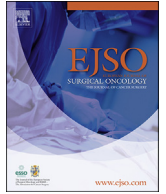




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## Individual data meta-analysis for the study of survival after pulmonary metastasectomy in colorectal cancer patients: A history of resected liver metastases worsens the prognosis

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## ABSTRACT

**Objectives:** To assess the impact of a history of liver metastases on survival in patients undergoing surgery for lung metastases from colorectal carcinoma.

**Methods:** We reviewed recent studies identified by searching MEDLINE and EMBASE using the Ovid interface, with the following search terms: lung metastasectomy, pulmonary metastasectomy, lung metastases and lung metastasis, supplemented by manual searching. Inclusion criteria were that the research concerned patients with lung metastases from colorectal cancer undergoing surgery with curative intent, and had been published between 2007 and 2014. Exclusion criteria were that the paper was a review, concerned surgical techniques themselves (without follow-up), and included patients treated non-surgically. Using Stata 14, we performed aggregate data and individual data meta-analysis using random-effect and Cox multilevel models respectively.

**Results:** We collected data on 3501 patients from 17 studies. The overall median survival was 43 months. In aggregate data meta-analysis, the hazard ratio for patients with previous liver metastases was 1.19 (95% CI 0.90–1.47), with low heterogeneity ( $I^2$  4.3%). In individual data meta-analysis, the hazard ratio for these patients was 1.37 (95% CI 1.14–1.64;  $p < 0.001$ ). Multivariate analysis identified the following factors significantly affecting survival: tumour-infiltrated pulmonary lymph nodes ( $p < 0.001$ ), type of resection ( $p = 0.005$ ), margins ( $p < 0.001$ ), carcinoembryonic antigen levels ( $p < 0.001$ ), and number and size of lung metastases (both  $p < 0.001$ ).

**Conclusions:** A history of liver metastases is a negative prognostic factor for survival in patients with lung metastases from colorectal cancer. We registered the meta-analysis protocol in PROSPERO (CRD42015017838).

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## Introduction

Pulmonary metastasectomy has become the standard treatment for patients with lung metastases from colorectal cancer (CRC) [1]. In Western countries, colon cancer is the most prevalent type of cancer considering both sexes [2], and 50% of patients with this type of cancer will develop metastases during the course of the disease, primarily in the liver, lung or both [2].

Although a large number of studies have been published with data on survival after surgical resection of lung metastases [3], there are certain outstanding issues, including a lack of agreement on the best prognostic factors. In 1997, to address this issue, the International Registry of Lung Metastases reported the prognostic factors associated with this type of surgery, after analysing survival rates in a sample of more than 5000 patients [4]. A decade later, in 2007, Pfannschmidt and colleagues conducted a systematic review to identify specific prognostic factors in patients with lung metastases from CRC [3]. Since then, many different factors have been found to be associated with prolonged survival after lung metastasectomy in patients with CRC [5–7]: prolonged disease-free interval, low pre-thoracotomy carcinoembryonic antigen (CEA) levels, a single lung metastasis less than 3 cm in diameter and the absence of thoracic lymph node involvement. However, the real impact of a history of resected liver metastases on survival outcomes following lung metastasectomy remains uncertain [5].

In 2013, Gonzalez et al. [8] published a systematic review and meta-analysis of papers published between 2000 and 2011. They analysed seven studies that took into account previous liver metastasis and concluded that a history of resected liver metastasis is not correlated with a higher risk of mortality in these patients (hazard ratio, HR 1.22, 95% CI: 0.91–1.64;  $p = 0.022$ ); however, the observed high heterogeneity of the data analysed might have influenced the interpretation and the conclusions in that analysis. Given the uncertainties about the impact of a history of resected liver metastasis on survival outcomes of CRC following lung metastasectomy, we sought to conduct a systematic review of recent scientific literature, considering papers published since Pfannschmidt's 2007 systematic review [3], and asking authors for their collaboration to enable us to perform an individual data meta-analysis. The aim of this study was to provide the best evidence on a question of great current interest, namely, the impact of a history of liver metastases on survival of patients undergoing surgery for lung metastases from CRC.

## Materials and methods

### Search strategy

Studies were identified by searching MEDLINE and EMBASE using the Ovid interface, supplemented by a manual search of the reference lists of the papers retrieved. The following terms were used: lung metastasectomy, pulmonary metastasectomy, lung metastases and lung metastasis. All the search terms were combined using the Boolean operator “OR” to increase the likelihood of retrieving all relevant articles, and the search was limited to publications between 2007 and 2014.

Fig. 1 is a diagram showing the flow of papers through the study. We sought to identify papers that analysed variables with an impact on survival after lung metastasectomy in patients with colorectal cancer. To identify papers that met all the inclusion criteria and none of the exclusion criteria, two reviewers independently assessed the relevance of the papers identified, by reading the titles, then the abstracts and, finally, by reading the full paper and confirming that they had some data relevant to our research question; disagreements were resolved by discussion and consensus. The inclusion criteria were that the research was in

consecutive patients with lung metastases from colorectal cancer undergoing surgery with curative intent, and had been published between 2007 and 2014, considering both retrospective and prospective studies. When a study led to more than one paper, we used data from the most recent publication. The exclusion criteria considered were that the paper was a review, concerned the surgical techniques themselves, did not report follow-up of patients undergoing surgery, or included patients treated with non-surgical approaches (stereotactic radiotherapy or radiofrequency ablation). This process resulted in the selection of a total of 29 papers.

### Data collection

We registered the protocol for the meta-analysis with PROSPERO (registration number CRD42015017838; [supplementary file 1](#)) and drafted a collaboration agreement to share specific data ([Supplementary file 2](#)). Additionally, we designed a database to store all the data we wanted to analyse from the studies of interest and the study was approved by the clinical research ethics committee of the Gipuzkoa health region. To contact study authors, we initially sent an email explaining our interest to the corresponding author cited on the paper retrieved. If we did not receive a reply, we sent emails directly to the other authors and we also attempted to contact some authors via social media, including Facebook, Twitter and ResearchGate.

### Statistical analysis

We performed two types of meta-analysis. First, we carried out conventional meta-analysis of aggregate data with both crude and adjusted estimates using a random-effect model. Second, we carried out one-step meta-analysis of individual participant data using a multilevel Cox model with the patients as level 1 units and the studies as level 2 units. We fitted both a univariate model with the main variable (previous liver metastasectomy) and a multivariate model. The variables in these models (as for the meta-analysis of aggregate data) were selected a priori with clinical criteria, seeking to control for confounding factors, with no modelling strategy. To be able to include random effects on the intercept and slope of the model (to allow for heterogeneity between studies in baseline risk and effect respectively), the Cox model was simulated using a Poisson model [9]. As a measure of heterogeneity, we used the median hazard ratio (MHR), that can be interpreted as the median relative change in the hazard of the occurrence of the outcome when comparing identical subjects from two randomly selected studies ordered by risk [10]. The assumption of proportional risk for the main variable given the other variables was tested by introducing a term for interaction with time.

## Results

### Studies included

We selected 29 papers that met all the selection criteria and divided them into two broad groups: 6 which did not analyse the variable of interest [2,6,7,11–13], that is, whether patients who underwent surgery had a history of resected liver metastases; and the other 23 which did consider this variable [1,5,14–33]. In this second group of 23 papers, there were 21 patient series, 1 prospective [15] and the others retrospective [5,14,16–32], and 2 meta-analyses [1,8] (these including several of the selected patient series). In total, we collected data from 17 studies [2,5,12–14,16–18,20,21,25–28,30,32,33], managing to obtain data on 3501 patients for the meta-analysis of individual data. The authors from three studies [6,15,31] replied to the first email, expressing interest in the study, but did not

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