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Original article

Review and update of the prognostic factors in lung metastasis surgery

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A B S T R A C T

Introduction: Since the International Registry of Lung Metastases established the factors that determine survival after performing lung metastasectomy in 1997, numerous studies have attempted to determine these prognostic factors of survival. Our objective has been to analyse the mortality, survival and disease-free survival lung metastasis surgery by studying the different variables that determine them.

Patients and method: All patients subjected to surgery for lung metastasectomy between 1998 and 2008 were included in this study. The Kaplan-Meier and log-rank tests were performed, as well as a Cox regression using multivariate analysis.

Results: A total of 178 lung metastases were removed in 146 patients during this period. The mean age was 62.22 years (median 63 years) and 64.6% were males. There were 2 cases (1.1%) of mortality and the incidence of complications was 5.02% (9 cases). The overall survival was 67.75 months with a 3 and 5 year survival of 67.4% and 52.4%, respectively. The variables that showed statistical significance in the multivariate analysis were: age disease free interval, number of nodules and size of nodules. The "state of the margins" variable was almost significant (P=.054).

Discussion: To have only one metastasis and it is less than 1 cm, a long disease free interval, and a resection with free margins, are the most favourable prognostic factors after resection of lung metastasis.

Revisión y actualización de los factores pronósticos en la cirugía de las metástasis pulmonares

Palabras clave:
Metástasis
Pulmón
Metastasectomía
Cirugía torácica
Supervivencia

R E S U M E N

Introducción: Desde que en 1997 el Registro Internacional de Metástasis Pulmonares estableció los factores que condicionan la supervivencia tras realizar metastasectomía pulmonar, numerosos trabajos han tratado de determinar las variables que condicionan dicha supervivencia. Nuestro objetivo principal es analizar la mortalidad, la supervivencia y la supervivencia libre de enfermedad de la cirugía de las metástasis pulmonares, estudiando las diferentes variables que puedan condicionarlas.

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Pacientes y método: Se ha incluido en este estudio a todos los pacientes intervenidos de metastasectomía pulmonar entre 1998 y 2008. Se ha realizado análisis de supervivencia de Kaplan-Meier y log-rank test y análisis multivariable mediante regresión de Cox.
Resultados: En este periodo se han realizado 178 metastasectomías a 146 pacientes. La edad media era 62,22 (mediana, 63) años y el 64,6% eran varones. La mortalidad ha sido del 1,1% (2 casos) y la incidencia de complicaciones, del 5,02% (9 casos). La supervivencia total media ha sido de 67,75 meses y la supervivencia a los 3 y 5 años, del 67,4 y el 52,4% respectivamente. Las variables que han mostrado significación estadística en el análisis univariable son edad, intervalo libre de enfermedad, número de nódulos y tamaño de nódulos. La variable estado de los bordes está próxima a la significación (p = 0,054).
Conclusiones: Presentar sólo una metástasis y que sea < 1 cm, un intervalo libre de enfermedad largo y resección con bordes libres son los factores pronósticos más favorables tras una resección de metástasis pulmonar.

Introduction

The first lung metastasectomy was performed in 1855, when a lung metastasis was detected by chance during the resection of a tumour of the chest wall. Later, in 1933, Barney and Churchill performed the first scheduled metastasectomy in the United States when they removed a tumour that had originated in the kidney. The patient survived for 23 years after the surgery.[1] There are no randomised studies which compare the survival rate of lung metastasis treatment with or without surgery.[2] However, many studies have found that survival rate increases after a metastasectomy. The most important of these studies was the article that Pastorino published in 1997.[3] This article showed the first results obtained from the analysis of 5206 metastasectomies included in the International Registry of Lung Metastases. In this study, there was a 5-year survival of 36% if the resection was complete and 13% if it was incomplete.

A classification of patients with lung metastases was created from the analysis of the survival rate in these patients, who were separated into 4 groups according to their prognosis. The groups going from the most favourable to the least favourable were the following: A, resectable tumour, no risk factors: disease-free interval (DFI)>36 months and single metastasis; B, resectable tumour, one risk factor: DFI<36 months or multiple metastases; C, resectable tumour, two risk factors: DFI<36 months and multiple metastases; and D, unresectable tumour.

In this same study,[3] the diagnostic accuracy of the CT scan was also analysed and they found that the assessment of the number of metastases was correct in 61% of patients. They therefore concluded that bilateral manual palpation is necessary for the final staging of the metastasis. This last point has been the object of much debate in recent years, as new imaging techniques have a greater diagnostic accuracy.[4] Video-assisted thoracic surgery (VATS) has started to become accepted, not only as a diagnostic option, but also as a therapeutic one[4-6] and only a small number of surgeons perform bilateral palpation on patients diagnosed with unilateral lung metastasis.[7]

Our main objective was to analyse the survival rate, mortality rate and complications of lung metastasis surgery by studying the different variables that may affect the survival of these patients. Furthermore, we wanted to establish the factors that determine recurrence by measuring not only survival, but also disease-free survival. Furthermore, we wanted to study the results of the first patients who underwent VATS in our hospital.

Material and method

We analysed all the patients who underwent surgery in the department of thoracic surgery of the Hospital Donostia from 1 January 1998 to 31 December 2008. The inclusion criteria for this study were: histological confirmation of metastasis by the department of pathological anatomy and the surgery was performed with intent to cure. The exclusion criteria were: diagnostic surgery and the cases when it was not possible to rule out it being a second primary lung tumour. The follow-up of these patients was drawn to a close on 25 November 2009 with an interview in person or by telephone with the patient and/or the oncologist in charge.

The data was collected in a database created for this study, where the following variables were recorded: demographic (age and sex), first surgery (location, histology and date), metastasectomy (disease-free interval, surgical approach, resection carried out, number and size of metastases resected, state of the lymph nodes and surgical margins, complications and mortality in the 30 days after the operation) and follow-up (relapse, survival and disease-free survival).

The quantitative variables are expressed using the interval, median and mean, and the qualitative variables using the absolute and relative frequency (as a percentage). We performed a Kaplan Meier survival analysis and log-rank test and multivariate analysis using a Cox regression model based on the variables that were found to have a statistical significance of $P<.25$ in the univariate analysis. Systat 12 statistical software was used for the statistical analysis.

Results

In this period, 146 patients underwent 178 metastasectomies (108 patients underwent 1 intervention, 26 patients underwent

2 interventions and 6 patients underwent 3 interventions). The mean age was 62.22 years (median 63) and 64.6% were male. DFI between surgery of the primary tumour and the metastasectomy ranged between 0 and 311 months, with a median of 35.56 and mean of 47.42.

A total of 66.5% of patients underwent treatment before the metastasectomy (38.4% chemotherapy, 5.5% radiotherapy and 22.6% combined chemotherapy and radiotherapy).

Lung recurrence was seen in 38 patients (26.02% of cases), recurrence in the same lung in 28 (19.17%), and 32 (21.92%) patients underwent surgery again as a result of metastasis. The time elapsed from surgery to recurrence varied between 3 and 60 months, with a median of 12.5 and a mean of 18.36.

The most used surgical approach was thoracotomy (149 procedures [83.7%]), followed by minithoracotomies (21 procedures [11.8%]) and VATS (8 procedures [4.5%]). A wedge resection of the metastasis was performed in 103 cases (57.9%), lobectomy in 57 (32%), bilobectomy in 1 (0.6%); pneumonectomy in 7 (3.9%), lobectomy with atypical resection in 6 (3.4%) and lung resection together with costal resection in 4 (2.2%). A lymphadenectomy was undertaken in all cases when it was suspected that the lymph nodes had been affected. Metastatic lymph nodes were found in 15 patients (8.4%).

A mean of 1.5 metastases were resected per procedure with a mean size of 2.66 cm and the surgical margins were positive in 9 cases (5.1%).

The mortality rate was 1.1% (2 cases) when taking into account any deaths that occurred up to 30 days after the intervention and the incidence of complications was 5.02% (9 cases). Among these, there were 4 persistent air leaks, 1 residual pneumothorax requiring drainage, 1 hospital-acquired pneumonia, 1 partial bowel obstruction, 1 atelectasis requiring a bronchoscopy due to retained secretions and 1 re-intervention due to haemothorax.

Table 1 shows the location of the primary tumour which caused the metastasis. Most tumours originated in the colon and rectum (54.8%).

Survival analysis

The overall mean survival was 67.75 months (median 56), (Figure 1). The 3-year and 5-years survival rates were 67.4% and 52.4%, respectively.

Table 1 – Location of the primary tumour

Location	Number	Frequency, %
Colon and rectum	85	54.8
Head and neck	2	1.4
Gynaecological	14	9.6
Breast	9	6.2
Uterus	4	2.7
Cervix	1	0.7
Urological	12	8.1
Kidney	9	6.2
Bladder	3	2
Limb (sarcoma)	18	12.3
Chest	7	4.8
Other	9	6.1

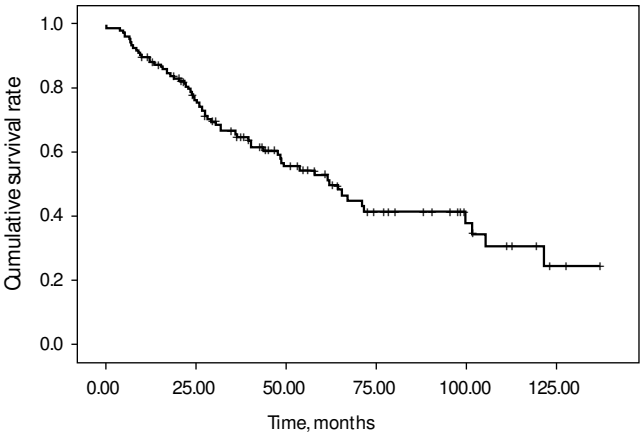

Figure 1 – Overall survival.

No statistically significant differences were observed in the univariate survival analysis (Table 2) for sex, laterality, surgical approach, lung recurrence, state of the lymph nodes and involvement of the surgical margins. Although we did

Table 2 – Univariate survival analysis

Variable	Survival in months, mean (median)	P
Sex		
Male	60.65 (51.4)	.593
Female	73 (56)	
Laterality		
Right	73.01 (61.66)	.128
Left	56.63 (48.8)	
Primary tumour		
Sarcoma	46.77 (26.87)	.017
Rest of tumours	75.25 (62.6)	
Approach		
VATS	46.04 (32.67)	.325
Open	67.78 (58.03)	
Number of nodules		
One	83.76 (71.7)	<.001
Multiple	40.81 (27.06)	
Size		
<1 cm	84.34 (66.97)	.044
>1 cm	70.74 (58.03)	
Lymph nodes		
Negative (130)	72.48 (62.03)	.38
Positive (12)	54.14 (58.03)	
Margins		
Negative (137)	73.01 (61.66)	.32
Positive (5)	56.57 (65.66)	
Disease-free interval		
<48 months	61.44 (48.43)	.004
>48 months	92.06 (101.63)	
Re-metastasectomy		
No	75.51 (65.66)	.27
Yes	54.24 (53.77)	

VATS indicates video-assisted thoracic surgery.

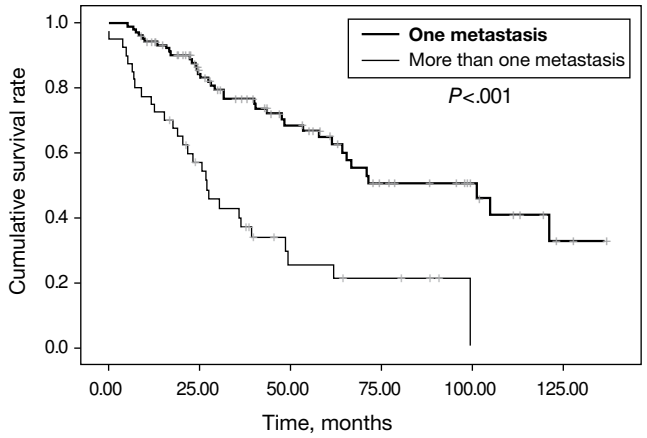

Figure 2 – Survival according to the number of metastases resected.

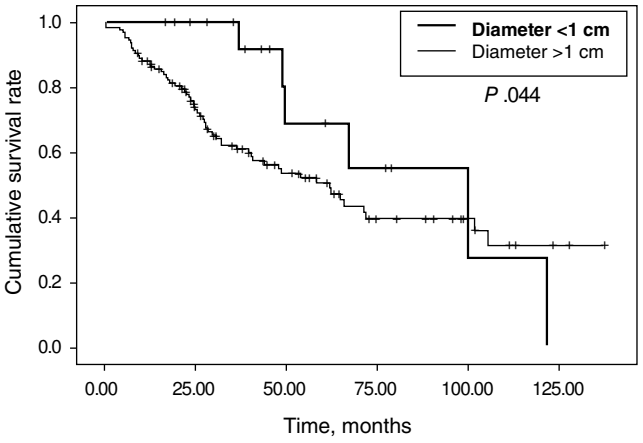

Figure 4 – Survival according to the size of the tumour resected.

not find any statistically significant differences between patients with positive and negative margins, 37% of those with negative margins were alive after 90 months and 100% of those with positive margins had died.

The observations that were found to be statistically significant are shown in Table 2: age, number of nodules (Figure 2), DFI (Figure 3) and size of nodules (Figure 4). The sarcoma category was also found to be statistically significant in the univariate analysis.

All the variables that were found to be statistically significant in the univariate analysis, except for sarcoma, were also found to be significant in the Cox regression multivariate analysis (Table 3). The "state of the margins" variable was nearly significant (*P*=.054).

With regard to the disease-free survival analysis (Figure 5), DFI, number of nodules and state of the lymph nodes (Figure 6) were found to be statistically significant in the univariate analysis (Table 4). However, we did not find any differences in surgical approach and state of the margins. Number of nodes, state of the lymph nodules and DFI were found to be statistically significant in the multivariate analysis (Table 5).

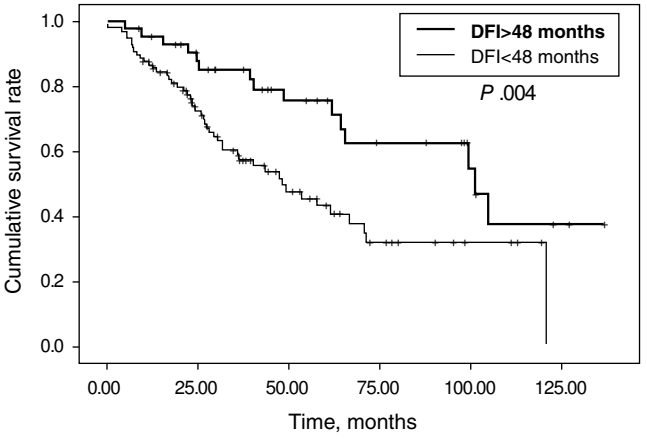

Figure 3 – Survival according to the disease-free interval (DFI).

Discussion

One of the main conclusions of the International Registry of Lung Metastases was that surgery needs to be radical, as patients with incomplete surgery or with positive margins have a lower survival rate. We only had 9 cases with positive margins in our series and we may not have found any significant statistical differences in the analysis due to the fact that there were so few patients to compare. In spite of the fact that we did not find any statistically significant differences, we did see that the group with positive margins tended to have a shorter survival (at 90 months all the patients with positive margins had died and 37% of the patients with negative margins were alive). Furthermore, the difference was nearly significant in the multivariate analysis and we can, therefore, come to the conclusion that positive margins after surgery worsens prognosis.

Disease-free interval was another of the definite prognostic factors, according to the International Registry of Lung Metastases. We observed the same trend in our study: a longer interval was linked to a longer survival. We did not find any statistically significant differences by using a cut-off point of DFI at 36 months, we did, however, at 48 months (*P*=.004). Furthermore, the longer the disease-free interval, the longer disease-free survival is.

Survival (*P*<.001) and disease-free survival (*P*<.001) are clearly reduced when a patient has more than one metastasis.

Table 3 – Multivariate survival analysis

Parameter	β	Standard error	t	*P*
DFI	−0.011	0.003	−3.17	.002
Number of nodules	0.582	0.12	4.388	<.001
Size	0.218	0.048	4.536	<.001
Margins	−1.564	0.812	−1.926	.054
Age	0.031	0.013	2.363	.018

DFI indicates disease-free interval.

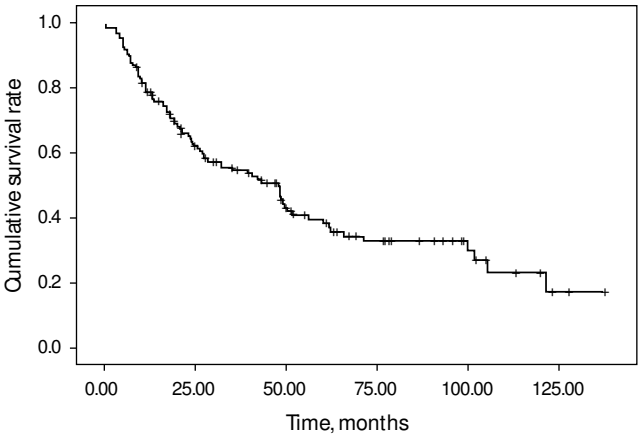

Figure 5 – Disease-free interval.

Figure 6 – Disease-free survival according to lymph node involvement.

In 2007, Welter et al published a study on the impact of lymph node involvement on the survival of patients with pulmonary metastases from colorectal cancer.[9] They came to the conclusion that mediastinal and hilar metastases have a strong impact on survival. In our study, node-positive patients had a similar survival rate to node-negative patients, although we did observe an earlier recurrence in the group of node-positive patients.

Metastases <1 cm have a higher overall survival rate. In 2008, Ayarra[1] published a series of 148 patients and found differences depending on the diameter, with the cut-off point set at 3.5 cm. In our study, we found a higher survival rate in smaller metastases when analysed as a continuous variable as well as when the patients were divided into two groups (cut-off point at 1 cm).

Table 4 – Univariate analysis of disease-free survival

	Disease-free survival, months, mean (median)	P
Disease-free interval		
<48 months	48.44 (28.2)	.001
>48 months	80.48 (99.76)	
Number of nodules		
1	67.95 (48.43)	<.001
>1	32.78 (20)	
Margins		
Negative	59.45 (43)	.515
Positive	45.3 (36)	
Lymph nodes		
Negative	59.36 (47)	.04
Positive	40.95 (18)	
Approach		
VATS	43.13 (22.93)	.89
Open	58.36 (43)	

VATS indicates video-assisted thoracic surgery.

Colorectal adenocarcinoma was the most common origin of the tumour in our series. The behaviour of these metastases has been studied the most to date,[2,4,8,9] with many publications mentioning this aetiology. We found that this group had a higher survival rate as its 3-year and 5-year survival rate was 73% and 53%, respectively. Sarcoma had the lowest survival rate, with a 3-year and 5-year rate of 35% and 22%, respectively. The cases of metastasectomy due to clear cell carcinoma originating in the kidneys were between these two values, with a 3-year and 5-year survival rate of 40% and 30%, respectively. When comparing the different origins of metastases using univariate analysis, we found that sarcoma had a statistically significant worse prognosis. However, this difference disappeared in the multivariate analysis. We, therefore, came to the conclusion that sarcoma has a worst prognosis not because of the type in itself, but rather because of the intrinsic characteristics: short DFI and multiple metastases.

Age is not mentioned as a variable that may have an effect on survival in studies published to date.[1-4,9,10] In our study, age, taken as a continuous variable, may be considered as a prognostic factor, given that statistically significant differences were seen in the multivariate analysis (P=.018). When we divided the patients into groups by age, we found that patients over 80 years old had a worse survival rate, followed by those under 40 years old. Patients between 41 and 79 years old had the best survival rate.

The role of VATS for resection of metastases is controversial.[6,11] According to a survey published in 2009,[7]

Table 5 – Multivariate analysis of disease-free survival

Parameter	β	Standard error	t	P
Number of nodules	0.202	0.072	2.817	.005
State of the lymph nodes	0.794	0.362	2.196	.028
DFI	–0.007	0.003	–2.615	.009

DFI indicates disease-free interval.

60.3% considered VATS only for diagnostic purposes, while 39.7% considered VATS to be a therapeutic tool. In our short experience with VATS, we have not found any difference in survival or recurrence in patients who underwent VATS compared to those who underwent a thoracotomy. These results match those of the trial published by Apostolos,[4] who compared 25 patients who underwent a thoracotomy with 27 VATS. No statistically significant differences were seen in survival, recurrence and recurrence in the same lung in this trial. Numerous previous studies have found that non-imaged nodules may remain after VATS,[5] but with these new results, the question is: Do the millimetric nodules that may go unnoticed using VATS affect survival or recurrence?

Lung metastasis surgery is a safe technique with a low morbidity and mortality that offers a good 3-year and 5-year survival rate. The factors that worsened prognosis in our series were short DFI, multiple metastases, tumours >1 cm, positive margins, lymph node infiltration and advanced age.

Conflict of interest

The authors affirm that they have no conflict of interest.

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