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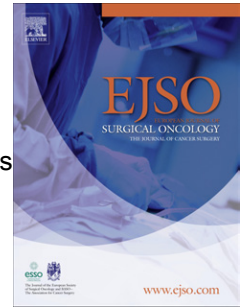
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Title: Survival after lung metastasectomy for colorectal cancer: importance of previous liver metastasis as a prognostic factor.

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Abstract

Aims: To analyse patient survival after the resection of lung metastases from colorectal carcinoma and specifically to verify whether presence of liver metastasis prior to lung metastasectomy affects survival. **Methods:** All patients who, between 1998 and 2008, underwent lung metastasectomy due to colorectal cancer were included in the study. Kaplan-Meier survival analysis was performed with the log-rank test and Cox regression multivariate analysis. **Results:** During this period, 101 metastasectomies were performed on 84 patients. The median age of patients was 65.4 years, and 60% of patients were male. The 30-day mortality rate was 2%, and incidence of complications was 7%. The overall survival was 72 months, with 3- and 5-year survival rates of 70% and 54%, respectively. A total of 17 patients (20%) had previously undergone resection of liver metastasis. No significant differences were found in the distribution of what were supposed to be the main variables between patients with and without previous hepatic metastases. Multivariate analysis identified the following statistically significant factors affecting survival: previous liver metastasectomy ($p=0.03$), tumour-infiltrated pulmonary lymph nodes ($p=0.04$), disease-free interval ≥ 48 months ($p=0.03$), and presence of more than one lung metastasis ($p<0.01$). In patients with previous liver metastasis, the shorter the time between primary colorectal surgery and the hepatectomy, the lower the survival rate after pulmonary metastasectomy ($p=0.048$). **Conclusions:** A previous history of liver metastasis shortens survival after lung metastasectomy. The time between hepatic resection and lung metastasectomy does not affect survival; however, patients with synchronous liver metastasis and colorectal neoplasia have poorer survival rates than those with metachronous disease.

Key words: metastasis, lung, metastasectomy, thoracic surgery, survival, colorectal cancer, liver.

Introduction

The lung is an ideal metastatic target for haematogenously disseminated cancer cells, given that lung parenchyma cells are very close to the pulmonary intravascular space and it is a nutrient-rich environment, where the blood supply and the partial pressure of oxygen are guaranteed [1].

There are no randomised studies that compare the survival after pulmonary metastases with and without surgery [2]. However, an analysis of 5206 lung metastasectomies recorded in the International Registry of Lung Metastases reported five-year survival rates of 36% and 13% for complete and incomplete tumour resection, respectively [3].

Colorectal cancer is the second most common cancer in most European countries [4,5], and the disease recurs after curative surgery in approximately half of patients, with the recurrence most often occurring in the liver or lungs [6,7]. The reported five-year survival rate for colorectal cancer patients with pulmonary metastases who did not undergo surgery is less than 5% [5,6].

In recent years, several factors have been found to be associated with prolonged survival after pulmonary metastasectomy in patients with colorectal cancer [5,7,8]: a) a longer disease-free interval (DFI); b) low levels of carcinoembryonic antigen (CEA) prior to thoracotomy (<5 ng/ml); c) a single metastasis less than 3 cm in diameter; and d) no lymphatic invasion. However, the role of a previous liver metastasectomy in the survival of these patients is controversial. [9,10]

Our main objective was to analyse patient survival after the resection of lung metastases from colorectal carcinoma, specifically to assess whether liver metastasectomy prior to pulmonary metastasectomy is an independent factor for predicting survival. In addition, we set out to analyse various factors that might affect the survival of patients with a history of previous liver metastasectomy.

Materials and Methods

Patient group

Data from all the patients who underwent surgery for pulmonary metastases of colorectal cancer origin from January 1998 to December 2008 were included in the study. The inclusion criteria were: a previous potentially curative resection of colorectal adenocarcinoma (M_0 stage and R_0 resection of the UICC) and histological confirmation of pulmonary metastasis after thoracic surgery performed with intent to cure (tumour-free resection margins). Cases that represented diagnostic surgery or for which it was not possible to rule out the existence of a primary lung tumour were excluded from the analysis. The follow-up period ended in August 2010, after outpatient clinic visit review or telephone interview with each of the patients.

Surgical intervention

We followed international criteria to select patients on whom to perform lung metastasectomy: the primary tumour is controlled or is controllable, no extra-pulmonary tumour exists, no better method of proven treatment value is available, adequate medical status for the planned resection exists, and complete resection is possible, based on computed tomographic evaluation.

Until 2007, we performed thoracotomy and entire lung palpation. Since then, we have treated all unique peripheral colorectal metastasis by video-assisted thoracic surgery (VATS). Then, we proceed to make a wedge resection and intraoperative anatomic pathology analysis. If metastatic tissue is identified, we finish the surgery. If the pathologic report cannot confirm metastasis or primary pulmonary neoplasm, we perform a lobectomy. If the lung metastasis is no peripheral, we perform a lobectomy or pneumonectomy. In the intraoperative view, we open the mediastinal pleura and

perform lymphadenectomy if we find enlarged lymph nodes. In the preoperative study that continued until 2006, all patients underwent CT scan. Since then, we have routinely performed CT scan and PET-CT.

Statistical methods

A database set up for this study was used to record the following variables: general demographic data, first surgery (site, histological findings and date), previous resected liver metastases (disease-free interval, histological findings, resection performed), pulmonary metastasectomy (disease-free interval, surgical access, resection performed, number and size of the metastases resected, lymph node status, complications and 30-day mortality after surgery), and follow-up (relapse, reiterative pulmonary metastasectomy, survival and disease-free survival). For all patients operated on from January 1, 2000 onwards, the levels of CEA prior to thoracotomy were also recorded.

We describe the quantitative variables using the rank, median and mean, and the qualitative variables using the absolute and relative frequencies, expressed as percentages. We carried out a Kaplan-Meier survival analysis, with the long-rank test and multivariate analysis using Cox regression, using those variables that had shown statistical significance with $p < 0.25$ in the univariate analysis. The SPSS 15.0 statistical package was used for this analysis.

Results

In the period covered by this study, 101 lung metastasectomies were performed on 84 patients. 71 patients were operated on once, while 9 and 4 patients underwent two and three surgical interventions, respectively. The median age of patients was 65 (range 40-82), and 71% were male.

A total of 17 patients had previously undergone resection of liver metastases. Table 1 shows the main demographic and clinical characteristics of the patients who form the groups with and without history of previous liver metastasis. Both groups are well matched and no statistically significant differences were found between them when comparing the main variables supposed to affect the survival of the two groups.

Overall, 64 patients had been given adjuvant chemotherapy (41 patients had chemotherapy alone) or combined chemo-radiotherapy (23 patients) prior to the lung metastasectomy. Rectal adenocarcinoma was the source of the metastasis in 54 patients, and, in the other 30, it was derived from colon adenocarcinoma.

Disease-free intervals

The disease-free interval between the primary colorectal surgery and lung metastasectomy (DFI₁) varied between 0 and 181 months, with a mean value of 39. The mean time elapsed between colorectal surgery and liver resection (DFI₂) was 18.5 months (range 0-56, 2 patients had synchronous metastases), while the mean time between the liver and the lung metastasectomy (DFI₃) was 29.1 months (range 0-84; 3 patients had synchronous metastasis in the liver and lungs).

Surgical technique

The type of surgical approach used and type of lung resection performed are shown in Table 1. All the patients with suspected lymph node involvement underwent

lymphadenectomy, and, in 11 cases, lymph node metastasis was confirmed. As regards the number of metastases, an average of 1.3 was resected per operation, with a mean diameter of 2.6 cm.

Complications

The 30-day postoperative mortality was 2% (2 patients), with further complications being observed in 7 patients. Of these, 3 were cases of persistent air leaks, one of nosocomial pneumonia, one of partial intestinal obstruction, one of atelectasis requiring bronchoscopy and one reintervention due to haemothorax. Two patients died after intestinal obstruction and respiratory insufficiency, on the 8th and 10th postoperative days, respectively.

Follow-up and recurrence

During the follow-up period, we lost the data for one patient who moved abroad 3 months after the lung resection. For the rest of the patients, the follow-up period lasted an average of 49 months (median 43; range 0-130).

There was recurrence in the lung in 21 patients; this recurrence was in the same lung in 18 cases. 13 patients were re-operated on for metastases; the time to recurrence varied from 3 to 50 months, with an average of 17.4 months. The other 8 patients were not considered for surgery for the following reasons: 4 cases of lung recurrence were also associated with metastases in other sites (positive lymph nodes, liver, vertebra); in 2 cases, the recurrence infiltrated the chest wall; 2 patients were not considered due to lung capacity and the location of metastasis.

In 5 patients (3 cases in the prior liver metastasectomy group and 2 cases de novo), liver metastases were diagnosed later. In addition, recurrences have been seen in:

bone (1 patient), brain (2 patients), ovary (1 patient), pancreas (2 patients), and rectal recurrence (2 patients).

Survival analysis

The overall median survival was 72 months (range 0-129 months), while the 3- and 5-year survival rates were 70.2% and 54.3%, respectively.

In the univariate analysis, we did not observe statistically significant differences as a function of sex, laterality, surgical approach, re-thoracotomy for new metastasis, size of metastases or site of the primary tumour. The presence of infiltrated lymph nodes ($p=0.06$) and DFI₁ of more than 48 months ($p=0.07$) were close to being statistically significant. However, differences were statistically significant for the following parameters: age ($p=0.04$), more than one lung metastasis ($p<0.01$), high levels of CEA ($p=0.04$) and prior liver metastasectomy ($p=0.04$; Figure 1). All the variables that had shown statistical significance with $p < 0.25$ in the univariate analysis were included in the multivariate analysis using Cox regression (Table 2). This analysis identified the following variables that significantly affected survival: prior liver metastasectomy ($p=0.03$), infiltrated lymph nodes ($p=0.04$), DFI₁>48 months ($p=0.03$) and presence of more than one metastasis ($p<0.01$).

Prior liver metastasectomy group

Considering just the group of 17 patients who underwent previous liver metastasectomy, the median survival was 41 months (range 0.2-103 months) and the 3- and 5-year survival rates were 50% and 39%, respectively. In this group of patients, we also performed a multivariate analysis with the following results significantly affecting survival: the time elapsed between resection of the primary colorectal tumour and liver resection ($p=0.05$), and the presence of tumour-infiltrated lymph nodes ($p=0.04$).

Discussion

Prior hepatic metastasectomy

In 2007, Pfannschmidt et al. published [5] a systematic review of the prognostic factors after lung metastasectomies of colorectal cancer origin, including 3 papers analysing the possible prognostic significance of a prior history of liver metastases. However, to date, only the study published in 2010 by Landes [10] pointed out that a previous liver metastasectomy is an independent prognostic factor for predicting survival after lung metastasectomy associated with colorectal cancer. This author reported a series of 40 patients with lung metastases of colorectal cancer origin, of which 16 (40%) had a previous history of resected liver metastases, representing the only prognostic factor identified by the multivariate survival analysis. On the other hand, in the same year, Riquet et al. [11] published a study based on 127 patients, 20% of whom had previous liver metastases, but in this case no statistically significant differences were found between the groups.

In our series, there were 17 (20%) patients with previous liver metastases, and the distribution of the main variables that affect survival (age, DFI, lymph node status, pre-thoracotomy CEA, and number of metastases) was similar in the groups with and without previous liver metastases. We found the presence of previous liver metastases to be an independent prognostic factor ($p=0.03$; HR 2.4; CI 95% 1-5.4). In addition, we carried out multivariate analysis to determine which factors affected survival within the group with previous liver metastasis, observing that the time elapsed between resection of the primary tumour and the appearance of liver metastasis was an independent prognostic factor ($p=0.05$), though there was no significant difference in survival as a function of the time between liver and lung metastasectomies.

Time between liver and lung metastasectomy

Several other studies have demonstrated that the disease-free interval between resection of the primary tumour and lung metastasectomy is an independent prognostic factor [2,4,6,12,13]. In a series of 39 patients, Shah et al. [14] did not find any statistically significant differences in survival based on whether the appearances of lung and liver metastases were synchronous or metachronous. In contrast, Nagakura et al. [15] and Miller et al. [16] both reported poorer survival in those patients who had synchronous liver and lung metastasis. In all cases, survival was measured as the time that elapsed between the first metastasectomy and the date of death, which might explain, to some extent, the finding that the longer the time elapsing between the first and the second metastasectomies, the higher the survival rate. In our study, in order to eliminate this type of bias, we defined survival as the time between the lung metastasectomy and the date of death. We observed that there was no difference in survival as a function of the time that elapsed between the appearance of metastasis in the lung and in the liver ($p=0.58$). However, we did find statistically significant differences in survival according to the time between colorectal surgery and liver metastasectomy ($p=0.05$), with the cases in which the diagnosis of liver metastasis were synchronous having a poorer prognosis.

Variables affecting survival in lung metastasectomy

With the multivariate analysis of our data, we observed that the strongest independent prognostic factor was the number of metastases resected, the hazard ratio being 4.23 (CI 95%: 1.8-9.6) when the patient had more than one metastasis. This finding supports the data in the International Registry of Lung Metastases [3], which records all the lung metastasectomies, and the findings published by Pfannschmidt et al.

[5] in their systematic review of the metastasectomies associated with colorectal carcinoma.

Another important prognostic factor in the International Registry of Metastases [3] is the disease-free interval between primary colorectal surgery and lung metastasectomy. In our series, we observed the same trend: the longer the interval, the higher the survival. However, we only observed statistically significant differences when the patients were divided in two groups, with the cut-off point being a DFI of 48 months ($p=0.03$), but not when the cut-off was set at 36 months.

In 2007, Welter et al. published a study concerning the influence of lymph node involvement on the survival of patients with lung metastasis derived from colorectal cancer [17], and concluded that mediastinal and hilar lymph node involvement had a strong impact on survival. These findings are in accordance with what we observed in our series, where lymph node involvement had a hazard ratio of 3.21 (CI 95% 1.0-9.6; $p=0.04$).

Conclusion

Previous liver metastasis is a negative survival prognostic factor after lung metastasectomy of colorectal origin. In addition, we found that the time elapsed between liver metastasectomy and the primary colorectal surgery was more significant than the time between metastatic liver resection and lung metastasectomy. Other factors that decrease survival include: presence of more than one lung metastasis, a disease-free interval of less than 48 months and mediastinal lymph node involvement.

The authors declare that they have no conflicts of interest.

TABLES

Table 1. Summary of the main variables and comparison of their distribution as a function of previous liver metastasectomy.

	Total (n=84)	No history of PLM (n=67)	History of PLM (n=17)	p
Mean age (median)	65.4 (65.5)	65.4 (65.0)	65.6 (68.0)	0.850
Sex (men)	60 (71.4%)	46 (68.6%)	14 (82.3%)	0.264
Source (rectum)	54 (64.3%)	44 (65.7%)	10 (58.8%)	0.599
Positive lymph nodes	10 (11.9%)	9 (13.4%)	1 (5.9%)	0.391
Lung metastasis > 2 cm	48 (57.1%)	40 (59.7%)	8 (47.1%)	0.347
More than 1 metastasis	19 (22.6%)	15 (22.4%)	4 (23.5%)	0.920
Positive CEA	22 (26.2%)	15 (22.4%)	7 (41.2%)	0.166
Re-thoracotomy	13 (15.48%)	10 (14.93%)	3 (17.65%)	0.782
DFI ₁ >48	24 (28.6%)	18 (26.9%)	6 (35.3%)	0.515
Other previous therapy:				
- Chemotherapy alone	41 (48.8%)	31 (46.3%)	10 (58.8%)	
- Chemotherapy and radiotherapy	23 (27.4%)	18 (26.9%)	5 (29.4%)	0.626
Lung recurrence:				

- present	21 (25%)	16 (23.9%)	5 (29.4%)	0.638
- in the same lung	18 (21.4%)	14 (20.9%)	4 (23.5%)	0.813
Surgical approach:				
- Thoracotomy	78 (77.2%) ^a	62 (77.5%) ^b	16 (71.4%) ^c	0.682
- Mini-thoracotomy	14 (13.9%) ^a	12 (15.0%) ^b	2 (9.5%) ^c	
- VATS	7 (6.5%) ^a	6 (7.5%) ^b	1 (4.8%) ^c	
- Other	2 (2.0%) ^a	0 (0.0%) ^b	2 (14.3%) ^c	
Type of resection:				
- Atypical resection	48 (47.5%) ^a	38 (47.5%) ^b	10 (47.6%) ^c	0.347
- Lobectomy	38 (37.6%) ^a	33(41.3%) ^b	5 (23.8%) ^c	
- Bilobectomy	1 (1.0%) ^a	1 (1.3%) ^b	0 (0.0%) ^c	
- Pneumonectomy	5 (5.0%) ^a	5 (6.3%) ^b	0 (0.0%) ^c	
- Lobectomy + Atypical	5 (5.0%) ^a	2 (2.5%) ^b	3 (14.3%) ^c	
Complications	7 (6.9%) ^a	5 (6.2%) ^b	2 (9.5%) ^c	0.567
30-Day Mortality	2 (2.02%) ^a	1 (1.25%) ^b	1 (4.76%) ^c	0.289

PLM: presence of previous liver metastases; VATS: Video-assisted thoracoscopic surgery. DFI₁: Disease-free interval between colectomy and lung metastasis. ^apercentage out of 101 surgical interventions. ^bpercentage out of 80 surgical interventions. ^cpercentage out of 21 interventions.

Table 2. Multivariate Survival Analysis

	Beta coefficient	Type II error	Level of significance	Hazard Ratio
Liver metastasis	0.883	0.414	0.033	2.418 (1.075-5.439)
Age \geq 65 years	0.725	0.402	0.071	2.064 (0.940–4.536)
Pre-thoracotomy CEA	0.572	0.399	0.152	1.772 (0.810-3.875)
Number of metastases	1.442	0.422	0.001	4.227 (1.848 – 9.669)
DFI ₁ \geq 48 m	1.161	0.534	0.030	3.194 (1.121 – 9.102)
Infiltrated lymph nodes	1.165	0.562	0.038	3.206 (1.066 - 9.644)

DFI₁: Disease-free interval between colectomy and lung metastasectomy.

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