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Survival Analysis of Resection of Lung Metastases From Colorectal Cancer

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ABSTRACT

Introduction: The publication of the International Registry of Lung Metastases (IRLM) in 1997 was a turning point in favor of surgical resection of lung metastases. Prognostic groups were defined according to resectability, number of metastases, and disease-free interval. The objective of this study was to determine survival in patients who underwent resection of lung metastases from colorectal carcinoma and to evaluate how applicable the prognostic factors established by the IRLM are in this specific patient group.
Patients and Methods: Patients with lung metastases from colorectal carcinoma who underwent resection between January 1, 2000, and November 30, 2006, were retrospectively analyzed. Survival was calculated using the Kaplan-Meier method, with log-rank comparisons between groups.
Results: Survivals at 1, 3, 5, and 6 years was 92%, 75%, 54%, and 43%, respectively. The main finding was that 3-year survival was better in patients who underwent atypical resection of the metastasis (75%) than those who required lobectomy (55%). There were no significant differences in survival in terms of number of lung metastases resected or disease-free interval.
Conclusions: Survival in patients requiring lobectomy for resection of lung metastases from colorectal carcinoma was worse than in those who underwent atypical resection. The number of metastases and disease-free interval may be questionable prognostic factors in the case of lung metastases from colorectal carcinoma.

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Analisis de supervivencia de la cirugía de resección de metastasis pulmonares de cáncer colorrectal

RESUMEN

Introducción: La publicación del Registro Internacional de Metástasis Pulmonares (IRLM, de International Registry of Lung Metastases) en 1997 supuso un punto de inflexión a favor de la cirugía de resección de metástasis pulmonares (MP). Se establecieron grupos pronósticos en función de la resecabilidad, el número de MP y el intervalo libre de enfermedad (ILE). El objetivo de este trabajo ha sido determinar la supervivencia de los pacientes intervenidos con resección de MP de carcinoma colorrectal y evaluar la aplicabilidad de los factores pronósticos establecidos por el IRLM a este grupo concreto de pacientes.
Pacientes y métodos: Se ha realizado un trabajo retrospectivo recogiendo los casos de MP de carcinoma colorrectal intervenidos entre el 1 de enero de 2000 y el 30 de noviembre de 2006. Para calcular la supervivencia se empleó el método de Kaplan-Meier con el test de rangos logarítmicos.
Resultados: La supervivencia a 1; 3; 5, y 6 años fue del 92, el 75, el 54 y el 43%, respectivamente. Como principal hallazgo, se observó que los pacientes a quienes se realizó resección atípica de las metástasis tuvieron

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mayor supervivencia que aquellos que necesitaron lobectomía: un 75% de supervivencia a los 3 años frente al 55%, respectivamente. No se encontraron diferencias significativas de supervivencia en cuanto al número de MP resecadas ni en cuanto al ILE.

Conclusiones: Los pacientes que requieren lobectomía para la resección de MP de carcinoma colorrectal presentan peor supervivencia que aquellos a los que se realiza resección atípica. El número de metástasis y el ILE pueden ser factores pronósticos cuestionables en el caso de MP de carcinoma colorrectal.

Introduction

The dissemination of neoplastic cells, with the subsequent appearance of metastases, is the strongest negative prognostic factor in patients with cancer. Despite the progress made in the prevention of metastases and multimodal treatment, metastatic disease is still the main cause of death in these patients.[1]

Given that the lungs act as the first filter for malignant cells from a large majority of malignant tumors, lung involvement should not always be considered a reflection of a systemic neoplastic state. This idea has led several authors to consider surgical removal of metastases as part of the therapeutic algorithm for cancer patients.[2] The publication, in 1997, of the results of the International Registry of Lung Metastases (IRLM), with a total of 5206 patients who underwent surgery at 18 sites in Europe, the United States, and Canada,[3] made a substantial contribution to the consideration of lung metastasectomy as an effective procedure in terms of survival. Analysis of the data led to the development of a prognostic model comprising 4 groups defined according to the number of lung metastases, their resectability, and the disease-free interval (DFI) from treatment of the primary tumor until the appearance of the lung metastasis (Table).

Colorectal cancer is one of the most common malignant diseases in industrialized countries.[4,5] It has been estimated that more than 148 000 new cases were diagnosed in 2006 in the USA alone and that more than 55 000 patients died as a result of the disease in that year.[6] Approximately 10% of patients with colorectal cancer suffer lung metastases, although the lung is the exclusive site of metastasis in only 2% to 4% of all patients.[7]

Although chemotherapy as treatment of metastatic 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%.[8] No prospective, randomized trials have yet been undertaken to compare the outcome of surgical removal of lung metastases from colorectal cancer with the outcome of other nonsurgical treatments. Resection of lung metastases from colorectal carcinoma therefore remains the only potentially curative treatment.[9]

The objective of this study was to analyze survival and prognosis in patients who underwent resection of lung metastases from colorectal carcinoma with curative intent. In addition, the study aimed to confirm the validity of the prognostic factors proposed by the IRLM when applied to a series of patients with lung metastases exclusively from colorectal carcinoma.

Table
Prognostic Groups and Factors in Lung Metastasis Resection According to the International Registry for Lung Metastases (1997)

Group 1	Resectable, with no risk factors (DFI of 36 months and solitary metastasis)
Group 2	Resectable, with 1 risk factor (DFI<36 months or multiple metastases)
Group 3	Resectable, with 2 risk factors (DFI<2 months and multiple metastases)
Group 4	Unresectable

Abbreviation: DFI, disease-free interval.

Patients and Methods

We performed a retrospective analysis of all resection procedures for lung metastases from colorectal carcinoma with curative intent performed consecutively in the Thoracic Surgery Department of the Hospital Regional Universitario Carlos Haya, Málaga, Spain, between January 2000 and November 2006. The medical histories of the patients who underwent surgery during the study period were reviewed. Surgical procedures performed exclusively for diagnostic purposes were excluded.

Lung metastases from colorectal carcinoma were resected provided the following conditions were met: unilateral or bilateral resectable pulmonary nodules detected by chest computed tomography (CT); absence of local recurrence of the primary tumor; absence of extrapulmonary metastases (except for resected or resectable liver metastases); and, finally, compliance with the criteria for operability applicable to any type of intervention involving lung resection. In most cases, a helical system was used for the chest CT, with 10 mm slices.

The standard procedure for this type of surgery was extensive palpation of the entire lung parenchyma by the surgeons and their assistant or assistants, with resection of all palpable nodules, while respecting as much healthy parenchyma as possible. The nodules were subsequently submitted for definitive clinicopathologic diagnosis. Systematic lymph node dissection was not employed, and lymph nodes were only resected during the intervention when there was visible evidence of disease.

The variables studied were age and sex of the patients, number of resected metastases per procedure, DFI (time from treatment of the primary tumor until detection of the metastasis), surgical approach, type of lung resection, agreement between the number of metastases detected in the chest CT and those confirmed by the definitive clinicopathology study, postoperative complications, and survival of patients operated between January 1, 2000, and November 30, 2006. The survival of the patients was ascertained by a telephone call or directly by a visit to the outpatient clinic.

Statistical Analysis

For the statistical analysis, descriptive statistics, contingency tables, and the χ^2 test were used. Kaplan-Meier survival curves were compared with the log rank test. Statistical analysis was performed using version 12.0 of the Statistical Package for Social Sciences (SPSS, Chicago, Illinois, USA) for Windows.

Results

Between January 1, 2000, and November 30, 2006, 126 lung metastases, were resected with curative intent from 106 patients (Figure 1). Of these procedures, 54 were resections of lung metastases from colorectal cancer in 45 patients.

The age range of patients undergoing surgery was 38 to 81 years, with a mean age of 62.9 years. Twenty-five of these patients were men (31 procedures) and 20 were women (23 procedures). A single metastasis was resected in 63.8% of the procedures, whereas 2 were

resected in 23.4%, 3 in 8.5%, and 4 in 4.3%. Only 6 patients (13.3%) had metastases in both lungs at the time of diagnosis. In 25% of the procedures, palpation during surgery detected a greater number of metastases than previously detected in chest CT. The DFI was between 0 and 11 months in 21.6% of the patients, between 12 and 35 months in 32.4%, and greater than 36 months in 45.9%.

A posterolateral thoracotomy was performed in 46 patients (85.18%), lateral thoracotomy in 2 patients, and simultaneous bilateral thoracotomy in a single patient with metastases in both lungs. In 4 procedures (7.7%), video-assisted thoracoscopy was used to rule out pleural invasion by the metastases before thoracotomy. Sternotomy was only done in 1 patient.

Of the resections, 35 were atypical (64.81%), 5 were segmentectomies (9.25%), 8 were simple lobectomies (14.81%), 1 was a bilobectomy, 1 was a sleeve lobectomy, 2 were lobectomies plus atypical resection, and 2 were atypical resections with removal of a part of the chest wall.

No postoperative complications were reported in 90.2% of the procedures. An air leak lasting more than 7 days, postoperative ileus, postoperative respiratory failure, and chylothorax which resolved with conservative management were experienced by 1 patient each. Only 1 postoperative death occurred (that is, within 30 days of the surgical procedure) due to pulmonary thromboembolism.

The mean postoperative stay was 8.63 days.

Survival at 1, 3, 5, and 6 years after the operation was 92%, 75%, 54%, and 43%, respectively, with a mean survival of 73.22 months (Figure 2) and a median survival of 66.6 months. There were no significant differences in survival according to sex, surgical approach, number of metastases, or DFI. In contrast, significant differences were reported according to the type of resection: 3-year survival in cases of atypical resection was 75%, with a mean survival of 94.41 months, compared to a 3-year survival of 55% and mean survival of 31.9 months in cases of lobectomy.

Discussion

Since the publication of the results of the IRLM,[3] resection of lung metastases with therapeutic intent has become a frequent indication in thoracic surgery departments.

The study by Pastorino et al[3] marks a watershed in surgical resection of lung metastases. As it was a multicenter study, the investigators were able to collect data from 5206 patients, making it the largest study to date on the subject. Its most important contribution was to establish prognostic groups defined according to the presence of certain risk factors: resectability, number of metastases, and DFI. The main drawback of the study was that the influence of prognostic factors specific to each type of primary tumor was not analyzed.[10] Although the results have been validated in other case series involving resection of lung metastases from different origins,[11] their applicability to a case series of patients with lung metastases exclusively from colorectal cancer has never been assessed.[10]

Two of the most important aspects to take into account with this type of surgery are the approach and the type of resection performed. One of the determining factors in the choice of approach is the disagreement between prior radiologic findings and definitive clinicopathologic ones. In our series, 25% more lung metastases were detected in the histopathologic study than in conventional chest CT performed before surgery. Even in recent studies with helical CT with 5-mm slices, the sensitivity for detecting lesions of less than 6 mm in diameter was still limited.[12-14]

Some authors are in favor of using video-assisted thoracoscopy when resecting lung metastases with curative intent,[15,16] arguing that it is less aggressive than other approaches, with a subsequent decrease in postoperative pain, complications, and duration of hospital stay. However, one of the strongest arguments against the use of video-assisted thoracoscopy for resection of lung metastases is provided by McCormack et al[17] in their much cited prospective study conducted at the Memorial Sloan-Kettering Cancer Center. That study, which aimed to compare video-assisted thoracoscopy with thoracotomy, had planned to include 50 patients but had to be terminated prematurely after only 18 patients had been enrolled because a statistically significant benefit was detected in terms of the number of metastases found with thoracotomy.

Currently, any thoracic approach for resection of lung metastases has to meet 3 essential requirements[2,18]: it has be as unaggressive as possible, allow manual palpation, and allow resection of all palpable metastases.

As mentioned above, video-assisted thoracoscopy has a minimal morbidity and offers excellent visualization of subpleural nodules but its capacity for locating small and intraparenchymatous nodules has been found wanting.[19,20] However, despite the disagreement between radiologic and clinicopathologic findings, recently published studies in series of patients with resected lung metastases using video-assisted thoracoscopy have reported similar results to those achieved with thoracotomy in terms of long-term survival.[21,22] Indeed, Pfannschmidt et al,[23] in their recent review, concluded that although thoracotomy continues to be the most widely used approach for resection of lung metastases from colorectal carcinoma, video-assisted thoracoscopy may play an important role in the resection of peripheral lung metastases.

In the series presented here, the main approach used was posterolateral thoracotomy. This approach allows the whole of the
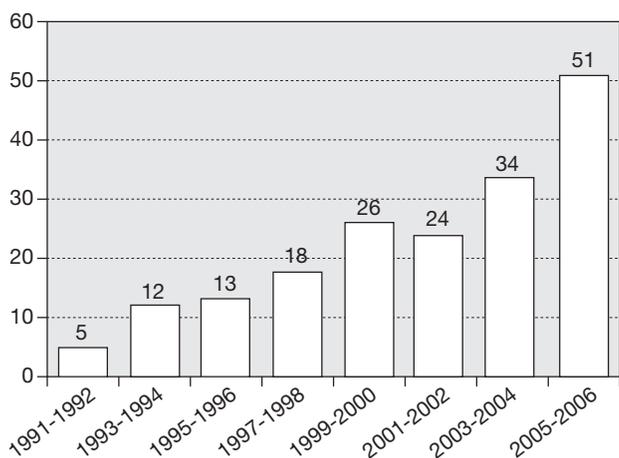

Figure 1. Change in the number of interventions for lung metastases in our department from 1991 to 2006.
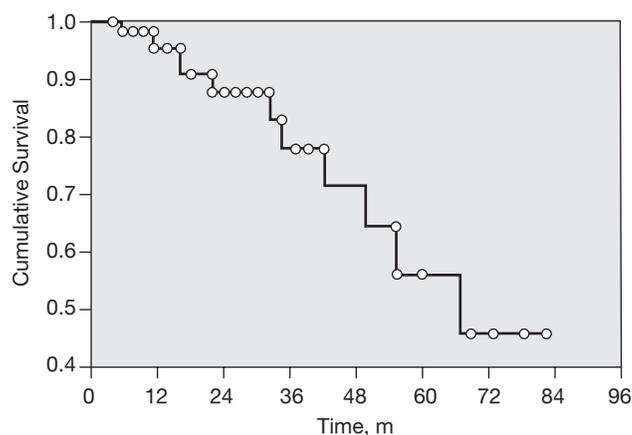

Figure 2. Survival in patients who underwent resection of lung metastases from colorectal carcinoma.

lung parenchyma to be palpated and resection of all palpable nodules. In cases of bilateral metastases, one side of the thorax is treated and the patient allowed to recover before operating on the other side (after approximately 3 weeks). Simultaneous bilateral thoracotomy is only used in young patients with good functional capacity as this approach may substantially affect respiration in the immediate postoperative period.

The choice of type of resection for removal of the lung metastases is based on 2 essential considerations—resection of all nodules with a healthy lung tissue margin while being as conservative as possible in terms of respecting the parenchyma.[2] Thus, metastasectomy or atypical resection of the metastatic nodule, preferably using surgical staplers, is the technique of choice as it is safe, associated with limited morbidity and mortality, and is just as effective as routine lung resections.[24,25] Pneumonectomy and/or removal of adjacent tissue is usually not indicated, except in certain exceptional cases.[2,24]

In the series presented here, the most relevant finding was that patients who underwent an atypical resection of metastases survived significantly longer than those who underwent major anatomical resections (lobectomies): 3-year survival in cases of atypical resection was 75%, with a mean survival of 94.41 months, compared to 3-year survival of 55% and mean survival of 31.9 months in cases of lobectomy. This difference may be because patients requiring lobectomies had more advanced disease given the larger size of the metastases, although this variable was not statistically significant in our series. A greater volume of visibly diseased tissue indicates a greater likelihood that other undetectable metastases are present.[10]

This finding, in line with that published by Vogelsang et al,[26] supports the traditional approach of attempting to resect all nodules while endeavoring to respect as much healthy parenchyma as possible, firstly, because further metastasectomies may have to be performed in the event of relapse and, secondly, because of the worse survival in cases of larger resections.

In contrast to the findings of the IRLM, in our study, we did not see any significant differences in survival according to the number of metastases or DFI, in agreement with the study published recently by Muñoz-Llarena et al.[10] In that study, not even dividing the patients into the prognostic groups of the IRLM, which include both number of metastases and DFI, yielded a different course among patients, prompting the authors to claim that those variables are of questionable use as prognostic factors in lung metastases from colorectal cancer. Those conclusions, although derived from retrospective studies, are in line with other recently published studies that cast doubt on what have been considered the underlying principles in the treatment of lung metastases from colorectal cancer until now. Pfannschmidt et al,[23] in their recent review, did not find the DFI to be a significant long-term prognostic factor, although they did think it followed that patients with a solitary lung metastasis benefit more from resection than those with multiple metastases. For their part, Tanaka et al[27] concluded that the optimum moment, in terms of survival, for resecting lung metastases from colorectal carcinoma is at least 3 months after radiologic diagnosis. We underline that these findings need to be confirmed in randomized, prospective studies in the future.

The percentage of postoperative complications reported in this series is similar to that published by the IRLM: 4.9% of serious complications, with a perioperative mortality of 1.7%.

With respect to overall survival, the results obtained in this series (54% survival at 5 years, with a mean survival of 73.22 months) lie within the ranges published to date: 38.3% to 63.7% with a median of 52.5%.[23] Many of the patients received adjuvant chemotherapy after resection of the metastases and, although this variable was not analyzed, it may contribute to the more than acceptable survival in this group of patients. This aspect has already been proposed recently

by more than one author,[10,23] and should perhaps be investigated in future studies.

In conclusion, resection of lung metastases from colorectal carcinoma is an effective therapeutic option for improving survival and one that is increasingly requested. Morbidity and mortality are relatively low. This approach remains the one that allows sufficient and extensive palpation of the entire lung parenchyma to detect metastases that do not show up with conventional radiologic techniques. Video-assisted thoracoscopy would seem to be indicated in some patients with peripheral metastases.[21-23] The type of resection should be one that allows the metastasis to be removed while respecting as much healthy lung parenchyma as possible, that is, mayor lung resections, such as lobectomies and pneumonectomies, should be avoided as far as possible. In the series presented, medium-term survival in patients undergoing atypical resections was better than in those undergoing other procedures. The number of lung metastases and the DFI are questionable as prognostic factors in patients with lung metastases from colorectal cancer. Last but not least, evidence in favor of resection of lung metastases has so far been based on retrospective analyses of case series.[23] Therefore, it is necessary to conduct prospective randomized studies comparing outcomes (in terms of survival and quality of life) after resection of lung metastases from colorectal carcinoma with those obtained after other nonsurgical therapeutic approaches in order to offer the best possible care to this group of patients.[28]

Acknowledgments

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