Current Concepts: Pulmonary Metastasectomy for Colorectal Cancer

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ABSTRACT

There is no good quality evidence for the effect of pulmonary metastasectomy in colorectal cancer. The practice has been in existence for over forty years and is increasing. Better evidence is needed to justify the continuing expansion of this practice and indeed for its continuance.

Pulmonary metastasectomy has become a common operation and is now a substantial part of the work of thoracic surgeons. A survey of practice in Europe conducted by the European Society of Thoracic Surgeons (ESTS) showed that beliefs concerning indications and limits vary widely, as do the surgical approach and resection techniques.[1] The ESTS formed a working group charged with the task of reviewing the pulmonary metastasectomy[2] and its conclusions are presented in a Supplement to the Journal of Thoracic Oncology in June 2010, which includes an up to date systematic review of the clinical evidence for factors influencing the outcome of metastasectomy in colorectal cancer.[3]

Colorectal cancer is the commonest epithelial cancer for which pulmonary metastasectomy is performed and usually features at the top of the list in the many reports of thoracic surgeons’ mixed metastasectomy series.[4] In a systematic review Fiorentino et al.[5] summarised data from 51 surgical follow up studies reporting surgery restricted to metastasectomy for colorectal cancer since the 1960s. The nature of cases operated upon has been remarkably consistent for over 40 years, with about 60% being male, average age about 60 years, 60% of operations being for a solitary metastasis, and 60% of operated patients die within 5 years.

The fundamental question is what is achieved by this surgery? Are patients cured? Do patients live longer? And if so how can we select the long survivors? Before addressing questions related to cure and extending survival, let us first consider if there is a palliative role for this surgery. Pulmonary metastases in colorectal cancer are characteristically asymptomatic and it is likely that this is the case in patients put forward for pulmonary metastasectomy. No reports include information on this point and no mention is made of alleviation or return of symptoms in the follow-up studies.[5,6]

We know that patients when patients with advanced colorectal cancer become symptomatic it is with pelvic, peritoneal, liver and local recurrence. It is not respiratory or other thoracic symptoms that trouble them so we can conclude that palliation is not, and should not be, used as a general indication for surgery in this disease. We confine further discussion to the question of survival.

Evidence for the practice of pulmonary metastasectomy

Contrary to the strict rules of Evidence Based Medicine (EBM)[7] much of surgical practice relies on forms of evidence other than randomised controlled trials (RCT).[8,9] A typical evidence sequence (as opposed to a hierarchy) has served us well and might be sufficient for many purposes.[10] In the case of pulmonary metastasectomy we will conclude that in this instance an RCT is required, and indeed is planned.[11,12] We set out the path taken to reach that conclusion.

A characteristic and time honoured sequence of assessing the evidence for surgery is set out below. Not all steps are necessary: the matter may be resolved one way or the other at steps 1, 2 or 3. It may be that step 8 on this route map is the gold standard but is a long time coming and we may be able to make decisions at an earlier step on the way, and at a much earlier point in time, and so spare many patients a lost opportunity of benefit.

1. Evident cause and effect
2. Accumulated clinical experience
3. Published peer reviewed of follow up studies
4. Prospective studies including registries
5. Formal comparative studies, non randomised
6. Mathematical models
7. Randomised controlled trials
8. Meta-analysis of controlled trials

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The evidence for pulmonary metastasectomy can be reviewed against this route map.

**Step 1. Evident cause and effect**

This form of evidence has been expounded by Glasziou et al.[13] It applies to conditions which are stable and/or predictably progressing. The relief attributed to the intervention must have a clear mechanistic relationship and an onset close in time to its application. Hip replacement and cataract surgery are good examples: after these the lame walk and the blind recover their sight.[14] In contrast, the progress of metastatic colorectal cancer is highly variable, multimodality treatments are common, and we count survivors after five years, and then they are the minority. Can survival be attributed to the surgery? Not reliably; it is not easy to be sure of the signal amongst the noise.[13]

**Steps 2&3. Accumulated clinical experience and published follow up studies**

Evidence based on clinical experience is plentiful in surgery but it has serious pitfalls as a means of assessing the effect of cancer surgery.[15] The authors of such reports always stress the need for careful selection but maybe they are selecting those who have disease compatible with longer survival? The point was made in the context of pulmonary metastasectomy years ago[16;17] and has never been refuted. Authors never put a number on the ratio of selected to non-selected patients because they never know the size of the population from which the patients were drawn in order to make it through the sequence of selection processes to reach the operating room. We can deduce from registry[18] and institutional data[19] that a very few in every hundred patients with pulmonary metastases that end up having a metastasectomy.

**Step 4. Registry data**

The International Registry of Lung Metastases[20;21] received returns from volunteer surgeons who are probably those writing up their follow up series. While the Registry might provide an aggregate it cannot be more reliable than the sum of its parts. Better mechanisms of comprehensive data collection[22] would be required to use it for robust and incontrovertible evidence of effectiveness.

**Steps 5,7 and 8. Studies which include a comparison group**

There are no comparative data provided in any of the publications.[5]

**Step 6. Mathematical models**

What is forgotten when the inference is drawn about survival in operated series, is that survival is not zero at five years. The selection process (which is extreme) must inevitably narrow down on the 5% destined to survive, so they are overrepresented amongst the operated patients as a result of selection rather than surgery.[23] It has proved possible to use data on (a) pathological case mix and (b) the time elapsed between resection of the primary cancer and metastasectomy surgery from two of the larger clinical series[24;25] to construct putative survival curves from cancer registry data. These curves display the survival of real cancer patients who were similar on the basis of these characteristics. Their survival might give an indication of the expectation of life for operated patients if the disease had been allowed to run its course without pulmonary metastasectomy. The results of this exercise do not support the belief that survival was better in the operated patients than it might have been if the operation had not been performed.[26;27]

**Pulmonary Metastasectomy in Colorectal Cancer: the PulMiCC trial**

On 17th March 2010 a multicentre RCT funded by Cancer Research UK was launched in London.[12]

**Inclusion and exclusion criteria**

Since there is no evidence for the effectiveness of pulmonary metastasectomy in any group of patients with colorectal cancer PulMiCC has no specified oncologically defined inclusion or exclusion criteria. Groups are asked to consider randomisation in patients where they do not have a clear preference for or against surgery.

**Likely exclusion factors**

There are a number of factors that are repeatedly found to be associated with worse five-year survival rates and most teams will already make absolute exclusions on the basis of these factors.

- Shorter interval between the operation on the primary cancer and the metastasectomy. The most recent analysis from Memorial Sloan Kettering Cancer Centre (MSKCC) finds this to be significant at one year.[28]
- The greater the number of pulmonary metastases. MSKCC analysis puts this at greater than 3.[28] In terms of those who are to become long term survivors it may be that the threshold is between one and multiple metastases.[29]
- High level of carcinoma embryonic antigen (CEA).[30]
- Evidence of involvement of mediastinal lymph nodes.[31]

However we know that they are not absolute and there is existing variation in practice.[1] Where there is clinical uncertainty about the recommendation the team wants to make, PulMiCC suggests allocation within the trial as being as rational and ethical as any other means of coming to a decision.

At the other end of the spectrum, that is for the most favourable patients, teams may have strong views that they would want to offer metastasectomy in particular patient groups.

People often put in a plea for young patients. In fact recent evidence is against them: patients over 65 survive longer after metastasectomy than do younger patients.[28]

There is a particular case to be made for operating on the solitary metastasis, or presumed metastasis. First, all newly appeared or growing solitary nodules merit diagnosis. In patients with a history of bowel cancer some of these will be a potentially curable lung cancer, maybe as many as 20-30% in some experiences, and although there are clinical criteria for probability of lung cancer[32] histological diagnosis is usually recommended. It is interesting to reflect on the fact that 60% of patients in reported series had a solitary metastasis.[5]
The retrospective nature of the data does not allow us to discover how many of these nodules were being excised for diagnosis. In at least some the characterisation as colorectal metastasis and inclusion in the follow up report was made after the event.

That apart, the data indicate that a solitary metastasis is consistently associated with longer five-year survival. There must be some cases where this is the only remnant of cancer and its removal will truly bring about cure. This was never the case with four or more in the MSKCC reported experience.[28]

Surgical approach

This is likely to be governed by the site, size, and number of the metastases and so the technique cannot be set out by protocol. Furthermore since radiofrequency ablation cannot be shown to achieve R0 resection, inclusion of this modality in PulMiCC will make it impossible to answer the primary question, does removal of pulmonary metastases extend survival in metastatic colorectal cancer.

OUTCOMES

The outcomes of interest are of course survival, but also some indicators of pulmonary functions (gained or lost) and overall quality of life. Advocates of pulmonary metastasectomy recommend an open approach so that the lung can always be palpated, and that bilateral surgery should be considered, because there may be unimaged metastases in the other lung.[33] In spite of the availability of minimal access approaches in the event this surgery may be burdensome.

REFERENCES