morbidity occurred in five patients (8%), including two bronchopleural fistulae (controlled with chemical pleurodesis), and acute renal insufficiency, haemorrhage, wound infection (one patient each). Follow-up was complete on September 30, 2007, or to death, for 56 of 61 patients (92%). The remaining five patients were excluded from statistical analysis, because all connections to the hospital were lost after surgery. Mean follow-up was 39 ± 37 months, ranging from 4 to 173 months.

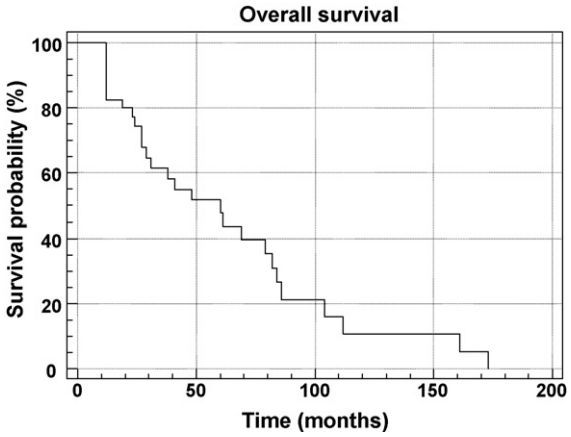

Fig. 1. Kaplan–Meier survival curve, from date of lung metastasectomy.

Metastatic disease recurred in 36 patients (64%), 8 were alive at the time of follow-up (14%) and 28 (50%) died because of progressive disease. Recurrence was limited to the lung in one third of patients (12 cases), the abdomen in 5 (14%), the brain, bone or other locations in 1 patient each. Relapse occurred in multiple organs in 16 patients (44%), 14 of whom had lung involvement. Altogether, pulmonary relapse occurred in 26 patients, 72% of those with recurrence. Eighteen patients (32%) were alive without any sign of relapse and 2 patients died of unrelated causes. Mean survival and disease-free survival were 67 ± 16 months and 52 ± 6 months, respectively. Overall, 3-, 5- and 10-year survival rates, from the date of lung resection, were 61%, 48% and 11%, respectively (Fig. 1). Overall, 3-, 5- and 10-year survival rates, from the date of primary colorectal resection, were 83%, 71% and 43% respectively (Fig. 2).

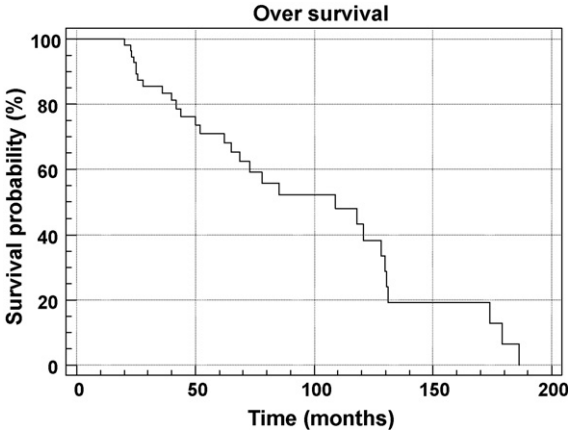

Fig. 2. Kaplan–Meier survival curve from date of primary colorectal resection.

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Table 2
Potential prognostic factors tested by univariate analysis.

Factor	*p* value
Sex	0.505
Primary location	0.307
DFI (≤6 vs >36 months)	0.045
Histological type	0.013
pTNM/UICC stage	0.045
Affected lung	0.022
Lung lesions	
Single/multiple	0.042
Number	0.053
Diameter	0.050
Symptomatic status	0.202
Complications	0.260
Adjuvant chemotherapy	0.017
Relapse of lung metastases	0.030
Prethoracotomy CEA	0.038

3.3. Analysis of risk factors for survival

The potential prognostic factors analysed are shown in Table 2. Of these factors, sex, location of the primary tumour, symptomatic status, the number and size of lung metastases, nodal involvement and postoperative complications did not significantly influence survival.

Five-year DF-survival rates, considering the definition of DFI used in by the International Registry of Lung Metastasis and adopted by other authors [8,14,15], were 51% and 92%, respectively for patients who had DFI of up to 35 months versus 36 months or more, and this observation was statistically significant ($p = 0.046$; Fig. 3).

We also analysed survival according to the grade of differentiation of the tumour and the TNM/UICC stage, as defined during surgery for the primary colorectal lesion. Five-year survival rates for patients of grade G1 versus grades G2–4 were 88% and 43%, respectively ($p = 0.013$). Concerning TNM/UICC stage, the 5-year survival rates were 56% and 32%, respectively for patients with stages II and III ($p = 0.045$). The number of stage I cases was too small for comparative analysis.

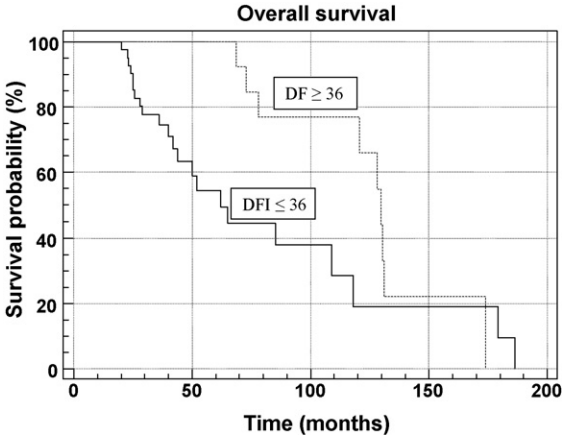

Fig. 3. Kaplan–Meier survival curve, according to the DFI: DFI ≤36 or >36 months. Log-rank test ($p = 0.0457$).

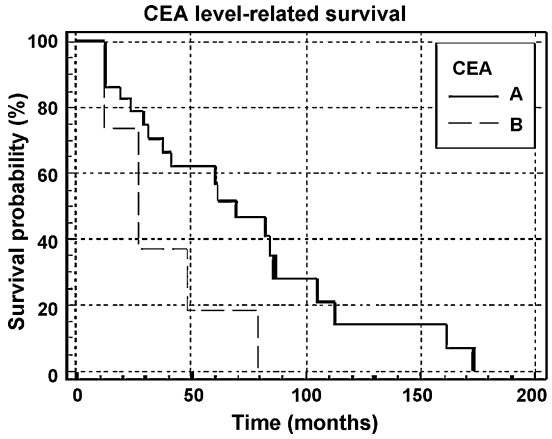

Fig. 4. Kaplan–Meier survival curve related to preoperative CEA serum level. Group A: CEA ≤5 ng/ml; group B >5 ng/ml. Log-rank test ($p = 0.0389$).

Patients with solitary lung lesions had a better long-term survival than those with multiple nodules. Three- and 5-year survival rates were 66% and 57% for the former and 53% and 27% for the latter ($p = 0.043$). Finally, the 5-year survival rate in patients submitted to adjuvant chemotherapy was 70%, versus 29% in those who had not ($p = 0.017$).

Among the study patients, those without recurrence of lung lesions after first metastasectomy had a 5-year survival of 63% as compared with 38% for the subgroup with relapse ($p = 0.031$).

Prethoracotomy CEA levels were measured in 53 patients (95%), and the 5-year survival rate was 57% for 31 patients with normal prethoracotomy CEA levels and 18% for the remainder with high (5 ng/ml) levels ($p = 0.039$; Fig. 4).

A multivariate analysis was carried out including all variables which revealed a statistically significant difference by univariate analysis. The results are shown in Table 3. Serum prethoracotomy CEA levels and solitary versus multiple lung lesions were the covariate factors of poor prognosis for patients ($p = 0.006$ and $p = 0.014$, respectively). Histological type or grade of primary tumour was not an indicator of poor prognosis, but tended towards significance ($p = 0.051$). The other factors were not found significant.

Patients were arbitrarily divided into three groups according to the presence or absence of the abovementioned prognostic factors: group I – patients with single metastasis, DFI >36 months, CEA ≤5 ng/ml; group II – patients with single metastasis and DFI ≤36 months or CEA >5 ng/ml; group III – patients with single or multiple metastasis, DFI ≤36

Table 3
Potential prognostic factors by multivariate analysis.

Variables	Hazard ratio	95% CI	*p* value
CEA level (<5 ng/ml; elevated)	3.762	0.382–2.267	0.0061
DFI[a]	0.438	0.096–1.746	0.0807
Histological differentiation[b]	0.212	0.001–3.106	0.0510
pTNM/UICC stage	1.277	0.513–1.002	0.5296
Solitary versus multiple lesions	0.316	0.236–2.068	0.0142

CI: confidence interval.
[a] Disease-free interval (≤36 months or >36 months).
[b] Grade 1 or 2–3, of primary colorectal cancer.

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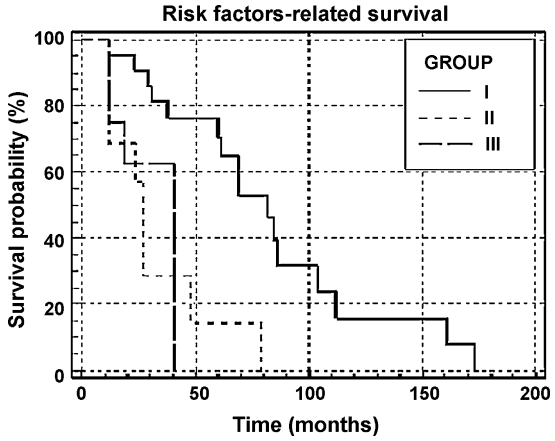

Fig. 5. Kaplan–Meier survival curve related to the presence of risk factors. Groups I–III (see text). Log-rank test ($p = 0.0066$).

months and CEA >5 ng/ml; The 3- and 5-year survival rates were 81% and 71%, respectively, for the first group (I), and 29% and 15%, respectively for the second group. None of the patients in the third group were alive after 41 months ($p = 0.007$; Fig. 5).

4. Comment

According to recent statistics, colorectal cancer is the second most frequent malignancy in Portugal, with an incidence similar to breast cancer in women and higher than cancer of the prostate in men, and contributes to 15% of total oncologic mortality. In Europe in 2004, an estimated 197,200 men were diagnosed with colorectal cancer, representing 13% of new cancer cases. In the same year, colorectal cancer was diagnosed in approximately 179,200 women, representing 13% of new cancer cases and making it the second most common incident form of cancer in women (http://www.eurekalert.org/pub_releases/2005-11/foec-cfi110205.php, accessed 17 June 2008). However, the death rate from colon cancer has declined over the past 15 years due to improved screening methods and advances in treatment [12,13].

Common sites of metastisation from colorectal cancer include liver and lung, with bone and brain metastasis occurring infrequently (approximately 6% and 1%, respectively) [14]. Therapeutic advances for patients with metastatic colorectal carcinoma have been associated with prolonged survival and this fact is associated with an increased incidence of metastases at uncommon sites [14,15]. But, to date, no effective chemotherapeutic, fully curative treatment is available and, consequently, resection of lung lesions has been accepted as appropriate therapy by most surgeons [9,16–19]. In recent years, we have been referred many cases of lung metastases from colorectal adenocarcinoma because early screening with highly efficient CT scan (helical or high-resolution) made diagnosis more accurate and more timely. Therefore, it seems appropriate to evaluate the prognostic factors for this population.

Until recently, general criteria for pulmonary metastasectomy from colorectal carcinoma were not consensually established, but several studies favour lung metastasectomy in all patients with potentially resectable metastases, no residual tumour at the primary site, no extrathoracic disease and ability to tolerate the degree of lung resection envisaged. Several authors consider that multiple and bilateral lesions are not a contraindication for lung resection, as long as they are completely excised. However, synchronic lung nodules had significantly lower survival than metachronous lesions [20].

Some authors defended that there is no considerable influence in survival rates related to multiple lesions, number, size, tumour location or bilaterality of lung nodules [4,8]. We found that cases with solitary lung lesions had a significantly better survival rate than those with multiple metastases, both by univariate and multivariate analysis. On the other hand, Iizasa [10], and Okumura [21] and their co-authors reported that the number and size of pulmonary nodules were independent prognostic factors. We believe that an accurate preoperative staging with lung CT scan, correctly evaluating the number and size of nodules, may have an influence on prognosis, becoming progressively more important in the diagnosis and therapy planning.

Human CEA expression, a member of CEA-related cell adhesion molecule family, is associated with progression of colorectal cancer, and was the most widely used human tumour marker [22]. Several investigators have analysed preoperative CEA as a prognostic factor after lung metastasectomy. The majority of the results demonstrated that prethoracotomy serum CEA was one of the most significant prognostic factors [7,9,24]. In this study, the preoperative serum CEA level was the most useful prognostic indicator for survival after metastasectomy, in both univariate and multivariate analyses. We assume that this factor could be one of the important indicators of dissemination of colorectal adenocarcinoma because elevated CEA expression is associated with poorer prognosis of either primary or metastatic colorectal cancer. Although Bcl-2 and galactin-3 are now commonly used as tumour markers, they were not available at time of this study.

We also suggest both the pTNM stage and the grade of differentiation of the primary tumour as reference factors for metastasectomy. Dukes classification or, more currently, pTNM/UICC stage has been reported to be a prognostic factor for patients undergoing hepatic metastasectomy for colorectal cancer [4,5,23], but the prognostic impact of Dukes stage in patients with pulmonary metastasis has not been sufficiently assessed. Nonetheless, Inoue [4] and Lucena [5] and their co-workers demonstrated that the Dukes/pTNM stage is an independent prognostic indicator. We also found the pTNM/UICC stage to be a statistically significant factor by univariate analysis, although this could not be confirmed by multivariate analysis. It may, however, suggest this indicator as a useful prognosis predictor, and it should be considered for operative indication in these patients. Only one other study, published by Ike et al. in 2002, found statistical significance related with the grade of differentiation of the primary growth [24].

From the classification in the three groups we defined above, we can conclude that patients with single nodules that are completely respectable, with DFI >36 months and normal prethoracotomy serum CEA levels have the best results after lung metastasectomy from colorectal cancer.

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However, in the absence of alternative therapy, patients without these favourable prognostic factors should not be denied resection.

In our experience, a limited wedge resection remains the procedure of choice for metastasectomy, permitting a R0, curative therapy. There was no operative mortality, and this approach was associated with very low perioperative morbidity. Several studies concerning lung metastasectomy from colorectal carcinoma reported 5-year survivals ranging from 21% to 63%, and most were around 40% [7—9,21,24,25]. Our overall 5-year survival rate was 48% from the time of lung resection and 71% from the time of surgery of the primary carcinoma.

In conclusion, our experience appears to indicate that pulmonary metastasectomy carries a potential survival benefit for patients with metastatic colorectal carcinoma. Low morbidity and mortality rates, parallel with the lack of any other effective therapy, justify the aggressive approach of surgical management. Resections should be carried out preserving maximal normal lung parenchyma, which could allow a safer re-excision, if necessary. Single deposits, DFI $>$36 months and normal prethoracotomy serum CEA levels were significant independent prognostic factors for medium-term survival.

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Appendix A. Conference discussion

Dr F. Carnochan (*Edinburgh, Scotland*): The patient that came with metastasis after about 10 years, how convinced was the pathologist that it was definitely a metastatic lesion and not a possible primary lung adenocarcinoma?

Dr Calvinho: This patient had a raised CEA level and we performed a fresh frozen section of the nodule and it was proved during surgery that it was a metastasis of colorectal cancer.

Dr Carnochan: And did they have a colonoscopy prior to their surgery?

Dr Calvinho: Everything was OK.

Dr A. Oliaro (*Torino, Italy*): In our department, now we associate with a lymphadenectomy. What is your opinion about lymphadenectomy to remove the metastases?

Dr Calvinho: We do not routinely perform lymphadenectomy. We only perform lymphadenectomy for microscopic nodules that we can find during surgery or preoperatively. In this series, 12% of patients had lymphadenectomy during surgery.

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