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1 **Review Article**

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5

6 **Electrochemotherapy for the palliative management of cutaneous metastases: a**  
7 **systematic review and meta-analysis**

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27 **Abstract**

28 Background: Electrochemotherapy combines electroporation in conjunction with  
29 chemotherapeutic agents and is used to treat tumours in many localisations, including  
30 cutaneous metastases. The symptoms associated with cutaneous malignant wounds can be  
31 distressing for patients and their management is a challenge in healthcare.

32 Aim: The purpose of this systematic review was to investigate the effectiveness of  
33 electrochemotherapy in the context of palliative care.

34 Design: All aspects of the systematic review were followed according to the Preferred  
35 Reporting Items for Systematic Reviews and Meta-Analyses statement.

36 Data Sources: The following databases were searched for English-language reviews;  
37 Medline, Embase, CINAHL, British Nursing Index and the Cochrane Library. The search  
38 was conducted between the publication of Standard Operating Procedures in 2006 and the  
39 third week of October 2017. Studies involving oral cancers and studies with fewer than 10  
40 patients were excluded. The selected studies were assessed for risk of bias and sub-group data  
41 were synthesised in a random-effects meta-analysis.

42 Results: From 425 studies, 29 studies were included involving 1,503 patients, the pooled  
43 results were 46.6% for complete response and 82.2% for objective response according to the  
44 Response Evaluation Criteria in Solid Tumours. The meta-analysis indicated that small  
45 tumours were over twice as likely (2.25) to have a complete response than large.

46 Conclusions: Electrochemotherapy is an effective, repeatable and minimally invasive  
47 intervention within the palliative population that can reduce symptom burden. This review is  
48 an update of previous systematic reviews by Mali et al [1,2] and highlights the need for  
49 tailored treatment depending on each individual case.

50 Keywords

51 MeSH headings: electrochemotherapy, treatment outcome, skin neoplasms, palliative care,  
52 systematic review, meta-analysis

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## 64 **1.0 Introduction**

### 65 1.1 Background

66 Cutaneous metastases are a result of primary cancers infiltrating the skin. Although their  
67 appearance can be the first detected sign of malignancy [3], cutaneous metastases are  
68 generally a sign of advanced disease. The primary aim of managing these lesions is palliative.  
69 Their presence can have a devastating impact on quality of life due to factors such as loss of  
70 body image, malodour, pain, bleeding and the inability to contain exudate [4]. Managing  
71 these symptoms can prove a challenge for health care providers due to a lack of evidence-  
72 based interventions for managing malodour as well as difficulties in managing exudate with  
73 dressings [5]. A number of skin directed therapies have been developed to try to mitigate the  
74 burden of cutaneous metastases with some varying levels of success [6]; in particular there is

75 mounting evidence for the use of electrochemotherapy as a palliative treatment for both  
76 primary skin cancers and cutaneous metastases [5].

77 Electrochemotherapy targets tumours in order to destroy or reduce their size. It consists of  
78 two stages; the first stage is the delivery of chemotherapeutic drugs, this is then followed by  
79 the application of electric pulses directly into the tumour approximately eight minutes later.  
80 This causes a temporary increase in the permeability of the plasma membrane of the tumour  
81 cells resulting in a rise in localised drug uptake [7]. Therefore, the aim of electroporation is to  
82 increase the absorption of chemotherapeutic drugs into cutaneous and subcutaneous  
83 cancerous cells, thereby increasing their concentration and thus their effectiveness.

84 A large study led by Marty et al. [8] led to the publication of Standard Operating Procedures  
85 and this defined the benchmark for best practice in this field and led to standardised practice  
86 of electrochemotherapy internationally. Further clinical trials with large sample sizes have  
87 established electrochemotherapy as an effective and safe treatment [9]. In 2018, the Standard  
88 Operating Procedures were updated to reflect the experiences obtained with its use in  
89 practice. The key changes noted in this update include robust recommendations regarding  
90 which treatment strategy to employ according to specific patient characteristics. For instance,  
91 in patients with less than seven tumours, smaller than 3cm in size local anaesthesia and local  
92 drug injection is suggested, whereas, in patients with more than 7 tumours, larger than 3cm in  
93 size general anaesthesia and intravenous drug administration is suggested. In addition, advice  
94 is given regarding the type of electrode to use according to the characteristics of individual  
95 tumours. The update also gives a comprehensive criteria that should be used to determine  
96 whether a patient is suitable for electrochemotherapy as well as standards for documentation  
97 and imaging, patient follow-ups and how to deal with reoccurrence [10].

98 Advantages of electrochemotherapy, such as its ability to eliminate or reduce tumours to a  
99 manageable size, in turn minimises distressing symptoms and avoids unnecessary surgery to

100 excise tumours [11]. These make it a highly significant intervention in the context of  
101 palliative care.

102 Two systematic reviews published in 2013 by Mali et al. [1-2] led to NICE (National Institute  
103 of Clinical Excellence) recognised electrochemotherapy as a palliative treatment for treating  
104 metastases in the skin from tumours of non-skin origin and melanoma [12]. A drawback of  
105 these reviews is that they included studies conducted before the publication of the Standard  
106 Operating Procedures in 2006 [8]. It is therefore worthwhile to review the evidence again  
107 since their publication, to exclusively evaluate the studies published since its implementation  
108 and minimise the heterogeneity which was present in the previous review.

109

110

## 111 **1.2 Objective**

112 The primary objective of this systematic review was to examine the available evidence for the  
113 use of electrochemotherapy to draw conclusions about its effectiveness with the primary  
114 objective of tumour response, and to make recommendations for its usage in the context of  
115 palliative care. A secondary objective was to examine the relationship between tumour size  
116 and response to treatment using a meta-analysis, again to update the previous reviews with  
117 the most recent evidence.

118

## 119 **2.0 Methods**

### 120 **2.1 Protocol and registration**

121 This systematic review and meta-analysis were conducted at King's College London (2018).

122 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement

123 (PRISMA) was used as a guide to the reporting of all aspects of this systematic review [13].

124

## 125 2.2 Eligibility criteria

126 Studies were eligible if they had been published after the publication of the Standard  
127 Operating Procedures in 2006 and reported data on tumour response after the delivery of  
128 electrochemotherapy with at least a four-week follow up. Case reports or studies involving  
129 fewer than 10 patients were unnecessary to include as there was an adequate number of  
130 studies with large sample sizes. Studies involving primarily oral cavity cancers were  
131 excluded as this was deemed a heterogeneous population. Studies were eligible for meta-  
132 analysis if they had separate data for tumour response according to size and were of an  
133 acceptable homogeneity.

134 The primary outcome was tumour response according to the RECIST (Response Evaluation  
135 Criteria In Solid Tumours) method [14]. These criteria define a complete response (CR) as  
136 the disappearance of all target lesions, partial response (PR) as a decrease of at least 30% in  
137 the sum of the longest diameters of all target lesions and objective response (OR) as sum of  
138 CR and PR.

139

## 140 2.3 Information Sources

141 The following databases were searched; Medline, Embase, CINAHL, British Nursing Index  
142 and the Cochrane Library. The search was performed during the third week of October 2017.  
143 Language restriction to English was applied as translation resources were unavailable for this  
144 review.

145

## 146 2.4 Search

147

148 To inform the search strategy the PICO format (population, intervention, comparison and  
149 outcome), was used to identify the key concepts in the review question. The Comparison

150 facet was omitted from the PICO table because only observational studies including  
151 prospective, retrospective studies and case series were identified in the preliminary literature  
152 search. The reason for the lack of randomised trials is likely due to the ethical concerns  
153 around conducting a trial in a palliative population and the lack of clinical equipoise relating  
154 to the intervention [15] (see supplementary material 1 for full search strategy).

155

156

#### 157 2.4.1 Study selection and data extraction

158 The study selection process was performed by one independent researcher. After removal of  
159 duplicates the title and abstracts of all remaining papers were screened against the  
160 inclusion/exclusion criteria and those deemed ineligible were removed. The full-text of the  
161 remaining papers was studied and the irrelevant studies were excluded with reasons (figure  
162 1).

163 The data were extracted from the selected studies by one researcher and displayed in  
164 evidence tables (tables 1 and 2). These studies were then screened again against the eligibility  
165 criteria for meta-analysis and the data on tumour size and response extracted (table 3).

166

#### 167 2.4.2 Data items

168 According to the PICO format [15]; the Population was cutaneous metastases, the  
169 Intervention was electrochemotherapy and Primary Outcome was clinical response, the  
170 Comparison facet was not included due to the lack of a comparator.

171 The information extracted from each study was as follows; study type, included number of  
172 evaluable patients, tumour response, response evaluation time, drug route, type of tumour and  
173 response evaluation method. These headings were chosen due to their similarity to the  
174 headings used in the previous systematic review [1], so comparisons could be made. A

175 further evidence table (table 2) extracted the available data relating to further cycles of  
176 electrochemotherapy and secondary outcomes such as survival analysis, as this information  
177 would provide context to the use of electrochemotherapy in the field of palliative care.  
178 The headings included in the evidence table for meta-analysis (table 3) were; total number of  
179 small tumours and number of those achieving complete response, number of large tumours  
180 and number achieving complete response. The criteria for small and large tumour sizes were  
181 set by the individual studies and therefore studies were only included if the definition of the  
182 groups were homogeneous between studies.

183

#### 184 2.5 Risk of bias in individual studies

185 In the case of this review the included studies were observational, prospective or  
186 retrospective case series designs. Although randomised controlled trials (RCTs) are  
187 considered the most rigorous method for determining the effectiveness of an intervention they  
188 were not present in the literature around electrochemotherapy during scoping searches. This  
189 is likely due to a lack of clinical equipoise, as electrochemotherapy has already been  
190 established as an effective palliative treatment; [1,2] therefore it would be deemed unethical  
191 to enter patients into an RCT where one intervention is believed superior to another [16]. In  
192 addition interventions for managing key symptoms (exudate and malodour) are currently  
193 lacking [5].

194 A tool developed to assess the methodology of observational case series studies was  
195 identified, which contains an 18-criteria checklist (see supplementary material 2 for checklist)  
196 [17]. This checklist has been validated in a systematic review of quality assessment tools [18]  
197 and was deemed the most appropriate tool to assess the quality of papers in this systematic  
198 review.

199

## 200 2.6 Summary Measures

201 The overall effectiveness of electrochemotherapy was determined by pooling the primary  
202 outcome data of all individual studies to calculate an overall weighted per patient Complete  
203 Response % (CR) and Objective Response % (OR).

204

## 205 2.7 Synthesis of results

206 A meta-analysis was used to compare sub-groups to evaluate the differences in anti-tumour  
207 effectiveness of electrochemotherapy on tumours of different sizes. For the purposes of sub  
208 group analysis, the studies with separate data for ‘small’ and ‘large’ tumours were used with  
209 ‘small’ defined as  $\leq 3$ cm and ‘large’ as  $> 3$ cm. The relative risk (or risk ratio) was used as the  
210 measure of the size of the effect.

211 The random- effects model was used in the meta-analysis as electrochemotherapy is a  
212 potential treatment for a wide range of tumour histologies and therefore applies to a wide  
213 patient population [19]. The I<sup>2</sup> statistic was used to measure the variability between studies  
214 and to interpret the impact of heterogeneity on the MA; with I<sup>2</sup><25% showing homogeneity  
215 and I<sup>2</sup>>75% showing considerable heterogeneity [20]. The calculations used were written in  
216 the Meta package which runs in the R programme according to the user manuals and forest  
217 plots were generated (figure 2) [21].

218

## 219 2.8 Risk of bias across studies

220 The concept of publication bias is an underlying issue within healthcare research and should  
221 be considered as a risk in systematic reviews and meta-analysis [22]. Investigating  
222 publication bias in a meta-analysis is usually done by performing a funnel plot, however, due  
223 to limited access to meta-analysis software this was not undertaken in this review.

224 Selective reporting of bias should be investigated by comparing the methodology of a paper  
225 with the reported outcomes to make sure there is consistency between the outcomes listed in  
226 the methods section and the results reported in the findings section [23]. Any obvious  
227 reporting failures in the studies included became obvious in the data extraction process and  
228 these studies scored less in the quality appraisal tool.

229

## 230 **3.0 Results**

### 231 3.1 Study Selection

232 The database search generated 425 studies after removal of duplicates. The title and abstracts  
233 of these studies were screened against the inclusion/exclusion criteria and 390 studies  
234 excluded as irrelevant. The 41 remaining studies were selected for further evaluation, the full  
235 text was obtained, read and screened against the eligibility criteria and 29 deemed eligible to  
236 be part of the review. Studies that did not meet the eligibility criteria were excluded and the  
237 reason for exclusion is detailed in the PRISMA flow chart (figure 1). The included studies  
238 were screened again against the inclusion criteria for the meta-analysis and five selected as  
239 satisfying the criteria.

240

241

### 242 3.2 Study Characteristics

243 All studies were observational and there was a combination of both prospective and  
244 retrospective approaches. The majority of studies used the Response Evaluation Criteria in  
245 Solid Tumours method [14] to measure tumour response and the follow-up period to tumour  
246 evaluation ranged between 30 days and three months.

247 As expected, there was a wide range of tumour types across the studies; the most common  
248 being Melanoma, Basal Cell Carcinoma (BCC) and metastatic Breast Cancer. All studies

249 with the exception of two [24, 25] reported the maximum number of electrochemotherapy  
250 cycles performed and the number of patients that received more than one course of  
251 electrochemotherapy. Where reported, the range of number of electrochemotherapy cycles  
252 was between two and six. Some studies reported patient outcomes such as pain and quality of  
253 life.

254 There was a lack of information across all the studies on the way survival analysis was  
255 calculated, perhaps due to the word restriction on publications. In addition, there was  
256 inconsistency between papers on the way they reported the survival analysis. Some reported  
257 progression free survival for the whole cohort of patients whereas others only calculated it for  
258 the patients with complete response.

259 Serious adverse events were minimal. The only serious adverse event that was considered  
260 related to the intervention was reported by Bertino et al. [9] where one patient with a large  
261 ulcerated tumour died from septic shock on the second day post-electrochemotherapy. The  
262 most common reported systemic reactions were mild, post-procedural nausea and dizziness  
263 being the most common. Pain was the second most reported adverse reaction, but this was  
264 reported as transient and although some reports of extreme pain were made immediately after  
265 the therapy, this settled to manageable pain within around 48 hours. The incidence and  
266 description of treatment toxicity was graded according to the Common Terminology Criteria  
267 for Adverse Events (CTCAE) in the majority of studies. The most frequently reported  
268 complications were skin-related such as ulceration, erythema, and other inflammatory  
269 reactions, the most severe of these were graded 4 according to the CTCAE. However, across  
270 the studies all of these were transient and did not result in permanent damage. A number of  
271 studies asked patients whether they would agree to further electrochemotherapy treatment  
272 after the initial session and the percentage of patients that answered favourably was high. For

273 instance, in Cabula et al. [24] 97% of 96 patients answered that they would agree to receive  
274 the treatment and in Matthiessen et al. [26] 90% of 51 patients were in favour of re-treatment.

275

276

### 277 3.3 Quality Appraisal and risk of bias across studies

278 The 18-criteria checklist was used to assess the quality of included studies [17]. A study  
279 scored a point when it fulfilled a criterion with the scores displayed in table 4. Overall, 17  
280 studies of the 21 assessed received a score of 14 or more and were deemed of satisfactory  
281 quality.

282 The researchers in this field have tried to overcome the weaknesses in their methodology by  
283 reporting the baseline characteristics of their patient populations in order to be transparent to  
284 the reader and to mitigate selection bias. This means judgements can be made about the  
285 suitability of the included patients and whether the conclusions made at the end of the study  
286 were robust. Only two of the included studies failed to report the baseline characteristics of  
287 participants, [27, 28] and these papers were awarded low scores in the quality appraisal tool.

288 Another aspect that increased rigour was the use of standardised outcome measurement tools.

289 In this case the majority of the papers (20 out of 29) used the Response Evaluation Criteria In  
290 Solid Tumours method [14] to measure tumour response, with the remaining using the WHO  
291 criteria [29] or stating their own measures, which in both cases were adequately similar to the  
292 Response Evaluation Criteria In Solid Tumours model. However, there was inconsistency  
293 across the studies in the timing of the tumour evaluation with a range of 30 days – three  
294 months, with three studies not reporting the time period to tumour evaluation and these  
295 papers were marked down in the quality appraisal [30-32].

296 The majority of studies in this review were prospective (n=21) with the remaining being  
297 retrospective analyses (n=8). It is generally the view that retrospective design is weaker in

298 the hierarchy of evidence than prospective design [33]. However, in this review there was not  
299 a significant difference in quality between the retrospective and prospective studies. This  
300 demonstrates that the labelling of studies does not automatically classify whether they are  
301 superior or inferior but a more thorough examination of what has been reported in the papers  
302 is required [34].

303

304

### 305 3.4 Synthesis of results

306 The pooled data across all the studies which evaluated the tumour response per patient was  
307 46.6% for complete response and 82.2% for objective response, the total number of patients  
308 being 1194. For six studies, the data were presented as ‘per tumour’ evaluation of response  
309 and the pooled result for these data was 53.6% for CR and 71.5% for OR, the total number of  
310 tumours was 599.

311

### 312 3.5 Meta-Analysis

313 The five studies found eligible for meta-analysis were among the highest scoring in the  
314 quality appraisal exercise with scores ranging from 15 – 17 out of 20. Table 3 shows the data  
315 extracted.

316 The total number of ‘small’ tumours included in the analysis was 602 and the pooled CR for  
317 this group was 67.4%. In contrast, the total number of ‘large’ tumours was 185 with a pooled  
318 complete response of 33.0%. The forest plot (figure 2) takes the ‘large’ tumour group as the  
319 control group and the ‘small’ tumour group as the experimental group. The overall relative  
320 risk in the random effects model is 2.25 95% confidence interval [1.58-3.2]. This means that  
321 ‘small’ tumours  $\leq 3$ cm are over twice as likely (2.25) to have a complete response than ‘large’

322 tumours >3cm. The test for overall effect generated a p value of <0.01 which is statistically  
323 significant, as the level of significance was set as p<0.05.

324 The I2 statistic was 52% indicating there is moderate heterogeneity. The p value associated  
325 with the Chi-squared test for heterogeneity is 0.08 which is statistically significant,  
326 demonstrating that the random-effects model was appropriate to use in this instance. It is  
327 important to note that the I2 in this meta-analysis will not be very precise due to the very  
328 small number of studies and the inability to detect the between study variance [19].

329

330

### 331 3.6 Risk of bias across studies

332 During the quality assessment process, the study by Di Monta et al. [37] only reported  
333 complete response data in the results section despite describing the Response Evaluation  
334 Criteria in Solid Tumours criteria and defining partial response as a primary outcome in the  
335 methods section. This meant that the objective response (the complete response + partial  
336 response) could not be calculated for this study and therefore there was an absent score for  
337 OR% when the data across all studies were pooled.

338 When selecting studies suitable for meta-analysis it was noticed that in the study by Curatola  
339 et al. [38] the percentage response data for small tumours and large tumours was reported,  
340 but, the number of tumours in the two sub-groups was not, which meant there was not enough  
341 raw data to be included. Similarly, the results for small versus large tumours in the study by  
342 Campana et al.[39] could not be included in the meta-analysis because only the statistical test  
343 results such as odds ratio and p-value were reported and not the raw data. It was not possible  
344 to contact the authors of these studies for the raw data due to time constraints.

345

## 346 **4.0 Discussion**

#### 347 4.1 Summary of Evidence

348 All the studies identified in the review reported results in favour of electrochemotherapy for  
349 the primary outcome of tumour response; it was well tolerated by patients and there were few  
350 reported serious adverse reactions.

351 The findings of this review are consistent with the previous systematic reviews on  
352 electrochemotherapy. It is noteworthy that in this review all the studies used bleomycin  
353 exclusively as the chemotherapeutic agent except for Campana et al. [30, 40] where cisplatin  
354 was used for a small proportion of study participants. In contrast, the previous review  
355 included six studies that used cisplatin exclusively. The reason for this move towards  
356 bleomycin as the drug of choice is likely due to further evidence generated since the  
357 publication of the previous studies which showed that the uptake of bleomycin is potentiated  
358 more effectively by electroporation pulses than the uptake of cisplatin and therefore future  
359 studies began to use the bleomycin drug exclusively [41].

360 The meta-analysis used to perform sub-group analysis comparing the treatment response  
361 found there was a statistically significant increase of 125% in the probability of complete  
362 response for tumours  $\leq 3$ cm compared to tumours  $>3$ cm. These findings are consistent with  
363 the previous meta-analysis [1, 2]. The reasons for this significant difference in the  
364 effectiveness of electrochemotherapy depending on tumour size has been considered in the  
365 literature [26, 42, 43] and it is believed to be multi-factorial. Firstly, in large tumours there  
366 may be insufficient exposure of the tumour to the chemotherapy drug due to inadequate blood  
367 flow across the tumour as it is harder for the drug to penetrate the centre of a larger tumour  
368 [44], therefore the drug is not adequately distributed to provide the optimum  
369 chemotherapeutic effect. Secondly, there may be insufficient coverage of the larger tumours  
370 by the electric fields simply due to the difficulty in applying the electrodes to the larger  
371 tumours, which will generally be of a less uniform size compared to the smaller tumours.

372 Another potential explanation for why small tumours respond better to electrochemotherapy  
373 is because they have faster healing times and the fact that large tumours may be more  
374 aggressive [36]. These potential shortfalls associated with treating larger tumours could be  
375 managed with individualised treatment planning to ensure the most effective choices of type  
376 of electrode and drug administration methods are assessed in all patients prior to instigation  
377 of the therapy. This review highlights the fact that electrochemotherapy is not a one-off  
378 treatment and can be repeated.

379 There were a number of further sub-group analyses across the studies in addition to tumour  
380 size. These include; in the study by Rotunno et al. [45] where response for  
381 electrochemotherapy performed under general versus local anaesthesia was compared and  
382 found a significant increase in CR% for patients who underwent general anaesthesia. In  
383 addition, in the study by Bertino et al. [9] the response of tumours that were treatment-naïve  
384 was compared with tumours that had been previously treated with surgical-excision or  
385 irradiation. The authors found the treatment-naïve tumours responded significantly better  
386 than the previously treated tumours. These additional analyses further enrich the breadth of  
387 knowledge about the usefulness of electrochemotherapy and provide valuable information for  
388 the review question and implications for future research.

389

#### 390 4.2 Limitations

391 Overall, the methodological quality of the included studies was acceptable. Baseline  
392 characteristics were reported in the majority of studies, the outcome measure was fairly  
393 consistent across the included studies. However, there was inconsistency across the studies in  
394 the timing of the tumour evaluation with a range of 30 days – three months, with three studies  
395 not reporting the time period to tumour evaluation [30-32]. This makes it very difficult to  
396 form any robust conclusions about their data. It is difficult to judge how much of an effect the

397 difference in time to evaluation had on the reliability of the results, but it is noteworthy that  
398 the Standard Operating Procedures recommended a period of four weeks before treatment  
399 efficacy of electrochemotherapy can be determined.

400 The survival analysis was poorly reported and inconsistent across the studies which is  
401 unfortunate as these data are of great interest to clinicians particularly when deciding whether  
402 a treatment is worthwhile in the context of palliative care. The data extracted from the studies  
403 do give an indication of the medium length of follow-up in each individual study and  
404 percentage of patients whose disease was kept at bay. It is therefore useful information to  
405 display regardless of the fact that it is not possible to obtain an overall pooled average  
406 survival statistic.

407 Another limitation of the included studies was the use of co-interventions. These are  
408 significant as they illustrate that there are fundamental differences in the experience of a  
409 portion of patients within the studies due to adjunct treatments which may affect the tumour  
410 response data. It may also be this was more widespread than can be identified in the full-text  
411 articles if some articles did not publish the additional interventions the patients underwent in  
412 their studies. However, it can be argued that due to the disease severity of the patients in  
413 these studies it would be considered unethical to deny them the opportunity to be exposed to  
414 other tumour-targeting therapies that may assist them to alleviate the burden of living with  
415 metastatic cutaneous tumours.

416 Overall, this systematic review includes a representative sample of the available literature on  
417 this topic area for meaningful conclusions to be made. The study selection, data extraction  
418 and study appraisal aspects of this review were carried out appropriately however, they would  
419 have been much more robust if there had been a second reviewer. Due to the availability of  
420 studies with large sample sizes, studies with less than ten participants were excluded to  
421 purposely limit the number of studies for analysis. However, the fact this occurred meant

422 some very pertinent articles were removed that would have increased the knowledge to  
423 answer the review question [46-48].

424

425 The methods of statistical analysis were appropriate and valid in this review and an academic  
426 statistician was consulted for guidance on conducting the meta-analysis. Unfortunately, there  
427 was poor precision due to the fact there were only five studies eligible for the analysis, and it  
428 may therefore be misleading to draw firm conclusions from the summary effect.

429

#### 430 **4.4 Conclusions**

431 This aim of this systematic review was to consolidate the recent literature on the effectiveness  
432 of electrochemotherapy for cutaneous metastases and update the previous systematic reviews  
433 [1, 2]. It was evident during the review process that the period of four weeks recommended  
434 by the Standard Operating Procedures as the time to measure tumour response to  
435 electrochemotherapy may not be long enough for large tumours to respond. In the study by  
436 Matthiessen et al. [26] the patients all had large tumours from breast cancer and used an eight  
437 week follow up instead of the four weeks to allow for this. Another factor noted in this  
438 review is that larger tumours may benefit from using different plates and electrodes.

439 Additionally, a higher concentration of drug in large tumours could be achieved by  
440 combining both intratumoural and systematic administration of chemotherapy. This review  
441 used meta-analysis to show that small tumours have a greater tumour response compared to  
442 large tumours, further meta-analyses comparing other sub-groups would be useful in future  
443 reviews such as whether previous irradiation and number of tumours per patient influences  
444 the effectiveness of electrochemotherapy. Matching the treatment modality and schedule to  
445 patient specific factors such as those identified above is crucial to ensure the most effective

446 coverage of the tumour by the electric field which means treatment needs to become more  
447 tailored to the individual.

448 Another implication for future treatment is that many of the studies reported some  
449 participants were able to obtain and/or maintain tumour response by undergoing repeated  
450 sessions of electrochemotherapy. Unfortunately, there was a lack of data providing the  
451 tumour responses to the additional cycles of electrochemotherapy. Further research should  
452 aim to explore this to set standards for the frequency of electrochemotherapy sessions to  
453 provide the highest benefit and lowest possible harm to patients. This could be done by better  
454 reporting of the number of cycles and results of the retreatments. Another issue this review  
455 has exposed is the lack of consistency in reporting of survival statistics as well as secondary  
456 outcomes such as QOL, pain and toxicity. Future research should address these outcomes as  
457 they inform health resource use and patient preference especially in palliative care.

458 This systematic review shows electrochemotherapy is an effective palliative treatment with  
459 minimal adverse reactions. Moreover, it should be considered early in the development of  
460 cutaneous metastases as the smaller the tumour the more effective the treatment. Larger  
461 tumours will need to have tailored approaches to maximise the effectiveness of the ECT  
462 treatment, such as using different plates and electrodes.

463 The evidence included in this review is based on the studies conducted following publication  
464 of the standard operating procedures in 2006 [8], it is noted that there has been an updated  
465 version of these standard operating procedures published in 2018 [10]. This update reflects  
466 the considerable experience gained in the use of the treatment in a wide range of tumour  
467 histologies. Future studies going forward, which use the updated standards may generate  
468 further clinically specific evidence to guide clinicians. The knowledge generated by this  
469 review provides evidence generated from clinical studies, which followed the 2006 Standard

470 Operating Procedures [8,] and inform clinical practice guidelines such as the NICE guidelines  
471 [12] to ensure they are brought up-to-date with current evidence.

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484 This is a systematic review of primary studies. Obtaining ethical approval was not applicable.

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1 **Review Article**

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5

6 **Electrochemotherapy for the palliative management of cutaneous metastases: a**  
7 **systematic review and meta-analysis**

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27 **Abstract**

28 Background: Electrochemotherapy ~~is a skin directed therapy involving combines~~  
29 ~~electro~~oporationie pulses in conjunction with chemotherapeutic agents and is used to treat  
30 tumours in many localisations, including cutaneous metastases. The symptoms associated  
31 with cutaneous malignant wounds can be distressing for patients and their management is a  
32 challenge in healthcare.

33 Aim: The purpose of this systematic review was to investigate the effectiveness of  
34 electrochemotherapy in the context of palliative care.

35 Design: All aspects of the systematic review were followed according to the Preferred  
36 Reporting Items for Systematic Reviews and Meta-Analyses statement.

37 Data Sources: The following databases were searched for English-language reviews;  
38 Medline, Embase, CINAHL, British Nursing Index and the Cochrane Library. The search  
39 was conducted between the publication of Standard Operating Procedures in 2006 and the  
40 third week of October 2017. Studies involving oral cancers and studies with fewer than 10  
41 patients were excluded. The selected studies were assessed for risk of bias and sub-group data  
42 were synthesised in a random-effects meta-analysis.

43 Results: From 425 studies, 29 studies were included involving 1,503 patients, the pooled  
44 results were 46.6% for complete response and 82.2% for objective response according to the  
45 Response Evaluation Criteria in Solid Tumours. The meta-analysis indicated that small  
46 tumours were over twice as likely (2.25) to have a complete response than large.

47 Conclusions: Electrochemotherapy is an effective, repeatable and minimally invasive  
48 intervention within the palliative population that can reduce symptom burden. This review is  
49 an update of previous systematic reviews by Mali et al [1,2] and highlights the need for  
50 tailored treatment depending on each individual case.

51 Keywords

52 MeSH headings: electrochemotherapy, treatment outcome, skin neoplasms, palliative care,  
53 systematic review, meta-analysis

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## 65 **1.0 Introduction**

### 66 1.1 Background

67 Cutaneous metastases are a result of primary cancers infiltrating the skin. Although their  
68 appearance can be the first detected sign of malignancy [3], cutaneous metastases are  
69 generally a sign of advanced disease. The primary aim of managing these lesions is palliative.  
70 Their presence can have a devastating impact on quality of life due to factors such as loss of  
71 body image, malodour, pain, bleeding and the inability to contain exudate [4]. Managing  
72 these symptoms can prove a challenge for health care providers due to a lack of evidence-  
73 based interventions for managing malodour as well as difficulties in managing exudate with  
74 dressings [5]. A number of skin directed therapies have been developed to try to mitigate the  
75 burden of cutaneous metastases with some varying levels of success [6]; in particular there is

76 mounting evidence for the use of electrochemotherapy as a palliative treatment for both  
77 primary skin cancers and cutaneous metastases [5].

78 Electrochemotherapy targets tumours in order to destroy or reduce their size. It consists of  
79 two stages; the first stage is the delivery of chemotherapeutic drugs, this is then followed by  
80 the application of electric pulses directly into the tumour approximately eight minutes later.  
81 This causes a temporary increase in the permeability of the plasma membrane of the tumour  
82 cells resulting in a rise in localised drug uptake [7]. Therefore, the aim of  
83 electroporationchemotherapy is to increase the absorption of chemotherapeutic drugs into  
84 cutaneous and subcutaneous cancerous cells, thereby increasing their concentration and thus  
85 their effectiveness. This occurs through the application of electric pulses directly into the  
86 tumour which causes a temporary increase in the permeability of the plasma membrane of the  
87 tumour cells resulting in a rise in localised drug uptake [7].

88 A large study led by Marty et al. [8] led to the publication of Standard Operating Procedures  
89 and this defined the benchmark for best practice in this field and led to standardised practice  
90 of electrochemotherapy internationally. Since then, F further clinical trials with large sample  
91 sizes have established electrochemotherapy as an effective and safe treatment [9]. In 2018,  
92 the Standard Operating Procedures were updated to reflect the experiences obtained with its  
93 use in practice. The key changes noted in this update include robust recommendations  
94 regarding which treatment strategy to employ according to specific patient characteristics.  
95 For instance, in patients with less than seven tumours, smaller than 3cm in size local  
96 anaesthesia and local drug injection is suggested, whereas, in patients with more than 7  
97 tumours, larger than 3cm in size general anaesthesia and intravenous drug administration is  
98 suggested. In addition, advice is given regarding the type of electrode to use according to the  
99 characteristics of individual tumours. The update also gives a comprehensive criteria that  
100 should be used to determine whether a patient is suitable for electrochemotherapy as well as

101 [standards for documentation and imaging, patient follow-ups and how to deal with](#)  
102 [reoccurrence \[10\]](#).

103 Advantages of electrochemotherapy, such as its ability to eliminate or reduce tumours to a  
104 manageable size, in turn minimises distressing symptoms and avoids unnecessary surgery to  
105 excise tumours [~~11~~10]. These make it a highly significant intervention in the context of  
106 palliative care.

107 Two systematic reviews published in 2013 by Mali et al. [1-2] led to NICE (National Institute  
108 of Clinical Excellence) recognised electrochemotherapy as a palliative treatment for treating  
109 metastases in the skin from tumours of non-skin origin and melanoma [~~12~~11]. A drawback of  
110 these reviews is that they included studies conducted before the publication of the Standard  
111 Operating Procedures in 2006 [8]. It is therefore worthwhile to review the evidence again  
112 since [its implementation](#) their publication, to exclusively evaluate the studies published since  
113 its implementation and minimise the heterogeneity which was present in the previous review.

114

115

## 116 **1.2 Objective**

117 The primary objective of this systematic review was to examine the available evidence for the  
118 use of electrochemotherapy to draw conclusions about its effectiveness with the primary  
119 objective of tumour response, and to make recommendations for its usage in the context of  
120 palliative care. A secondary objective was to examine the relationship between tumour size  
121 and response to treatment using a meta-analysis, again to update the previous reviews with  
122 the most recent evidence.

123

## 124 **2.0 Methods**

125 2.1 Protocol and registration

126 This systematic review and meta-analysis were conducted at King's College London (2018).  
127 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement  
128 (PRISMA) was used as a guide to the reporting of all aspects of this systematic review  
129 | [\[1312\]](#).

130

## 131 2.2 Eligibility criteria

132 Studies were eligible if they had been published after the publication of the Standard  
133 Operating Procedures in 2006 and reported data on tumour response after the delivery of  
134 electrochemotherapy with at least a four-week follow up. Case reports or studies involving  
135 fewer than 10 patients were unnecessary to include as there was an adequate number of  
136 studies with large sample sizes. Studies involving primarily oral cavity cancers were  
137 excluded as this was deemed a heterogeneous population. Studies were eligible for meta-  
138 analysis if they had separate data for tumour response according to size and were of an  
139 acceptable homogeneity.

140 The primary outcome was tumour response according to the RECIST (Response Evaluation  
141 | Criteria In Solid Tumours) method [\[1413\]](#). These criteria define a complete response (CR) as  
142 the disappearance of all target lesions, partial response (PR) as a decrease of at least 30% in  
143 the sum of the longest diameters of all target lesions and objective response (OR) as sum of  
144 CR and PR.

145

## 146 2.3 Information Sources

147 The following databases were searched; Medline, Embase, CINAHL, British Nursing Index  
148 and the Cochrane Library. The search was performed during the third week of October 2017.  
149 Language restriction to English was applied as translation resources were unavailable for this  
150 review.

151

## 152 2.4 Search

153

154 To inform the search strategy the PICO format (population, intervention, comparison and  
155 outcome), was used to identify the key concepts in the review question. The Comparison  
156 facet was omitted from the PICO table because only observational studies including  
157 prospective, retrospective studies and case series were identified in the preliminary literature  
158 search. The reason for the lack of randomised trials is likely due to the ethical concerns  
159 around conducting a trial in a palliative population and the lack of clinical equipoise relating  
160 to the intervention [15] (see supplementary material 1 for full search strategy).

161

162

### 163 2.4.1 Study selection and data extraction

164 The study selection process was performed by one independent researcher. After removal of  
165 duplicates the title and abstracts of all remaining papers were screened against the  
166 inclusion/exclusion criteria and those deemed ineligible were removed. The full-text of the  
167 remaining papers was studied and the irrelevant studies were excluded with reasons (figure  
168 1).

169 The data were extracted from the selected studies by one researcher and displayed in  
170 evidence tables (tables 1 and 2). These studies were then screened again against the eligibility  
171 criteria for meta-analysis and the data on tumour size and response extracted (table 3).

172

### 173 2.4.2 Data items

174 | According to the PICO format [1514]; the Population was cutaneous metastases, the  
175 | Intervention was electrochemotherapy and Primary Outcome was clinical response, the  
176 | Comparison facet was not included due to the lack of a comparator.  
177 | The information extracted from each study was as follows; study type, included number of  
178 | evaluable patients, tumour response, response evaluation time, drug route, type of tumour and  
179 | response evaluation method. These headings were chosen due to their similarity to the  
180 | headings used in the previous systematic review [1], so comparisons could be made. A  
181 | further evidence table (table 2) extracted the available data relating to further cycles of  
182 | electrochemotherapy and secondary outcomes such as survival analysis, as this information  
183 | would provide context to the use of electrochemotherapy in the field of palliative care.  
184 | The headings included in the evidence table for meta-analysis (table 3) were; total number of  
185 | small tumours and number of those achieving complete response, number of large tumours  
186 | and number achieving complete response. The criteria for small and large tumour sizes were  
187 | set by the individual studies and therefore studies were only included if the definition of the  
188 | groups were homogeneous between studies.

189

## 190 2.5 Risk of bias in individual studies

191 | In the case of this review the included studies were observational, prospective or  
192 | retrospective case series designs. Although randomised controlled trials (RCTs) are  
193 | considered the most rigorous method for determining the effectiveness of an intervention they  
194 | were not present in the literature around electrochemotherapy during scoping searches. This  
195 | is likely due to a lack of clinical equipoise, as electrochemotherapy has already been  
196 | established as an effective palliative treatment; [1,2] therefore it would be deemed unethical  
197 | to enter patients into an RCT where one intervention is believed superior to another [1615].

198 In addition interventions for managing key symptoms (exudate and malodour) are currently  
199 lacking [5].  
200 A tool developed to assess the methodology of observational case series studies was  
201 identified, which contains an 18-criteria checklist (see supplementary material 2 for checklist)  
202 [17+6]. This checklist has been validated in a systematic review of quality assessment tools  
203 [18+7] and was deemed the most appropriate tool to assess the quality of papers in this  
204 systematic review.

205

## 206 2.6 Summary Measures

207 The overall effectiveness of electrochemotherapy was determined by pooling the primary  
208 outcome data of all individual studies to calculate an overall weighted per patient Complete  
209 Response % (CR) and Objective Response % (OR).

210

## 211 2.7 Synthesis of results

212 A meta-analysis was used to compare sub-groups to evaluate the differences in anti-tumour  
213 effectiveness of electrochemotherapy on tumours of different sizes. For the purposes of sub  
214 group analysis, the studies with separate data for ‘small’ and ‘large’ tumours were used with  
215 ‘small’ defined as  $\leq 3$ cm and ‘large’ as  $> 3$ cm. The relative risk (or risk ratio) was used as the  
216 measure of the size of the effect.

217 The random- effects model was used in the meta-analysis as electrochemotherapy is a  
218 potential treatment for a wide range of tumour histologies and therefore applies to a wide  
219 patient population [19+8]. The I<sup>2</sup> statistic was used to measure the variability between studies  
220 and to interpret the impact of heterogeneity on the MA; with I<sup>2</sup><25% showing homogeneity  
221 and I<sup>2</sup>>75% showing considerable heterogeneity [20+9]. The calculations used were written

222 in the Meta package which runs in the R programme according to the user manuals and forest  
223 | plots were generated (figure 2) [2120].

224

## 225 2.8 Risk of bias across studies

226 The concept of publication bias is an underlying issue within healthcare research and should  
227 | be considered as a risk in systematic reviews and meta-analysis [2221]. Investigating  
228 | publication bias in a meta-analysis is usually done by performing a funnel plot, however, due  
229 | to limited access to meta-analysis software this was not undertaken in this review.

230 Selective reporting of bias should be investigated by comparing the methodology of a paper  
231 | with the reported outcomes to make sure there is consistency between the outcomes listed in  
232 | the methods section and the results reported in the findings section [2322]. Any obvious  
233 | reporting failures in the studies included became obvious in the data extraction process and  
234 | these studies scored less in the quality appraisal tool.

235

## 236 **3.0 Results**

### 237 3.1 Study Selection

238 The database search generated 425 studies after removal of duplicates. The title and abstracts  
239 | of these studies were screened against the inclusion/exclusion criteria and 390 studies  
240 | excluded as irrelevant. The 41 remaining studies were selected for further evaluation, the full  
241 | text was obtained, read and screened against the eligibility criteria and 29 deemed eligible to  
242 | be part of the review. Studies that did not meet the eligibility criteria were excluded and the  
243 | reason for exclusion is detailed in the PRISMA flow chart (figure 1). The included studies  
244 | were screened again against the inclusion criteria for the meta-analysis and five selected as  
245 | satisfying the criteria.

246

247

### 248 3.2 Study Characteristics

249 All studies were observational and there was a combination of both prospective and  
250 retrospective approaches. The majority of studies used the Response Evaluation Criteria in  
251 Solid Tumours method [[1413](#)] to measure tumour response and the follow-up period to  
252 tumour evaluation ranged between 30 days and three months.

253 As expected, there was a wide range of tumour types across the studies; the most common  
254 being Melanoma, Basal Cell Carcinoma (BCC) and metastatic Breast Cancer. All studies  
255 with the exception of two [[2423](#), [2524](#)] reported the maximum number of  
256 electrochemotherapy cycles performed and the number of patients that received more than  
257 one course of electrochemotherapy. Where reported, the range of number of  
258 electrochemotherapy cycles was between two and six. Some studies reported patient  
259 outcomes such as pain and quality of life.

260 There was a lack of information across all the studies on the way survival analysis was  
261 calculated, perhaps due to the word restriction on publications. In addition, there was  
262 inconsistency between papers on the way they reported the survival analysis. Some reported  
263 progression free survival for the whole cohort of patients whereas others only calculated it for  
264 the patients with complete response.

265 Serious adverse events were minimal. The only serious adverse event that was considered  
266 related to the intervention was reported by Bertino et al. [9] where one patient with a large  
267 ulcerated tumour died from septic shock on the second day post-electrochemotherapy. The  
268 most common reported systemic reactions were mild, post-procedural nausea and dizziness  
269 being the most common. Pain was the second most reported adverse reaction, but this was  
270 reported as transient and although some reports of extreme pain were made immediately after  
271 the therapy, this settled to manageable pain within around 48 hours. The incidence and

272 description of treatment toxicity was graded according to the Common Terminology Criteria  
273 for Adverse Events (CTCAE) in the majority of studies. The most frequently reported  
274 complications were skin-related such as ulceration, erythema, and other inflammatory  
275 reactions, the most severe of these were graded 4 according to the CTCAE. However, across  
276 the studies all of these were transient and did not result in permanent damage. A number of  
277 studies asked patients whether they would agree to further electrochemotherapy treatment  
278 after the initial session and the percentage of patients that answered favourably was high. For  
279 instance, in Cabula et al. [2423] 97% of 96 patients answered that they would agree to receive  
280 the treatment and in Matthiessen et al. [2625] 90% of 51 patients were in favour of re-  
281 treatment.

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283

### 284 3.3 Quality Appraisal and risk of bias across studies

285 The 18-criteria checklist was used to assess the quality of included studies [1746]. A study  
286 scored a point when it fulfilled a criterion with the scores displayed in table 4. Overall, 17  
287 studies of the 21 assessed received a score of 14 or more and were deemed of satisfactory  
288 quality.

289 The researchers in this field have tried to overcome the weaknesses in their methodology by  
290 reporting the baseline characteristics of their patient populations in order to be transparent to  
291 the reader and to mitigate selection bias. This means judgements can be made about the  
292 suitability of the included patients and whether the conclusions made at the end of the study  
293 were robust. Only two of the included studies failed to report the baseline characteristics of  
294 participants, [2726, 2827] and these papers were awarded low scores in the quality appraisal  
295 tool.

296 Another aspect that increased rigour was the use of standardised outcome measurement tools.  
297 In this case the majority of the papers (20 out of 29) used the Response Evaluation Criteria In  
298 Solid Tumours method [1413] to measure tumour response, with the remaining using the  
299 WHO criteria [2928] or stating their own measures, which in both cases were adequately  
300 similar to the Response Evaluation Criteria In Solid Tumours model. However, there was  
301 inconsistency across the studies in the timing of the tumour evaluation with a range of 30  
302 days – three months, with three studies not reporting the time period to tumour evaluation and  
303 these papers were marked down in the quality appraisal [3029-3234].  
304 The majority of studies in this review were prospective (n=21) with the remaining being  
305 retrospective analyses (n=8). It is generally the view that retrospective design is weaker in  
306 the hierarchy of evidence than prospective design [3332]. However, in this review there was  
307 not a significant difference in quality between the retrospective and prospective studies. This  
308 demonstrates that the labelling of studies does not automatically classify whether they are  
309 superior or inferior but a more thorough examination of what has been reported in the papers  
310 is required [3433].

311

312

### 313 3.4 Synthesis of results

314 The pooled data across all the studies which evaluated the tumour response per patient was  
315 46.6% for complete response and 82.2% for objective response, the total number of patients  
316 being 1194. For six studies, the data were presented as ‘per tumour’ evaluation of response  
317 and the pooled result for these data was 53.6% for CR and 71.5% for OR, the total number of  
318 tumours was 599.

319

### 320 3.5 Meta-Analysis

321 The five studies found eligible for meta-analysis were among the highest scoring in the  
322 quality appraisal exercise with scores ranging from 15 – 17 out of 20. Table 3 shows the data  
323 extracted.

324 The total number of ‘small’ tumours included in the analysis was 602 and the pooled CR for  
325 this group was 67.4%. In contrast, the total number of ‘large’ tumours was 185 with a pooled  
326 complete response of 33.0%. The forest plot (figure 2) takes the ‘large’ tumour group as the  
327 control group and the ‘small’ tumour group as the experimental group. The overall relative  
328 risk in the random effects model is 2.25 95% confidence interval [1.58-3.2]. This means that  
329 ‘small’ tumours  $\leq 3$ cm are over twice as likely (2.25) to have a complete response than ‘large’  
330 tumours  $> 3$ cm. The test for overall effect generated a p value of  $< 0.01$  which is statistically  
331 significant, as the level of significance was set as  $p < 0.05$ .

332 The I2 statistic was 52% indicating there is moderate heterogeneity. The p value associated  
333 with the Chi-squared test for heterogeneity is 0.08 which is statistically significant,  
334 demonstrating that the random-effects model was appropriate to use in this instance. It is  
335 important to note that the I2 in this meta-analysis will not be very precise due to the very  
336 small number of studies and the inability to detect the between study variance [[1918](#)].

337

338

### 339 3.6 Risk of bias across studies

340 During the quality assessment process, the study by Di Monta et al. [[3736](#)] only reported  
341 complete response data in the results section despite describing the Response Evaluation  
342 Criteria in Solid Tumours criteria and defining partial response as a primary outcome in the  
343 methods section. This meant that the objective response (the complete response + partial  
344 response) could not be calculated for this study and therefore there was an absent score for  
345 OR% when the data across all studies were pooled.

346 When selecting studies suitable for meta-analysis it was noticed that in the study by Curatola  
347 et al. [3837] the percentage response data for small tumours and large tumours was reported,  
348 but, the number of tumours in the two sub-groups was not, which meant there was not enough  
349 raw data to be included. Similarly, the results for small versus large tumours in the study by  
350 Campana et al.[3938] could not be included in the meta-analysis because only the statistical  
351 test results such as odds ratio and p-value were reported and not the raw data. It was not  
352 possible to contact the authors of these studies for the raw data due to time constraints.

353

## 354 **4.0 Discussion**

### 355 4.1 Summary of Evidence

356 All the studies identified in the review reported results in favour of electrochemotherapy for  
357 the primary outcome of tumour response; it was well tolerated by patients and there were few  
358 reported serious adverse reactions.

359 The findings of this review are consistent with the previous systematic reviews on  
360 electrochemotherapy. It is noteworthy that in this review all the studies used bleomycin  
361 exclusively as the chemotherapeutic agent except for Campana et al. [3029, 4039] where  
362 cisplatin was used for a small proportion of study participants. In contrast, the previous  
363 review included six studies that used cisplatin exclusively. The reason for this move towards  
364 bleomycin as the drug of choice is likely due to further evidence generated since the  
365 publication of the previous studies which showed that the uptake of bleomycin is potentiated  
366 more effectively by electroporation pulses than the uptake of cisplatin and therefore future  
367 studies began to use the bleomycin drug exclusively [4140].

368 The meta-analysis used to perform sub-group analysis comparing the treatment response  
369 found there was a statistically significant increase of 125% in the probability of complete  
370 response for tumours  $\leq 3$ cm compared to tumours  $>3$ cm. These findings are consistent with

371 the previous meta-analysis [1, 2]. The reasons for this significant difference in the  
372 effectiveness of electrochemotherapy depending on tumour size has been considered in the  
373 literature [~~2625~~, ~~4241~~, ~~4342~~] and it is believed to be multi-factorial. Firstly, in large tumours  
374 there may be insufficient exposure of the tumour to the chemotherapy drug due to inadequate  
375 blood flow across the tumour as it is harder for the drug to penetrate the centre of a larger  
376 tumour [~~4443~~], therefore the drug is not adequately distributed to provide the optimum  
377 chemotherapeutic effect. Secondly, there may be insufficient coverage of the larger tumours  
378 by the electric fields simply due to the difficulty in applying the electrodes to the larger  
379 tumours, which will generally be of a less uniform size compared to the smaller tumours.  
380 Another potential explanation for why small tumours respond better to electrochemotherapy  
381 is because they have faster healing times and the fact that large tumours may be more  
382 aggressive [~~3635~~]. These potential shortfalls associated with treating larger tumours could be  
383 managed with individualised treatment planning to ensure the most effective choices of type  
384 of electrode and drug administration methods are assessed in all patients prior to instigation  
385 of the therapy. This review highlights the fact that electrochemotherapy is not a one-off  
386 treatment and can be repeated.

387 There were a number of further sub-group analyses across the studies in addition to tumour  
388 size. These include; in the study by Rotunno et al. [~~4544~~] where response for  
389 electrochemotherapy performed under general versus local anaesthesia was compared and  
390 found a significant increase in CR% for patients who underwent general anaesthesia. In  
391 addition, in the study by Bertino et al. [9] the response of tumours that were treatment-naïve  
392 was compared with tumours that had been previously treated with surgical-excision or  
393 irradiation. The authors found the treatment-naïve tumours responded significantly better  
394 than the previously treated tumours. These additional analyses further enrich the breadth of

395 knowledge about the usefulness of electrochemotherapy and provide valuable information for  
396 the review question and implications for future research.

397

#### 398 4.2 Limitations

399 Overall, the methodological quality of the included studies was acceptable. Baseline  
400 characteristics were reported in the majority of studies, the outcome measure was fairly  
401 consistent across the included studies. However, there was inconsistency across the studies in  
402 the timing of the tumour evaluation with a range of 30 days – three months, with three studies  
403 not reporting the time period to tumour evaluation [[3029-3231](#)]. This makes it very difficult  
404 to form any robust conclusions about their data. It is difficult to judge how much of an effect  
405 the difference in time to evaluation had on the reliability of the results, but it is noteworthy  
406 that the Standard Operating Procedures recommended a period of four weeks before  
407 treatment efficacy of electrochemotherapy can be determined.

408 The survival analysis was poorly reported and inconsistent across the studies which is  
409 unfortunate as these data are of great interest to clinicians particularly when deciding whether  
410 a treatment is worthwhile in the context of palliative care. The data extracted from the studies  
411 do give an indication of the medium length of follow-up in each individual study and  
412 percentage of patients whose disease was kept at bay. It is therefore useful information to  
413 display regardless of the fact that it is not possible to obtain an overall pooled average  
414 survival statistic.

415 Another limitation of the included studies was the use of co-interventions. These are  
416 significant as they illustrate that there are fundamental differences in the experience of a  
417 portion of patients within the studies due to adjunct treatments which may affect the tumour  
418 response data. It may also be this was more widespread than can be identified in the full-text  
419 articles if some articles did not publish the additional interventions the patients underwent in

420 their studies. However, it can be argued that due to the disease severity of the patients in  
421 these studies it would be considered unethical to deny them the opportunity to be exposed to  
422 other tumour-targeting therapies that may assist them to alleviate the burden of living with  
423 metastatic cutaneous tumours.

424 Overall, this systematic review includes a representative sample of the available literature on  
425 this topic area for meaningful conclusions to be made. The study selection, data extraction  
426 and study appraisal aspects of this review were carried out appropriately however, they would  
427 have been much more robust if there had been a second reviewer. Due to the availability of  
428 studies with large sample sizes, studies with less than ten participants were excluded to  
429 purposely limit the number of studies for analysis. However, the fact this occurred meant  
430 some very pertinent articles were removed that would have increased the knowledge to  
431 answer the review question [4645-4847].

432  
433 The methods of statistical analysis were appropriate and valid in this review and an academic  
434 statistician was consulted for guidance on conducting the meta-analysis. Unfortunately, there  
435 was poor precision due to the fact there were only five studies eligible for the analysis, and it  
436 may therefore be misleading to draw firm conclusions from the summary effect.

437

#### 438 **4.4 Conclusions**

439 This aim of this systematic review was to consolidate the recent literature on the effectiveness  
440 of electrochemotherapy for cutaneous metastases and update the previous systematic reviews  
441 [1, 2]. It was evident during the review process that the period of four weeks recommended  
442 by the Standard Operating Procedures as the time to measure tumour response to  
443 electrochemotherapy may not be long enough for large tumours to respond. In the study by  
444 Matthiessen et al. [2625] the patients all had large tumours from breast cancer and used an

445 eight week follow up instead of the four weeks to allow for this. Another factor noted in this  
446 review is that larger tumours may benefit from using different plates and electrodes.  
447 Additionally, a higher concentration of drug in large tumours could be achieved by  
448 combining both intratumoural and systematic administration of chemotherapy. This review  
449 used meta-analysis to show that small tumours have a greater tumour response compared to  
450 large tumours, further meta-analyses comparing other sub-groups would be useful in future  
451 reviews such as whether previous irradiation and number of tumours per patient influences  
452 the effectiveness of electrochemotherapy. Matching the treatment modality and schedule to  
453 patient specific factors such as those identified above is crucial to ensure the most effective  
454 coverage of the tumour by the electric field which means treatment needs to become more  
455 tailored to the individual.

456 Another implication for future treatment is that many of the studies reported some  
457 participants were able to obtain and/or maintain tumour response by undergoing repeated  
458 sessions of electrochemotherapy. Unfortunately, there was a lack of data providing the  
459 tumour responses to the additional cycles of electrochemotherapy. Further research should  
460 aim to explore this to set standards for the frequency of electrochemotherapy sessions to  
461 provide the highest benefit and lowest possible harm to patients. This could be done by better  
462 reporting of the number of cycles and results of the retreatments. Another issue this review  
463 has exposed is the lack of consistency in reporting of survival statistics as well as secondary  
464 outcomes such as QOL, pain and toxicity. Future research should address these outcomes as  
465 they inform health resource use and patient preference especially in palliative care.

466 This systematic review shows electrochemotherapy is an effective palliative treatment with  
467 minimal adverse reactions. Moreover, it should be considered early in the development of  
468 cutaneous metastases as the smaller the tumour the more effective the treatment. Larger

469 tumours will need to have tailored approaches to maximise the effectiveness of the ECT  
470 treatment, such as using different plates and electrodes.  
471 The evidence included in this review was based on the studies conducted following  
472 publication of the standard operating procedures in 2006 [8], it is noted that there has been an  
473 updated version of these standard operating procedures published in 2018 [10]. This update  
474 reflects the considerable experience gained in the use of the treatment in a wide range of  
475 tumour histologies. Future studies going forward, which use the updated standards may  
476 generate ~~more~~ further clinically specific evidence to guide clinicians. The knowledge  
477 generated by this review can ~~provide~~ provides further validation evidence generated from  
478 clinical studies, which followed the 2006 ~~for inform~~ publications such as the Standard  
479 Operating Procedures [8, 10] and inform clinical practice guidelines such as the NICE  
480 guidelines [124] to ensure they are brought up-to-date with current evidence.

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493 This is a systematic review of primary studies. Obtaining ethical approval was not applicable.

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Table 1 + 2

First author, year published	Original Data		Data used in evaluation										Eligibility for meta-analysis	
	Study type	Included no. of evaluable patients/tumours	Response of skin cancer (%)					response evaluation time	Drug/route	Type of tumour(s)	Response evaluation	follow-up median(range)	Tumour types	Tumour size
			CR (%)	PR (%)	NR/SD (%)	PD (%)	NA (%)							
<sup>a</sup> Benevento et al.[27]	Prospective, observational	12/142	107(75.3)	24(17)	11(7.7)	-	-	At least 30 days	Bleo i.v.	breast	RECIST	210days (30-354)	no	no
<sup>a</sup> Bertino et al.[9]	Prospective, observational, longitudinal	99/99	62(~62.6)	19(~19.2)	13(~13.1)	4(~4)	1(~1)	2 months	Bleo i.v or i.t.	H&N (BCC,SCC,MM, others <sup>c</sup> )	RECIST (1.1)	6 months (15 days- 12 months)	yes	yes
<sup>a</sup> Cabula et al.[34]	Retrospective cohort study	113/214	66(58.4)	36(31.8)	8(7.1)	2(1.8)	1(0.9)	2 months	Bleo i.v or i.t.	breast	RECIST (1.1)	5.9 months (3-58 months)	no	yes
Campana et al.[35]	Retrospective observational	84/185	42(50)	30(36)	12(14)	-	-	1-2 month	Bleo i.v or i.t.	BCC <sup>d</sup>	RECIST	49.2 months (3.6 – 121.1)	no	yes
Campana et al.[40]	Prospective observational	226/811	113(50)	75(33.2)	30(13.3)	7(3.1)	1(0.4)	60 days	Bleo i.v or bleo/cisp i.t.	Breast, BCC,SCC, KS, STS, melanoma, others <sup>e</sup>	RECIST	13.9 months(0.4-63.2)	yes	yes
Campana et al.[30]	retrospective	39/-	15(38)	8(21)	15(38)	1(3)	-	-	Bleo i.v or bleo/cisp i.t.	Oral/oropharynx, non-melanoma	RECIST	14 months (3-82)	no	yes
Campana et al.[49]	Phase II trial	35/196	19(54.3)	13(37.1)	3(8.6)	-	-	2 months	Bleo i.v.	Chest wall	RECIST	32 months (6-53)	no	no
Campana et al.[39]	observational	85/894	41(48)	39(46)	3(4)	2(2) patient	-	1 month	Bleo i.v or i.t.	melanoma	RECIST	26 (6-47) months	no	yes
Campana et al.[42]	Prospective, phase II	52/608	26(50)	24(46)	2(4)	-	-	1 month	Bleo i.v or i.t.	Melanoma, breast, STS, SCC, H&N	RECIST	9(2-21) months	no	yes
<sup>b</sup> Caraco et al.[50]	observational	89/-	43(48.3)	34(38.2)	12(13.5)	-	-	3 months	Bleo i.v.	Metastatic melanoma	WHO	27.5(6-67) months	no	no
<sup>b</sup> Caraco et al.[51]	observational	60/-	29(48.4)	23(38.3)	8(13.3)	-	-	3 months	Bleo i.v.	Metastatic melanoma	WHO	27.5(6-67) months	no	no
Curatolo et al.[38]	Prospective, phase II	23/-	14(60.9)	9(39.1)	-	-	-	4 weeks	Bleo i.v.	KS	RECIST 7 tumours	1.5 years (2 months-4.2 yrs)	no	yes
Di Monta et al.[25]	retrospective	22/-	5(22.7)	13(59)	3(13.6)	1(4.5)	-	4 weeks	Bleo i.v.	Locally advanced SCC	RECIST	34(5-48) months	No	no
Di Monta et al.[37]	prospective	19/-	14(73.6)	-	-	-	-	4 weeks	Bleo i.v.	KS	RECIST	16(6-31) months 13 (3-28) months	-	-

Gargiulo et al.[52]	retrospective	25/-	18(72)	7(28)	-	-	-	6 weeks	Bleo i.v.	H&N: SCC, BCC, adenocarcinoma	WHO, biopsy	21.9(4-42) months	no	yes	
Guida et al.[53]	retrospective	19/54	8(42)	4(21)	6(32)	1(5)	-	2 months	Bleo i.v.	angiosarcomas	RECIST 7 tumours	12(4.7-12.8) months	no	no	
Kreuter et al.[31]	retrospective	56/	6(10.7)	19(33.9)	7(12.5)	24(42.9)	-	-	Bleo i.v.	Melanoma, BC, carcinoma, sarcoma	RECIST		yes	no	
Kunte C. et al.[36]	prospective	114/394	55(48)	29(25)	26(23)	3(3)	1(1)	60 days	Bleo i.v or i.t.	Metastatic melanoma	RECIST	116(66-201) days	no	yes	
Latini et al.[54]	prospective	18/-	16(89)	2(11)	-	-	-	4 weeks	Bleo i.v.	KS	WHO	(6 – 48 months)	no	no	
<sup>a</sup> Mevio et al.[55]	prospective	14/31	19(61.5) <sup>g</sup>	10(32.5) <sup>g</sup>	1(3) <sup>g</sup>	1(3) <sup>g</sup>		8 weeks	Bleo i.v.	H&N	RECIST	8.75(2-20)months	-	-	
Mir-Bonafe et al.[56]	retrospective	31/-	7(23)	15(49)	-	9(28)		1 month	Bleo i.v.	Melanoma	Own measures	1 year (no median)	-	-	
Quaglino et al.[43]	prospective	14/233	7	6	1	-	-	8 weeks	Bleo i.v.	Melanoma	WHO 4-7 tumours	21(5-28) months	no	yes	
Ricotti et al.[28]	prospective	30/654	6(20)	24(80)	-	-	-	4 weeks	Bleo i.v.	melanoma	WHO	20 months (no median)	no	yes	
Rotunno et al.[45]	prospective	55/-	33(60)	17(31)	4(7)	1(1.8)		8 weeks	Bleo i.v.	H&N	RECIST, biopsy	8 months (327)	no	no	
Skarlatos et al.[57]	prospective	47/-	30(63.83)	15(31.91)	2(4.26)	-	-	2 months	Bleo i.v or i.t.	Melanoma, KS, H&N, BC, others <sup>f</sup>	Own measures	At least 6 months	yes	no	
Solari et al.[58]	prospective	Total = 39: 20/- melanoma						-	Bleo i.v.	Melanoma, BC, KS,BCC, SCC, MC, AS, AC	RECIST	At least 6 months	yes	yes	
			2(10)	9(45)	3(15)	6(30)	-								
			19/- other	7(36.8)	8(42.1)	-	4(21.1)								-
<sup>a</sup> Tomassini et al.[32]	prospective	Total= -/16:						2 months	Bleo i.v.	MM, NMSC	RECIST	-	yes	no	
			MM -/9 'target'	3(33.3)	0	4(44.4)	2(22.3)								0
			-/7 NMSC 'target'	6(85.7)	0	1(14.3)	0								0
Matthiessen et al.[26]	Phase II	12/25	1	1	9	1	-	8 weeks	Bleo i.v or i.t.	BC	RECIST, PET/CT	79(11-378) days	no	no	

<sup>a</sup> Matthiessen et al.[11]	Phase II	24/97	58(60)	18(10)	11(11)	7(7)	3(3)	>60 days	Bleo i.v or i.t.	BC	RECIST	47(16-110) days	no	yes
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Table 1. Summary of studies and characteristics of tumours included in the systematic review

Key

- a) Number of responses per tumour reported
- b) Caraco et al. [48] is an update of Caraco et al.[49] with an increased data set of patients
- c) 3 undifferentiated carcinoma, 3 adenocarcinoma, 1 lentigo maligna, 1 syringoma, 1 sarcomatous tumour
- d) BCC local 40(48%), locally advanced 41 (49%) and metastatic 3(3%)
- e) Merkel cell carcinoma, vulvar carcinoma, H&N
- f) Solid tumours including liposarcoma, anal, vulvar, uterine cervix, renal, pancreatic

CR = complete response; PR = partial response; NR = no response; - = no data; bleo = bleomycin; cisp = cisplatin; i.t. = intratumoural; i.v. = intraveonou; BC = breast cancer; BCC = basal cell carcinoma; SCC = squamous cell carcinoma; H&S = Head and neck; KS = Kaposi sarcoma; STS = soft tissue sarcoma; AS = angiosarcoma; MC = merkel cell; AC = adenocarcinoma; MM= melanoma metastases; NMSC= non melanoma skin cancer



Mir-Bonafe et al.[54]	3	24	-	-	-	-	-	-	-	-	-	-	-
Quaglino et al.[42]	3	10	-	-	-	-	-	no	no	no	-	-	74.5%(2 years)
Ricotti et al.[27]	2	25	-	-	-	-	-	no	no	no	-	-	72%(24 month)
Rotunno et al.[44]	3	23	-	-	-	-	-	yes	yes	yes	-	-	-
Skarlatos et al.[55]	3	18	-	-	-	-	-	no	no	no	-	-	-
Solari et al.[56]	4	17	-	-	-	-	-	-	-	-	-	-	-
Tomassini et al.[31]	2	4	-	-	-	-	-	-	-	-	-	-	-
Matthiessen et al.[25]	4	7	-	-	-	-	-	yes	yes	no	-	-	-
Matthiessen et al.[10]	2	11	-	-	-	-	-	no	yes	no	-	-	-

Table 3

Author, year of publication	Tumour sizes	Number of tumours (small)= n <sub>1</sub>	Complete response of tumours (small) number (%)	Number of tumours (large) = n <sub>2</sub>	Complete response of tumours (large) number (%)
Bertino et al. 2016 <sup>9</sup>	≤ 3 cm > 3cm	68	53(78)	31	9(29)
Cabula et al. 2015 <sup>24</sup>	< 3 cm ≥ 3cm	55	44(80.3)	58	27(46.1)
Campana et al. 2017 <sup>35</sup>	≤ 3 cm > 3cm	52	36(69.2)	32	6(18.7)
Kunte et al. 2016 <sup>36</sup>	≤ 3 cm > 3cm	343	216(62.9)	51	18(35.3)
Wichmann Matthesse n et al. 2011 <sup>11</sup>	≤ 3 cm > 3cm	84	57(68)	13	1(8)

Table 1. Data for small and large tumours included in meta-analysis



Table 4	Study reference	Question no.																		Score n/18		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		19	20
	Benevento et al.[27]	Y	Y	N	Y	U	Y	U	Y	P	Y	U	Y	N	y	Y	N	Y	Y	Y	P	11.5
	Bertino et al.[9]	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	U	Y	N	Y	Y	Y	Y	Y	Y	Y	17
	Cabula et al.[24]	Y	N	Y	U	Y	Y	Y	Y	N	Y	U	Y	N	Y	Y	Y	Y	Y	Y	Y	15
	Campana et al.[35]	Y	N	N	Y	Y	Y	Y	Y	Y	Y	U	Y	N	Y	Y	N	Y	Y	Y	Y	15
	Campana et al.[40]	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	U	Y	N	Y	Y	Y	Y	Y	Y	Y	17
	Campana et al.[30]	Y	N	Y	U	Y	N	Y	Y	P	Y	U	Y	N	Y	U	Y	Y	Y	Y	Y	13
	Campana et al.[49]	Y	Y	N	U	Y	Y	Y	Y	P	Y	U	Y	N	Y	Y	N	Y	Y	Y	Y	14
	Campana et al.[39]	Y	Y	Y	U	Y	Y	Y	Y	P	Y	U	Y	N	Y	Y	Y	Y	Y	Y	Y	16
	Campana et al.[42]	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	U	Y	N	Y	Y	Y	Y	Y	Y	N	16
	Caraco et al.[50]	Y	U	N	U	Y	N	Y	Y	P	Y	U	Y	N	y	Y	Y	Y	Y	Y	Y	12.5
	Caraco et al.[51]	Y	U	U	U	Y	N	Y	Y	P	Y	U	Y	N	y	Y	Y	Y	Y	Y	Y	12.5
	Curatolo et al.[38]	Y	Y	Y	U	Y	Y	Y	Y	P	Y	U	Y	N	Y	Y	Y	Y	Y	Y	N	15
	Di Monta et al.[25]	Y	N	N	Y	Y	Y	Y	Y	P	Y	U	Y	N	Y	Y	Y	Y	Y	Y	Y	15
	Di Monta et al.[37]	Y	Y	N	Y	Y	N	Y	Y	P	Y	U	Y	N	y	Y	Y	Y	Y	Y	Y	15.5
	Gargiulo et al.[52]	Y	N	N	U	Y	Y	Y	Y	P	Y	U	Y	N	Y	Y	Y	Y	Y	Y	Y	14
	Guida et al.[53]	Y	N	Y	U	Y	N	Y	Y	P	Y	U	Y	N	Y	Y	N	Y	Y	Y	Y	13
	Kreuter et al.[31]	Y	N	Y	U	Y	N	Y	Y	P	Y	U	Y	N	Y	U	N	N	Y	Y	P	10
	Kunte et al.[36]	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	U	Y	N	Y	Y	Y	Y	Y	Y	Y	17
	Latini et al.[54]	Y	Y	N	U	Y	N	Y	Y	P	Y	U	N	N	y	Y	Y	Y	N	Y	N	11.5
	Mevio et al.[55]	Y	U	N	U	Y	Y	Y	Y	P	Y	U	Y	N	y	Y	Y	Y	Y	Y	Y	12.5
	Mir-Bonafe et al.[56]	Y	N	N	U	Y	P	Y	Y	P	Y	U	Y	N	y	Y	Y	N	Y	Y	Y	11.5
	Quaglino et al.[43]	Y	Y	U	Y	Y	Y	Y	Y	P	Y	U	Y	N	Y	Y	Y	Y	Y	Y	P	14
	Ricotti et al.[28]	Y	Y	N	Y	N	N	Y	Y	P	Y	U	Y	N	y	Y	Y	Y	Y	Y	N	12.5
	Rotunno et al.[45]	Y	Y	Y	U	Y	Y	Y	Y	P	Y	U	Y	N	Y	Y	Y	Y	Y	Y	N	15
	Skarlatos et al.[57]	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	U	Y	N	y	Y	Y	N	Y	Y	N	14.5
	Solari et al.[58]	Y	Y	N	U	Y	Y	Y	Y	p	Y	U	Y	N	Y	U	Y	Y	Y	Y	P	13
	Tomassini et al.[32]	Y	Y	N	U	Y	Y	Y	Y	P	Y	U	Y	N	Y	Y	Y	N	Y	Y	N	13

Matthiessen et al.[26]	Y	Y	U	U	Y	Y	Y	Y	P	Y	U	Y	N	y	Y	Y	Y	Y	Y	Y	14.5
Matthiessen et al.[11]	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	U	Y	N	y	Y	Y	Y	Y	Y	Y	16.5

Key: Y = yes, y = yes but less advanced, N = no, U = unclear, P = partial

Table 4. Quality Appraisal Tool Scores

Figure 1. Selection process for the studies included in the systematic review

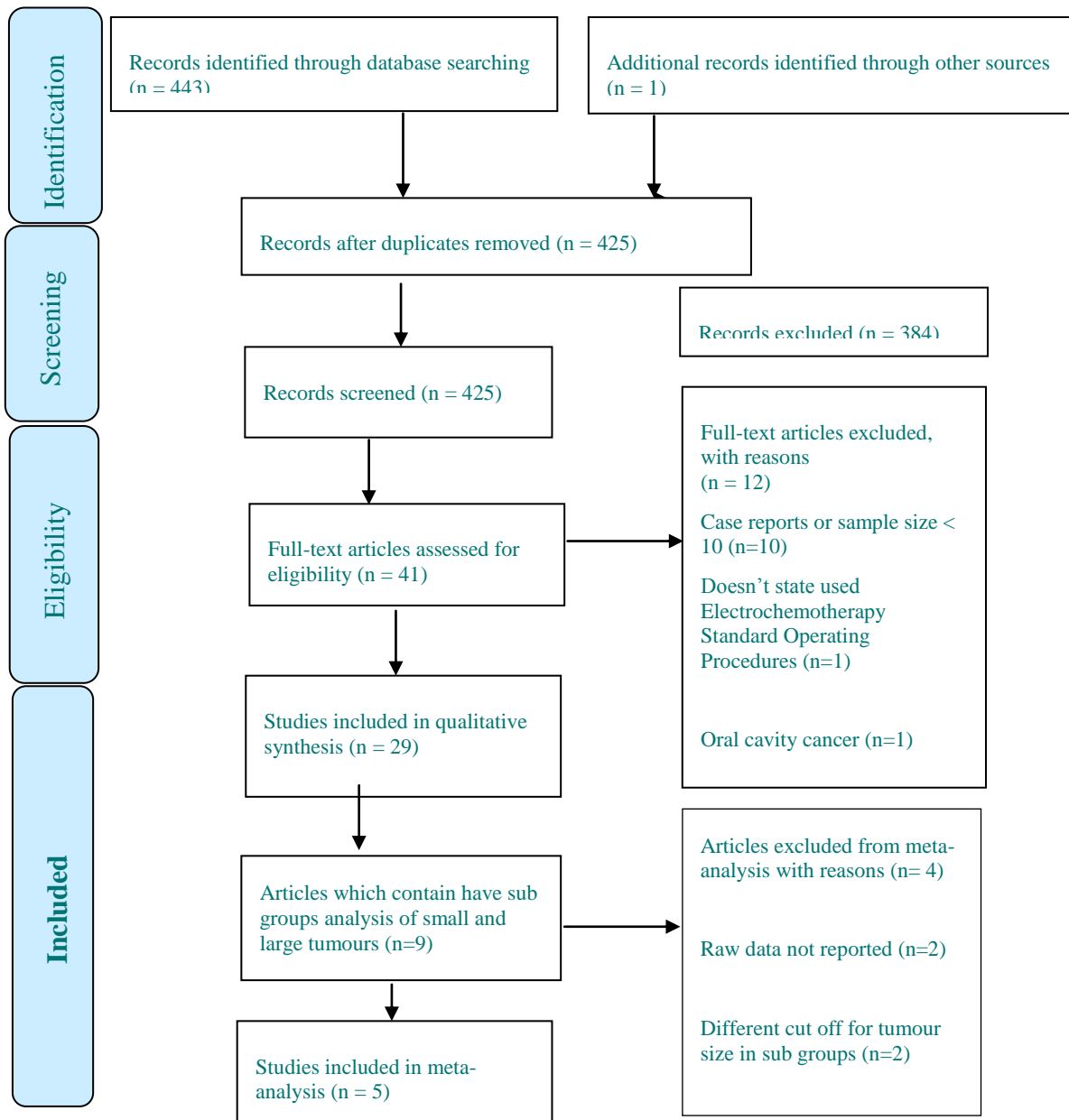
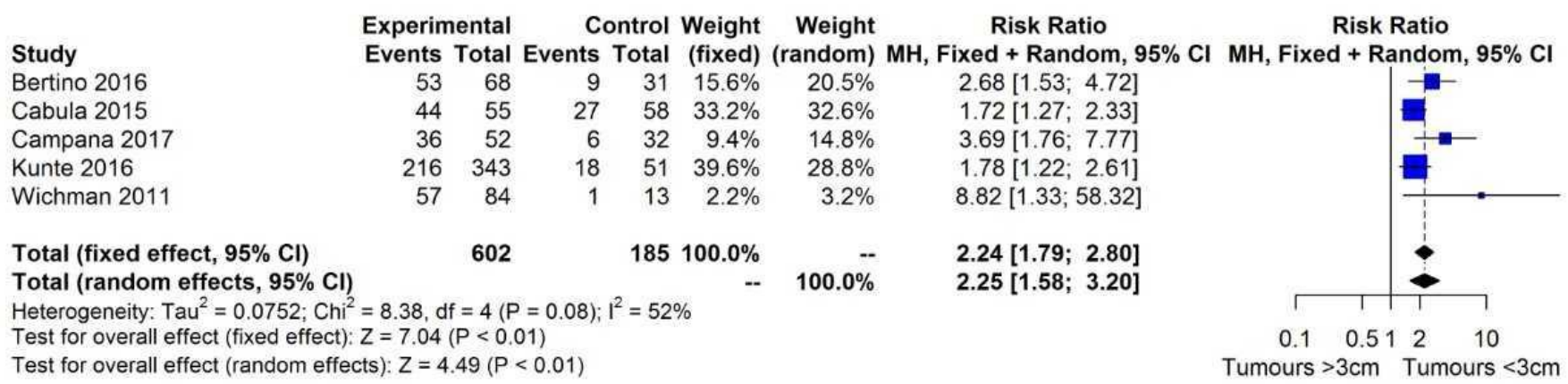


Figure 2

Figure 2. Results of meta-analysis



**Supplementary Material 1 Search Strategy**

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