Review Article

Corresponding Author: Josephine Morley

J. Morley, North Bristol NHS Trust, Southmead Road, Bristol, BS10 5NB, United Kingdom

E-mail: josephine.morley@nbt.nhs.uk

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

Josephine Morley (a), Patricia Grocott (b), Edward Purssell (c), Trevor Murrells (b)

a North Bristol NHS Trust, Southmead Road, Bristol, BS10 5NB b King's College London, Florence Nightingale Faculty of Nursing, Midwifery & Palliative care c School of Health Sciences, City, University of London

Abstract

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

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

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

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

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

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

Keywords

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

1.0 Introduction

1.1 Background

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

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

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

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

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

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

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

1.2 Objective

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

2.0 Methods

2.1 Protocol and registration

This systematic review and meta-analysis were conducted at King's College London (2018). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) was used as a guide to the reporting of all aspects of this systematic review [13].

2.2 Eligibility criteria

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

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

2.3 Information Sources

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

2.4 Search

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

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

2.4.1 Study selection and data extraction

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

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

2.4.2 Data items

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

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

further evidence table (table 2) extracted the available data relating to further cycles of electrochemotherapy and secondary outcomes such as survival analysis, as this information would provide context to the use of electrochemotherapy in the field of palliative care.

The headings included in the evidence table for meta-analysis (table 3) were; total number of small tumours and number of those achieving complete response, number of large tumours and number achieving complete response. The criteria for small and large tumour sizes were set by the individual studies and therefore studies were only included if the definition of the groups were homogeneous between studies.

2.5 Risk of bias in individual studies

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

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

2.6 Summary Measures

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

2.7 Synthesis of results

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

The random- effects model was used in the meta-analysis as electrochemotherapy is a potential treatment for a wide range of tumour histologies and therefore applies to a wide patient population [19]. The I2 statistic was used to measure the variability between studies and to interpret the impact of heterogeneity on the MA; with I2<25% showing homogeneity and I2>75% showing considerable heterogeneity [20]. The calculations used were written in the Meta package which runs in the R programme according to the user manuals and forest plots were generated (figure 2) [21].

2.8 Risk of bias across studies

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

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

3.0 Results

3.1 Study Selection

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

3.2 Study Characteristics

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

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

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

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

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

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

3.3 Quality Appraisal and risk of bias across studies

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

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

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

The majority of studies in this review were prospective (n=21) with the remaining being 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 ≤3cm are over twice as likely (2.25) to have a complete response than 'large'

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

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

3.6 Risk of bias across studies

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

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

4.0 Discussion

4.1 Summary of Evidence

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

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

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

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

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

4.2 Limitations

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

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

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

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

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

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

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

4.4 Conclusions

This aim of this systematic review was to consolidate the recent literature on the effectiveness of electrochemotherapy for cutaneous metastases and update the previous systematic reviews [1, 2]. It was evident during the review process that the period of four weeks recommended by the Standard Operating Procedures as the time to measure tumour response to electrochemotherapy may not be long enough for large tumours to respond. In the study by Matthiessen et al. [26] the patients all had large tumours from breast cancer and used an eight week follow up instead of the four weeks to allow for this. Another factor noted in this review is that larger tumours may benefit from using different plates and electrodes. Additionally, a higher concentration of drug in large tumours could be achieved by combining both intratumoural and systematic administration of chemotherapy. This review used meta-analysis to show that small tumours have a greater tumour response compared to large tumours, further meta-analyses comparing other sub-groups would be useful in future reviews such as whether previous irradiation and number of tumours per patient influences the effectiveness of electrochemotherapy. Matching the treatment modality and schedule to patient specific factors such as those identified above is crucial to ensure the most effective

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

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

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

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

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

Acknowledgements

The first author of this paper is Josephine Morley who conducted the systematic review and meta-analysis and was supervised by Professor Patricia Grocott and Trevor Murrells at King's College London. Statistical support was provided by Dr Edward Purssell Senior Lecturer at City, University of London. This paper has not been submitted for publication elsewhere.

Funding

The Author(s) received no financial support for the research, authorship, and/ or publication of this article.

Declaration of conflicts of interest

The author(s) declare(s) that there is no conflict of interest.

Ethics/research governance approvals

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

References

[1] Mali B, Jarm T, Snoj M, et al. Antitumor effectiveness of electrochemotherapy: a systematic review and meta-analysis. Eur J Surg Oncol 2013; 39(1):4-16.

[2] Mali B, Miklavcic D, Campana LG, et al. Tumor size and effectiveness of electrochemotherapy. Radiology and oncology 2013;47(1):32-41.

[3] Schwartz RA. Cutaneous metastatic disease. J Am Acad Dermatol 1995;33(2):161-185.

[4] Alexander S. Malignant fungating wounds: epidemiology, aetiology, presentation and assessment. J Wound Care 2009;18(7):273-280.

[5] Grocott P, Gethin G, Probst S. Malignant wound management in advanced illness: new insights. Current opinion in supportive and palliative care 2013;7(1):101-105.

[6] Spratt DE, Gordon Spratt EA, Wu S, et al. Efficacy of skin-directed therapy for cutaneous metastases from advanced cancer: a meta-analysis. J Clin Oncol 2014;32(28):3144-3155.

[7] Miklavcic D, Corovic S, Pucihar G, et al. Importance of tumour coverage by sufficiently high local electric field for effective electrochemotherapy. European Journal of Cancer Supplements 2006;4(11):45-51.

[8] Marty M, Sersa G, Garbay JR, et al. Electrochemotherapy–An easy, highly effective and safe treatment of cutaneous and subcutaneous metastases: Results of ESOPE (European Standard Operating Procedures of Electrochemotherapy) study. European Journal of Cancer Supplements 2006;4(11):3-13.

[9] Bertino G, Sersa G, De Terlizzi F, et al. European Research on Electrochemotherapy in Head and Neck Cancer (EURECA) project: Results of the treatment of skin cancer. Eur J Cancer 2016;63:41-52.

[10] Gehl et al. Updated standard operating procedures for electrochemotherapy of cutaneous tumors and skin metastases. Acta Oncol. 2018;57(7):874-882

[11] Matthiessen LW, Chalmers RL, Sainsbury DCG, et al. Management of cutaneous metastases using electrochemotherapy. Acta Oncol 2011;50(5):621-629

[12] National Institute of Clinical Excellence, NICE. Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma. 2013; Available at: https://www.nice.org.uk/guidance/ipg446. Accessed 07/03, 2018.

[13] Moher D, Liberati A, Tetzlaff J, et al. Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097 (accessed on 07/03, 2018)

[14] Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92(3):205-216.

[15] Boland A, Cherry MG, Dickson R. Doing a systematic review a students guide. London: SAGE Publication Ltd; 2014.

[16] Sibbald B, Roland M. Understanding controlled trials. Why are randomised controlled trials important? BMJ 1998;316(7126):201.

[17] Moga C, Guo B, Schopflocher D, et al. Development of a Quality Appraisal Tool for Case Series Studies Using a Modified Delphi Technique. 2012; Available at: https://www.researchgate.net/publication/281411226_Development_of_a_Quality_Appraisal_Tool_for_Case_Series_Studies_Using_a_Modified_Delphi_Technique. (accessed on 07/03, 2018)

[18] Zeng X, Zhang Y, Kwong JS, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta- analysis, and clinical practice guideline: a systematic review. Journal of evidence-based medicine 2015;8(1):2-10.

[19] Borenstein M, Hedges L, Higgins J.et al. Introduction to meta-analysis. West Sussex, England: Wiley & Sons Ltd 2009.

[20] Ried K. Interpreting and understanding meta-analysis graphs: a practical guide. Australian Family Physician, 2006; 35(8):635-638

[21] Del Re A. A practical tutorial on conducting meta-analysis in R. The Quantitative Methods for Psychology 2015;11(1):37-50.

[22] Sutton AJ. Evidence concerning the consequences of publication and related biases. Publication bias in meta-analysis: Prevention, assessment, and adjustments. John Wiley & Sons, Ltd, 2005:175-192.

[23] Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. : John Wiley & Sons; 2011.

[24] Cabula C, Campana LG, Grilz G, et al. Electrochemotherapy in the Treatment of Cutaneous Metastases from Breast Cancer: A Multicenter Cohort Analysis. Annals of Surgical Oncology 2015;22:442-450.

[25] Di Monta G, Caraco C, Simeone E, et al. Electrochemotherapy efficacy evaluation for treatment of locally advanced stage III cutaneous squamous cell carcinoma: A 22-cases retrospective analysis. Journal of Translational Medicine 2017;15: 82

[26] Matthiessen LW, Johannesen HH, Hendel HW, et al. Electrochemotherapy for large cutaneous recurrence of breast cancer: a phase II clinical trial. Acta Oncol 2012;51(6):713-721.

[27] Benevento R, Santoriello A, Perna G, et al. Electrochemotherapy of cutaneous metastasis from breast cancer in elderly patients: a preliminary report. BMC surgery 2012;12(1):S6.

[28] Ricotti F, Giuliodori K, Cataldi I, et al. Electrochemotherapy: an effective local treatment of cutaneous and subcutaneous melanoma metastases. Dermatologic Therapy 2014;27(3):148-152.

[29] Miller A, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment. Cancer 1981;47(1):207-214.

[30] Campana LG, Mali B, Sersa G, et al. Electrochemotherapy in non-melanoma head and neck cancers: a retrospective analysis of the treated cases. Br J Oral Maxillofac Surg 2014;52(10):957-964.

[31] Kreuter A, van Eijk T, Lehmann P, et al. Electrochemotherapy in advanced skin tumors and cutaneous metastases - a retrospective multicenter analysis. Journal der Deutschen Dermatologischen Gesellschaft 2015;13(4):308-315.

[32] Tomassini GM, Covarelli P, Tomassini MA, et al. Electrochemotherapy with intravenous bleomycin for advanced non-melanoma skin cancers and for cutaneous and subcutaneous metastases from melanoma. Giornale Italiano di Dermatologia e Venereologia 2016;151(5):499-506.

[33] Euser AM, Zoccali C, Jager KJ, et al. Cohort studies: prospective versus retrospective. Nephron Clin Pract 2009;113(3):c214-7.

[34] Vandenbroucke JP. Prospective or retrospective: what's in a name? BMJ 1991;302(6771):249-250.

[35] Campana LG, Marconato R, Valpione S, et al. Basal cell carcinoma: 10-year experience with electrochemotherapy. Journal of Translational Medicine 2017;15:122.

[36] Kunte C, Letule V, Gehl, et al. Electrochemotherapy in the treatment of metastatic malignant melanoma: a prospective cohort study by InspECT. Br J Dermatol 2017;176(6):1475-1485.

[37] Di Monta G, Caraco C, Benedetto L, et al. Electrochemotherapy as "new standard of care" treatment for cutaneous Kaposi's sarcoma. European Journal of Surgical Oncology 2014;40(1):61-66.

[38] Curatolo P, Quaglino P, Marenco F, et al. Electrochemotherapy in the treatment of Kaposi sarcoma cutaneous lesions: a two-center prospective phase II trial. Annals of Surgical Oncology 2012;19(1):192-198.

[39] Campana LG, Valpione S, Mocellin S, et al. Electrochemotherapy for disseminated superficial metastases from malignant melanoma. Br J Surg 2012;99(6):821-830.

[40] Campana LG, Testori A, Curatolo P, et al. Treatment efficacy with electrochemotherapy: A multi-institutional prospective observational study on 376 patients with superficial tumors. European Journal of Surgical Oncology 2016;42(12):1914-1923.

[41] Mir LM. Bases and rationale of the electrochemotherapy. European Journal of Cancer Supplements 2006;4(11):38-44.

[42] Campana LG, Mocellin S, Basso M, et al. Bleomycin-based electrochemotherapy: clinical outcome from a single institution's experience with 52 patients. Annals of Surgical Oncology 2009;16(1):191-199.

[43] Quaglino P, Mortera C, Osella-Abate S, et al. Electrochemotherapy with intravenous bleomycin in the local treatment of skin melanoma metastases. Annals of Surgical Oncology 2008;15(8):2215-2222.

[44] Sersa G, Jarm T, Kotnik T, et al. Vascular disrupting action of electroporation and electrochemotherapy with bleomycin in murine sarcoma. Br J Cancer 2008;98(2):388.

[45] Rotunno R, Marenco F, Ribero S, et al. Electrochemotherapy in non-melanoma head and neck skin cancers: A three-center experience and review of the literature. Giornale Italiano di Dermatologia e Venereologia 2016;151(6):610-618.

[46] Kis E, Oláh J, Ócsai H, et al. Electrochemotherapy of cutaneous metastases of melanoma—a case series study and systematic review of the evidence. Dermatologic Surgery 2011;37(6):816-824.

[47] Kis E, Szegesdi I, Ócsai H, et al. Electrochemotherapy of melanoma cutaneous metastases. Orv Hetil 2010;151(3):99-101.

[48] Seccia V, Muscatello L, Dallan I, et al. Electrochemotherapy and its controversial results in patients with head and neck cancer. Anticancer Res 2014;34(2):967-972.

[49] Campana LG, Valpione S, Falci C, et al. The activity and safety of electrochemotherapy in persistent chest wall recurrence from breast cancer after mastectomy: a phase-II study. Breast Cancer Research & Treatment 2012;134(3):1169-1178.

[50] Caraco C, Marone U, Simeone E, et al. Electrochemotherapy in melanoma patients: A single institution experience. Melanoma Management 2015;2(2):127-132.

[51] Caraco C, Mozzillo N, Marone U, et al. Long-lasting response to electrochemotherapy in melanoma patients with cutaneous metastasis. BMC Cancer 2013;13:564.

[52] Gargiulo M, Papa A, Capasso P, et al. Electrochemotherapy for non-melanoma head and neck cancers: clinical outcomes in 25 patients. Ann Surg 2012;255(6):1158-1164.

[53] Guida M, Campana LG, Curatolo P, et al. Local treatment with electrochemotherapy of superficial angiosarcomas: Efficacy and safety results from a multi-institutional retrospective study. J Surg Oncol 2016;114(2):246-253.

[54] Latini A, Bonadies A, Trento E, et al. Effective treatment of Kaposi's sarcoma by electrochemotherapy and intravenous bleomycin administration. Dermatologic Therapy 2012;25(2):214-218

[55] Mevio N, Bertino G, Occhini A, et al. Electrochemotherapy for the treatment of recurrent head and neck cancers: preliminary results. Tumori 2012;98(3):308-313.

[56] Mir-Bonafe JM, Vilalta A, Alarcon I, et al. Electrochemotherapy in the treatment of melanoma skin metastases: a report on 31 cases. Actas Dermo-Sifiliogr 2015;106(4):285-291.

[57] Skarlatos I, Kyrgias G, Mosa E, et al. Electrochemotherapy in cancer patients: first clinical trial in Greece. In Vivo 2011;25(2):265-274.

[58] Solari N, Spagnolo F, Ponte E, et al. Electrochemotherapy for the management of cutaneous and subcutaneous metastasis: a series of 39 patients treated with palliative intent. J Surg Oncol 2014;109(3):270-274.

644

645

Review Article

Corresponding Author: Josephine Morley

J. Morley, North Bristol NHS Trust, Southmead Road, Bristol, BS10 5NB, United Kingdom

E-mail: josephine.morley@nbt.nhs.uk

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

Josephine Morley (a), Patricia Grocott (b), Edward Purssell (c), Trevor Murrells (b)

a North Bristol NHS Trust, Southmead Road, Bristol, BS10 5NB b King's College London, Florence Nightingale Faculty of Nursing, Midwifery & Palliative care c School of Health Sciences, City, University of London

Abstract

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

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

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

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

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

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

Keywords

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

1.0 Introduction

1.1 Background

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

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

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

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

standards for documentation and imaging, patient follow-ups and how to deal with reoccurrence [10].

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

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

1.2 Objective

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

2.0 Methods

2.1 Protocol and registration

This systematic review and meta-analysis were conducted at King's College London (2018). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) was used as a guide to the reporting of all aspects of this systematic review [13~~12~~].

2.2 Eligibility criteria

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

The primary outcome was tumour response according to the RECIST (Response Evaluation Criteria In Solid Tumours) method [14~~13~~]. These criteria define a complete response (CR) as the disappearance of all target lesions, partial response (PR) as a decrease of at least 30% in the sum of the longest diameters of all target lesions and objective response (OR) as sum of CR and PR.

2.3 Information Sources

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

2.4 Search

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

2.4.1 Study selection and data extraction

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

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

2.4.2 Data items

According to the PICO format [15~~14~~]; the Population was cutaneous metastases, the Intervention was electrochemotherapy and Primary Outcome was clinical response, the Comparison facet was not included due to the lack of a comparator.

The information extracted from each study was as follows; study type, included number of evaluable patients, tumour response, response evaluation time, drug route, type of tumour and response evaluation method. These headings were chosen due to their similarity to the headings used in the previous systematic review [1], so comparisons could be made. A further evidence table (table 2) extracted the available data relating to further cycles of electrochemotherapy and secondary outcomes such as survival analysis, as this information would provide context to the use of electrochemotherapy in the field of palliative care.

The headings included in the evidence table for meta-analysis (table 3) were; total number of small tumours and number of those achieving complete response, number of large tumours and number achieving complete response. The criteria for small and large tumour sizes were set by the individual studies and therefore studies were only included if the definition of the groups were homogeneous between studies.

2.5 Risk of bias in individual studies

In the case of this review the included studies were observational, prospective or retrospective case series designs. Although randomised controlled trials (RCTs) are considered the most rigorous method for determining the effectiveness of an intervention they were not present in the literature around electrochemotherapy during scoping searches. This is likely due to a lack of clinical equipoise, as electrochemotherapy has already been established as an effective palliative treatment; [1,2] therefore it would be deemed unethical to enter patients into an RCT where one intervention is believed superior to another [16~~15~~].

In addition interventions for managing key symptoms (exudate and malodour) are currently lacking [5].

A tool developed to assess the methodology of observational case series studies was identified, which contains an 18-criteria checklist (see supplementary material 2 for checklist) [17~~16~~]. This checklist has been validated in a systematic review of quality assessment tools [18~~17~~] and was deemed the most appropriate tool to assess the quality of papers in this systematic review.

2.6 Summary Measures

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

2.7 Synthesis of results

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

The random- effects model was used in the meta-analysis as electrochemotherapy is a potential treatment for a wide range of tumour histologies and therefore applies to a wide patient population [19~~18~~]. The I2 statistic was used to measure the variability between studies and to interpret the impact of heterogeneity on the MA; with I2<25% showing homogeneity and I2>75% showing considerable heterogeneity [20~~19~~]. The calculations used were written

in the Meta package which runs in the R programme according to the user manuals and forest plots were generated (figure 2) [21~~20~~].

2.8 Risk of bias across studies

The concept of publication bias is an underlying issue within healthcare research and should be considered as a risk in systematic reviews and meta-analysis [22~~21~~]. Investigating publication bias in a meta-analysis is usually done by performing a funnel plot, however, due to limited access to meta-analysis software this was not undertaken in this review.

Selective reporting of bias should be investigated by comparing the methodology of a paper with the reported outcomes to make sure there is consistency between the outcomes listed in the methods section and the results reported in the findings section [23~~22~~]. Any obvious reporting failures in the studies included became obvious in the data extraction process and these studies scored less in the quality appraisal tool.

3.0 Results

3.1 Study Selection

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

3.2 Study Characteristics

All studies were observational and there was a combination of both prospective and retrospective approaches. The majority of studies used the Response Evaluation Criteria in Solid Tumours method [14~~13~~] to measure tumour response and the follow-up period to tumour evaluation ranged between 30 days and three months.

As expected, there was a wide range of tumour types across the studies; the most common being Melanoma, Basal Cell Carcinoma (BCC) and metastatic Breast Cancer. All studies with the exception of two [24~~23~~, 25~~24~~] reported the maximum number of electrochemotherapy cycles performed and the number of patients that received more than one course of electrochemotherapy. Where reported, the range of number of electrochemotherapy cycles was between two and six. Some studies reported patient outcomes such as pain and quality of life.

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

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

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

3.3 Quality Appraisal and risk of bias across studies

The 18-criteria checklist was used to assess the quality of included studies [1716]. A study scored a point when it fulfilled a criterion with the scores displayed in table 4. Overall, 17 studies of the 21 assessed received a score of 14 or more and were deemed of satisfactory quality.

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

Another aspect that increased rigour was the use of standardised outcome measurement tools. In this case the majority of the papers (20 out of 29) used the Response Evaluation Criteria In Solid Tumours method [14~~13~~] to measure tumour response, with the remaining using the WHO criteria [29~~28~~] or stating their own measures, which in both cases were adequately similar to the Response Evaluation Criteria In Solid Tumours model. However, there was inconsistency across the studies in the timing of the tumour evaluation with a range of 30 days – three months, with three studies not reporting the time period to tumour evaluation and these papers were marked down in the quality appraisal [30~~29~~-32~~31~~].

The majority of studies in this review were prospective (n=21) with the remaining being retrospective analyses (n=8). It is generally the view that retrospective design is weaker in the hierarchy of evidence than prospective design [33~~32~~]. However, in this review there was not a significant difference in quality between the retrospective and prospective studies. This demonstrates that the labelling of studies does not automatically classify whether they are superior or inferior but a more thorough examination of what has been reported in the papers is required [34~~33~~].

3.4 Synthesis of results

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

3.5 Meta-Analysis

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

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

The I2 statistic was 52% indicating there is moderate heterogeneity. The p value associated with the Chi-squared test for heterogeneity is 0.08 which is statistically significant, demonstrating that the random-effects model was appropriate to use in this instance. It is important to note that the I2 in this meta-analysis will not be very precise due to the very small number of studies and the inability to detect the between study variance [19~~18~~].

3.6 Risk of bias across studies

During the quality assessment process, the study by Di Monta et al. [37~~36~~] only reported complete response data in the results section despite describing the Response Evaluation Criteria in Solid Tumours criteria and defining partial response as a primary outcome in the methods section. This meant that the objective response (the complete response + partial response) could not be calculated for this study and therefore there was an absent score for OR% when the data across all studies were pooled.

When selecting studies suitable for meta-analysis it was noticed that in the study by Curatola et al. [38~~37~~] the percentage response data for small tumours and large tumours was reported, but, the number of tumours in the two sub-groups was not, which meant there was not enough raw data to be included. Similarly, the results for small versus large tumours in the study by Campana et al.[39~~38~~] could not be included in the meta-analysis because only the statistical test results such as odds ratio and p-value were reported and not the raw data. It was not possible to contact the authors of these studies for the raw data due to time constraints.

4.0 Discussion

4.1 Summary of Evidence

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

The findings of this review are consistent with the previous systematic reviews on electrochemotherapy. It is noteworthy that in this review all the studies used bleomycin exclusively as the chemotherapeutic agent except for Campana et al. [30~~29~~, 40~~39~~] where cisplatin was used for a small proportion of study participants. In contrast, the previous review included six studies that used cisplatin exclusively. The reason for this move towards bleomycin as the drug of choice is likely due to further evidence generated since the publication of the previous studies which showed that the uptake of bleomycin is potentiated more effectively by electroporation pulses than the uptake of cisplatin and therefore future studies began to use the bleomycin drug exclusively [41~~40~~].

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

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

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

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

4.2 Limitations

Overall, the methodological quality of the included studies was acceptable. Baseline characteristics were reported in the majority of studies, the outcome measure was fairly consistent across the included studies. However, there was inconsistency across the studies in the timing of the tumour evaluation with a range of 30 days – three months, with three studies not reporting the time period to tumour evaluation [30~~29~~-32~~31~~]. This makes it very difficult to form any robust conclusions about their data. It is difficult to judge how much of an effect the difference in time to evaluation had on the reliability of the results, but it is noteworthy that the Standard Operating Procedures recommended a period of four weeks before treatment efficacy of electrochemotherapy can be determined.

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

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

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

Overall, this systematic review includes a representative sample of the available literature on this topic area for meaningful conclusions to be made. The study selection, data extraction and study appraisal aspects of this review were carried out appropriately however, they would have been much more robust if there had been a second reviewer. Due to the availability of studies with large sample sizes, studies with less than ten participants were excluded to purposely limit the number of studies for analysis. However, the fact this occurred meant some very pertinent articles were removed that would have increased the knowledge to answer the review question [46~~45~~-48~~47~~].

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

4.4 Conclusions

This aim of this systematic review was to consolidate the recent literature on the effectiveness of electrochemotherapy for cutaneous metastases and update the previous systematic reviews [1, 2]. It was evident during the review process that the period of four weeks recommended by the Standard Operating Procedures as the time to measure tumour response to electrochemotherapy may not be long enough for large tumours to respond. In the study by Matthiessen et al. [26~~25~~] the patients all had large tumours from breast cancer and used an

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

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

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

tumours will need to have tailored approaches to maximise the effectiveness of the ECT treatment, such as using different plates and electrodes.

The evidence included in this review ~~was~~is based on the studies conducted following publication of the standard operating procedures in 2006 [8], it is noted that there has been an updated version of these standard operating procedures published in 2018 [10]. This update reflects the considerable experience gained in the use of the treatment in a wide range of tumour histologies. Future studies going forward, which use the updated standards may generate ~~more~~further clinically specific evidence to guide clinicians. The knowledge generated by this review ~~can provide~~provides ~~further validation~~evidence generated from clinical studies, which followed the 2006 ~~for inform publications such as~~ ~~the~~ Standard Operating Procedures [8, 10] and inform clinical practice guidelines such as the NICE guidelines [12~~11~~] to ensure they are brought up-to-date with current evidence.

Acknowledgements

The first author of this paper is Josephine Morley who conducted the systematic review and meta-analysis and was supervised by Professor Patricia Grocott and Trevor Murrells at King's College London. Statistical support was provided by Dr Edward Purssell Senior Lecturer at City, University of London. This paper has not been submitted for publication elsewhere.

Funding

The Author(s) received no financial support for the research, authorship, and/ or publication of this article.

Declaration of conflicts of interest

The author(s) declare(s) that there is no conflict of interest.

Ethics/research governance approvals

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

References

[1] Mali B, Jarm T, Snoj M, et al. Antitumor effectiveness of electrochemotherapy: a systematic review and meta-analysis. Eur J Surg Oncol 2013; 39(1):4-16.

[2] Mali B, Miklavcic D, Campana LG, et al. Tumor size and effectiveness of electrochemotherapy. Radiology and oncology 2013;47(1):32-41.

[3] Schwartz RA. Cutaneous metastatic disease. J Am Acad Dermatol 1995;33(2):161-185.

[4] Alexander S. Malignant fungating wounds: epidemiology, aetiology, presentation and assessment. J Wound Care 2009;18(7):273-280.

[5] Grocott P, Gethin G, Probst S. Malignant wound management in advanced illness: new insights. Current opinion in supportive and palliative care 2013;7(1):101-105.

[6] Spratt DE, Gordon Spratt EA, Wu S, et al. Efficacy of skin-directed therapy for cutaneous metastases from advanced cancer: a meta-analysis. J Clin Oncol 2014;32(28):3144-3155.

[7] Miklavcic D, Corovic S, Pucihar G, et al. Importance of tumour coverage by sufficiently high local electric field for effective electrochemotherapy. European Journal of Cancer Supplements 2006;4(11):45-51.

[8] Marty M, Sersa G, Garbay JR, et al. Electrochemotherapy–An easy, highly effective and safe treatment of cutaneous and subcutaneous metastases: Results of ESOPE (European Standard Operating Procedures of Electrochemotherapy) study. European Journal of Cancer Supplements 2006;4(11):3-13.

[9] Bertino G, Sersa G, De Terlizzi F, et al. European Research on Electrochemotherapy in Head and Neck Cancer (EURECA) project: Results of the treatment of skin cancer. Eur J Cancer 2016;63:41-52.

[10] Gehl et al. Updated standard operating procedures for electrochemotherapy of cutaneous tumors and skin metastases. Acta Oncol. 2018;57(7):874-882

[11~~10~~] Matthiessen LW, Chalmers RL, Sainsbury DCG, et al. Management of cutaneous metastases using electrochemotherapy. Acta Oncol 2011;50(5):621-629

[12~~11~~] National Institute of Clinical Excellence, NICE. Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma. 2013; Available at: https://www.nice.org.uk/guidance/ipg446. Accessed 07/03, 2018.

[13~~12~~] Moher D, Liberati A, Tetzlaff J, et al. Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097 (accessed on 07/03, 2018)

[14~~13~~] Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92(3):205-216.

[15~~14~~] Boland A, Cherry MG, Dickson R. Doing a systematic review a students guide. London: SAGE Publication Ltd; 2014.

[16~~15~~] Sibbald B, Roland M. Understanding controlled trials. Why are randomised controlled trials important? BMJ 1998;316(7126):201.

Formatted: Font: (Default) Times New Roman

[1716] Moga C, Guo B, Schopflocher D, et al. Development of a Quality Appraisal Tool for Case Series Studies Using a Modified Delphi Technique. 2012; Available at: https://www.researchgate.net/publication/281411226_Development_of_a_Quality_Appraisal_Tool_for_Case_Series_Studies_Using_a_Modified_Delphi_Technique. (accessed on 07/03, 2018)

[1817] Zeng X, Zhang Y, Kwong JS, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta- analysis, and clinical practice guideline: a systematic review. Journal of evidence-based medicine 2015;8(1):2-10.

[1918] Borenstein M, Hedges L, Higgins J.et al. Introduction to meta-analysis. West Sussex, England: Wiley & Sons Ltd 2009.

[2019] Ried K. Interpreting and understanding meta-analysis graphs: a practical guide. Australian Family Physician, 2006; 35(8):635-638

[2120] Del Re A. A practical tutorial on conducting meta-analysis in R. The Quantitative Methods for Psychology 2015;11(1):37-50.

[2221] Sutton AJ. Evidence concerning the consequences of publication and related biases. Publication bias in meta-analysis: Prevention, assessment, and adjustments. John Wiley & Sons, Ltd, 2005:175-192.

[2322] Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. : John Wiley & Sons; 2011.

[2423] Cabula C, Campana LG, Grilz G, et al. Electrochemotherapy in the Treatment of Cutaneous Metastases from Breast Cancer: A Multicenter Cohort Analysis. Annals of Surgical Oncology 2015;22:442-450.

[2524] Di Monta G, Caraco C, Simeone E, et al. Electrochemotherapy efficacy evaluation for treatment of locally advanced stage III cutaneous squamous cell carcinoma: A 22-cases retrospective analysis. Journal of Translational Medicine 2017;15: 82

[2625] Matthiessen LW, Johannesen HH, Hendel HW, et al. Electrochemotherapy for large cutaneous recurrence of breast cancer: a phase II clinical trial. Acta Oncol 2012;51(6):713-721.

[2726] Benevento R, Santoriello A, Perna G, et al. Electrochemotherapy of cutaneous metastasis from breast cancer in elderly patients: a preliminary report. BMC surgery 2012;12(1):S6.

[2827] Ricotti F, Giuliodori K, Cataldi I, et al. Electrochemotherapy: an effective local treatment of cutaneous and subcutaneous melanoma metastases. Dermatologic Therapy 2014;27(3):148-152.

[2928] Miller A, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment. Cancer 1981;47(1):207-214.

[3029] Campana LG, Mali B, Sersa G, et al. Electrochemotherapy in non-melanoma head and neck cancers: a retrospective analysis of the treated cases. Br J Oral Maxillofac Surg 2014;52(10):957-964.

[3130] Kreuter A, van Eijk T, Lehmann P, et al. Electrochemotherapy in advanced skin tumors and cutaneous metastases - a retrospective multicenter analysis. Journal der Deutschen Dermatologischen Gesellschaft 2015;13(4):308-315.

[3231] Tomassini GM, Covarelli P, Tomassini MA, et al. Electrochemotherapy with intravenous bleomycin for advanced non-melanoma skin cancers and for cutaneous and subcutaneous metastases from melanoma. Giornale Italiano di Dermatologia e Venereologia 2016;151(5):499-506.

[3332] Euser AM, Zoccali C, Jager KJ, et al. Cohort studies: prospective versus retrospective. Nephron Clin Pract 2009;113(3):c214-7.

[3433] Vandenbroucke JP. Prospective or retrospective: what's in a name? BMJ 1991;302(6771):249-250.

[3534] Campana LG, Marconato R, Valpione S, et al. Basal cell carcinoma: 10-year experience with electrochemotherapy. Journal of Translational Medicine 2017;15:122.

[3635] Kunte C, Letule V, Gehl, et al. Electrochemotherapy in the treatment of metastatic malignant melanoma: a prospective cohort study by InspECT. Br J Dermatol 2017;176(6):1475-1485.

[3736] Di Monta G, Caraco C, Benedetto L, et al. Electrochemotherapy as "new standard of care" treatment for cutaneous Kaposi's sarcoma. European Journal of Surgical Oncology 2014;40(1):61-66.

[3837] Curatolo P, Quaglino P, Marenco F, et al. Electrochemotherapy in the treatment of Kaposi sarcoma cutaneous lesions: a two-center prospective phase II trial. Annals of Surgical Oncology 2012;19(1):192-198.

[3938] Campana LG, Valpione S, Mocellin S, et al. Electrochemotherapy for disseminated superficial metastases from malignant melanoma. Br J Surg 2012;99(6):821-830.

[4039] Campana LG, Testori A, Curatolo P, et al. Treatment efficacy with electrochemotherapy: A multi-institutional prospective observational study on 376 patients with superficial tumors. European Journal of Surgical Oncology 2016;42(12):1914-1923.

[4140] Mir LM. Bases and rationale of the electrochemotherapy. European Journal of Cancer Supplements 2006;4(11):38-44.

[4241] Campana LG, Mocellin S, Basso M, et al. Bleomycin-based electrochemotherapy: clinical outcome from a single institution's experience with 52 patients. Annals of Surgical Oncology 2009;16(1):191-199.

[4342] Quaglino P, Mortera C, Osella-Abate S, et al. Electrochemotherapy with intravenous bleomycin in the local treatment of skin melanoma metastases. Annals of Surgical Oncology 2008;15(8):2215-2222.

[4443] Sersa G, Jarm T, Kotnik T, et al. Vascular disrupting action of electroporation and electrochemotherapy with bleomycin in murine sarcoma. Br J Cancer 2008;98(2):388.

[4544] Rotunno R, Marenco F, Ribero S, et al. Electrochemotherapy in non-melanoma head and neck skin cancers: A three-center experience and review of the literature. Giornale Italiano di Dermatologia e Venereologia 2016;151(6):610-618.

[4645] Kis E, Oláh J, Ócsai H, et al. Electrochemotherapy of cutaneous metastases of melanoma—a case series study and systematic review of the evidence. Dermatologic Surgery 2011;37(6):816-824.

[4746] Kis E, Szegesdi I, Ócsai H, et al. Electrochemotherapy of melanoma cutaneous metastases. Orv Hetil 2010;151(3):99-101.

[4847] Seccia V, Muscatello L, Dallan I, et al. Electrochemotherapy and its controversial results in patients with head and neck cancer. Anticancer Res 2014;34(2):967-972.

[4948] Campana LG, Valpione S, Falci C, et al. The activity and safety of electrochemotherapy in persistent chest wall recurrence from breast cancer after mastectomy: a phase-II study. Breast Cancer Research & Treatment 2012;134(3):1169-1178.

[5048] Caraco C, Marone U, Simeone E, et al. Electrochemotherapy in melanoma patients: A single institution experience. Melanoma Management 2015;2(2):127-132.

[5149] Caraco C, Mozzillo N, Marone U, et al. Long-lasting response to electrochemotherapy in melanoma patients with cutaneous metastasis. BMC Cancer 2013;13:564.

[5250] Gargiulo M, Papa A, Capasso P, et al. Electrochemotherapy for non-melanoma head and neck cancers: clinical outcomes in 25 patients. Ann Surg 2012;255(6):1158-1164.

[5351] Guida M, Campana LG, Curatolo P, et al. Local treatment with electrochemotherapy of superficial angiosarcomas: Efficacy and safety results from a multi-institutional retrospective study. J Surg Oncol 2016;114(2):246-253.

[54~~52~~] Latini A, Bonadies A, Trento E, et al. Effective treatment of Kaposi's sarcoma by electrochemotherapy and intravenous bleomycin administration. Dermatologic Therapy 2012;25(2):214-218

[55~~53~~] Mevio N, Bertino G, Occhini A, et al. Electrochemotherapy for the treatment of recurrent head and neck cancers: preliminary results. Tumori 2012;98(3):308-313.

[56~~54~~] Mir-Bonafe JM, Vilalta A, Alarcon I, et al. Electrochemotherapy in the treatment of melanoma skin metastases: a report on 31 cases. Actas Dermo-Sifiliogr 2015;106(4):285-291.

[57~~55~~] Skarlatos I, Kyrgias G, Mosa E, et al. Electrochemotherapy in cancer patients: first clinical trial in Greece. In Vivo 2011;25(2):265-274.

[58~~56~~] Solari N, Spagnolo F, Ponte E, et al. Electrochemotherapy for the management of cutaneous and subcutaneous metastasis: a series of 39 patients treated with palliative intent. J Surg Oncol 2014;109(3):270-274.

Table 1 + 2

	Original Data		Data used in evaluation										Eligibility for meta-analysis	
First author, year published	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 (%)							
[a] 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
[a] 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[c])	RECIST (1.1)	6 months (15 days- 12 months)	yes	yes
[a] 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[d]	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[e]	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
[b]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
[b]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
[a]Mevio et al.[55]	prospective	14/31	19(61.5)[g]	10(32.5)[g]	1(3)[g]	1(3)[g]		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[f]	Own measures	At least 6 months	yes	no
Solari et al.[58]	prospective	Total = 39: 20/- melanoma	2(10)	9(45)	3(15)	6(30)	-	-	Bleo i.v.	Melanoma, BC, KS,BCC, SCC, MC, AS, AC	RECIST	At least 6 months	yes	yes
		19/- other	7(36.8)	8(42.1)	-	4(21.1)	-							
[a] 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

[a] 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

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

Table 2. Summary of the studies including number of ECT cycles and secondary outcomes reported

First author, year published	Maximum number of ECT cycles performed	No. of patients that received 2 + courses	Response of skin cancer (%) for second cycle					Secondary outcomes reported					
			CR (%)	PR (%)	NR/SD (%)	PD (%)	NA (%)	Quality of life/PROS (patient reported outcome measures)	toxicity	pain	Progression free survival % (CI) Whole cohort	Progression free survival % (CI) CR	Local control rate (%)
Benevento et al.[26]	3	4	-	-	-	-	-	-	-	-	-	-	
Bertino et al.[9]	2	19	-	-	-	-	-	yes	-	yes	-	89(69-97) 1 year	
Cabula et al.[23]	-	-	-	-	-	-	-	no	yes	yes	86.2(79.3-93.8) 1 year	96.4(91.6-100)	
Campana et al.[34]	3	24	11(45.8)	11(45.8)	2(8.4)	-	-	-	yes	yes	70(58-82) (5 years)	-	
Campana et al.[39]	6	89(23.7%)	-	-	-	-	-	yes	yes	-	73.7(68.4-37.6) one year	-	
Campana et al.[29]	3	15(38)	-	-	-	-	-	no	yes	no			
Campana et al.[48]	3	21(59.7)	-	-	-	-	-	-	yes	yes			81% 3 year
Campana et al.[38]	6	61	30	31	-	-	-	no	yes	no	87% (2 year)		
Campana et al.[41]	5	20	13(65)	7(35)	-	-	-	yes	yes	yes	-	-	96% 9(2-21) months
Caraco C. et al.[48]	6	50	-	-	-	-	-	no	no	no	-	-	-
Caraco et al.[49]	5	26	-	-	-	-	-	no	no	no	-	-	-
Curatolo et al.[37]	3	5	-	-	-	-	-	no	no	no	-	-	76.2% (2 years)
Di Monta et al.[24]	-	-	-	-	-	-	-	no	no	no	-	-	-
Di Monta et al.[36]	3	5	-	-	-	-	-	no	no	no	-	-	-
Gargiulo et al.[50]	2	4	-	-	-	-	-	no	yes	no	-	-	-
Guida et al.[51]	3	4	-	-	-	-	-	no	yes	yes	45%(12-69)	-	-
Kreuter et al.[30]	-	-	-	-	-	-	-	no	no	no	-	-	-
Kunte C. et al.[35]	4	31	-	-	-	-	-	no	yes	yes	74(64-68) 1 year LPFS	-	-
Latini et al.[52]	3	9	8(89)	1(11)	-	-	-	-	-	-	-	-	-
Mevio et al.[53]	3	-	-	-	-	-	-	-	-	-	-	-	-

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_1	Complete response of tumours (small) number (%)	Number of tumours (large) = n_2	Complete response of tumours (large) number (%)
Bertino et al. 2016[9]	≤ 3 cm > 3cm	68	53(78)	31	9(29)
Cabula et al. 2015[24]	< 3 cm ≥ 3cm	55	44(80.3)	58	27(46.1)
Campana et al. 2017[35]	≤ 3 cm > 3cm	52	36(69.2)	32	6(18.7)
Kunte et al. 2016[36]	≤ 3 cm > 3cm	343	216(62.9)	51	18(35.3)
Wichmann Matthiessen et al. 2011[11]	≤ 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.																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Score n/18
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

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

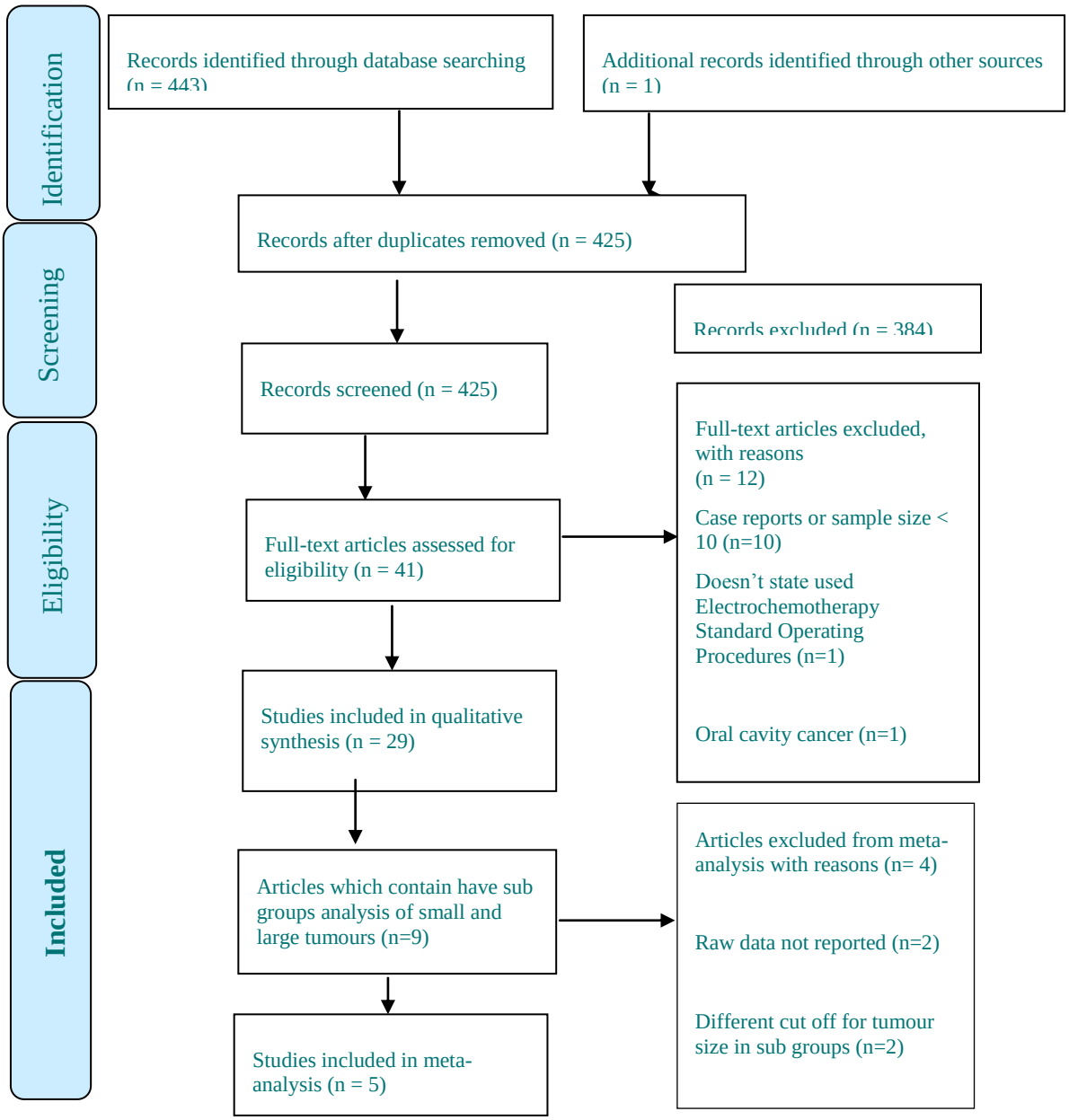
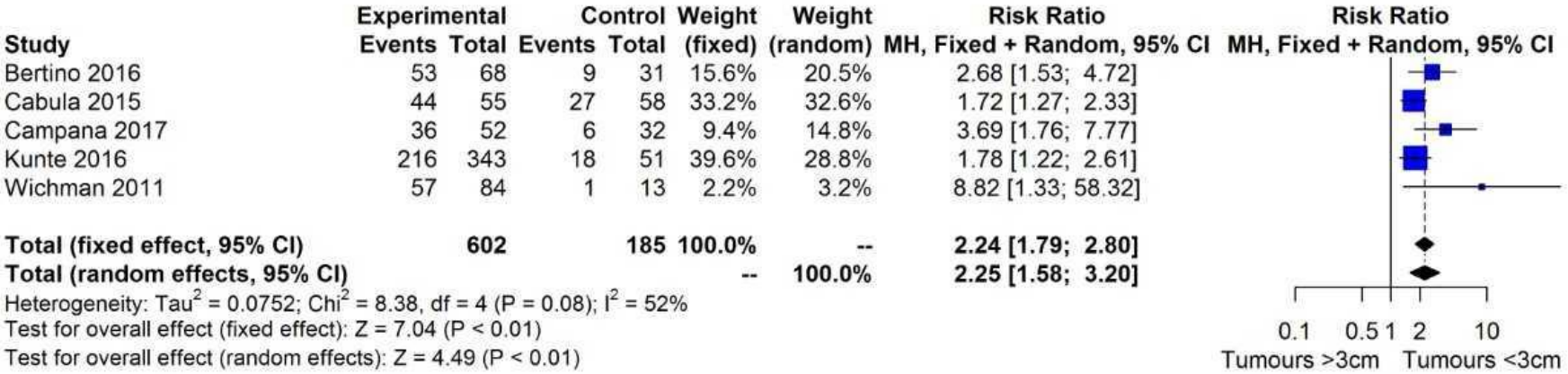


Figure 2

Figure 2. Results of meta-analysis



Supplementary Material 1 Search Strategy

Click here to download Supplementary files: Supplementary Material 1 Search Strategy.docx

Supplementary 2 Quality Appraisal Tool

Click here to download Supplementary files: Supplementary Material 2 Quality Appraisal Tool.docx

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

1. Identifying information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

Definitions.

Entity: government agency, foundation, commercial sponsor, academic institution, etc.
Grant: A grant from an entity, generally [but not always] paid to your organization
Personal Fees: Monies paid to you for services rendered, generally honoraria, royalties, or fees for consulting , lectures, speakers bureaus, expert testimony, employment, or other affiliations
Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
Issued: The patent has been issued by the agency
Licensed: The patent has been licensed to an entity, whether earning royalties or not
Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Josephine
2. Surname (Last Name): Morley
3. Date: 05-April-2019

4. Are you the corresponding author? ☑ Yes ☐ No

5. Manuscript Title: Electrochemotherapy for the palliative management of cutaneous metastases: a systematic review and meta-analysis

6. Manuscript Identifying Number (if you know it):

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Miss. Morley has nothing to disclose.

Evaluation and Feedback

Please visit http://www.icmje.org/cgi-bin/feedback to provide feedback on your experience with completing this form.