



## REVIEW

# Survival after pulmonary metastasectomy in colorectal cancer patients: does a history of resected liver metastases worsen the prognosis? A literature review

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### ABSTRACT

**Objective:** To assess the impact of past liver metastases on the survival duration of patients who are undergoing surgery for lung metastases.

**Methods:** We conducted a review of literature published from 2007 to 2014. The studies were identified by searching PubMed, MEDLINE, and Embase and were supplemented by a manual search of the references listed by the retrieved studies. The following search terms were used: lung metastasectomy, pulmonary metastasectomy, lung metastases, and lung metastasis. We selected retrospective and prospective studies published from 2007 to 2014 on patients with lung metastases from colorectal cancer and were undergoing surgery with curative intent. We excluded reviews, studies that focused on surgical techniques, patients who were treated non-surgically, analyses of specific subgroups of patients, and those that did not report follow-up of the patients undergoing surgery.

**Results:** We identified 28 papers that assessed survival after lung metastases, 21 of which were mostly retrospective studies that identified previous liver metastases to explore their impact on patient survival. In more than half of the papers analyzed (63.2%), patients with a history of resected liver metastases had a lower survival rate than those who did not have such a history, and the difference was statistically significant in eight of these studies. However, data were presented differently, and authors reported mean survival time, survival rates, or hazard ratios.

**Conclusions:** A history of liver metastases seems to be a negative prognostic factor, but the individual data need to undergo a meta-analysis.

### KEYWORDS

Lung; metastasis; liver; colorectal cancer; review

## Introduction

Pulmonary metastasectomy has become a standard therapeutic strategy for patients with pulmonary metastases from colorectal cancer<sup>1</sup>. In Western countries, colon cancer is the most prevalent type of cancer in both sexes<sup>2</sup>, and 50% of patients with this type of cancer will develop metastases during the course of the disease<sup>2</sup>, primarily in the liver, lungs, or both<sup>2</sup>.

Although a large number of studies has been published with data on survival after surgical resection of lung metastases<sup>3</sup>, certain issues have yet to be settled. The need to identify prognostic factors, which is one of these outstanding issues, was addressed in 1997 by the International Registry of

Lung Metastases by reporting the prognostic factors associated with this type of surgery after analyzing the survival rates of a sample of more than 5000 patients<sup>4</sup>. In 2007, Pfannschmidt et al.<sup>3</sup> conducted a systematic review and meta-analysis to identify the specific prognostic factors of lung metastases from colorectal cancer. Various factors have since been found to be associated with prolonged survival after lung metastasectomy in patients with colorectal carcinoma<sup>3,5,6</sup>: prolonged disease-free intervals, low pre-thoracotomy levels of carcinoembryonic antigen (CEA), a single lung metastasis less than 3 cm in diameter, and the absence of thoracic lymph node involvement. However, the real impact of past liver metastases on survival is uncertain<sup>7</sup>. Thus, we systematically reviewed scientific papers published since Pfannschmidt's<sup>3</sup> in 2007 and summarized the conclusions of the most recent papers on lung metastasectomy in patients with colorectal cancer about an ongoing debate<sup>8</sup>: does a history of resected liver metastases have a negative impact on survival after lung surgery?

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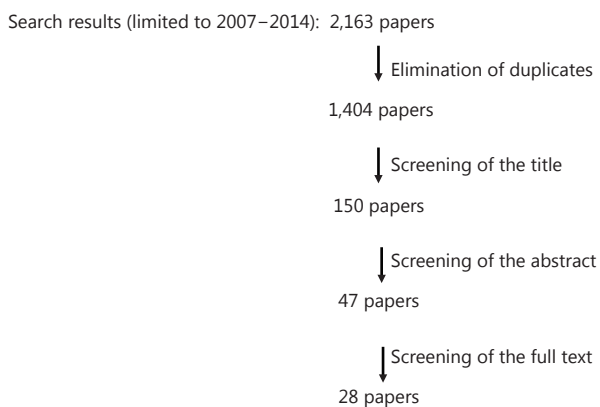
## Material and methods

Studies were identified by searching PubMed, Medline, and Embase and supplemented by a manual search of the references 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 studies published between 2007 and 2014.

The inclusion criteria were that the research: 1) could be retrospective or prospective, 2) was about patients with lung metastases from colorectal cancer and were undergoing surgery with curative intent, and 3) was published between 2007 and 2014. When a study led to more than one paper, we used data from the most recent publication. The exclusion criteria were that the paper 1) was a review, 2) was a study concerned with the utilized surgical techniques, patients treated with non-surgical approaches (stereotactic radiotherapy or radiofrequency ablation) or specific subgroups of patients (for example, only patients with liver and lung metastases), and 3) did not report follow-up of the patients undergoing surgery. **Figure 1** illustrates the data cleansing process used to identify the papers that analyzed variables that influence survival after lung metastasectomy in patients with colorectal cancer. To identify papers that contained data that were relevant to our research question and met the inclusion criteria and none of the exclusion criteria, papers were filtered first by the title, then by the abstract, and finally by the main text. This filtering process left us with 28 papers.

## Results

We selected 28 papers and divided them into two broad



**Figure 1** Flow chart of the search and selection process.

groups: 7 that did not analyze the variable of interest<sup>9-14</sup>, that is, whether patients who underwent surgery had a history of resected liver metastases, and 21 that did consider this variable<sup>1,7,15-33</sup>. In this second group of 21 papers, 19 were patient series (1 prospective<sup>15</sup> and 18 retrospective<sup>7,16-32</sup>) and 2 were meta-analyses<sup>1,33</sup> (including several of the retrospective patient series).

**Table 1** summarizes the main characteristics of the 19-patient series in which past liver metastases were considered in the survival analysis. Among these 19 studies, 12 (63.2%) found survival to be shorter in patients who had previously undergone resection of liver metastases<sup>7,15-25</sup> than those who had not, and the difference was significant in 8 of these 12 studies<sup>7,16-22</sup>. By contrast, two studies<sup>26,27</sup> (10.5%) found shorter survival in patients with no history of liver metastases than those who had such a history. Four studies (21.1%) concluded that the two groups did not significantly differ in terms of survival and reported *P* values but not the length of survival of each group of patients (with or without past liver metastases)<sup>28-31</sup>. Finally, the study published by Welter et al.<sup>32</sup> reported similar survival rates between the two groups.

In 2013, Gonzalez et al.<sup>33</sup> reviewed papers published between 2000 and 2011. They analyzed 7 studies that considered previous liver metastases and concluded that a history of resected liver metastases is not correlated with a higher risk of mortality in these patients (HR 1.22, 95% CI: 0.91-1.64) but highlighted the high heterogeneity of the data analyzed (*P*=0.022).

Meanwhile, Salah<sup>1</sup> conducted a meta-analysis of individual data for 927 patients, which were collected from 8 studies. They attempted to construct a model to predict survival after lung metastasectomy using these original data and concluded that past liver metastases do not have an impact on survival using multivariate analysis.

## Discussion

The factors prognostic of lung metastases are a topic of ongoing debate, as shown by the numerous studies that analyze potentially relevant factors<sup>1,3,4,33</sup>. In 1997, the International Registry of Lung Metastases published its own study, which found only disease-free survival, radicality of surgery, and number of removed lymph nodes to be the determinants. Since then, several studies have shown a wide range of prognostic factors, including mediastinal lymph node involvement, preoperative CEA levels and age<sup>5,6,8</sup>.

However, no results from clinical trials have been published so far on lung metastasectomy. We await the results of the PulMICC trial for good scientific evidence to

**Table 1** Main characteristics of the 19 patient series found.

Author	Country and year	Patients, n (% with liver metastases)	OS (months)	OS with no history of HM (months)	OS with history of HM (months)	Variables affecting survival
Perera NK	Australia 2013	66 (24.0)	At 5 years 39.6%	Not reported	Not reported	None
Kamiyoshihara M	Japan 2014	73 (37.0)		At 5 years 70%, 33.7 m	At 5 years 59.5%, 39.5 m	CEA level, number of metastases, female
Renaud S	France 2013	320 (15.0)		74 m (60–87)	47 m (21–76)	Lymph node involvement, Liver metastases
Matsui T	Japan 2013	186 (13.4)		At 5 years 63%	At 5 years 54%, 60 m	ASA class, Metastasis size
Javed MA	UK 2014	66 (39.0)	45 m	43 m	33 m	Age, Number of metastases, DFS, CEA
Cho S	Korea 2013	84 (26.2)	31 m	45.1 m	26.3 m	Age, Number of metastases, DFS, CEA
Iida T	Japan 2013	1223 (18.8)	69.5 m	At 5 years 55.3%, 75.7 m	At 5 years 44.6% 49.4 m	Age, Number of metastases, Metastasis size
Hattori N	Japan 2013	96 (30.2)	At 5 years 61.3%	At 5 years 69%	At 5 years 43%	Lymph node involvement, Liver metastases, DFS
Jarabo JR	Spain 2011	79 (27.8)	At 5 years 53.3%	At 5 years 50.1%	At 5 years 62.5%	Age, CEA level, Lymph node involvement
Zabaleta J	Spain 2011	90 (18.7)	84 m	89.2 m (74.1–104.2)	58.8 m (34.4–83.1)	DFI, Age, Lymph node involvement, Early recurrence, Metastasis size, History of liver metastases
Borano P	Italy 2011	137 (31.4)	At 5 years 55.4%		HR 0.919	Number of metastases, DFS
Chen F	Japan 2011	75 (25.3)	At 5 years 59.7%	Not reported	Not reported	TNM stage of primary tumour
Suemitsu R	Japan 2011	57 (56.1)	53.9% 65.2 m	At 5 years 71.5%	At 5 years 43.1%	Early recurrence, Non-pulmonary metastasis, CEA level, Lymph node involvement
Hwang MR	Korea 2010	125 (29.6)		At 5 years 58%	At 5 years 13.7%	Liver metastasis
Landes U	Switzerland 2010	40 (60.0)		87 m, at 5 years 53.8%	40 m At 5 years 29.2%	Vascular invasion
Riquet M	France 2010	127 (24.4)	At 5 years 41%	At 5 years 39.2%	At 5 years 53.3%	CEA level, Lymph node involvement
Watanabe K	Japan 2009	122 (29.2)	At 5 years 67.8%	Not reported	Not reported	Surgical approach, Liver metastasis, DFS
Lin BR	Taiwan 2009	63 (23.8)	At 5 years 43.9%	At 5 years 26.8%	At 5 years 45.9%	

OS: overall survival; HM: hepatic metastasectomy; CEA: carcinoembryonic antigen; DFS: disease-free survival

clarify uncertainties related to this type of surgery<sup>34</sup>. In the meantime, systematic reviews of case series are the best source of scientific evidence. In 2007, Pfannschmidt et al.<sup>3</sup> researched lung metastases from colorectal cancer in detail by conducting a systematic review and a meta-analysis to assess prognostic factors and found that little attention had been paid to past liver metastases in patients up to that point. Later, Gonzalez<sup>33</sup> carried out a new systematic review and meta-analysis of four studies that had been published after 2007. Three out of these four studies found that a history of resected liver metastases decreased survival<sup>7,21,22</sup>. Despite this negative effect, none of these studies recommended not operating patients with previous liver metastases.

In the current systematic review, we found 19 papers published since 2007 that assessed survival after resection of lung metastases from colorectal cancer while considering patients' history of liver metastases. Similar to Gonzalez<sup>33</sup>, we found considerable heterogeneity in the studies. Some authors reported their results as mean survival time<sup>7,16-18</sup> (with or without confidence intervals), 5-year survival rates<sup>20,27</sup> or hazard ratios<sup>30</sup>, whereas others simply concluded that differences were not statistically significant without reporting the actual results<sup>28,30</sup>.

Besides the 5 studies that were included in Gonzalez's meta-analysis<sup>7,21,22</sup>, 3 out of the 19 studies published after 2007 found better survival in patients with no history of liver metastases than those with past liver metastases<sup>16-20</sup>. Furthermore, the series with the largest numbers of patients among these studies, which were published by Renaud<sup>16</sup> (320 patients) and by Iida<sup>18</sup> (1,223 patients), both found better survival in patients with no history of liver metastases.

By contrast, Riquet et al.<sup>27</sup> analyzed 127 patients who underwent surgery in a single center in 2010 and observed that patients who had history of liver metastases lived longer than those who did not. The authors explained this apparently paradoxical finding by the changing context in which the patients were treated. Survival, after all, is determined by numerous prognostic factors, such as disease-free interval, mediastinal lymph node involvement, number of resected lung metastases and pre-thoracotomy CEA levels<sup>4-6,8</sup>. Riquet et al.<sup>27</sup> found that survival was poorer among the patients in their series who underwent surgery before 2000 than those who had operations after that year; moreover, the improvements in systemic treatments and surgical techniques that have been implemented since 2000 have resulted in a significant increase in the number of patients with a history of resected liver metastases undergoing pulmonary resection. The authors concluded that the longer survival found in patients with past liver

metastases than those who did not was attributable to these improvements and other patient-related factors and not to their history of liver metastasis resection per se.

Recent findings call the conclusions of previous systematic reviews into question. What is particularly interesting is that poor levels of survival were found in large series of patients with a history of liver metastases<sup>16,18</sup>.

Meanwhile, as previously noted by Gonzalez<sup>33</sup>, performing a high-quality meta-analysis is difficult with the currently available data, with research authors often only presenting grouped data. The two main problems are the different ways the results are presented and the differences in patient characteristics other than their history of liver metastases. For example, different surgical teams can be more or less aggressive in treating metastatic patients, and their various approaches need to be considered in survival analysis (age, surgical margins, number of lung metastases, mediastinal lymph node involvement, and disease-free survival, among others). A meta-analysis should be conducted using individual patient data to provide better scientific evidence than what is currently available and to address the controversial question of whether a history of liver metastases has a negative impact on survival after a lung metastasectomy. Therefore, we propose to conduct a new research study (registered in Prospero with reference number CRD42015017838) and invite colleagues who have analyzed and published their results on patients with lung metastases and past liver metastases to contact the corresponding author of this paper to take part in our analysis.

## Conclusions

The alleged negative role of prior liver metastases in poor prognosis after resection of lung metastases from colorectal carcinoma is gaining support from a growing number of recent evidence. However, a meta-analysis should be done using individual patient data to produce better scientific evidence than what is currently available in this area.

## Conflict of interest statement

No potential conflicts of interest are disclosed.

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