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Study Protocol

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Electrochemotherapy vs radiotherapy in the treatment of primary cutaneous malignancies or cutaneous metastases from primary solid organ malignancies: a protocol for a systematic review and meta-analysis

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Abstract

Electrochemotherapy has emerged as a valuable tool in the treatment of cutaneous malignancies that are unamenable to surgical resection. Despite growing recognition and recommendation in national guidelines, to date, no Level 1 evidence exists comparing its use to radiotherapy in the management of cutaneous malignancies. A systematic review and meta-analysis will be undertaken in line with the Cochrane Handbook and Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and checklist. A comprehensive search strategy will be applied to MEDLINE, Embase, CINAHL, CENTRAL and ClinicalTrials.gov from the time period from inception to December 2021. Supplementary searches of the grey literature will also be undertaken. Studies in humans which compare treatment with electrochemotherapy to radiotherapy and report tumour response with at least a 4-week follow-up will be eligible. Studies will be included regardless of publication language or country of origin. Screening of studies and data extraction will be undertaken independently by two authors. Our primary outcome will be tumour volume response according to Response Evaluation Criteria in Solid Tumors. We will also extract any secondary outcomes reported, such as patient-reported outcome measures, pain, toxicity/adverse events and progression-free survival. Included studies will be assessed for risk of bias using recognized tools. Evidence quality will be appraised using the Grading of Recommendations, Assessment, Development and Evaluation approach. If studies are of acceptable clinical homogeneity and suitable data is extracted, a meta-analysis will be performed. If adequate data are present, various subgroup analyses will be performed. Publication bias will be assessed using a funnel plot and Egger's test.

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INTRODUCTION

Skin cancer accounts for a significant proportion of new cancer diagnoses globally each year [1]. The mainstay of treatment in the majority of cases is surgical resection with or without reconstruction [2, 3]. However, in some patients, the malignancy may be aggressive or locally advanced, or there may be metastatic deposits from a primary malignancy elsewhere in the body. Skin malignancies also often occur in the clinically frail patient in whom elevated rates of post-operative complications are seen [4, 5]. For some, tumour size, location, plurality and co-morbidity may limit the feasibility of treatment with surgical resection. Radiotherapy is a well-established treatment modality that may provide symptomatic control in these patients [6]. Electrochemo therapy is an alternative treatment in which electroporation is used to increase the permeability of cells to cytotoxic agents [7]. Since the publication of standard operating procedures for its use [8, 9], electrochemotherapy has gained international traction in specialist centres. Use of electroporation in conjunction with chemotherapy has been shown to have greater efficacy than the administration of the chemotherapy agents alone [10], and NICE has issued guidance for its use in a specialist setting [11]. However, to date, no Level 1 evidence has been published comparing electrochemotherapy with radiotherapy in the management of cutaneous malignancy.

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The aim of this study, therefore, is to systematically examine the published literature comparing electrochemotherapy and radiotherapy in the treatment of patients with primary cutaneous malignancies unsuitable for curative surgical resection or cutaneous metastases from other primary solid organ malignancies and, where possible, synthesize the data with meta-analysis.

METHODS AND ANALYSIS

This protocol is registered on PROSPERO International Prospective Register of Systematic Reviews [12] with the protocol ID 'CRD42021285415'. The methodology of the review has been developed in line with the Cochrane Handbook for Systematic Reviews of Interventions [13], and the review will be undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and checklist [14].

Eligibility

Studies will be eligible for inclusion if they compare treatment with electrochemotherapy to treatment with radiotherapy and report on tumour response after treatment delivery with at least a 4-week follow-up period. Studies will be deemed suitable for inclusion in a meta-analysis if they present comparable data for tumour response between electrochemotherapy and radiotherapy treatment groups and are of suitable clinical homogeneity.

Only studies applying to humans will be included. Studies will be included regardless of their publication language or country of origin.

Search strategy

A search strategy will be developed to encompass all relevant works relating to the review. The help of an information specialist has been sought to identify appropriate MeSH and free-text search terms, which will be combined with Boolean operators. Table 1 gives an example of the MeSH and free-text terms used in the search strategy. This search strategy will then be applied to the following databases: MEDLINE, Embase and CINAHL from the time period from database inception to 28 December 2021. Additionally, searches of trial registries CENTRAL and ClinicalTrials.gov will be performed. Supplementary searches of the grey literature via Web of Science, SCOPUS and Zetoc will also be undertaken.

The results from the searches will be combined, and any duplicates will be removed. Search results will be uploaded to Rayyan, an open source tool designed for systematic reviews [15]. Titles and abstracts will then be independently screened by two authors (A.M. and L.M.) against the inclusion/exclusion criteria. Any disagreement will be moderated by a third author (J.P.T.), who will make a final decision on inclusion. Following title and abstract screening, articles will be retrieved, and full text screening will be undertaken by two authors (A.M. and L.M.) acting independently. Any disagreement will again be moderated by a third author (J.P.T.), with disagreements resolved through discussion. Bibliography screening of the final included studies will be undertaken to identify any studies missed by the search strategy. A list of included studies and their citations will be managed using EndNote (Clarivate Analytics, Boston, MA, USA).

Study selection

All studies comparing electrochemotherapy and radiotherapy in the treatment of primary cutaneous malignancies or cutaneous metastases from other primary solid organ malignancies will be eligible for inclusion. Criteria for study selection were defined using the Population, Intervention, Comparison, Outcome framework.

Participants

Participants will be patients diagnosed with either primary cutaneous malignancies or cutaneous metastases from other primary solid organ malignancies. There will be no restriction to inclusion based on patient demographics, clinical setting, tumour types or anatomical location of the neoplasm(s). To reduce heterogeneity, any data reported on the treatment of lymph node metastases or metastases from haematological malignancies will be excluded. If these data are inseparable from data reported on primary cutaneous malignancies or cutaneous metastases from other primary solid organ malignancies, then the study will be excluded from the review.

Intervention

All publications reporting on the use of electrochemotherapy for the treatment of primary cutaneous malignancies or cutaneous metastases from solid organ malignancies will be included. *In vitro* and animal studies will be excluded. Any studies reporting on multiple treatment modalities will only be included if data on the use of electrochemotherapy are distinguishable and additional treatment modalities are appropriately matched with the comparator group.

Comparator

The comparator for this study is radiotherapy, delivered as a monotherapy, either with palliative or curative intent.

Outcome

The primary outcome will be tumour volume response according to Response Evaluation Criteria in Solid Tumors (RECIST) [16]:

- Complete response: disappearance of tumour at 4 weeks.
- Partial response: tumour volume reduction by 30% or more at 4 weeks.
- Stable disease: neither partial response nor progressive disease criteria fulfilled.
- Progressive disease: tumour volume increase by 20% or more with no previous complete or partial

Table 1. Search strategy for MEDLINE electronic database

	Concept 1	AND	Concept 2	AND	Concept 3
MeSH term					
OR	Skin neoplasms		Electrochemotherapy		Radiotherapy
OR	Neoplasms, squamous cell		Electroporation		
OR	Neoplasms, basal cell				
OR	Carcinoma, squamous cell				
OR	Carcinoma, basal cell				
OR	Carcinoma, Merkel cell				
OR	Melanoma				
OR	Sarcoma				
OR	Sarcoma, Kaposi				
Free-text keywords					
OR	cutaneous ADJ (carcinoma* OR Neoplasm* OR malignanc* OR metastas* OR cancer*)		electrochemotherap*		radiotherap*
OR	skin ADJ (carcinoma* OR Neoplasm* OR malignanc* OR metastas* OR cancer*)		electroporat*		radiation ADJ (therap* OR treatment*)
OR	'Squamous Cell' ADJ (carcinoma* OR Neoplasm* OR malignanc* OR metastas* OR cancer*)		ECT		electron ADJ (therap* OR treatment* OR beam OR radiat*)
OR	'Basal Cell' ADJ (carcinoma* OR Neoplasm* OR malignanc* OR metastas* OR cancer*)				x?ray ADJ (therap* OR treatment* OR beam OR radiat*)
OR	'Merkel Cell' ADJ (carcinoma* OR Neoplasm* OR malignanc* OR metastas* OR cancer*)				kilovoltage ADJ (therap* OR treatment* OR beam OR radiat*)
OR	melanoma*				kv ADJ (therap* OR treatment* OR beam OR radiat*)
OR	metastas*s				
OR	sarcoma*				
OR	'Kaposi* sarcoma*'				

response or stable disease documented before increased disease.
- Objective response: complete response plus partial response.

Studies reporting tumour volume response outcome (according to the World Health Organization criteria [17]) will have results for partial response and progressive disease considered to be adequately similar to the same tumour response categories reported by those using RECIST. A complete or objective response will be recorded as a successful primary outcome.

Any secondary outcomes reported by included studies will also be examined, including, but not limited to, progression-free survival, patient-reported quality of life and amenability to future successful surgical resection. Any outcomes related to safety will also be collected, including rates of pain, side-effects and adverse events. Any unpublished data or ongoing trials be excluded, but reasonable attempts will be made to contact the study authors for usable data, if such data exist.

Study design

Randomized control trials, cohort studies, case control studies and case series will all be eligible for inclusion in the review. Case series will not be eligible for inclusion in any meta-analysis. There will be no limitations made based upon patient selection criteria or study size. Letters, opinion pieces, literature reviews and case reports will all be excluded. The reference lists of literature reviews will be hand-searched for suitable articles.

Data extraction

All data collection and analyses will be undertaken in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [13]. Two authors (A.M. and L.M.) will individually extract the data and record it in a pre-designed electronic form. The two authors will compare collected data and if a consensus cannot be reached a third author (J.P.T.) will resolve any disagreement between authors.

The following data will be collected for comparison:

1. Study characteristics, funding source, patient demographics, response evaluation time, recruitment/sampling procedures and tumour volume response evaluation method.
2. Tumour anatomy, number, size and histotype.
3. Electrochemotherapy agent, route and operating procedure technique.
4. Radiotherapy technique and characteristics.
5. Tumour volume response, which will be our primary outcome, and any secondary outcomes reported by the study such as patient reported outcome measures, pain, toxicity/adverse events and progression-free survival.

If unable to directly extract any of these data from a study, the authors of the study will be contacted by email.

If there is no response, the study will be excluded from the analysis and this outcome will be recorded on the PRISMA flowchart.

Risk of bias assessment

For each study included in the review, which incorporates randomization of participants, a risk of bias assessment will be undertaken using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [18]. For each study included in the review, which does not randomize participants, a risk of bias assessment will be undertaken using the ROBINS-I tool [19]. These tools will be used to stratify studies into those at low, moderate and high risk of bias. The quality of evidence for each study outcome will be appraised using the Grading of Recommendations, Assessment, Development and Evaluation approach [20].

Data analysis

Simple descriptive statistics will be presented for the demographics of patients included in each study. For the primary outcome, dichotomous data will be analysed as odds ratios (ORs) with a corresponding 95% confidence interval and continuous data as either mean difference or standardized mean difference. Where appropriate and feasible, we will use random effects meta-analysis to synthesize the results using an appropriate statistical software. An appropriate estimator of variance will be used based upon the number of studies identified and the sample size of each study. A Knapp-Hartung adjustment will be used to account for uncertainty in between-study heterogeneity. ORs will be presented as the meta-analysis statistic and forest plots will be used for graphical representation.

Should a formal meta-analysis not be feasible or possible due to concerns over a lack of data, or due to clinical heterogeneity of data, results will be presented in a narrative synthesis.

Assessment of heterogeneity

Statistical heterogeneity of compared studies will be calculated and presented using the I^2 statistic. Interpretation of this will be according to the following guideline [21]:

- 0–40%: heterogeneity might not be important;
- 30–60%: may represent moderate heterogeneity;
- 50–90%: may represent substantial heterogeneity and
- 75–100%: considerable heterogeneity.

If substantial heterogeneity is found, this will be reported in the final manuscript and possible reasons for this will be discussed. We will also look to explore potential sources of heterogeneity through pre-planned subgroup analyses.

Pre-planned subgroup analyses

If there are enough studies available to support valid subgroup comparisons, we will perform subgroup analyses to assess potential sources of heterogeneity. We will consider the following categories:

- Tumour histotype (e.g. cutaneous melanoma versus cutaneous SCC vs metastatic deposit of other/unknown primary).
- Treatment regime (e.g. studies following European Standard Operating Procedures on Electrochemotherapy [9] vs non-standard regime for electrochemotherapy).
- Small (defined as ≤3 cm) and large (defined as >3 cm) tumours.
- Therapy delivered with curative vs palliative intent.

Other sources of heterogeneity that become apparent during the analysis will be considered for further subgroup analysis; these will be outlined in the final manuscript as 'additional *post hoc* analyses'.

Assessment of reporting bias

A funnel plot will be used to assess the included studies for publication bias, with a corresponding formal statistical test (Egger's test) to assess for asymmetry that may indicate publication bias.

ETHICS AND DISSEMINATION

As this study will draw from the results of previous studies, in which informed consent was gained by the primary researchers, no ethical approval will be required.

The results of this study will be disseminated by publication in a mainstream PubMed indexed journal, preferably open access. The results will also be presented at any relevant national or international conference should the opportunity arise.

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CONFLICT OF INTEREST STATEMENT

None declared.

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