Surgical resection of pulmonary metastases from colorectal cancer: a systematic review of published series

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CRD summary
This review assessed the resection of pulmonary metastases secondary to colorectal cancer. Only retrospective surgical case series were identified. Peri-operative mortality was low and median 5-year survival was 52.5%. Most of the factors examined did not have a clear influence on long-term survival. Despite the limitations of the data, the conclusions appear consistent with the data presented.

Authors' objectives
To assess the effectiveness of pulmonary metastasectomy in patients with colorectal cancer, focusing on patient selection for surgery by examination of potential prognostic factors for long-term survival.

Searching
PubMed, MEDLINE and EMBASE were searched for studies published between 1995 and December 2006; the search terms were listed. The search was restricted to studies published in English. The reference lists of retrieved studies were also checked.

Study selection
Study designs of evaluations included in the review
No randomised controlled trials had been conducted in this field, so any prospective and retrospective studies fulfilling the remaining inclusion criteria were eligible for inclusion. The studies had to involve at least 40 patients, and have a minimum follow-up of 30 days for data on post-operative morbidity and mortality and at least 24 months for the inclusion of survival data. Only studies with recruitment of patients from 1980 were eligible. All of the identified studies were retrospective case series. Where reported, the median follow-up ranged from 20 to 62 months.

Specific interventions included in the review
Studies of surgical resection with curative intent of colorectal pulmonary metastases were eligible for inclusion. Studies of repeat pulmonary resection and hepatic and pulmonary resection were also included. Fourteen studies included R0 resections (no residual disease), five also included a small number of patients with R1 resections (histologic involved margins), and six gave no details. Surgical procedures included wedge, lobectomy, pneumonectomy and segmentectomy.

Participants included in the review
Studies were eligible if they assessed patients with pulmonary metastases from colorectal cancer. Where reported, the mean age of the patients was between 55 and 65 years (range: 23 to 85).

Outcomes assessed in the review
Studies were eligible if they assessed overall 5-year survival, operative mortality and post-operative mortality. Fourteen factors were consistently investigated with respect to prognostic relevance: patient demographics (age and gender), primary tumour characteristics (TNM, stage, histology, origin), lung metastases (number, size, laterality, type of resection, thoracic lymph node involvement), timing of metastases (disease-free interval), pre-thoracotomy carcinoembryonic antigen value, and different histological patterns of the primary and lung metastases.

How were decisions on the relevance of primary studies made?
The authors did not state how the studies were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state how they assessed study validity, or how many reviewers performed the validity assessment.
**Data extraction**

The data were extracted into pre-designed data extraction forms. The authors did not state how many reviewers performed the data extraction.

**Methods of synthesis**

How were the studies combined?
The studies were combined in a narrative.

How were differences between studies investigated?
Differences between the studies were reported in the body of the text.

**Results of the review**

Twenty studies (n=1,870), including 3 studies with resection of colorectal metastases to the liver and lung (n=186), were included.

The authors stated that the quality of reporting was poor in many studies. Almost half of the studies did not state if post-operative mortality was excluded from the survival analysis, and patients lost to follow-up were not reported or included in the analysis appropriately. Several studies did not report the distribution of important confounding factors. The patients were highly selected and the treatment centres highly specialised.

Peri-operative death (within 30 days of pulmonary resection or not defined) ranged from 0 to 2.5% of patients (13 studies).

Overall 5-year survival after pulmonary resection was 48% (median; range: 41.1 to 5). In studies not distinguishing between R0 and R1/2 resection, there was a median 5-year survival of 52.5% (range: 38.3 to 63.7). Thirteen studies reported the survival of patients with R0 resections: the median 5-year survival was 39.6% (range: 24 to 56). Three studies reported the survival of patients with R1/2 resections: the median 5-year survival was 0% (range: 0 to 21). In 3 studies of patients with pulmonary and hepatic resection, the median 5-year survival was 31% (range: 30 to 38).

With respect to prognostic factors, in 8 of 9 studies no effect on long-term survival was seen for patients in different tumour stages. There was no significant difference in survival dependent on uni- or bilateral distribution in any of the studies (12 studies). Nine of 16 studies found a significant effect of elevated carcinoembryonic antigen levels (>5 ng/mL or >10 ng/mL) on survival. Only 1 of 19 studies found significantly better survival in patients with longer disease-free intervals between resection of the primary tumour and pulmonary metastasectomy. No difference in survival could be seen for different surgical approaches (7 studies). In most studies, the type of lung resection (wedge resection /segmentectomy, lobectomy, pneumonectomy) was not a prognostic factor for survival. Two of 5 studies found significantly improved survival after achieving clear surgical margins, while three did not find radicality of resection to be an independent prognostic factor. None of 7 studies found repeat resection to be a prognostic factor for survival. No significant difference in median 5-year survival was found (where reported) between patients with and without previously resected hepatic metastases at the time of pulmonary resection. Five studies suggested that patients with single metastases had better survival outcomes than patients with multiple metastases, but this was not confirmed by a further 14 studies. Maximum tumour size was found to be a significant prognostic factor (with more survivors with smaller tumour sizes) in only 2 of 14 studies reporting on this factor. Mediastinal and pulmonary lymph node involvement was only shown to be a prognostic factor for survival in studies where nearly all of the patients had undergone a systematic mediastinal and hilar lymph node dissection at the same time as undergoing pulmonary metastasectomy. Lymph node involvement was no prognostic factor in studies where lymph node dissection was not carried out at the same time as pulmonary resection, or where lymph node dissection was only carried out in case of node enlargement. None of 12 studies found adjuvant chemotherapy after resection of the primary tumour or pulmonary metastasectomy to have a significant effect on long-term survival. In general, age and intestinal localisation of the primary tumour were not prognostic factors for survival. Various histopathologic and immunohistochemical measurements have also been tested for prognostic significance. However, there was insufficient information available to exclude patients from metastasectomy based on these measurements.
Authors' conclusions
Colorectal pulmonary metastases can be resected safely with a low mortality rate; for a subset of highly selected patients, the outcomes exceed those normally associated with colorectal metastatic cancer. Gender, distribution of pulmonary metastases, repeat pulmonary resection and additional chemotherapy were not reported to be significant prognostic factors for survival. The role of technical aspects of pulmonary metastasectomy is unclear. The role of radicality of the resection of pulmonary metastases is not entirely clear, but complete resection should be aimed at wherever possible. Lymph node involvement appeared to have a negative effect on survival, as did elevated carcinoembryonic antigen levels. Patients with solitary metastases potentially benefit more from resection than patients with multiple metastases. Several histological characteristics of the primary tumour or the metastases may also play a role in prognosis.

CRD commentary
This review had clearly stated inclusion criteria with respect to the study design, participants, interventions and outcomes. The authors searched relevant databases and efforts were made to identify supplemental information. However, the search was restricted to publications in English, thereby leading to the potential for language bias. The methods used to select studies, assess validity and extract the data were not clearly described, thus the likelihood of reviewer error or bias at these stages cannot be assessed. Study details were tabulated extensively. All of the studies were retrospective clinical case series and in many cases the reporting was poor. Since the patients were highly selected and the centres highly specialised, it is unclear to what extent the results can be generalised. Despite the methodological problems of this review, the conclusions appear consistent with the data presented.

Implications of the review for practice and research
Practice: The authors suggested that there is not enough evidence to exclude patients from colorectal pulmonary metastasectomy based on most of the potential prognostic factors investigated.

Research: The authors stated that new strategies based on intensive systemic chemotherapy combined with pulmonary metastasectomy should be evaluated in future prospective randomised studies.

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