Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) cohort study: analysis of case selection, risk factors and survival in a prospective observational study of 512 patients

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Title Page
Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) Cohort Study: analysis of case selection, risk factors and survival in a prospective observational study of 512 patients.

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Key words
Lung metastasectomy, prospective observational study

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Abstract

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Aim

We wanted to examine survival in patients with resected colorectal cancer (CRC) whose lung metastases are and whose are not resected.

Methods

Teams participating in the study of Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) identified potential candidates for lung metastasectomy and invited their consent to join Stage 1. Baseline data related to CRC and fitness for surgery were collected. Eligible patients were invited to consent for randomisation in the PulMiCC RCT (Stage 2). Sites were provided with case report forms for non-randomised patients to record adverse events and death at any time. They were all reviewed at one year. Baseline and survival data were analysed for the full cohort.

Results

Twenty-five clinical sites recruited 512 patients from October 2010 to January 2017. Data collection closed in October 2020. Before analysis 28 patients with non-CRC lung lesions were excluded and 3 had withdrawn consent leaving 481. The date of death was known for 292 patients, 136 were alive in 2020, and 53 at earlier time points. Baseline factors and five-year survival were analysed in three strata: 128 non-randomised patients did not have metastasectomy; 263 had elective metastasectomy; 90 were from the randomised trial. The proportions of solitary metastases for electively operated and non-operated patients were 69% and 35%. Their respective five-year survivals were 47% and 22%.

Conclusion

Survival without metastasectomy was greater than widely presumed. Difference in survival appeared to be largely related to selection. No inference can be drawn about the effect of metastasectomy on survival in this observational study.

What this study adds to the literature

The assumed near zero survival without resection of patients with lung metastases from colorectal cancer was not supported by this study. It seems likely that a much smaller part of the 40% observed five-year survival can be attributed to lung metastasectomy than is widely believed.
The Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) study enrolled 512 patients who were being considered for lung metastasectomy from October 2010 to January 2017. Nested within this observational study was the PulMiCC randomised controlled trial (RCT) in 93 patients. The RCT was reported in Colorectal Disease in 2020.(1) The widely believed large survival benefit from lung metastasectomy was not evident although a small late effect cannot be excluded. Patient reported outcomes—Quality of Life and Health Utility—declined at a similar rate in the metastasectomy and the unoperated control arms.(2, 3)

The PulMiCC study was run in the context of a firm belief in the clinical effectiveness of lung metastasectomy. In response to a paper arguing the case for a trial,(4) the European Journal of Cardio-Thoracic Surgery published an Editorial in 2017 proclaiming “Surgery for pulmonary metastases is a pillar of modern thoracic surgery”.(5) In support of lung metastasectomy for colorectal cancer (CRC), the authors cited two retrospective single institution studies.(6, 7) These provided a pooled five-year survival of 60% in groups of 165 and 113 patients collected over 10 and 12 years. The Work Force of Evidence Based Surgery of the Society of Thoracic Surgeons (STS) based its recommendations for lung metastasectomy on the assumption that five-year survival without resection is zero.(8) Neither statement was supported by control data. These publications in the leading thoracic surgical journals invite the conclusion that lung metastasectomy provides 60% survival benefit. This widely held belief and the climate of certainty resulted in multidisciplinary teams (MDTs) having difficulty randomising patients into the PulMiCC trial. (Fig.1)

Although PulMiCC found no difference in survival, a small survival advantage due to resection of lung metastases that prove to be the only site of residual CRC, cannot be discounted. But the trial was large enough to refute the improbable 0%.(8) and the less extreme estimate of 5% more generally cited.(9) The five-year survival in the control group was 30% (95% CI, 15.3-45.7%) significantly above 5% (P<0.001).(1)

Colorectal Disease has recently published a Big Data study of pulmonary metastasectomy for colorectal cancer (CRC).(10) Among 173,354 patients who had a CRC resection from 2005 to 2013, lung resection was subsequently reported in 3,434 patients which averages 2% over the time span of the study. From this can be estimated an average number of pulmonary metastasectomy operations for CRC of about 380 per annum in the National Health Service in England. During an overlapping period from late 2010 to early 2016 the PulMiCC Cohort recruited more than 300 patients who had a lung metastasectomy for CRC which is equivalent to about 14% of all patients having this procedure in England.

Here we report data from the full PulMiCC Cohort. The large majority of the patients were not randomised and so we cannot draw any valid inferences about survival attributable to lung metastasectomy. Nevertheless, the characteristics of the large sample of patients and
their outcomes are available to inform the Association of Coloproctology IMPACT initiative and the design of future research in this uncertain area. (11, 12)
General Methods

Recruitment
The PulMiCC Cohort Study was planned around the PulMiCC RCT. The study was administered by clinical trials staff based at the recruiting hospitals under the direction of the site’s principal investigator (PI) who was either a thoracic surgeon or an oncologist. Patients who were potential candidates for lung metastasectomy were given written information and an explanatory DVD to take home. A healthcare professional training DVD was also available for clinicians to aid their discussions with patients.

Interested patients were invited to sign Stage 1 to be assessed for lung metastasectomy within PulMiCC and to be registered by the Trials Unit. They consented to collection of baseline information: sex, age, height and weight to derive body mass index (BMI), the interval since primary colorectal cancer (CRC) resection, whether they had prior liver metastasectomy, the number of lung metastases, carcinoembryonic antigen assay (CEA) and tests of lung function.

Stage 1 consent included one-year follow-up by a Case Report Form (CRF) to record treatments since evaluation, including lung metastasectomy, and other cancer directed local interventions. The sites were given CRFs to report death, serious adverse events, new lung metastases, new liver metastases and other cancer recurrence.

The local MDT considered whether patients should have lung metastasectomy and if they were uncertain, agreed to offer patients randomisation in the PulMiCC RCT. When PulMiCC was closed, in view of the size and wealth of baseline data about the 82.2% non-randomised patients we sought Research Ethics Committee agreement to approach sites for follow-up data. Approval was readily granted as an audit of practice on 11th February 2019. All patients who gave consent on entry to Stage 1 are included in this analysis.

From 11th February 2019 all the site PIs and trials staff were approached with an individualised CRF request for each patient in Stage 1 asking for a date of death or when last known alive. We repeated the requests for missing survival information until the end of October 2020.

Statistical Methods
Data from the full PulMiCC Cohort were used to investigate baseline factors that influenced survival. Patients not known to have died were censored at the last time they were known to be alive in all analyses of survival. These investigations were based on Cox’s relative risk model with time to death as the outcome and time from cohort entry as the time scale. The observational nature of the cohort does not support the estimation of treatment effects. Three strata were defined and all analyses were stratified on this basis.

1. The first stratum included all patients who were not randomised and did not have a metastasectomy. They entered the analysis from their time of cohort entry.
2. Patients receiving an elective metastasectomy formed the second stratum, entered at
the time of their operation.

3. Patients in the RCT formed the third stratum entering at the time of randomisation.

Results are summarised as hazard ratios (HRs) with confidence intervals (CIs). An HR
greater than 1 indicates that larger values of the risk factor are associated with poorer survival
and an HR less than one indicates that larger values are associated with improved survival.
For categorical risk factors, an HR > 1 indicates poorer survival is associated with the
presence of the risk factor (e.g. for male sex) or with a risk factor category compared to the
reference category as for performance status using the Eastern Cooperative Oncology Group
(ECOG) scores.

For descriptive purposes, survival curves were also estimated based on the fixed grouping of
the patients into these three strata. The times of origin for these three curves are different and
are the dates of cohort entry. These classifications are retrospective and therefore analyses
using these from the time of cohort entry are ad hoc because the classes are determined after
cohort entry and, more importantly, by decisions made by the patient and MDT following
cohort entry.

Results
Sources of patients and composition of the three strata
512 patients were recruited into Stage 1 of the PulMiCC trial from October 2010 to January
2017 from 25 clinical sites, mainly in England but also China, Scotland, Serbia, and Sicily.
(Table 1) Of the 512 patients 31 were excluded for reasons given in Table 2. This left 481
patients in the cohort, of whom 90 had been randomised in the PulMiCC RCT. Of these 41
never had a metastasectomy and 49 had a lung metastasectomy 0 to 627 days after
randomisation (median 51; IQR 27-160 days) including some late crossovers.

We received a record of the date of death for 292 of them. Four patients who had
metastasectomy group died on the day of surgery. For the 189 patients without death dates,
136 were known to be alive in 2020, 33 in 2019, and for 20 patients last alive dates were
longer ago than the end of December 2018. (Fig.2, Table 3) Data collected up to October
2020 are used in this analysis. The source, mix, and eventual outcome of the three strata are
shown in Fig.3.

Mortality risk factors
The baseline risk factors for the patients in the three strata are in Table 4. The proportions of
metastases in the three strata (Fig.4) shows the predominance of solitary metastases (69%) in
the elective metastasectomy group. (Table 5).

Table 5a presents the results from single factor analyses of baseline factors derived from
stratified Cox regression models. The table includes the number of deaths examined in each
analysis as these vary depending on the number of patients for whom information is available.
on the various potential risk factors. The factors demonstrating evidence of a higher mortality risk were higher values of log(CEA), a shorter interval from CRC to cohort entry, and higher ECOG classes with a suggestive effect for male sex. Multiple lung metastases and prior liver metastases also demonstrated limited potential for an increase in mortality so were also considered for multi-factor analyses. There was some evidence that the effect for log(CEA) was different in different strata. Estimated HRs and 95% CIs were 1.73(1.37,2.19), 1.16(0.93,1.44) and 1.58(1.22,2.05) in the elective no metastasectomy, elective metastasectomy and randomised groups respectively with no effect being demonstrable in the elective metastasectomy group.

Table 6b presents results from multi-factor stratified Cox regression models including variables demonstrating some potential for a relationship in single factor analyses. The set of models presented are based on gradually decreasing numbers of deaths depending on the availability of risk factor information for the variables included with a final model with the 4 most significant variables. These were male sex, interval (shorter) from CRC to cohort entry, prior liver metastases and log(CEA). Again, there was evidence of differential effects for log(CEA) with estimated HRs and 95% CIs of 1.57(1.20,2.04), 1.14(0.92,1.43) and 1.52(1.16,1.98) in the elective no metastasectomy, elective metastasectomy and randomised groups respectively.

Survival

With a time origin of cohort entry, Fig.5 a,b,c display Kaplan-Meier estimated survival curves, and 95% confidence intervals of three groups of patients retrospectively classified in the strata: non-randomised and no metastasectomy, elective metastasectomy, and randomised.

Fig.6 displays the estimated survival after metastasectomy curves for randomized and elective metastasectomy patients. The curve in Fig.6 begins at a value of 0.989 for elective patients because there were 3 patients with a death date the same as the day of metastasectomy. The curve for randomised patients begins at 0.980 with 1 death on the day of metastasectomy. Overall, in the six months after metastasectomy there were 9/288 deaths compared with 2/166 among those who did not have an operation in the six months after cohort entry.

Over the time period after metastasectomy, the overall estimated HR(95% CI) for multiple metastases versus a single metastasis, stratified by elective/randomised status, in PulMICC patients having a metastasectomy is 1.33(0.94,1.88) \( [p=0.10] \). The separate estimates based on elective and randomized metastasectomies are 1.18(0.80,1.76) \( [p=0.40] \) and 2.15(0.93,4.99) \( [p=0.07] \) respectively providing suggestive evidence for a much more marked effect in the randomised patients. The difference in survival for those having elective resection of solitary and multiple metastases is shown in Fig.7. The number of lung metastases is a risk factor of particular relevance for metastasectomy patients and is considered further under the heading “Interpretation of Results”.

Interpretation of results
All the curves in Fig.5, 6 and 7 show a relatively slow rate of decline initially. This is a hallmark of many cancer survival studies—whether randomised or observational—in contrast to cancer registry data presentations when there is characteristically an early sharp fall which becomes progressively flatter. For randomised patients the plateau may be because patients have to have a good probability of short-term survival (1-2 years) often defined by entry criteria. This is also seen among patients in whom the decision is individualised. All patients in the cohort were being considered for lung metastasectomy and therefore had favourable features. This provides for a further bias in addition to the selection of patients on prognostic features. The median interval from registration to elective metastasectomy was 21 days with the upper quartile of delayed decisions ranging from 39 to 431 days. Lung metastasectomy is used highly selectively, not undertaken for imminently life-threatening disease. The time needed to check that there are no further metastases or disease at other sites allows for a further manifestation of selection bias seen in the initial parts of the curves in Figures 5b and 5c. This effect carries over to the initial period after the metastasectomy as seen by the initial plateaus in Figure 6 after deaths on the day of operation. We suggest this is a form of guarantee-time bias (GTB).(13) It can occur when survival is timed from enrolment, and is compared across groups defined by a classifying event occurring sometime during the subsequent passage of time. In this case patients who show other sites of disease, or other adverse features, fall outside the standard criteria for metastasectomy.(14) But metastasectomy remains an option for patients whose progression trajectory indicates the likelihood of longer survival. It is carried out if survival appears to be “guaranteed” for a reasonable length of time. In assessment for liver metastasectomy there is a period of assessment before the final decision is made. It is a conscious policy referred to by liver surgeons as the “test of time”. (15, 16)

The early deaths in the elective metastasectomy stratum merit attention. There were three deaths on the day of surgery and a further five in the six months after operation. Although lung metastasectomy is comparatively low risk, thoracic surgery is associated with non-trivial rates of pneumothorax, persistent air leak, bleeding, lung infection and pleural space infection all of which take their toll on wellbeing and may contributed to deterioration and earlier death than would have otherwise been the case. Deaths in the months after operation for selected patients with very limited colorectal cancer are probably related to surgery. A similar inference was drawn in the analysis of deaths within 90 days after primary resection in the National Bowel Cancer Audit.(17)

The relatively low hazard ratio of 1.19 for multiple versus single metastases in Table 6a is not directly comparable with results derived only from metastasectomy patients. In the meta-analysis of 24 reports including 2589 patients already referred to, the hazard ratio for multiple versus solitary metastases, for patients having a metastasectomy, was 2.04.(9) The better survival of patients with a solitary metastasis has been found repeatedly in case series, in the International Registry of Lung Metastases(18) and in systematic reviews.(19, 20) Fig.4 shows that among patients selected for the elective metastasectomy stratum the solitary metastasis rate was nearly double that in the unoperated patients (69% versus 35%). A large difference was seen in survival after two years among patients with a difference in this risk factor.
The analysis of the randomised stratum in PulMiCC produced a hazard ratio of 2.15 which is comparable with that in the meta-analysis of Gonzalez and colleagues. (9) A likely explanation is that in more recent practice, aware of the hazard of multiple metastases, the MDT will only recommend metastasectomy if the balance of other risk factors is favourable. In randomised patients minimisation prevents trading off risk factors.

However, erosion of the effect of a risk factor as the practice becomes more selective has been observed in the use of risk factors in case selection. (21) A simple analogy might help explain. Looking at performance data of a large pool of high school basketball players an analyst noted that youths ≥2 metres tall were higher scorers. They were preferentially picked for the county team. When the analysis was run for elite teams, height was no longer such a strong discriminator. They were nearly all very tall. Blackstone has called this effect “work up bias”. (22) The coach however continued to select for the squad one or two players ≤1.7 metres tall who could almost unerringly shoot and score from 15-20 metres away. As does the coach, an MDT looks at all the factors. If a patient has 2-3 metastases that have remained much the same over a year of observation, they know that patient is likely to have a longer survival.

Discussion

The major limitation of the PulMiCC Cohort Study is that it is not a randomised comparison and cannot provide evidence about survival benefit attributable to metastasectomy. The best currently available data is in the PulMiCC RCT report. (1)

We can confidently state that the five-year survival of people with lung metastases from colorectal cancer is not zero. Among 481 patients in the cohort, 169 patients did not have a metastasectomy and 37 of them were five-year survivors (22% 95%:CL 16%-29%). It is possible but very unlikely that a few of these survivors did not in fact have malignant lung lesions. We specifically sought information on long survivors, however treated, and the PIs did not report any case in whom the diagnosis of CRC had been wrong.

In most cases after lung metastasectomy CRC recurs sooner or later but it is quite feasible that in some cases the lung metastases are the only residual site of disease and metastasectomy is curative. We hear anecdotal accounts (23) but documented proof of disease-free survival at a long interval after lung metastasectomy are yet to be seen. Reported long term survivors have usually also had systemic treatments. The majority of patients in this cohort with and without metastasectomy had systemic treatments. An analysis of those treatments is the subject of a further report.

The Big Data study in the English NHS already referred to showed that lung metastasectomy is highly selective being used on only 2.3% of patients with resected colorectal cancer in 2013. (10) A study in the Korean National Health Insurance Database of 2573 CRC lung metastasectomy patients found a similar rate of 2.5%. (24) The lung metastasectomy operations referred to as “a pillar of modern thoracic surgery” were performed at a rate of
about one a month in the two series cited in support. (5) More a flying buttress than a pillar.

This is a highly selective practice.

At this point discussants of observational studies tend to point to “the need for trials”. In this instance we refer to the PulMiCC RCT, a trial already done. It refutes the zero assumption and substantially narrows the plausible effect size from the assumed 40% difference.

NICE has considered the question of lung metastasectomies and the recommendation was to “consider” metastasectomy. While it might have been intended as a weak recommendation, it sends out a signal for “business as usual”. The guideline development group advising NICE discounted PulMiCC as too small. (25) Instead they chose to use a non randomised follow-up study in which 48 had metastasectomy. PulMiCC’s metastasectomy arm fell short of their unspecified cut off with only 46 patients but there was a control group. Also recommended for consideration was peritoneal surgery. They cited an RCT in support. It had the same surgery in both arms but the authors concluded “that high-quality surgery is of value” which cannot be derived from the abstract cited. The position with respect to liver resection was summed up by surgeons at Memorial Sloan-Kettering: “We took as our point of departure the assumption that there will never be an RCT to answer the question of if liver resection has a role in the management of CRLM (colorectal liver metastases), or even to quantify its exact benefits.” (26) It seems questionable that the practitioners of a particular form of surgery should seek to bar the way to its evaluation. We are aware that the IMPACT initiative of ACPGB&I includes active detection of metastases for resection but meta-analysis of the many trials of more versus less intensive screening protocols have found no overall survival benefit. (27, 28)

Thoracic surgeons have addressed the question of the clinical effectiveness of lung metastasectomy by participating in the PulMiCC studies, the RCT and this cohort, but resolution of this matter is unlikely to come from specialist thoracic surgeons engaged in a very small part of the overall treatment of advanced colorectal cancer. ACPGB&I have made a commitment to improving the care of patients with advanced colorectal cancer. (11) That should include reducing and avoiding the use of ineffective treatments if only to make room in the budget for adopting new ones. It is noteworthy that in the process of prioritising patients for cancer treatments during the Covid-19 pandemic, metastasectomy was deemed low priority. The use of stereotactic radiotherapy (SABR) to treat “oligometastases” has been commissioned by NHS England on the basis of very weak evidence, and this may well supersede the use of surgical metastasectomy. (29)

Colorectal MDTs are in the best position to implement trials of treatments for advanced CRC. Commenting on yet another round of the homoeopathy versus allopathy debate The Lancet recognised that allopathy might have RCT evidence but homoeopathy has a following and while “doctors need to be bold and honest with their patients about homoeopathy’s lack of benefit” they should also be honest “with themselves about the failings of modern medicine to address patients’ needs for personalised care”. The IMPACT initiative seeks to personalise...
care(11) but all systemic treatments have been introduced on the basis of controlled trial
evidence. To paraphrase The Lancet, doctors need to be bold and honest with themselves
about the failure to even seek proof in the effectiveness of local treatments. This is a declared
research priority of the Association of Coloproctology.(12)
| Site  | City and Institution                                      | Participants Enrolled |
|-------|----------------------------------------------------------|-----------------------|
| 076   | Sheffield, Northern General Hospital                     | 101                   |
| 073   | Liverpool, Heart and Chest Hospital                      | 88                    |
| 062   | Bristol, Royal Infirmary                                 | 77                    |
| 078   | Serbia, Institute for Lung Diseases of Vojvodina         | 41                    |
| 070   | Middlesbrough, James Cook Hospital                       | 29                    |
| 029   | Cambridge, Papworth Hospital                             | 29                    |
| 028   | London Guy's Hospital                                    | 22                    |
| 060   | Basildon, Basildon Hospital                              | 15                    |
| 065   | Plymouth, Derriford Hospital                             | 15                    |
| 068   | Glasgow, Golden Jubilee Hospital                         | 15                    |
| 071   | Sutton in Ashfield, King's Mill Hospital                 | 12                    |
| 063   | Manchester, Christie                                     | 11                    |
| 067   | Leicester, Glenfield Hospital                            | 10                    |
| 074   | Wolverhampton, New Cross Hospital                        | 9                     |
| 105   | Zhengzhou, Henan Cancer Hospital                         | 6                     |
| 066   | Newcastle, Royal Victoria Hospital                       | 5                     |
| 075   | Norwich, Norfolk and Norwich Hospital                    | 5                     |
| 080   | Catania, Policlinico Hospital                            | 5                     |
| 082   | London, Royal Brompton Hospital                          | 5                     |
| 018   | London, Royal Free Hospital                              | 4                     |
| 061   | Belfast, City Hospital                                   | 2                     |
| 069   | Birmingham, Heartlands Hospital                          | 2                     |
| 084   | London, St George's Hospital                             | 2                     |
| 072   | Leeds, St James' Hospital                                | 1                     |
| 081   | Burton, New Cross Hospital                               | 1                     |

**Total Patients**: 512
Table 2 Reasons for exclusion

| Reasons for exclusion          |   |
|-------------------------------|---|
| Total Stage 1 Recruitment     | 512|
| Non-neoplastic nodules        | 13|
| Primary lung cancer           | 13|
| Carcinoid tumour              | 1 |
| Hamartoma                     | 1 |
| Consent withdrawn             | 3 |
| Total exclusions              | 31|
| Included patients             | 481|
| Status                  | From        | To          | Number |
|-------------------------|-------------|-------------|--------|
| Known dates of death    | 31/07/2012  | 11/08/2020  | 292    |
| Known to be alive to 2020 | 01/01/2020  | 29/10/2020  | 136    |
| Known to be alive to 2019 | 03/01/2019  | 30/12/2019  | 33     |
| Last known to be alive  | 22/10/2014  | 10/12/2018  | 20     |
| <2019                   |             |             |        |
| Total                   |             |             | 481    |

Table 3. Recorded date of alive or dead status in all 481 cohort patients.
### Table 4 revision 210128

|                          | Data available† | %     | Min | 0.25 | Median | 0.75 | Max  |
|--------------------------|----------------|-------|-----|------|--------|------|------|
| **Age in years**         |                |       |     |      |        |      |      |
| Elective no metastasectomy | 128            | 99.2% | 42.4| 65.7 | 71.9   | 77.7 | 87.9 |
| Elective metastasectomy   | 263            | 100.0%| 30.8| 60.0 | 67.0   | 72.8 | 85.6 |
| Randomised                | 90             | 100.0%| 35.3| 59.8 | 67.1   | 73.8 | 86.5 |
| **Body Mass Index**       |                |       |     |      |        |      |      |
| Elective no metastasectomy | 105            | 81.4% | 17.9| 25.0 | 27.8   | 30.9 | 57.8 |
| Elective metastasectomy   | 259            | 98.5% | 17.0| 24.6 | 27.7   | 31.4 | 56.8 |
| Randomised                | 86             | 95.6% | 18.7| 26.1 | 28.6   | 31.7 | 40.9 |
| **Carcinoembryonic antigen ng/L** |            |       |     |      |        |      |      |
| Elective no metastasectomy | 82             | 63.6% | 0.3 | 1.7  | 3.0    | 5.9  | 57.0 |
| Elective metastasectomy   | 144            | 54.8% | 0.3 | 1.3  | 2.0    | 4.0  | 151.0|
| Randomised                | 78             | 86.7% | 0.3 | 1.9  | 3.0    | 4.6  | 74.0 |
| **Forced Expiratory Volume % predicted** |            |       |     |      |        |      |      |
| Elective no metastasectomy | 90             | 70.3% | 44.0| 76.0 | 86.6   | 101.5| 145.0|
| Elective metastasectomy   | 233            | 96.2% | 0.0 | 14.3 | 24.7   | 37.1 | 138.7|
| Randomised                | 84             | 93.3% | 46.0| 78.0 | 93.1   | 109.3| 139.0|
| **Months from primary CRC resection to metastasectomy or registration** |            |       |     |      |        |      |      |
| Elective no metastasectomy | 117            | 91.4% | 1.3 | 13.9 | 25.6   | 49.7 | 145.4|
| Elective metastasectomy   | 253            | 96.2% | 0.0 | 14.3 | 24.7   | 37.1 | 138.7|
| Randomised                | 84             | 93.3% | 0.8 | 13.8 | 25.6   | 36.9 | 130.3|
| **Number of metastases**  |                |       |     |      |        |      |      |
| Elective no metastasectomy | 107            | 82.9% | 1   | 1    | 2      | 3    | 17   |
| Elective metastasectomy   | 245            | 93.2% | 1   | 1    | 1      | 2    | 8    |
| Randomised                | 90             | 100.0%| 1   | 1    | 2      | 3    | 9    |
| **% Solitary**            |                |       |     |      |        |      |      |
| Elective no metastasectomy | 107            | 83.6% | 22  | 38   | 69     | 35.5%|      |
| Elective metastasectomy   | 245            | 93.2% | 18  | 169  | 76     | 69.0%|      |
| Randomised                | 90             | 100.0%| 0   | 30   | 60     | 33.3%|      |
| **ECOG**                  |                |       |     |      |        |      |      |
| Elective no metastasectomy | 90             | 70.3% | 29.7| 35.9 | 29.7   | 4.7  |      |
| Elective metastasectomy   | 215            | 81.7% | 18.3| 67.9 | 31.6   | 0.5  |      |
| Randomised                | 74             | 82.2% | 21.6| 73.0 | 25.7   | 1.4  |      |
| **Sex**                   |                |       |     |      |        |      |      |
| Elective no metastasectomy | 128            | 100.0%| 42  | 87   | 36.4%  |      |      |
| Elective metastasectomy   | 263            | 100.0%| 100 | 163  | 38.0%  |      |      |
| Randomised                | 90             | 100.0%| 34  | 56   | 37.8%  |      |      |
| **Prior liver metastasectomy** |            |       |     |      |        |      |      |
| Elective no metastasectomy | 121            | 94.5% | 44  | 77   | 36.4%  |      |      |
| Elective metastasectomy   | 256            | 97.3% | 71  | 185  | 27.7%  |      |      |
| Randomised                | 83             | 92.2% | 26  | 57   | 31.3%  |      |      |
†There are usually more missing data in the elective non-metastasectomy group because if metastasectomy is decided against for any reason, other investigations may serve no purpose. CEA is an exception. It was required for minimisation but the value was not always in the record. It is a paradoxical marker because its elevation on screening may prompt a search for metastases but its elevation is a negative predictor for survival after metastasectomy and may contribute to a decision against operating.
|                | Solitary | Two  | Three | Four | Five | Polymetastatic | Available |
|----------------|----------|------|-------|------|------|----------------|-----------|
| Elective no metastasectomy | 38       | 33   | 16    | 8    | 1    | 11             | 107/128   |
| Elective metastasectomy      | 169      | 44   | 18    | 10   | 2    | 2              | 245/263   |
| Randomised                  | 30       | 31   | 16    | 4    | 4    | 5              | 90/90     |

Table 5
Results from single factor analyses using a stratified Cox regression model.

Strata: Elective no metastasectomy or randomisation

Elective metastasectomy

Randomised

| Variable                              | Categories | No. of deaths | HR (95% CI)      | p-value |
|---------------------------------------|------------|---------------|------------------|---------|
| Age (cont.)                           |            | 292           | 1.00 (0.99, 1.01)| 0.73    |
| Male sex                              |            | 292           | 1.24 (0.98, 1.58)| 0.08    |
| Log(CEA)                              |            | 200           | 1.42 (1.25, 1.62) | * <0.001 |
| Liver Mets (Y/N)                      |            | 280           | 1.22 (0.95, 1.56) | 0.12    |
| # Lung Mets > 1                       |            | 265           | 1.19 (0.92, 1.54) | 0.181   |
| Interval CRC to Start (years)         |            | 274           | 0.90 (0.84, 0.97) | 0.003   |
| BMI                                   |            | 269           | 1.00 (0.98, 1.02) | 0.99    |
| ECOG                                  | 0          | 219           | 1.00             |         |
|                                       | 1          |               | 1.28 (0.97, 1.69) | 0.09    |
|                                       | 2          |               | 1.11 (0.49, 2.56) | 0.80    |
| %FEV                                  |            | 247           | 1.00 (0.99, 1.00) | 0.20    |

*some evidence of effects being different in different strata.
Table 6b:

Results from multi-factor analyses using a stratified Cox regression model.

**Strata:** Elective no metastasectomy or randomisation

|           | Model A          | Model B          | Model C          | Model D          | Model E          |
|-----------|------------------|------------------|------------------|------------------|------------------|
| No. deaths| 274              | 270              | 251              | 191              | 192              |
| Male sex  | 1.30 (1.02,1.67) | 1.29 (1.00,1.65) | 1.20 (0.93,1.55) | 1.25(0.93,1.69)  | 1.45 (1.07,1.98) |
|           | [P=0.036]        | [P=0.051]        | [P=0.167]        | [P=0.144]        | [P=0.018]        |
| Interval  | 0.90 (0.84,0.96) | 0.88 (0.81,0.94) | 0.89 (0.82,0.95) | 0.86 (0.79,0.94) | 0.84 (0.77,0.92) |
| CRC to Start | [P=0.002] | [P<0.001] | [P<0.001] | [P<0.001] | [P<0.001] |
| Liver Mets(Y/N) | 1.33(1.02,1.74) | 1.27 (0.96,1.67) | 1.23 (0.89,1.70) | 1.29 (0.94,1.76) | 1.29 (0.94,1.76) |
|           | [P=0.035] | [P=0.092] | [P=0.210] | [P=0.113] | [P=0.113] |
| # Lung Mets > 1 | 1.19 (0.91,1.55) | 1.23 (0.90,1.68) | 1.23 (0.90,1.68) | 1.35 (1.17,1.55) | 1.35 (1.17,1.55) |
|           | [P=0.208] | [P=0.191] | [P=0.191] | [P<0.001] | [P<0.001] |
| ECOG (0)  |                  |                  |                  |                  | 1.00             |
| ECOG (1)  |                  |                  |                  | 1.31 (0.97,1.78) | 1.31 (0.97,1.78) |
|           |                  |                  |                  | [P=0.081] | [P=0.081] |
| ECOG (2)  |                  |                  |                  | 0.96 (0.38,2.44) | 0.96 (0.38,2.44) |
|           |                  |                  |                  | [0.938]   | [0.938]   |
| Log(CEA)  |                  |                  |                  |                  | 1.35 (1.17,1.55) |
|           |                  |                  |                  |                  | [P<0.001]        |

Legend: HR (95% CI) [p-value]
Legends to Figures

Figure 1
Concerned by the low rate of randomisation into the RCT the IDMC asked for an investigation. The three largest recruiting centres (Bristol, Liverpool and Sheffield) provided reasons for not randomising in 155 patients. Among 78 patients for whom the MDT overrode the patients’ wishes to be in a controlled trial, 77 (99%) were operated on. When patients made their own decision they were more evenly divided, demonstrating group equipoise. The results are given in the Sankey chart. Diagram created using SankeyMATIC (http://sankeymatic.com/).

Figure 2
For 189 patients where a death form had not been returned this chart gives the date at which they were last known to be alive in order from the earliest to the most recent. Requests continued until October 2020 when we closed the study for analysis. Some centres regarded the close of the RCT as the end of their commitment to give time to the PulMiCC study.

Figure 3
The total 512 Stage 1 enrolled patients divide into the 93 in the RCT and the remaining 419 in the observational study. After 31 exclusions for the reasons given in Table 2, 481 patients form the PulMiCC Cohort who are analysed in three strata: elective non-metastasectomy 128, elective metastasectomy 263 and the 90 patients who were randomised. Diagram created using SankeyMATIC (http://sankeymatic.com/)

Figure 4
The numbers of lung metastases in the three strata based on available data as in Table 5. 1. N=128 non-randomised patients who did not have a metastasectomy. 2. N=263 non-randomised patients who had a metastasectomy. 3. N=90 randomised patients.

Figure 5
Survival in three strata with 95% confidence intervals. The curves are displayed separately because the entry points into the analyses and the baseline prognostic factors of those in the three strata are different. No direct comparison of these curves is appropriate.

Figure 6
Survival curves for all 312 patients who had pulmonary metastasectomy separated into those in the elective and randomised strata.

Figure 7
Survival for elective metastasectomy patients with solitary or multiple metastases. The difference in survival does not appear until nearly two years.
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