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1 **Title page**

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3 Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) randomised controlled trial: a systematic  
4 review of published responses.

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44 Full word count 6473

45 Data availability

46 All data used in this study are available on appropriately justified request to the corresponding  
47 author.

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48 **Graphical abstract**

49

50 Key question

51 What is the clinical reaction to the PulMiCC  
 52 randomised controlled trial of lung  
 53 metastasectomy in colorectal cancer?

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55 Key findings

56 A systematic citation search found 64  
 57 publications of which 57 (89%) dismissed  
 58 the RCT without providing data.

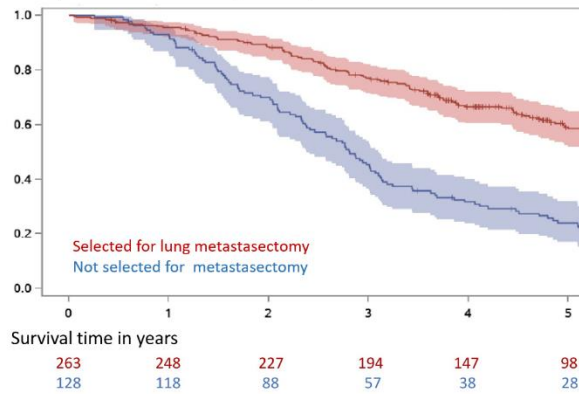
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60 Take-home message

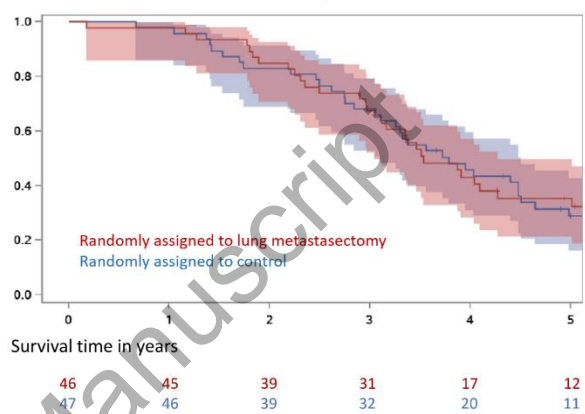
61 The apparent widespread disregard for  
 62 controlled trial data among  
 63 interventionalists treating metastatic  
 64 cancer is a cause for concern.

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Prospective cohort study in 391 patients



Randomised controlled trial in 93 patients



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## **Abstract and Keywords**

### Objectives

The objective of this review was to assess the nature and tone of the published responses to the Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) randomised controlled trial.

### Methods

Published articles that cited the PulMiCC trial were identified from Clarivate Web of Science (©). Duplicates and self-citations were excluded and relevant text extracted. Four independent researchers rated the extracts independently using agreed scales for the representativeness of trial data and the textual tone. The ratings were aggregated and summarised. Two PulMiCC authors carried out a thematic analysis of the extracts.

### Results

Sixty-four citations were identified and relevant text was extracted and examined. The consensus rating for data inclusion was a median of 0.25 out of 6 (range 0 to 5.25, IQR 0-1.5) and for textual tone the median rating was 1.87 out of 6 (range 0 to 5.75, IQR 1-3.5). The majority of citations did not provide adequate representation of the PulMiCC data and the overall the textual tone was dismissive. Although some were supportive, many discounted the findings because the trial closed early and was underpowered to show non-inferiority. Two misinterpreted the authors' conclusions but there was acceptance that five-year survival was much higher than widely assumed.

### Conclusions

Published comments reveal a widespread reluctance to consider seriously the results of a carefully conducted randomised trial. This may be because the results challenge accepted practice because of 'motivated reasoning'. But there is a widespread misunderstanding of the fact that though PulMiCC with 93 patients was underpowered to test non-inferiority, it still provides reliable evidence to undermine the widespread belief in a major survival benefit from metastasectomy.

Key words. Pulmonary metastasectomy; colorectal cancer; randomised controlled trial; motivated reasoning; citation index.

96 Text

97 **Introduction**

98 *It ought to be remembered that there is nothing more difficult to take in hand, more perilous*  
99 *to conduct, or more uncertain in its success, than to take the lead in the introduction of a*  
100 *new order of things.*

101 *This ... arises partly ... from the incredulity of men, who do not readily believe in new things*  
102 *until they have had a long experience of them. Niccolò Machiavelli, The Prince*

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104 The prospective cohort study Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC), with its  
105 embedded randomised controlled trial (RCT), was presented to the European Association for  
106 Cardiothoracic Surgery (EACTS) at its 35<sup>th</sup> Annual Meeting in Barcelona, in 2021. The study was  
107 proposed at the Workshop on Pulmonary Metastasectomy in Cluj-Napoca, Romania, in 2006 before  
108 a meeting of the European Society of Thoracic Surgeons (ESTS) (1). The launch of the PulMiCC trial  
109 was announced in the full report of the ESTS Lung Metastasectomy Project in 2010(2).

110

111 Lung metastasectomy for colorectal cancer (CRC) is based on surgical follow-up studies since the  
112 1970s, gaining momentum in the 1980s and 1990s.(3) The publication in 1997 of the International  
113 Registry of Lung Metastases with data on 5206 patients(4) showed that survival after  
114 metastasectomy was better if the metastases were solitary and there was longer elapsed time since  
115 primary resection. There were no RCTs but there had been one comparative study published in  
116 1980(5). Åberg and colleagues identified patients in the pre-metastasectomy era whose  
117 characteristics would make them candidates for metastasectomy in the 1980s. They found, in a  
118 small series of a dozen patients, that survival was similar to that attributed to lung metastasectomy.  
119 (Fig.1) Åberg returned to the debate in 2016 in an EJCTS editorial(6) making the case for an evidence  
120 based approach. Schirren et al. countered in an editorial opening “Surgery for lung metastases is a  
121 pillar of modern thoracic surgery”(7). The cited data for CRC showed a 60% five-year survival. The  
122 Society of Thoracic Surgeons (STS) Expert Consensus Document states that “metastatic disease  
123 survival is assumed to be zero”(8). The implication is that all five-year survival is attributable to  
124 metastasectomy.

125

126 The two-stage PulMiCC study recruited well; 512 patients consented to Stage 1 registration in 25  
127 centres between 2010 and 2016(9). After assessment 28 did not fit the study inclusion criteria  
128 leaving 484 patients. After Stage 2 consent 93 patients were randomly assigned to lung  
129 metastasectomy or control(10). The sample size calculation for non-inferiority of control versus

130 metastasectomy required 300 randomised patients. The two prominently published opinion  
131 papers(7,8) indicating a supposed five-year survival gain, attributable to metastasectomy, from 0%  
132 to 60% made randomisation difficult. Accrual into the RCT slowed and the trial steering committee  
133 closed the trial and instigated analysis(9,10). Before making the decision the trialists were asked to  
134 investigate the reasons for not randomising. Full details are provided in the first RCT report(9) and  
135 the full 512 participant cohort study report(11). The three most actively recruiting centres analysed  
136 reasons in 155 non-randomised patients. Of them 41 fully informed patients had chosen to make  
137 their own decision and chose metastasectomy or not in approximately equal numbers. For 78 fully  
138 eligible patients the clinician made the decision and 99% had a metastasectomy.(9,11) For the 36  
139 remaining patients 10 had non-CRC pathology or were deemed ineligible locally.

140

141 The elective cohort provided a wealth of trial-quality prospective data on 391 patients of whom 263  
142 (67%) had an elective lung metastasectomy.(11) Five-year survival (Graphical Abstract) after  
143 metastasectomy was 58.5% (95%CI:52.0-64.8) confirming that the PulMiCC cohort replicated the  
144 best of “real world” results. Critically important were the hitherto missing data on those who were  
145 clinically selected to not have metastasectomy. Their five-year survival, 24.0% (95%CI:16.9-31.9),  
146 was much higher than assumed.

147

148 From baseline data characteristics collected to RCT standards there is reliable information about  
149 prognostic factors. The proportion of solitary metastases in the 263 electively operated patients was  
150 69% versus 35% in the 128 unoperated. Fewer operated patients had raised carcinoembryonic  
151 antigen (CEA) (12% versus 20%). By meta-analysis(12) the hazard ratios were 2.04 for non-solitary  
152 metastases and 1.91 for elevated CEA. That is about twice the likelihood of death for each. The five-  
153 year death rates were 41% and 76%, a difference compatible with the hazard ratios. Also fewer  
154 operated patients had liver involvement (28% versus 36%), they had better lung function (FEV1 96%  
155 versus 87%), a higher rate of zero ECOG (Eastern Cooperative Oncology Group) performance scores  
156 (68% versus 36%) and were on average five years younger (67 versus 72 years). In the RCT there was  
157 excellent balance in metastasis numbers, CEA, primary cancer stage, the interval since primary  
158 resection, liver involvement, lung function, performance status, age and sex. There was no survival  
159 difference at any time point. We cannot escape the conclusion that the perception of survival  
160 benefit in uncontrolled observational follow up studies is mainly — maybe all — due to  
161 selection of those more likely to survive. Because of the wide confidence intervals we cannot  
162 exclude a small eventual difference in survival but it cannot be as large as is widely believed or what  
163 patients are told.

164

165 Opening the discussion at EACTS in 2021 Tim Batchelor remarked that the PulMiCC trial had received  
166 'a mixed reception'. That prompted this systematic review of publications citing the PulMiCC  
167 RCT(9,10) to investigate its reception.  
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170 **Materials and Methods**171 **Ethics Statement**

172 The material for analysis is from 64 papers all of which are published (14-77). Central ethical approval  
 173 for the PulMiCC trial was granted by the National Research Ethics Committee London – Hampstead  
 174 (No.10/H0720/5) but the work referred to here is all previously published (9-11).

175

176 **Search methods**

177 A search was conducted for publications providing survival results of the PulMiCC RCT and the  
 178 cohort study(9,10, 11). Citations were derived from Clarivate Web of Science (© Copyright Clarivate  
 179 2021) on 31 October 2021. The publications were searched for content related to PulMiCC.

180 **Rating publications citing the PulMiCC randomised controlled trial**

181 Potential raters were identified by HP and TT. They needed experience of systematic reviewing and  
 182 no prior involvement in PulMiCC. Four PulMiCC-independent researchers volunteered: AA, FF, HP  
 183 and MS.

184 Before presenting the material to the raters, the papers were filed in alphabetical order by the  
 185 surname of the first author and individually searched for all text related to PulMiCC. Blocks of text  
 186 were extracted and copied verbatim, including all statements and comments about PulMiCC, erring  
 187 on the side of overinclusion. Word counts were made with MS Word and quartiles were calculated  
 188 using MS Excel. The blocks of text were assigned an identity by sequential numbering masking the  
 189 authors and their affiliations.

190 The extent of representation of PulMiCC data from none to a full summary of the results was rated  
 191 using a numeric ordinal rating system from 0-6. On a similar system the tone of the comments from  
 192 dismissive to supportive was rated 0-6.

193 The agreed scales were:

194 (a)Representation of the data in the PulMiCC RCT

195 None Omits CIs and Significance Representative Full and fair summary

196 0 1 2 3 4 5 6

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198 (b)Tone of the text related to the PulMiCC RCT

199 Dismissive Balanced appraisal Supportive

200 0 1 2 3 4 5 6



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Working individually in undisclosed practice runs, the raters were invited to refine and agree the scales as fit for purpose. They then returned their 64 ratings individually. These were entered on a single spread sheet by the corresponding author. The standard deviation of the four ratings were calculated for each of the 64 papers giving a simple but robust indication of the spread of the ratings. The rows of four ratings were colour coded to indicate how close or dispersed they were and returned to the raters who could see their colleagues' ratings alongside their own, providing an opportunity to reconsider them in a Delphi consensus process. Inter-rater reliability was assessed by ordinal weighted agreement coefficients and confidence limits calculated by the method of Gwet(13) [Inter-Rater Reliability using the SAS System, 2nd Edition, K Gwet, 2021, AgreeStat Analytics] using SAS software (copyright © 2021 SAS Institute Inc., Cary, NC, USA).

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## 214 **Results**

215 Of 123 titles found, 46 were by PulMiCC authors and in 12 there was no reference found to PulMiCC.  
216 (Fig.2) There was only one independent citation to the cohort study which was excluded leaving 64  
217 publications for analysis(14-77) of which 40 cited the preliminary report (9), 12 cited the full RCT  
218 report (10), and 12 cited both.

219  
220 All 64 publications were from teams engaged in local treatment of lung metastases. Three sub-  
221 groups were identified: 28 original research reports, 24 opinion pieces (editorials, commentaries and  
222 letters) and 12 reviews (10 narrative and 2 systematic). (Fig.2) The contributors were thoracic  
223 surgical teams (30/64), other interventionalists (16/64), colorectal oncology multidisciplinary groups  
224 (12/64), head and neck surgeons (4/64) and hepatobiliary surgical groups (2/64). Of the 28 research  
225 papers 17 were follow-up studies on the treatment of lung metastases. (Table 1)

226  
227 The 64 blocks of texts provided for the raters totalled 8,444 words, of individual length varying from  
228 19 to 673 (median 81, IQR 39-164). The numbers of each of the 0-6 ratings assigned in the first and  
229 second rounds and the range, medians and interquartile ranges are given in Table 2. The inter-rater  
230 reliability association coefficients (Gwet's AC2 with confidence interval) are given in Table 3 and  
231 Fig.3 showing higher association coefficients after the second round. There were some differences in  
232 inter-rater reliability within the subgroups of papers. The presentation of PulMiCC numerical data  
233 was predictably the easier task and had 'very good' reliability. The rating of textual tone showed  
234 more variation but association was 'good' for all categories.

235 The majority of ratings for data content were <2 (58/64) indicating that they did not provide  
236 sufficient PulMiCC data to inform a reader. (Table 2, Fig.4) For textual tone the comments were  
237 predominantly dismissive, with 35/64 rated at  $\leq 2$ , rather than balanced or supportive. The patterns  
238 of the presentation of the data and textual tone are illustrated Fig.4 and the relationship between  
239 them in Fig.5.

240

## 241 **Textual analysis**

242

### 243 **Opinions on the methods of the PulMiCC trial**

244 Of six of the publications commenting on the method and conduct of the trial, five were  
245 favourable(16,18,40,53,54). It was noted to be "the world's only randomized pulmonary  
246 metastasectomy study" and that the "well-constructed study showed no advantage in the surgical

247 arm”(16). Other favourable comments were “The results of the PulMiCC study are impressive”(40)  
248 and “The PulMiCC study had the most interesting design and showed no advantage from lung  
249 metastasectomy.”(53)

250 There was only one response overtly critical of the nature of the study. In this rhetorical question the  
251 authors invoked the parachute analogy. “Would you perform a randomized trial of whether to  
252 deploy a parachute when jumping out of an airplane at high altitudes?”(56)

### 253 **Power considerations**

254 Twelve publications referred to the question of the “power” of PulMiCC but the statistical issues  
255 were not addressed in any detail (15,20,25,35,36,39,50,58,64,65,67,70). Most of the publications  
256 questioning the power failed to include any substantial data that could support their claim.

257

### 258 **Reasons for discounting the conclusions of the PulMiCC trial**

259 Nine texts described PulMiCC as a “failure”(16,77) or a “failed trial”(24,30,51,55,58,65,67) often in a  
260 short comment after which its findings were, to varying degrees, discounted.

261

262 Fourteen publications said that the trial was “stopped”(19-21,25,37,38,41,43,45,50,52,62,63,70,77)  
263 that it “closed early”(22,29,32,57,59,64,69,77) or “prematurely”(26,51,53,54,76.)

264

265 The numbers of patients in the RCT — 65 in the first report(9) and 93 in the full report(10) — were  
266 often seen as sufficient reason to discount the findings. For example “small sample size precluded  
267 definitive conclusions”(15) “due to poor accrual”(20) “failed to accrue patients adequately” (24)  
268 “insufficient number”(31) “small sample size”(34) and “poor recruitment”(35).

269

270 However one author interpreted the small size as evidence of resistance of the clinical teams: “Its  
271 small size again bears testament to entrenched surgical practice”. (16)

272

273

### 274 **PulMiCC’s refutation of the assumed zero survival without metastasectomy**

275 One firm conclusion of PulMiCC was that the STS “zero survival” assumption(8) was refuted. This was  
276 acknowledged in ten publications(17,18,20,23,34,44,65,67,74, 5) with one author, counter to the  
277 STS Consensus Statement(8) writing “The 5-year OS of large numbers of unselected patients with  
278 stage IV colorectal cancer has been >8% even before potential improvements from recent advances  
279 in systemic therapies.”(23)

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### **The question of survival benefit**

Three commentators explicitly considered that the PulMiCC RCT results were a signal that there might be no survival benefit(15, 39, 76) or “that any survival advantage from resection of colorectal lung metastases is, in all likelihood, very much smaller than has been assumed”(48). But it was clear that most authors discounted the possibility that there was no benefit and there seemed to be a note of incredulity in this statement “some authors openly doubt that PM might even provide a survival advantage”(33). Others suggested that the results show benefit: “the partial results of this suspended trial should be considered, in my opinion, as further support for the local treatment of pulmonary metastases”(59). Another paper had misinterpreted the conclusion of the PulMiCC trialists writing “We agree with the authors of the PulMiCC trial, who state that (although non-significant), a hazard ratio of 0.82 suggests that it is likely that in some patients, for whom isolated lung metastasis remains the only remnant of their otherwise fully-treated colorectal cancer, pulmonary metastasectomy is likely to convey benefit”(65).

### **Is PulMiCC applicable to practice?**

Amongst the comments was one specifically noting the applicability to clinical practice: “These findings are interesting, relevant, and important to keep in mind during both multidisciplinary tumor board discussions as well as in informed consent discussion with patients”(18). There were some personal plaudits for the PulMiCC trialists who were called “the true trail blazers in challenging established dogma surrounding treatment of CRC metastases” and “The PulMiCC trial was intrepid in reminding us to assess the true benefit of therapies we provide, particularly in conditions like metastatic CRC where cure is rarely guaranteed”(15).

**305 Discussion**

306

307 There was a “mixed reception” to the PulMiCC trial shown in the analysis of the 64 citing  
308 publications revealing a spread of opinions from dismissing the PulMiCC trial’s worth to some very  
309 supportive comments (Fig.4). But only a small minority reported the results adequately. Most over  
310 simplified the key issues and 44/64 were rated <3 on the 0-6 scale. But those who commented on  
311 the PulMiCC conclusions implicitly agreed that the five-year survival benefit from metastasectomy  
312 was likely to be much less than the widely believed 40% and none of the 64 publications restated  
313 the zero assumption of the STS Consensus Statement(8).

314

315 The phrase “a negative trial” for a study which does not show a treatment effect is an  
316 oversimplification. High quality RCT data where none existed before may answer part of the bigger  
317 question. Most observational studies report ~40% five-year survival(12) and by implication attribute  
318 all of that to metastasectomy. PulMiCC is the first study to report on potential metastasectomy  
319 candidates who remained unoperated and their survival was 20-30%(9, 10). So the prior belief in a  
320 ~40% improvement in five-year survival from metastasectomy is seriously challenged. A  
321 mathematical modelling study using cancer registry data, undertaken during planning the sample  
322 size for PulMiCC study, had found that the 40% five-year survival then widely reported(3) could be  
323 explained by case selection(78). It may in fact be only 10% or less. In the introduction we stress the  
324 importance of the non-randomised cohort of 391 operated and non-operated patients(11) in giving  
325 context to the RCT data (Fig.2). As seen in the visual abstract, the elective non-operated cohort —  
326 who were the less favoured patients — show a clear refutation of the “zero survival” assumption.

327

328 No quantitative data were found in 31/64 citing publications and a further 27 (ratings of <2/6) give  
329 no more than the number of randomised patients. In publications where there were few or no data  
330 there was often a summary dismissal of the PulMiCC RCT (Fig.5). In fairness, at the time of writing,  
331 the authors of 40/64 of the publications had only seen the incomplete report of 65 randomised  
332 patients, published in 2019. The full report was published in 2020, but it seems that it was not seen  
333 by many of the 64 sets of authors; however, it makes no material difference because the increased  
334 number, from 65 to 93 randomised patients, narrowed the confidence intervals but did not change  
335 the conclusion. The impression is that the authors were very ready to disregard PulMiCC. Some  
336 controlled data are surely an improvement on none at all. The STS Expert Consensus had stated  
337 “Only a randomized clinical trial will definitively determine the value of PM for colorectal cancer”.

338 The findings of the PulMiCC study in its totality, with patients treated by clinical decision and random  
339 assignment, make high “value” unlikely.

340

341 All 64 of the publications citing the PulMiCC RCT were from authors involved in the local treatment  
342 of lung metastases and among them were 17 reports of clinical follow-up with a total of 4795  
343 patients (Table 1). There may well be vested interests in maintaining the status quo, which raises  
344 the possibility of “motivated reasoning” Human beings tend to place more reliance on information  
345 that confirms their beliefs and seek arguments against evidence that contradicts them(79). But as  
346 can be seen from the textual analysis, there were laudatory statements, commending the trialists for  
347 their efforts. A group of hepato-biliary authors agreed that the practice of metastasectomy had  
348 expanded due to lack of contrary evidence subtitled their letter “When to Draw the Line”.(15)

349

350 The “pillar of modern thoracic surgery” authors alluded to the parachute analogy(7) as did one of  
351 the commenting papers in this rhetorical question: “Would you perform a randomized trial of  
352 whether to deploy a parachute when jumping out of an airplane at high altitude?”(56) The analogy is  
353 to a circumstance when death is virtually certain within seconds, but patients who are offered lung  
354 metastasectomy are not at imminent risk of death. Lung metastasectomy is not remotely analogous  
355 to a parachute jump(80).

356

357 It is perhaps understandable why so many authors dismissed the findings of the PulMiCC RCT  
358 especially on seeing the first publication including only 65 patients. But the 17 clinical reports (Table  
359 1) included seven(30,32,37,55,69,73,75) which drew conclusions from groups of 33-66 patients  
360 (mean 43) which is fewer than PulMiCC but authors nevertheless commented on the RCT as  
361 small(37,73) insufficient(30), poorly accruing(55,69) and a failure(75). Now that the full study  
362 including the observational cohorts is published, the results need to be considered carefully and the  
363 uncertainty about the extent of benefit from metastasectomy should be acknowledged and honestly  
364 discussed with those highly selected patients to whom it is offered.

365

366 Thoracic surgeons are aware of the incursions being made in the treatment of lung metastases from  
367 stereotactic radiotherapy (SABR/SBRT) and image guided thermal ablation (IGTA). Trials have been  
368 mooted suggesting direct comparisons between these methods to see if similar results can be shown  
369 with less invasive methods. If such trials are proposed and designed, funders and ethicists might  
370 reasonably ask to check on the foundations of what is claimed to be “a pillar of thoracic surgery”.

371 Among many things we have learned in the time of Covid 19 is that it is possible to get regulatory

372 approval at speed and patients are willing to come forward to be randomised. But this can only  
373 happen if the medical profession can admit to not having all the answers.

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## 375 Acknowledgement

376 We are grateful to the 512 patients, the many research nurses and trials and the 25 Principal  
377 Investigators staff at the local sites who contributed to the PulMiCC study

378

379

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382 not funded and undertaken with the help of researchers who gave their time unpaid.

383

384

## 385 Conflict of interest statement

386 None of the authors has any conflict of interest to disclose

387

388

## 389 Author contribution statement

390 NRW, FM and TT devised the concept of the study. MM was the largest contributor to the PulMiCC  
391 RCT. The search was undertaken by NRW. The organisation of the 64 publications and text extraction  
392 was by TT. AA, FF, HP and MS were initially blinded to the origin of the texts but were unblinded  
393 after the first round of ratings. Data analysis was by NRW and TT. TT and FM collaborated on writing  
394 the first draft and all authors shared in the revisions and editing of the final manuscript.

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399 Figure legends

400

401 Central image

402 Kaplan Meier analysis of survival over 5 years with 95% confidence intervals and numbers at risk for  
403 484 patients with colorectal lung metastases. The clinical teams took an elective decision in 391 and  
404 their survival was analysed by the Kaplan Meier method and is shown in the upper panel. Lung  
405 metastasectomy was carried out in 263 (survival and 95% confidence intervals in red) and not in 128  
406 (blue). Differences in risk factors all favoured those selected for operation. Risk factors were very  
407 well balanced in the 93 randomised patient shown in the lower panel.

408

409 Legend to Figure 1

410 Control patients were sought from the records in the era before the introduction of lung  
411 metastasectomy from which time they would have been candidate for the operation.(5) There is no  
412 difference in five- year survival. Survival for non-operated patients was about 20%, not zero.

413

414 Legend to Figure 2. Sankey flow diagram. On the left are the numbers of publications retrieved.  
415 Citations to either or both RCT reports (N=64) are categorised above. Reasons for exclusion (N=59)  
416 are shown below. More details are in the text.

417

418 Legend to Figure 3 of inter-rater reliability coefficient

419 The inter-rater reliability coefficients in Table 3 are shown graphically (blue for data and orange for  
420 textual tone) with the 95% confidence intervals for all 64 publications (All) and for opinion pieces  
421 (Op), research papers (Res) and reviews (Rev).

422

423 Legend to Figure 4 of ratings

424 The arithmetic mean of the four ratings are shown above for of the presentation of PulMiCC data set  
425 out in ascending sequence to aid interpretation and below a similar display of the rating of textual  
426 tone.

427

428 Legend to Figure 5

429 The ratings of PulMiCC 'data presentation' (horizontal axis) plotted against the ratings of 'textual  
430 tone' The overall trend was that publications presenting fuller data had a more supportive textual  
431 tone. Top left are authors who cited PulMiCC and commented favourably without providing data in  
432 support.  $r=0.43$ ,  $r^2 0.185$ , linear regression  $y=0.39x$  (95%CI:0.18-0.60) + 1.85

433 Table 1

434

Author	Start Year	End Year	Study	Intervention	Pathology	N	Solitary Mets	Survival 5 year	Median months
Corsini <sup>28</sup>	2011	2017	SC F-up	Surgery	Colorectal	194	NF	57%	76
Dudek <sup>30</sup>	2008	2018	SC F-up	Surgery	Head and Neck	44	48%	41%	28
Dudek <sup>31</sup>	2008	2018	SC F-up	Surgery	Mixed	281	57%	47%	NF
Forster <sup>32</sup>	2003	2018	SC F-up	1st Surgery	Mixed	198	61%	56%	NF
				Repeat	Mixed	66	NF	79%	32
Fukada <sup>33</sup>	2000	2019	SC F-up	Surgery	Colorectal	126	71%	61%	
Gossling <sup>37</sup>	1985	2019	SC F-up	Surgery	Colorectal	59	53%	50%	58
Mamma <sup>42</sup>	2001	2017	SC F-up	Surgery	Colorectal	129	89%	NF	90
Markowiak <sup>44</sup>	2009	2017	SC F-up	Surgery	Mixed	251	86%	50%	61
Palma <sup>55</sup>	2012	2016	RCT	SABR	Mixed	66	46%	42%	50
				Control		33	36%	18%	28
Sponholz <sup>60</sup>	1999	2014	SC F-up	Surgery	Colorectal	233	47%	47%	57
van Dorp <sup>65</sup>	2012	2017	DLCA	Surgery	Mixed	2090	70%	NA	NA
Vidarsdottir <sup>66</sup>	2000	2014	SC F-up	Surgery	Colorectal	216	70%	56%	68
Yaftian <sup>68</sup>	2000	2017	MC F-up	Surgery	Mixed	476	58%	50%	NF
Yildiz <sup>69</sup>	2012	2019	SC F-up	Surgery	Colorectal	33	91%	NF	55
Yun <sup>70</sup>	2011	2017	SC F-up	Surgery	Colorectal	173	61%	52%	NF
Zhao <sup>73</sup>	2001	2018	PMS	Surgery	Nasopharyngeal	45	NF	76%	NF
				Control		22	NF	48%	NF
Zhong <sup>75</sup>	2008	2014	RSC	RFA±Surgery	Colorectal	60	NF	44%	52

435

DLCA	Dutch Lung Cancer Audit
MC F-up	Multicentre follow-up study
NA	Not available
NF	Not found
PMS	Propensity matched case control study
RFA	Radiofrequency ablation
RSC	Retrospective single centre
SABR	Stereotactic ablative radiotherapy
SC F-up	Single centre follow-up study

436

437

438

Quartiles	Data R1	Data R2	Text R1	Text R2
Minimum	0	0	0	0
25%	0	0	0	0
Median	1	1	3	2
75%	1	1	3	2
Maximum	4	2	4	4

Scale 0-6	Data R1	Data R2	Text R1	Text R2
0	30	31	2	2
1	22	27	17	29
2	7	6	12	23
3	4	0	23	6
4	1	0	7	4
5	0	0	3	0
6	0	0	0	0
Totals	64	64	64	64

439

440 Table 2. R1 and R2 refer to the first and second rounds of rating publications.

441 Above distribution of the ratings. 0 indicates unanimity, 1 no ratings more than one rank apart with  
 442 the possible maximum of 6. Ratings were for data and textual tone. The dispersion was  
 443 reduce by the Delphi process.

444 Below are the averaged ratings from 0-6. These data are illustrated in Figure 4

445

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446 Table 3: Inter-rater agreement  
447

n	Category	Round1	Round2	Diff	S.E.(Diff)	t-Stat	P-Value
	<b>Data</b>						
64	All publications	0.9411	0.9645	0.0234	0.0107	2.1820	0.0328
24	Opinion	0.9492	0.9629	0.0137	0.0108	1.2674	0.2177
28	Research	0.9394	0.9485	0.0091	0.0071	1.2834	0.2102
12	Reviews	0.8481	0.9440	0.0958	0.0667	1.4368	0.1786
	<b>Text</b>						
64	All publications	0.6293	0.7739	0.1446	0.0262	5.5252	<0.0001
24	Opinion	0.6344	0.7837	0.1494	0.0476	3.1389	0.0046
28	Research	0.6244	0.6858	0.0614	0.0401	1.5316	0.1373
12	Reviews	0.7437	0.7745	0.0308	0.0404	0.7630	0.4615

448  
449 Inter-rater agreement coefficients in the two rounds. The t-stat is the statistic from a paired t-test  
450 for testing 2 correlated agreement coefficients, assuming ordinal weights using the method  
451 described by Gwet. All the agreement coefficients increased and significantly ( $P < 0.05$ ) when all 64  
452 were considered. See also Fig.3 which depicts the data from Round 2.  
453

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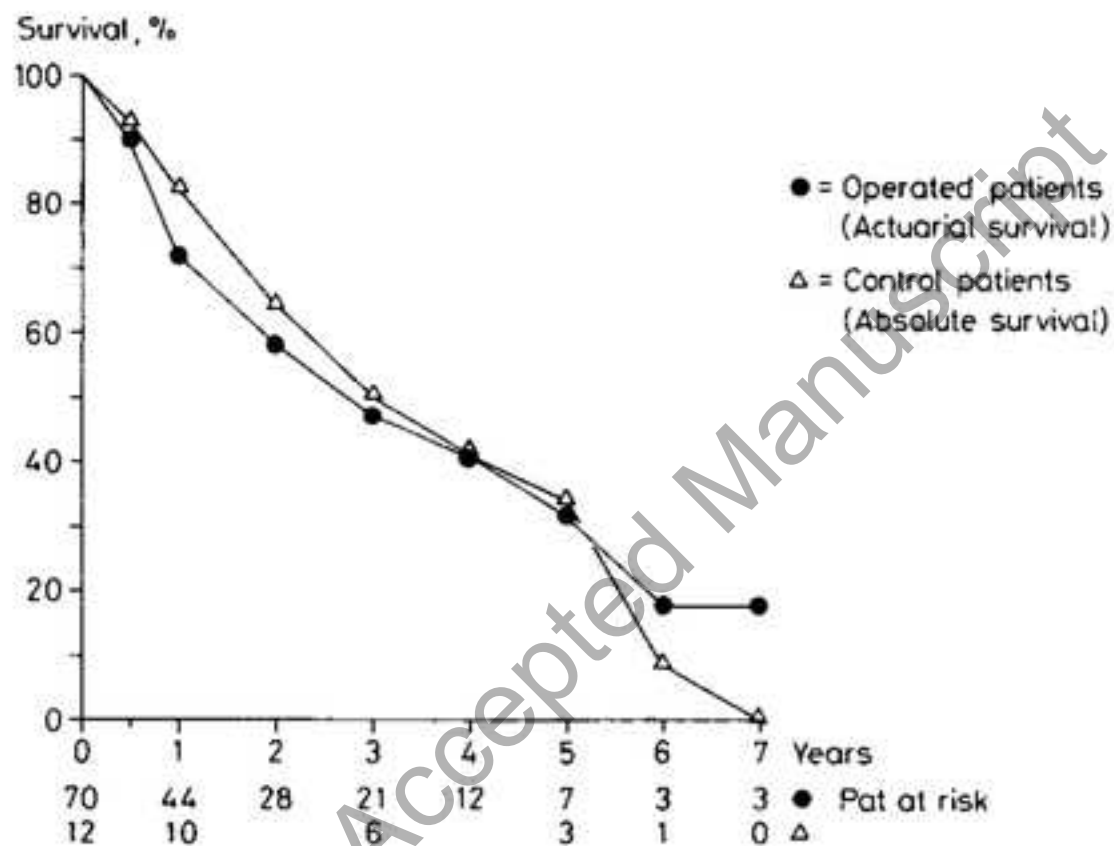
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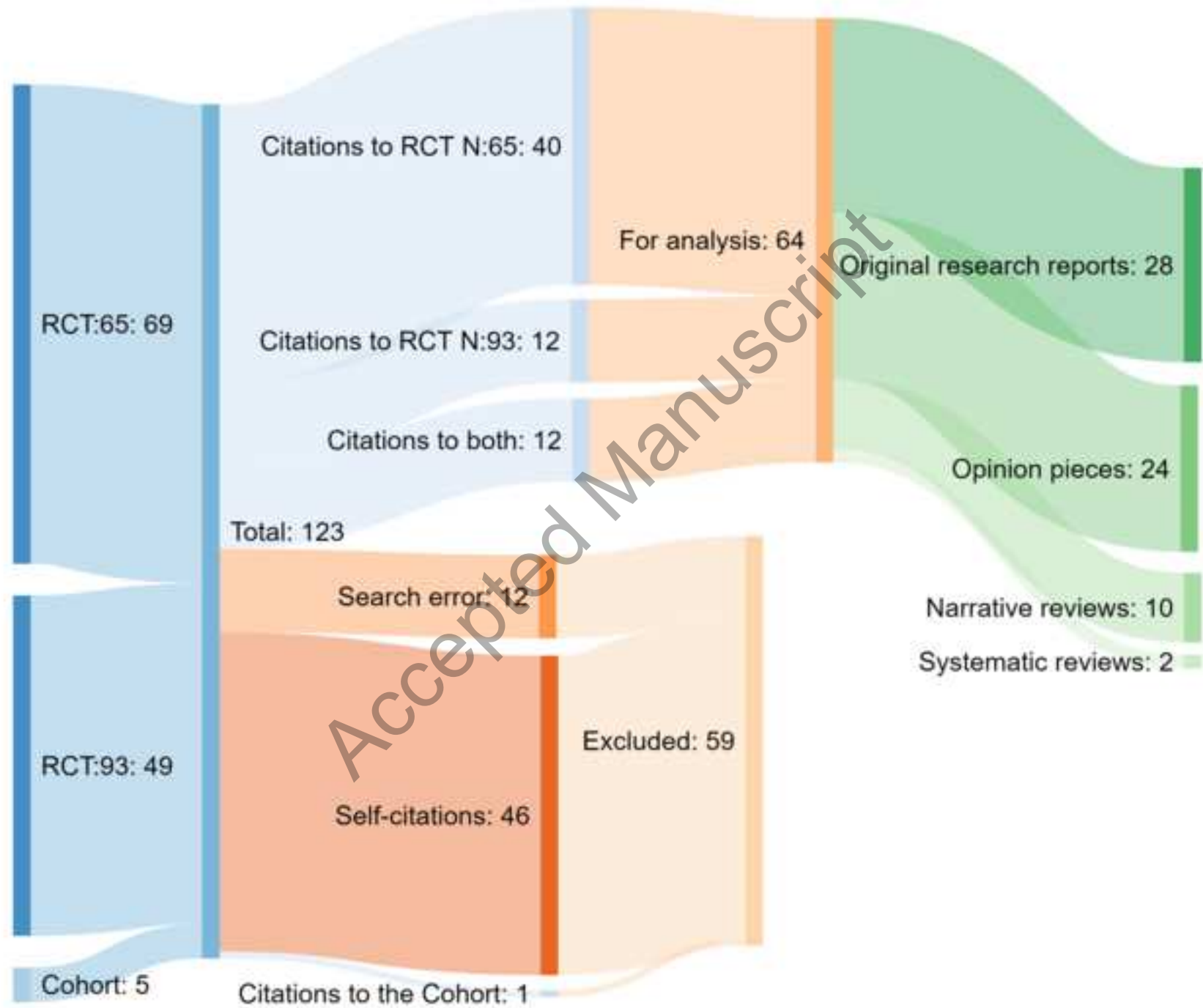
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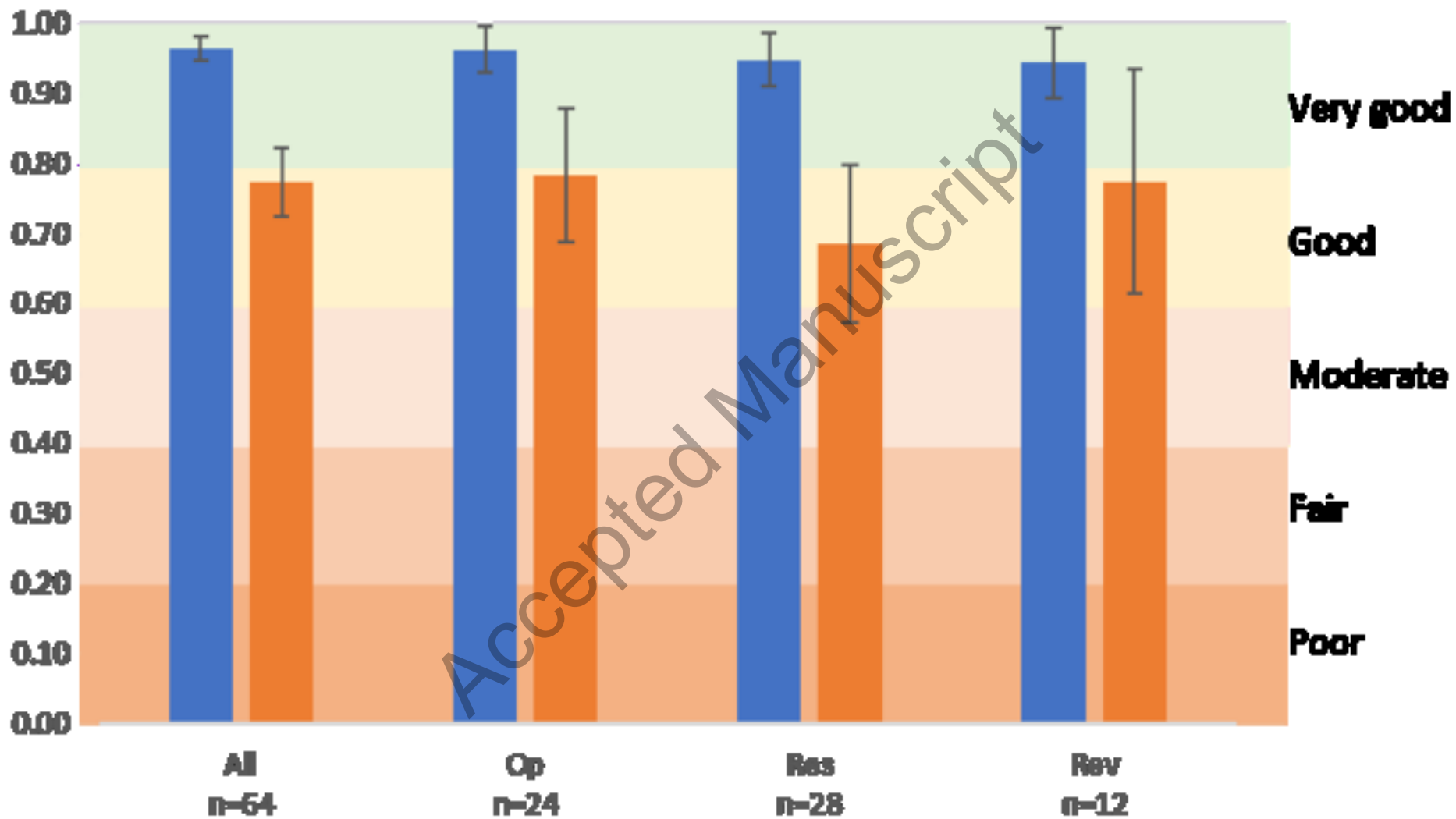
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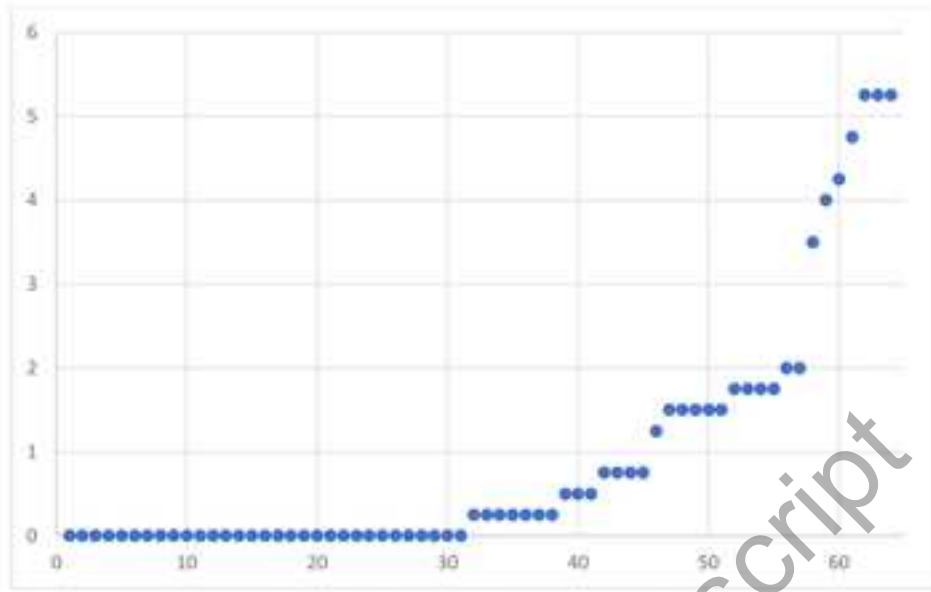




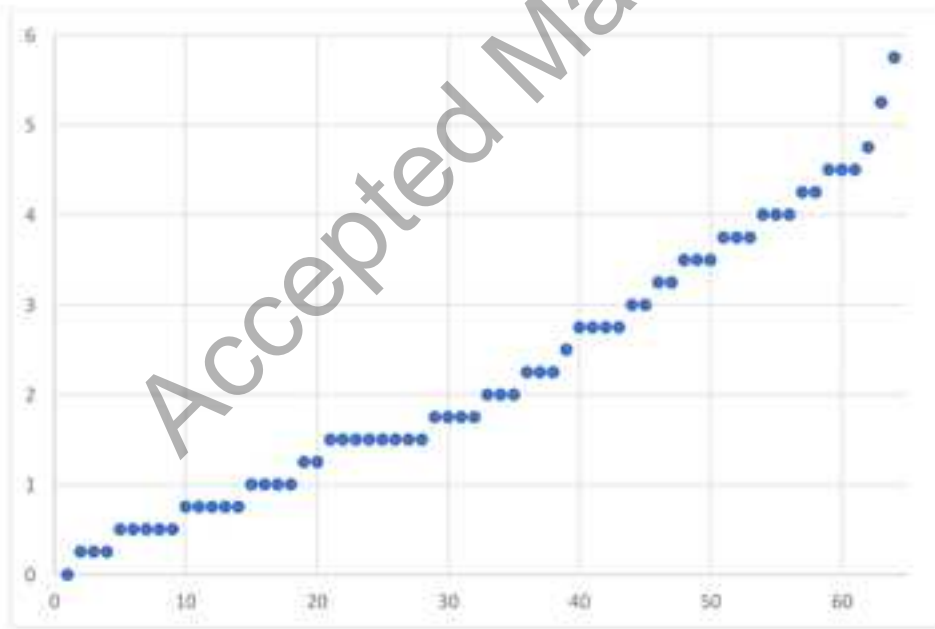
*Fig 2. Survival after metastasectomy or diagnosis in 70 operated and 12 control patients.*



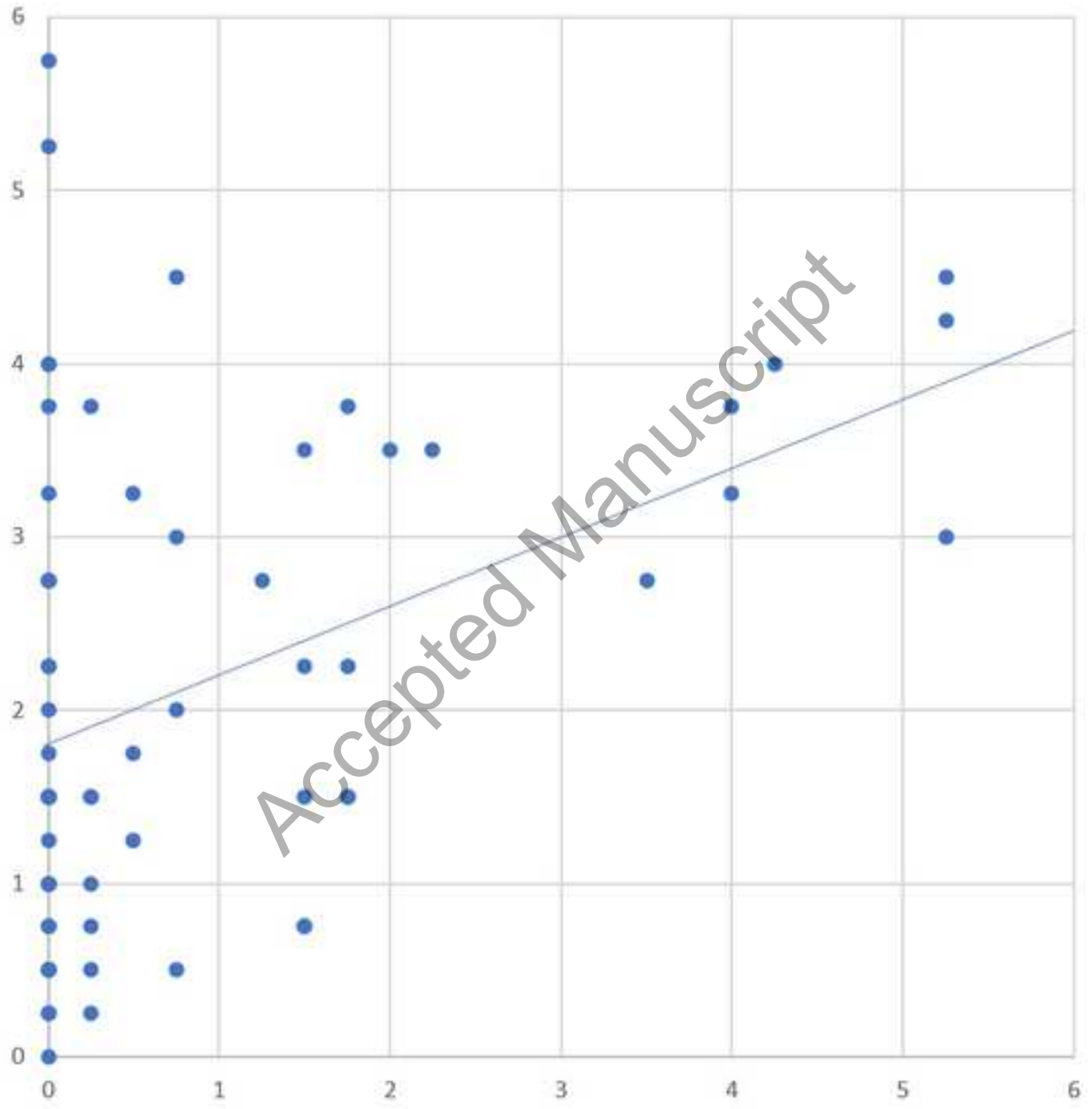




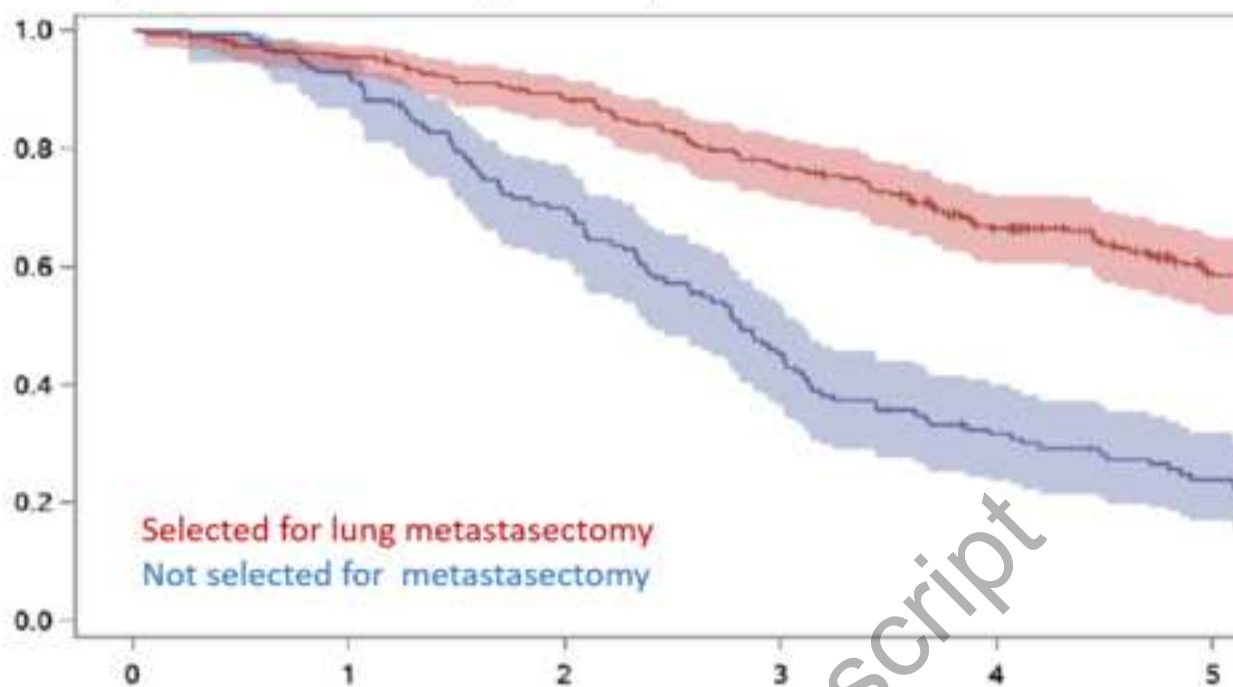
Grades of data presentation (vertical) in the 64 publications (horizontal)  
0 1 2 3 4 5 6  
None Omits CIs and Significance Representative Full and fair summary



Grades of textual tone of the 64 publications  
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Dismissive Balanced appraisal Supportive



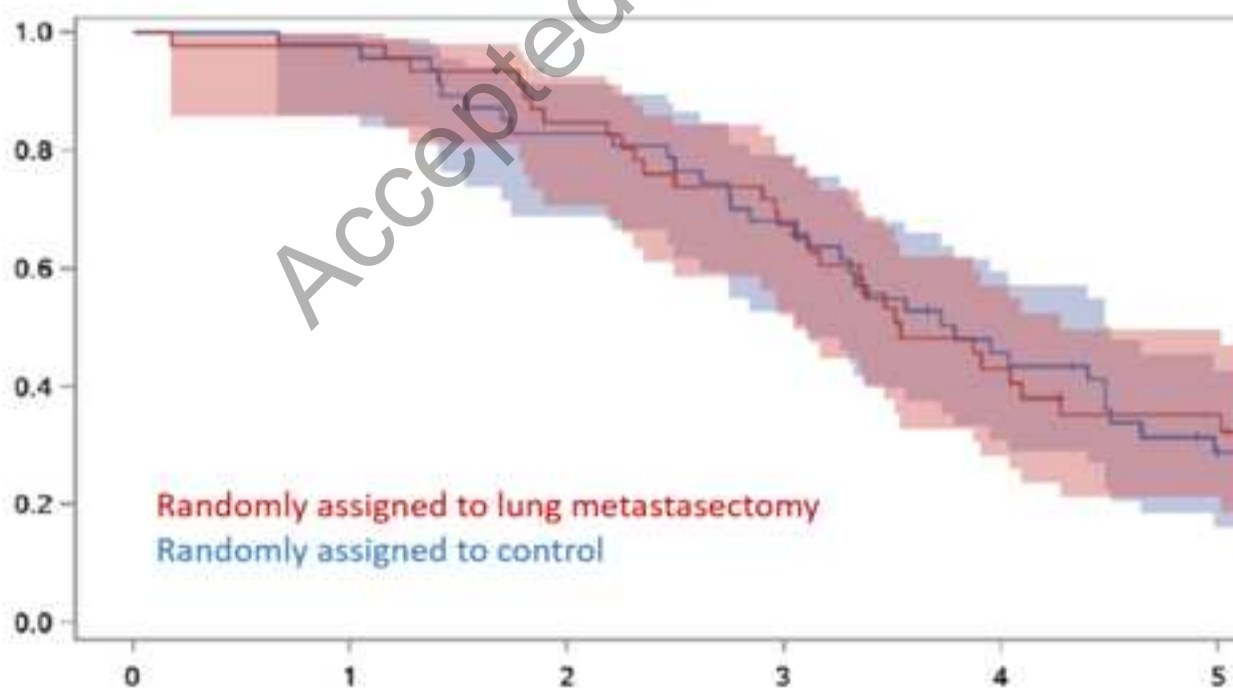
### Prospective cohort study in 391 patients



Survival time in years

263	248	227	194	147	98
128	118	88	57	38	28

### Randomised controlled trial in 93 patients



Survival time in years

46	45	39	31	17	12
47	46	39	32	20	11