



Pulmonary metastasectomy in colorectal cancer: a systematic review and quantitative synthesis

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DECLARATIONS

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None declared

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Summary

Objectives Surgical removal of pulmonary metastases from colorectal cancer is undertaken increasingly but the practice is variable. There have been no randomized trials of effectiveness. We needed evidence from a systematic review to plan a randomized controlled trial.

Design A formal search for all studies concerning the practice of pulmonary metastasectomy was undertaken including all published articles using pre-specified keywords. Abstracts were screened, reviewed and data extracted by at least two of the authors. Information across studies was collated in a quantitative synthesis.

Results Of 101 articles identified, 51 contained sufficient quantitative information to be included in the synthesis. The reports were published between 1971 and 2007, and reported on 3504 patients. There was little change over time in patient characteristics such as age, sex, the time elapsed since resection of the primary cancer, its site or stage. The proportion with multiple metastases or elevated carcinoma embryonic antigen (CEA) did not change over time but there was an apparent increase in the proportion of patients who also had hepatic metastasectomy. Differences in 5-year survival between groups defined by CEA or by single versus multiple metastases persisted over time. Few data were available concerning postoperative morbidity, postoperative lung function or change in symptoms.

Conclusion The quality of evidence available concerning pulmonary metastasectomy in colorectal cancer is not sufficient to draw inferences concerning the effectiveness of this surgery. There is great variety in what was reported and its utility. Given the burdensome nature of the surgery involved, better evidence, ideally in the form of a randomized trial, is required for the continuance of this practice.

and extracted data; the screening of papers for overlapping or duplication of content was performed by FF, TT and MU; TT, MU and FF wrote the first draft and all revisions. All authors have read successive drafts and approved the final version

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Introduction

Pulmonary metastasectomy for colorectal cancer is widespread but a survey in Europe shows great variation in belief and practice.¹ There is growing pressure to operate on these patients to remove metastases from the lung, not infrequently in patients who have already undergone liver resection for metastatic disease. There are systematic reviews of surgery for both liver² and for lung metastasectomy;³ the authors found no randomized trials in either case. In the absence of randomized trials a formal meta-analysis was not deemed possible, and for pulmonary metastasectomy Pfannschmidt *et al.* presented a textual summary of 20 papers chosen on the basis of size (40 cases or more) and criteria concerning follow-up.

At the time the practice was increasing the degree of selection was examined in the USA Veterans Administration database.⁴ Of 35,921 cases of colorectal cancer, 22,715 had the primary cancer removed. Pulmonary metastasectomy was performed in 76 patients and a five-year survival rate of 36% was projected. The possibility that survivors were a result of the extreme selection of cases rather than being attributable to the pulmonary metastasectomy was mooted by Åberg,⁵ a proposition that has never been refuted.

Mathematical modelling has been used to show that the survival rates presented in two of the larger and most complete of the follow-up studies^{6,7} are not inconsistent with what would be expected among the broader population of patients with colorectal cancer when account is taken of the stage mix and the period between treatment of the primary cancer and the pulmonary metastasectomy.⁸

Systematic review is a prerequisite to planning a randomized trial. Given our own uncertainties about the evidence for benefit⁹ and prior to embarking on a randomized trial¹⁰ we sought the best evidence available to guide practice. We performed an inclusive systematic review and a quantitative synthesis of the data they contain.

Methods

The literature was searched using a formal strategy. This is shown in Appendix 1, available online at <http://jrsm.rsmjournals.com/cgi/content/full/103/2/60/DC1>. Manuscript titles were searched to

identify papers that might include data concerning pulmonary metastasectomy for colorectal cancer. These were reviewed by IH, KT and TT. No exclusions were made on the basis of the language of publication. Papers excluded at the first selection included teaching and review articles, technical reports and those containing no relevant data concerning surgical treatment. A second selection was made by FF, MU and TT to remove any residual reports which pertained to multiple primary cancer sites; registries that overlapped with institutional reports; single institutional studies that were superseded by later reports from the same institution; or specific subgroups of the patient population. Obvious exclusions were made on the basis of abstracts, the remainder with reference to the full articles.

In instances where uncertainty could not be resolved by careful reading of the manuscripts, the authors of the manuscripts concerned were contacted and asked to clarify matters.

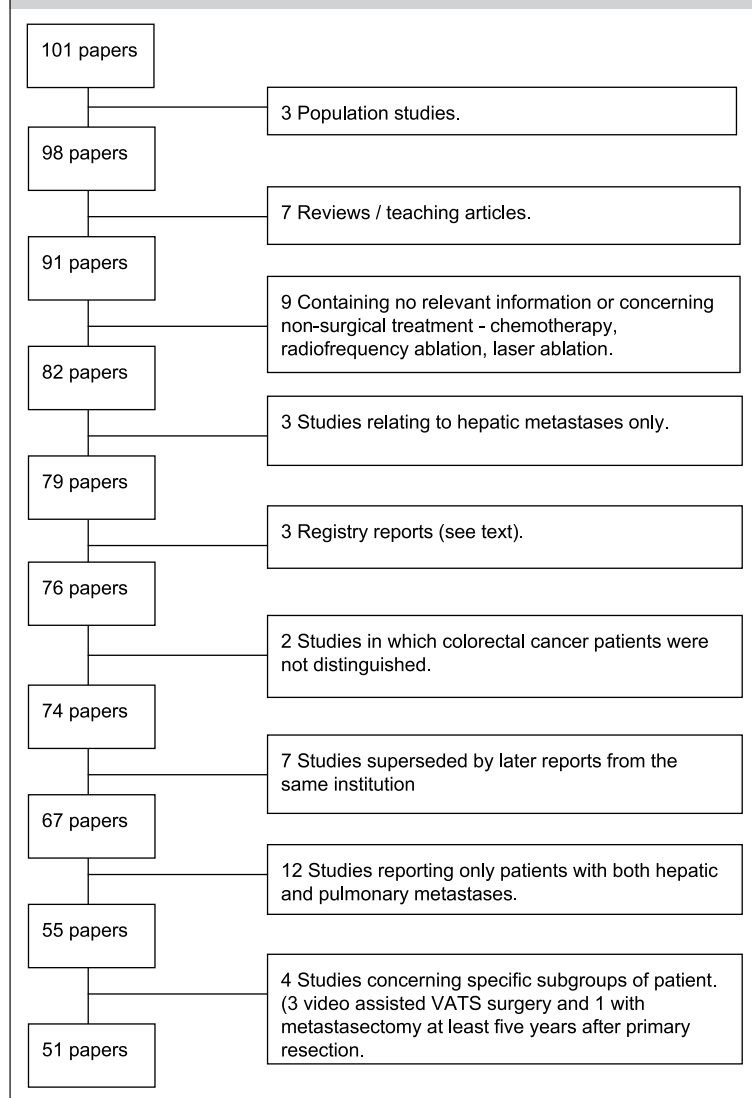
The resulting selected papers were individually searched and data extracted.

Series with over 50 cases were inspected first and all items of data contained were collated in a spreadsheet. From these we identified the most commonly reported items of data and systematically searched the smaller series for these and other elements that we deemed important for informing practice. We tabulated the presence of data grouped according to whether these were pre-operative features that describe the case-mix being operated upon, operative and pathological findings, or outcome data.

We recorded the start and end dates of the reported series. Where not reported, the series was deemed to have ended a year before the publication date and the start date was approximated with reference to the longest duration of follow-up in the publication. The mid-point of the period was used to order the papers and the cumulative sum of cases was used to define five epochs chosen to give groups of as near equal case volume as possible.

A series of graphical displays were constructed to depict the presenting features, clinicopathological findings and post-metastasectomy course, aggregating data by epoch where feasible. On inspection of these, additional graphical displays were constructed to further explore particular features of the data. Given the very large number of

Figure 1
Flow chart of papers found and progressive selection of 51 providing data in the quantitative synthesis



hypotheses that might be raised on inspection of the data, we have not performed any statistical hypothesis testing.

Results

Having excluded technical reports, teaching and review articles, and those containing no relevant data concerning surgical treatment, 101 papers remained. The flow chart (Figure 1) shows the number of these papers rejected on the basis

of each criterion; 51 papers remained for data extraction.

The 51 included series had mid-point dates from 1965 to 2000 and included a total of 3504 patients (Figure 2).^{4,6,7,11-58} The presence of data pertaining to each of the specified domains in each of the 51 papers is indicated by a bar in Figure 3. Where data were present for a particular domain they were often inconsistently reported, with various definitions and summary statistics.

For the specified factors where there were sufficient data across a number of studies, graphical displays similar in layout to Figure 4 were prepared. A further 12 figures are available online at <http://jrsm.rsmjournals.com/cgi/content/full/103/2/60/DC2>. Some of the data they contain are in an abbreviated form in Table 1.

The majority of operations in case series are for a single metastasis, as opposed to two or more pulmonary metastases, but with a wide range of their relative proportions (Figure 4). In the 25 papers where five-year survival was given after single pulmonary metastasectomy, it was of the order of 50% \pm 5%. Fewer papers provide survival data for multiple metastasectomy and where they do it is lower.

Elevated carcinoma embryonic antigen (CEA) has been shown to be strongly associated with shorter survival in a number of multivariable analyses³ and this is in line with summary data presented here (Figure 15 online). The level of CEA was reported in fewer than half of the papers.

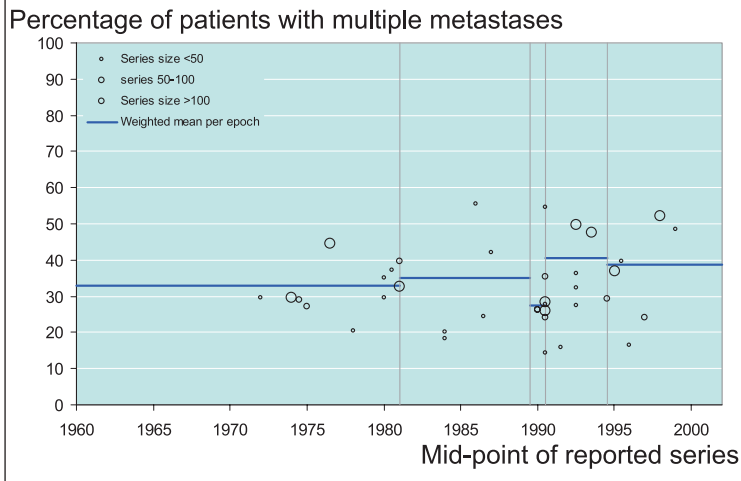
There may be an upward trend in the proportion of patients operated on with bilateral disease, previous pulmonary metastasectomy, and those who also have hepatic metastasectomy.

Little or no data exist within this literature concerning important considerations such as change in symptoms, change in respiratory function or other aspects of what would now be termed quality of life.

Discussion

The outcome data contained within the surgical follow-up reports found in our review are almost exclusively related to survival. There are no control groups provided of outcome among patients with similar features to those operated upon and in the

Figure 4
Percentage of patients who had multiple metastasectomy according to 38/51 papers in which data were presented



The weaknesses of the literature, relying on follow-up studies, are inevitably carried into this synthesis. There is variable and incomplete reporting. One conclusion that we can draw is that there is surely no purpose in compiling and reporting further small, uncontrolled studies. They are unlikely to add further knowledge^{59,60} and yet they continue to appear in the surgical literature.⁶¹⁻⁶³

There are circumstances where the immediacy of cause and effect, the mechanistically obvious

relationship between intervention and benefit, and the large and incontrovertible effect leads us to accept a treatment because we can see that it works.⁶⁴ In the practice of pulmonary metastasectomy in colorectal cancer, these conditions do not prevail.

In the context of colorectal cancer, the claims of survival benefit from pulmonary metastasectomy rely on an implicit belief that survival for any of this population of patients at five years (say) is an extreme rarity, and that any survivors five years after operation are attributable to surgical metastasectomy. We explored the validity of that assumption using mathematical modelling using cancer registry data and it did not hold.⁸ This review of the literature does not resolve our doubts.

The reports often state that pulmonary metastasectomy is safe and indeed reported mortality rates are often zero. A recent report detailed how well these patients recover.⁶⁵ Nevertheless, it should be remembered that when one operates on a patient, one does not have the opportunity to modify the dose or discontinue treatments which are not achieving the desired effect. There are certain harms which are permanent and irretrievable such as the loss of lung parenchyma for all and for some long-term pain and other complications. One of the weaknesses of the literature reviewed in this study is that these are not reported.

The authors of the previous systematic review of pulmonary metastasectomy for advanced

Table 1
Prognostic factors among patients in the five epochs

	1	2	3	4	5
<i>Prognostic factors and case-mix</i>					
<i>Cases by epoch (%)</i>					
Multiple metastases reported in 38 studies comprising 2676 patients in total	33	35	27	40	39
Bilateral metastases reported in 13 studies comprising 624 patients in total	11	15	*	13	19
Previous pulmonary metastasectomy reported in 21 studies comprising 1608 patients in total	15	22	16	14	19
Also with hepatic metastases reported in 34 studies comprising 2356 patients in total	15	16	19	19	22
Elevated CEA reported in 18 studies comprising 1409 patients in total	46	51	41	49	32
<i>Prognostic factors and survival</i>					
<i>Alive at five years (%)</i>					
Multiple metastases reported in 15 studies comprising 1516 patients in total	30	29	31	22	37
Solitary metastasis reported in 25 studies comprising 2227 patients in total	46	45	48	49	54
CEA normal reported in 11 studies comprising 1159 patients in total	47	38	42	53	43
CEA elevated reported in 11 studies comprising 1159 patients in total	16	22	33	22	0**
* No report in this epoch provided information on this factor					
** Only one series reported this factor in this epoch					

colorectal cancer concluded by opining that randomized trials are not now possible. We draw a different conclusion – it is time for a randomized trial.¹⁰ A randomized trial is now essential because the evidence for the benefit of surgery is small, the practice is very widespread¹ and probably increasing, and the certain harm being done, if there is no benefit, is too great.

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