

REVIEW



Electrochemotherapy with intravenous bleomycin for patients with cutaneous malignancies, across tumour histology: a systematic review

Freya A. Bastrup^{a,b}, Mille Vissing^{a,b} and Julie Gehl^{a,b}

^aDepartment of Clinical Oncology and Palliative Care, Zealand University Hospital, Roskilde, Denmark; ^bDepartment of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

ABSTRACT

Background: Electrochemotherapy (ECT) is an established treatment for primary and secondary cutaneous tumours. The method combines chemotherapy with electroporation, thus increasing the cytotoxic effect of the chemotherapeutic drug. Bleomycin is the drug of choice for ECT, as it is already well established as a treatment for several cancer types and has the largest increase in efficacy after electroporation, enhancing the cytotoxic effect several hundred fold. The response rates of ECT have over the past 30 years been high and consistent. Case based reports point out that the efficacy possibly can be maintained even when the dose of bleomycin is reduced. Consequently in 2018, studies began investigating reducing the bleomycin dose.

Aim: The purpose of this review is to summarise all data published using intravenous bleomycin for cutaneous malignancies and is to our knowledge the first review to examine the use of a reduced bleomycin dose in ECT.

Methods: This study is a systematic review. Fifty-five clinical studies investigating ECT with intravenous bleomycin for patients with cutaneous malignancies were included.

Results: Studies published from 1993 to 2021 investigating the effect of ECT include 3729 patients and indicate a consistent and high response with a mean objective response rate (ORR) of 81.5%. Interestingly, studies using lower doses of bleomycin observe a similar ORR (85.5%), opening the possibility that a lower dose may not be inferior.

Conclusion: This study gives an overview of published studies on ECT with intravenous bleomycin for patients with cutaneous malignancies, including the use of a reduced bleomycin dose, as preparation for a randomised study.

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Introduction

Electrochemotherapy (ECT) is a combination of chemotherapy and reversible electroporation, where electric pulses are administered to the tumour after administration of chemotherapy, which permeabilizes cell membranes and thus increases the cytotoxic effect of the chemotherapeutic drug [1,2]. ECT has proven to be highly effective and reliable in the treatment of cutaneous malignancies and is a treatment option when standard treatment is not sufficient or applicable [3–9]. Cutaneous malignancies can be difficult to manage. These tumours can become exuding, bleeding and odorous and may have a large influence on a patient's quality of life (QOL) [10,11].

Electroporation destabilises the cell membrane and allows different hydrophilic substances to enter the cell [1], such as the cytotoxic drug bleomycin. Bleomycin is favourable for ECT compared to other anticancer drugs, in that it is already established as a treatment for cancer and has the largest increase in efficacy after electroporation, enhancing the

cytotoxic effect 300–5000 fold [1,2,12]. ECT is indicated for cutaneous malignancies of any histology, size and quantity, which either are symptomatic or which other treatment modalities have not been possible to treat [9]. Contraindications include pregnancy, allergy or hypersensitivity. ECT is applicable all over the surface of the body and shows high response rates across different tumour subtypes [13]. Often the procedure is performed with general anaesthesia, which requires hospitalisation [9].

Since the first clinical study in 1993, ECT has been reported with a consistently high response rate [3,13,14]. The standard operating procedures (SOP) published in 2006 [4] and updated in 2018 [9] have been helpful in harmonising use of the procedure. The SOP recommends a standard bleomycin dose of 15,000 IU/m² when administered intravenously, originally based on the treatment for testicular cancer [15].

A study investigating bleomycin pharmacokinetics, suggest that age matters possibly explained by decreases in

CONTACT Julie Gehl  kgehl@regionsjaelland.dk  Department of Clinical Oncology and Palliative Care, Zealand University Hospital, Sygehusvej 10, Roskilde 4000, Denmark

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kidney function and different body compositions regarding water/fat ratio [16]. In 2018 and 2021, two studies therefore attempted to reduce the dose of bleomycin (10.000 IU/m²) when performing ECT in patients older than 65 years old [17–19]. Both studies conclude that ECT with a reduced dose of bleomycin is a feasible treatment option for older patients, with similar efficacy to standard dose treatment (Objective response rate (ORR) from 87 to 100%) and should be considered as a treatment in aged patients with comorbidities [17,18].

The purpose of this review is to provide a systematic overview of published data on ECT using intravenous bleomycin for cutaneous malignancies, as well as examine the possibilities and indications of reducing the bleomycin dose in ECT.

Electrochemotherapy from 1993 to 2021

Standard treatments of cutaneous malignancies include surgery, radiotherapy and chemotherapy [20]. Other treatments include isolated limb perfusion [21], oncolytic viruses (TVEC) [22] and for some diagnoses systemic therapy e.g., with BRAF/MEK [23] inhibitors, hedgehog inhibitors [24] or immune checkpoint inhibitors such as anti-CTLA-4 and anti-PD-1 [25]. Over the previous 30 years, ECT has been implemented for treatment in cases where the standard treatments are not sufficient [4,9,13,14,26,27]. ECT is performed by either intravenous or intratumoural injection of bleomycin, followed by the insertion of an electrode. Different electrodes may be applied depending on tumour localisation and size [9]. This review has limited the scope and does not focus on the electric field or electrode types.

Bleomycin was introduced in the pivotal study by Einhorn in 1977 for the treatment of testicular cancer using combination chemotherapy [15]. Different doses were applied in the first use of ECT [14,26,28] and the standard dose used today was recommended and implemented in the first standard operating procedure (SOP) in 2006 [4]. Since the first SOP was published, several centres have been using this treatment for patients with cutaneous malignancies. Due to the expanded experience within the area, an updated SOP was developed in order to integrate the knowledge obtained from the different centres, recommending the same standard dose of bleomycin [9]. As a result of the consistently high response rates, studies have in 2018 reported the possibility of lowering the dose of bleomycin in ECT [19,29] and suggested that this could be as effective as the standard treatment, especially in patients that have impaired lung or renal function or patients who are candidates for multiple ECT-cycles [29].

The results raised important questions as to what is the optimal drug concentration needed for favourable antitumour effectiveness of ECT and if it is possible to safely decrease the intravenously administered dose of bleomycin without loss of efficacy [19].

Aim of review

We performed a systematic review in order to evaluate the potential role and possibilities of reducing the bleomycin dose in ECT for cutaneous malignancies. Additionally, our aim was to evaluate the ORR found in studies using a standard bleomycin dose compared with studies using a reduced bleomycin dose, in order to investigate if the effect could be similar.

Methods

This review was constructed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [30]. There was no available protocol for this review. An institutional or ethical board approval was not necessary, as all data were retrieved from previously published data. The endpoint of the analysis was overall tumour response after ECT.

A systematic literature search was conducted on the 17 November 2021 from PubMed, Scopus and Cochrane libraries. The following search terms were used: 'electrochemotherapy' AND 'bleomycin'.

Two authors independently performed the process of screening abstracts and full text assessment.

Inclusion criteria

Eligible studies had to be full text in English and describe the use of ECT with intravenous bleomycin in patients with cutaneous malignancies, including more than four patients. Clinical trials and original studies were included.

Exclusion criteria

Papers concerning ECT with intratumoural chemotherapy and treatment of other cancers than cutaneous malignancies or ECT in combination with immunotherapy were not included. *In vitro* treatments, veterinary studies, general reviews, editorials and letters to the editor were not included.

Data extraction

Full text assessment retrieved the following data: study design, patient number, tumour localisation, tumour size, histology, type of anaesthesia, route of bleomycin administration, choice of electrodes, side effects, length of follow-up and ORR.

Response rate evaluation

The studies included in Table 1 and 2, evaluate the response to treatment according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria [75].

Table 1. Studies performing ECT with standard dose of intravenous bleomycin performed from 1993 to 2021 for treatment of cutaneous malignancies. Studies written in *italics* are from the InspECT network.

	Study	Patients/nodes	Tumour histology	Bleomycin administration (1000 IU = 0.66mg)	Electrodes	Size mm (median)	Response rates (%)	Objective response rate (%)
1	Behrdradek 1993 [14]	8/40	HNSCC	IV 10mg/m ² (~15,000IU/m ²) 15 mg/m ² (1 pt) (~22,700IU/m ²) IV 10mg/m ² (~15,000IU/m ²) 15 mg/m ² (~22,700IU/m ²) Patients received in some cases additional bleomycin.	Hex	16–17	CR 57 PR 15 NC 7.5	72
2	Domenge 1996 [28]	7/53	HNSCC, BC	IV 10mg/m ² (~15,000IU/m ²) 15 mg/m ² (~22,700IU/m ²) Patients received in some cases additional bleomycin.	Hex	10–200	CR 11 PR 11 NC 56 PD 22	22
3	Mir 1998 [26]	50 (15 incl in previous)/291	BCC, MM, BC, HNSCC	IT or IV 10mg/m ² (~15,000IU/m ²), 15 mg/m ² (~22,700IU/m ²), 10,000 IU/m ² (6 pt's)	Plate, needle	2–125 (11)	CR 56.4 PR 28.9	85.3
4	Rols 2000 [31]	4/55	MM	IV 10mg/m ² (~15,000IU/m ²)	Plate	2–35	CR 9 PR 84 NC 7	93
5	Marty 2006 [5]	62/290	MM, carcinom, sarcoma	IT or IV 15,000 IU/m ²	Hex, lin or plate	Not described	CR 73.7 PR 11.1	84.8
6	Larkin 2007 [32]	30/111	SCC, BC	IT or IV 15,000 IU/m ²	Plate, lin	90/111 < 3 cm	CR 60 PR 22 NC 18	82
7	Quaglino 2008 [33]	14/233	MM	IV 15mg/m ² (~22,700IU/m ²)	Not described	Not described	CR 58 PR 34 NC 8	92
8	Campana 2009 [34]	52/608	MM, BC, SCC, HNC	IT or IV 15,000 IU/m ²	Plate/ hex	1–30	CR 58 PR 34 NC 7	93
9	Kis 2011 [35]	9/158	MM	15 mg/m ² (~22,700IU/m ²)	Lin, hex	5–56 (14.7)	CR 23 PR 39 NC 30 PD 8	62
10	Matthiessen 2011 [36]	52/196	MM, BC	IT or IV 15,000 IU/m ²	Plate/ hex	1–200 (10)	CR 60 PR 19 SD 11 PD 7	58.5 <3 cm: 86 >3 cm: 31
11	Skarlatos 2011 [37]	51/52	MM, KS, HNC + solid	IT or IV 15,000 IU/m ²	Lin, hex or plate	Not described	CR 63.8 PR 31.9	95.7
12	Matthiessen 2012 [38]	17/25	BC	IT or IV 15,000 IU/m ²	Plate, hex	32–250 (65)	CR 83 PR 8.3	23.6
13	Curatolo 2012 [39]	23/25	KS	IV 15mg/m ² (~22,700IU/m ²)	Plate, hex	Not described	CR 60.9 PR 39.1 SD 75	100
14	Latini 2012 [40]	18/29	KS	IV 15,000 IU/m ²			CR 86 PR 14	100
15	Campana 2012 [41]	85/894	MM	IT or IV 15,000 IU/m ² or in combination	Needle	3–73 (24)	CR 48 PR 46 NC 4 PD 2	94
16	Campana 2012 [42]	35/516	BC	IV 15,000 IU/m ²	Hex	10–220 (20)	CR 54.3 PR 37.1 SD 8.6	92.3
17	Benevento 2012 [43]	12/142	BC	IV 15,000 IU/m ²	Hex	5–30	CR 75.3 PR 17 NC 7.7	91.4

(continued)

Table 1. Continued.

	Study	Patients/nodules	Tumour histology	Bleomycin administration (1000 IU = 0.66mg)	Electrodes	Size mm (median)	Response rates (%)	Objective response rate (%)
18	Gargiulo 2012 [44]	25/25	SCC, BCC, adenocarcinoma	IV 15,000 IU/m ²	Hex, finger	Not described	CR 72 PR 28	100
19	Caraco 2013 [45]	60	MM	IV 15,000 IU/m ² 10% received reduced dose	Lin, hex	0.8–20 (5)	CR 48.4 PR 38.3 PD 13.3	86.7
20	Di Monta 2014 [46]	19	KS	IV 15,000 IU/m ²	Plate, lin	Not described	CR 73.6	100
21	Campana 2014 [47]	34/210	soft tissue sarcoma	IV 15,000 IU/m ²	Hex	20–120 (40)	CR 32.3 PR 52.9 SD 14.7	85.2
22	Campana 2014 [48]	55	Metastatic BC	IT or IV 15,000 IU/m ²	Needle	10–320 (20)	CR 40 PR 47.3 SD 12.7	87.3
23	Campana 2014 [49]	42/81	SCC, BCC, adenocarcinoma	IT or IV 15,000 IU/m ²	Plate, lin, hex, finger	10–100 (35)	CR 41 PR 18	59
24	Solari 2014 [50]	39	MM, BC, KS, BCC, SCC	IV 15,000 IU/m ²	Hex	Not described	For MM: CR 10 PR 45 For others: CR 36.8 PR 42.1 CR 20 PR 80	67 For MM: 55 For others: 78.9 100
25	Ricotti 2014 [51]	30/654	MM	IV 15,000 IU/m ²		0.2–10cm ²	CR 68.5 PR 23.5 SD 6.6	92
26	Cabula 2015 [52]	125/239	BC	IT or IV 15,000 IU/m ²	Plate, lin or hex	15–45 (21)	PD 0.9 CR 10.7 PR 33.9 SD 12.5 PD 42.9	44.6
27	Kreuter 2015 [53]	56	MM, BC, SCC + others	IV 15mg/m ² (~22,700IU/m ²)	Plate, lin of hex	Not described	CR 23 PR 49 PD 28 CR 34 PR 32 CR 48 PR 26 SD 19 PD 6	72
28	Mir-Bonafe 2015 [54]	31	MM	IV 15,000 IU/m ²	Hex	0.8–15 (4.4)	CR 23 PR 49 PD 28 CR 34 PR 32 CR 48 PR 26 SD 19 PD 6	72
29	Quaglino 2015 [55]	121	MM, SCC, BC, BCC	IT or IV 15,000 IU/m ²	Plate, lin, hex	3–400 (23)	CR 30.1 PR 45.5 SD 21 CR 66.7 PR 18.5 SD 9.3 PD 5.6	66
30	Bertino 2016 [8]	105/105	SCC, BCC, MM and others.	IT or IV 15,000 IU/m ²	Plate, hex or finger	2–145 (20)	CR 30.1 PR 45.5 SD 21 CR 66.7 PR 18.5 SD 9.3 PD 5.6	74
31	Campana 2016 [56]	376/1304	MM, SCC, KS, BC, BCC and others	IT or IV 15,000 IU/m ² – (251 pt)	Hex, lin, plate, multiple	6–20 (10)	CR 30.1 PR 45.5 SD 21 CR 66.7 PR 18.5 SD 9.3 PD 5.6	82.7
32	Guida 2016 [57]	19	AS	IV 15,000 IU/m ²	Lin	15–35 (20)	CR 66.7 PR 18.5 SD 9.3 PD 5.6	85.5
33	Groselj 2016 [58]	24/47	BCC, SCC, BC	IV 15,000 IU/m ²	Plate, hex	<50	CR 82.6 PR 15.2 SD 2.2	97.8
34	Bourke 2017 [59]	24/161	BC	IT or IV 15,000 IU/m ²	Plate, lin or hex	Not described	CR 64.4 PR 15.3 NC 19.3	79.7

(continued)

Table 1. Continued.

	Study	Patients/nodules	Tumour histology	Bleomycin administration (1000 IU = 0.66mg)	Electrodes	Size mm (median)	Response rates (%)	Objective response rate (%)
35	Di Monta 2017 [60]	22/22	SCC	IV 15,000 IU/m ²	Lin, hex	Not described	CR 22.7 PR 59 SD 13.6 PD 4.5	81.7
36	Campana 2017 [61]	84/185	BCC	IT or IV 15,000 IU/m ²	Lin, hex	5–267 (20)	CR 50 PR 35.7 CR 58 PR 20 SD 20	85.7
37	Kunte 2017 [62]	151/394	MM	IT or IV 15,000 IU/m ²	Plate, lin, hex	5–20 (9)	PD 2 CR 50 PR 21 SD 18 PD 8	78
38	Matthiessen 2018 [63]	90/207	BC	IT or IV 15,000 IU/m ²	Plate, hex	1–550 (25)	CR 71.4 PR 28.6 CR 74 PR 14 NR 8.5 CR 42 PR 29 NR 11 PD 18 CR 82 PR 18 CR 58.3 (100 after several treatments) CR 5 PR 40 PD 20 SD 34 CR 61 PR 22 SD 18 PD 2	71
39	Gargiulo 2018 [64]	21/21	Lower lip SCC	IV 15,000 IU/m ²	Lin	Not described	CR 71.4 PR 28.6 CR 74 PR 14 NR 8.5 CR 42 PR 29 NR 11 PD 18 CR 82 PR 18 CR 58.3 (100 after several treatments) CR 5 PR 40 PD 20 SD 34 CR 61 PR 22 SD 18 PD 2	100
40	Al-Hadithy 2018 [65]	48	MM, BC, AS, SCC	IV 15,000 IU/m ²	Lin, hex or finger	1.33–2.1 m ²	CR 71.4 PR 28.6 CR 74 PR 14 NR 8.5 CR 42 PR 29 NR 11 PD 18 CR 82 PR 18 CR 58.3 (100 after several treatments) CR 5 PR 40 PD 20 SD 34 CR 61 PR 22 SD 18 PD 2	88
41	Wichtowski 2019 [66]	38	BC	IV 15,000 IU/m ²	Hex	Not described	CR 71.4 PR 28.6 CR 74 PR 14 NR 8.5 CR 42 PR 29 NR 11 PD 18 CR 82 PR 18 CR 58.3 (100 after several treatments) CR 5 PR 40 PD 20 SD 34 CR 61 PR 22 SD 18 PD 2	71
42	Bonadies 2019 [67]	33	HNSC	IV 15,000 IU/m ²	Plate, lin, hex, finger	Not described	CR 71.4 PR 28.6 CR 74 PR 14 NR 8.5 CR 42 PR 29 NR 11 PD 18 CR 82 PR 18 CR 58.3 (100 after several treatments) CR 5 PR 40 PD 20 SD 34 CR 61 PR 22 SD 18 PD 2	100
43	Kis 2019 [68]	12/12	Eyelid-periocular BCC	IT or IV 15,000 IU/m ² (9 pts)	Lin, hex	1–108	CR 71.4 PR 28.6 CR 74 PR 14 NR 8.5 CR 42 PR 29 NR 11 PD 18 CR 82 PR 18 CR 58.3 (100 after several treatments) CR 5 PR 40 PD 20 SD 34 CR 61 PR 22 SD 18 PD 2	58.3
44	Longo 2019 [69]	93	HNSC	IV 15,000 IU/m ²	Lin, hex, finger	>30 or <30	CR 71.4 PR 28.6 CR 74 PR 14 NR 8.5 CR 42 PR 29 NR 11 PD 18 CR 82 PR 18 CR 58.3 (100 after several treatments) CR 5 PR 40 PD 20 SD 34 CR 61 PR 22 SD 18 PD 2	45
45	Campana 2019 [70]	20/20	cAS	IT or IV 15,000 IU/m ²	Lin, hex	10–200 (23)	CR 71.4 PR 28.6 CR 74 PR 14 NR 8.5 CR 42 PR 29 NR 11 PD 18 CR 82 PR 18 CR 58.3 (100 after several treatments) CR 5 PR 40 PD 20 SD 34 CR 61 PR 22 SD 18 PD 2	83
46	Pirc 2020 [71]	23	MM	IT or IV 15,000 IU/m ²	Hex, plate, lin	Not described	CR 71.4 PR 28.6 CR 74 PR 14 NR 8.5 CR 42 PR 29 NR 11 PD 18 CR 82 PR 18 CR 58.3 (100 after several treatments) CR 5 PR 40 PD 20 SD 34 CR 61 PR 22 SD 18 PD 2	100
47	Fabrizio 2020 [72]	41	SCC, KS, BCC, MM, BC	IT or IV 15,000 IU/m ²	Lin, hex	17–350 (60)	CR 71.4 PR 28.6 CR 74 PR 14 NR 8.5 CR 42 PR 29 NR 11 PD 18 CR 82 PR 18 CR 58.3 (100 after several treatments) CR 5 PR 40 PD 20 SD 34 CR 61 PR 22 SD 18 PD 2	83
48	Clover 2020 [13]	987/2482	MM, BC, SCC, BCC and KS	IT or IV 15,000 IU/m ²	Lin, hex	5–500 (23)	CR 71.4 PR 28.6 CR 74 PR 14 NR 8.5 CR 42 PR 29 NR 11 PD 18 CR 82 PR 18 CR 58.3 (100 after several treatments) CR 5 PR 40 PD 20 SD 34 CR 61 PR 22 SD 18 PD 2	83
49	Borgognoni 2020 [73]	68/699	MM, NMSC	IT or IV 15,000 IU/m ²	Plate, lin or hex	Not described	CR 71.4 PR 28.6 CR 74 PR 14 NR 8.5 CR 42 PR 29 NR 11 PD 18 CR 82 PR 18 CR 58.3 (100 after several treatments) CR 5 PR 40 PD 20 SD 34 CR 61 PR 22 SD 18 PD 2	89.7
50	Groselj 2021 [16]	25	BCC, SCC, MM and others	IV 15,000 IU/m ²	Lin	Not described	CR 71.4 PR 28.6 CR 74 PR 14 NR 8.5 CR 42 PR 29 NR 11 PD 18 CR 82 PR 18 CR 58.3 (100 after several treatments) CR 5 PR 40 PD 20 SD 34 CR 61 PR 22 SD 18 PD 2	96.5

Tumour histology: BCC: Basal cell carcinoma; SCC: Squamous cell carcinoma; MM: Malignant melanoma; BC: Breast cancer; HNSC: Head and neck SCC; KS: Kaposi's sarcoma; AS: Angiosarcoma; NMSC: Non-melanoma skin cancer.

Drug administration: IV: Intravenous; IT: Intratumoural.

Response: ORR: Objective response rate, CR: Complete response, SD: Stable disease, PD: Progressive disease, NC: No change, ND: Not determined.

Electrodes: Hex: Hexagonal needle electrodes; Lin: Linear needle electrodes; Needle: Other types of needle electrodes; Plate: Surface electrode with opposing plates [9].

Table 2. Studies performing ECT with a reduced dose of intravenous bleomycin for treatment of cutaneous malignancies.

Study	Patients/nodes	Tumour histology	Bleomycin administration	Electrodes	Size mm (median)	Response rates (%)	Objective response rate (%)
51 Heller 1996 [74]	6/18	MM, BCC, BC	IV 10 IU/m ² (~10,000 IU/m ²)	Plate	4–16	CR 33 PR 39	72
52 Rotunno 2018 [29]	57/147	MM, SCC, BCC, BC, KS and others	Three groups: 50% reduction – 7,500 IU/m ² 33% reduction – 10,000 IU/m ² 10% reduction – 13,500 IU/m ²	Plate, lin, hex	5–190 (10)	CR 82 PR 9 CR 64 PR 20 CR 74 PR 15	90 84 89
53 + 54 Groselj 2018; Jamsek 2020 [17,19]	28 (>65yo)	NMSC	IV two groups: 10,000 IU/m ² (12 pt's) 15,000 IU/m ² (16 pt's) IT or IV	Hex, lin, plate	6–80 (21)	CR 96–100	100
55 Sersa 2021 [18]	61 (>90yo)	SCC, BCC, MM, BC + others	2 × 10,000 IU/m ² 15,000 IU/m ²	Hex, lin, plate	4–50 (17) 5–450 (15)	CR 64.7 PR 23	96 87.7
	122 (<90yo)					CR 57.4 PR 30	87.4

Tumour histology: BCC: Basal cell carcinoma; SCC: Squamous cell carcinoma; MM: Malignant melanoma; BC: Breast cancer; KS: Kaposi's sarcoma; NMSC: Non-melanoma skin cancer.
 Drug administration: IV: Intravenous; IT: Intratumoural.
 Response: ORR: Objective response rate; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; NC: No change; ND: Not determined.
 Electrodes: Hex: Hexagonal needle electrodes; Lin: Linear needle electrodes; Plate: Surface electrode with opposing plates [9].

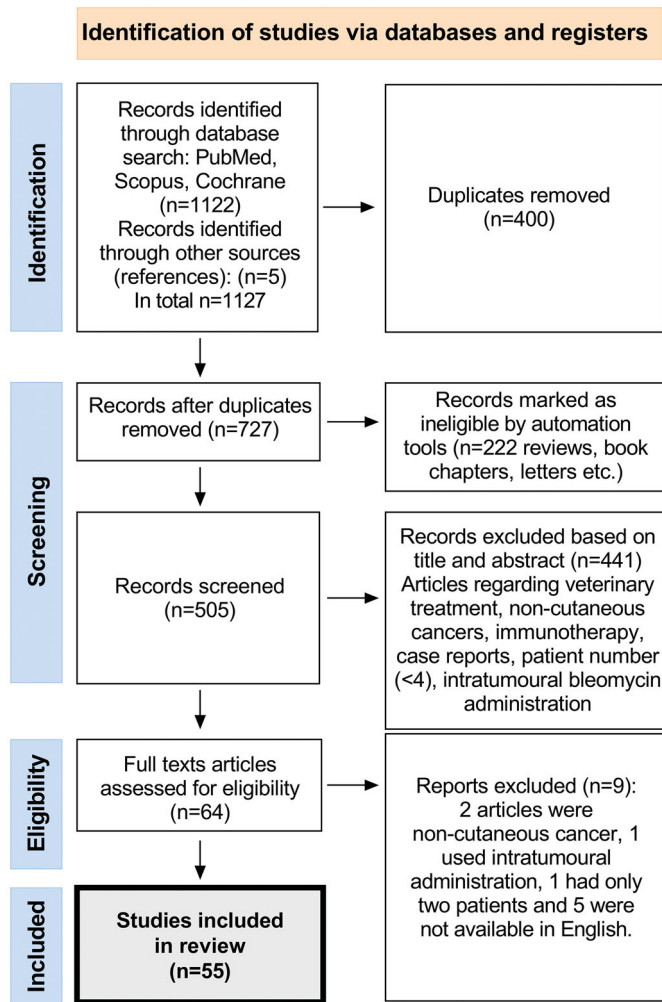


Figure 1. PRISMA flowchart depicting the search and screening process.

Results

Figure 1 shows the PRISMA flowchart of the study selection. In the initial search, 1127 articles were found. All duplicates were removed ($n=400$) and all reviews, books, letters etc. ($n=222$) were excluded through automation tools. All abstracts were examined and screened, excluding 441 studies with veterinary treatments, studies treating non-cutaneous tumours, studies solely using intratumoural bleomycin administration, case reports, immunotherapy and studies with a patient number below four. Full text assessments of the remaining 64 articles, resulted in 55 eligible articles published from 1993 to 2021.

The included studies and their characteristics are detailed in Tables 1 and 2. These studies collectively report 3729 patients in total, who received ECT for cutaneous malignancies. To the best of our ability, studies written by the same author have been thoroughly reviewed in order to note patients presented multiple times. One study mentions that 15 patients were included in preliminary reports, which have already been published [26]. Studies that are listed under the InspECT network are listed in *italics*. Among these, there can be overlaps between e.g., studies on special cancers and global evaluations.

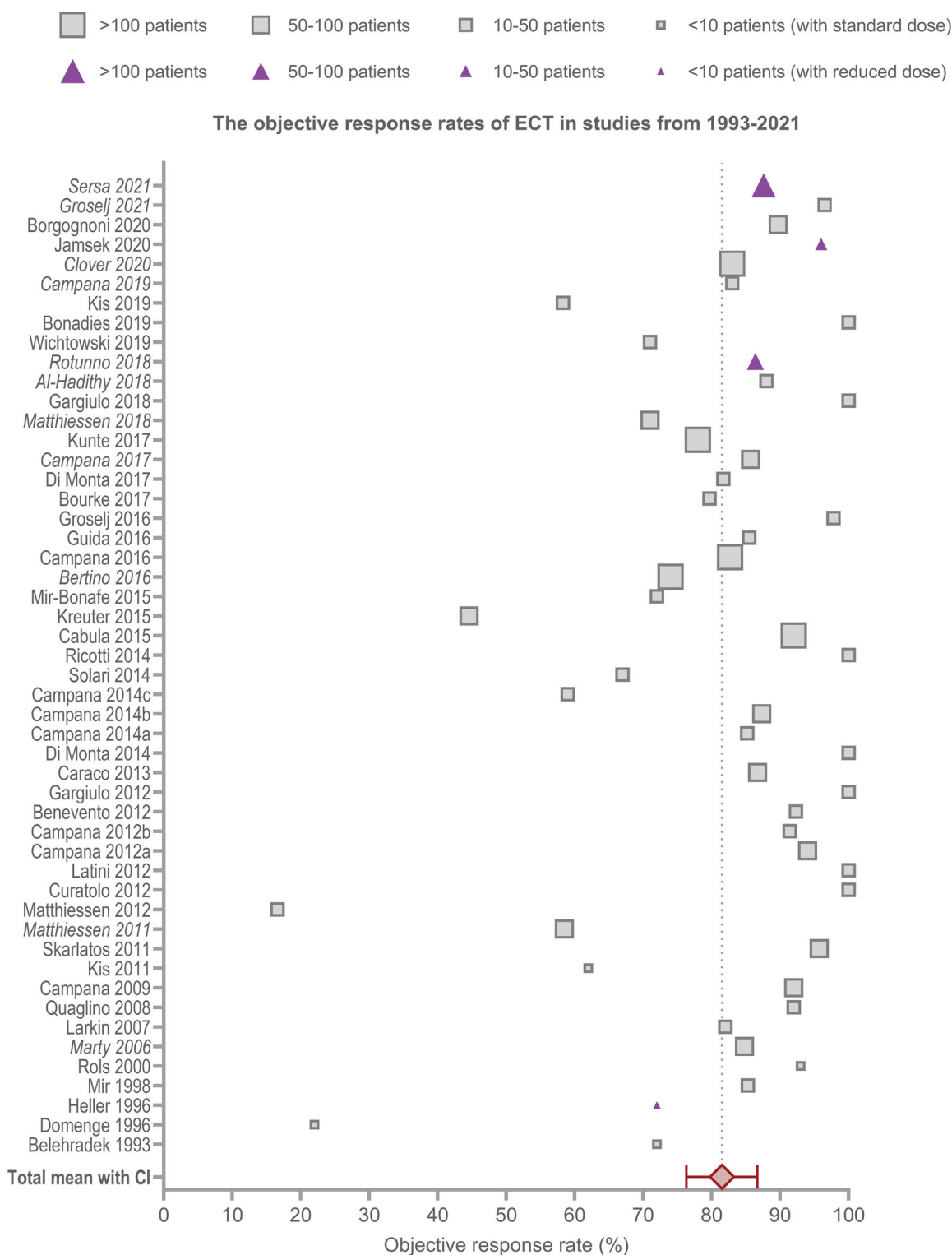


Figure 2. Forest plot of the objective response rates reported in the 55 studies mentioned in Tables 1 and 2, including the pooled mean with confidence intervals (CI). Squares indicate studies with standard dose of bleomycin and triangles indicate studies with reduced dose of bleomycin. The size of square/triangle is dependent on study size. Studies written in *italics* are from the InspECT network.

All studies administer bleomycin intravenously, 25 of these utilise either intravenous or intratumoural administration. All studies provided information regarding choice of electrode and 51 describe response to treatment. The four studies that do not aim to evaluate tumour response are included in the Table 1 but are excluded from the

forest plot in Figure 2 [55,69,71,72]. One of these studies focuses on pain associated to ECT [55], one on mucosal tumours compared to cutaneous tumours [69], one describes the cost-effectiveness of ECT [71] and the last one describes the possibilities of ECT as a neoadjuvant treatment [72].

Tumour response

Figure 2 depicts all studies included in this review. These data suggest that despite the many parameters investigated in the studies, the ORR remains high, with a mean of 81.5% [CI 76.3; 87.5] and a standard deviation (SD) of 18.76. Three studies stand out, with an ORR under 55% [28,38,53], without these studies the SD is 11.99. One of these studies is Domenge's study from 1996, which was one of the first studies conducted and included only seven patients and used electrodes not commercially produced [28]. The other two studies, Matthiessen and Kreuter, include only larger tumours and heavily pre-treated patients, which are well-known parameters that can affect the response [38,53]. Matthiessen and colleagues conclude that evaluation only by clinical examination may lead to an underestimation of the treatment effect in larger tumours. Also, the healing time may be longer in larger tumours and therefore a longer follow-up period would have been beneficial and perhaps lead to better results [38]. Kreuter and colleagues suggest that their study includes patients with markedly advanced disease and larger tumour nodules, which is why they observe a lower ORR [53]. Another five studies stand out with an ORR below 70% [35,36,49,50,68], excluding these studies the SD is 9.03. Three of these studies suggest tumour size causing the more modest response [35,36,49]. One observes an ORR of 86% in tumours <3cm, however when including tumours >3cm the ORR is reduced to 58% [36]. Clover and colleagues also observe highest response rates in smaller tumours (up to 3 cm), but very large tumours (up to 50cm) still exhibit response at lower levels [13].

Kis et al. observes a CR of 58.3% after one treatment with ECT and 83.3% after two treatments [68], thus indicating the need for multiple treatments in some cases. One study observes an ORR of 67% when including melanoma (MM) and when excluding MM, the ORR increases to 79% [50]. This is however not consistent with studies investigating solely MM, which observe an ORR of 72–100% [31,33,41,45,51,54,76].

Clover and colleagues published the largest study in 2020 involving 987 patients and 2483 tumours [13]. They conclude a slight difference of ORR in tumours with different histology. Basal cell carcinoma (BCC) and Kaposi's sarcoma (KS) show the highest ORR of 96% and 98% respectively. KS has a high vascularity, which is one of the explanations for the high ORR, due to ECT's anti-vascular effect. Breast cancer metastases, MM and squamous cell carcinoma (SCC) have similar objective responses of 77%, 82% and 80%, thus concluding a small though significant difference in tumour histology ($p < 0.0001$). In general non-melanoma tumours show a higher ORR than MM [5,13,77]. Clover and colleagues also observe no significant difference between intravenous administrations and intratumoural injections when treating smaller lesions (<2cm), however when treating larger lesions (>2cm) the complete response rate goes from 48% to 57% using intratumoural and intravenous administration, respectively ($p < 0.05$) [13]. These data suggest that despite the significant difference between the many parameters

investigated in the study, the mean ORR in ECT only differs from 61% to 98% [13].

In summary, most studies observe an ORR between 70 and 100%, indicating a consistent and high response rate of ECT.

Reduced bleomycin dose

This review includes four studies investigating the use of a lower bleomycin dose [17–19,29,74]. These show an ORR of 85.5%, which is similar to the studies using the standard dose of bleomycin. An overview of these studies can be found in Table 2, with a total of 77 patients receiving a bleomycin dose below the standard dose.

Side effects

All studies, except seven, describe observed side effects. In general, there are limited side effects and ECT is well tolerated. A common side effect is post-ECT pain. This was mentioned in 31 studies, with a frequency between 5 and 100% in various grades of severity. However, most studies describe the pain being manageable with simple analgesia [34,40,64]. This has also been described in Quaglino's study from 2015, reporting that 74% of the patients presented with low pain scores, 13% with moderate and 13% with severe pain after treatment [55]. This pain was significantly associated with pain before treatment ($p < 0.0001$), enabling the possibility for making a pain management strategy before ECT. Hyperpigmentation of the skin is mentioned in 13 out of the 55 studies, with a frequency between 5 and 44% [8,18,29,34,38,42,47,52,53,62,66,67,72]. Only three studies observe serious adverse events (SAEs) [5,8,65] and only one case (sepsis-related death post-treatment) out of the 3729 patients included, was thought related to ECT [8]. No studies reported lung fibrosis, which is a known dose-dependent side effect of bleomycin [78,79]. This can be explained by the low cumulative dose used for ECT, compared with the use of bleomycin for other treatments e.g., testicular cancer [15] and the screening of patients for eligibility with exclusion of patients with lung disease. The same analysis of side effects was observed in the review from Petrelli and colleagues in 2021, which concludes no significant concerns regarding systemic toxicity [80]. Only one study mentions side effects dependent on bleomycin dose and concludes that less side effects are observed when using a reduced bleomycin dose compared to the standard dose [18].

Quality of life

Thirty-six out of the 55 studies mention a reduced QOL being an issue in patients with cutaneous malignancies. In the ESOPE from 2006, QOL is mentioned in their patient monitoring and included in the case report forms [5], however only eight studies have since performed an assessment of QOL using either EORTC, EQ-5D, PGA or SQOLIT questionnaires [8,34,39,47,56,65,69,71]. ECT is often performed as a

palliative treatment and it is therefore important to evaluate if the treatment leads to an improvement or deterioration of QOL. Thus, future studies should include this important element.

Discussion

When comparing the 55 studies published from 1993 to 2021 (Table 1 and 2), we get an overview of the development in ECT over the past 30 years. The ORR has remained high and consistent, which indicates that ECT is a reliable treatment option for patients with cutaneous malignancies. The SOP published in 2006 and updated in 2018 [9] has been helpful in harmonising use of the procedure, according to drug administration, administration time and use of electric pulses. In this review, we have limited the scope to focus solely on drug administration.

It should be noted that 15 studies have evaluated response according to WHO criteria and the remaining studies evaluate according to RECIST criteria. We assume however, that this has a minimal effect on the comparison of tumour response in the studies. Additionally, the time of evaluation differs from four weeks to three months. This can affect the response rates, in that an evaluation after four weeks may not provide the most accurate result. In general however, we can see in Table 1 and 2 that the response rate does not differ much. This was already reflected in the ESOPE from 2006, which found no difference in success rate among the four different oncological centres using different protocols with a lack of homogeneity [5]. This was also observed in a review from 2018 [81] and in Clover's study published in 2020 investigating differences in histology and drug administration [13]. These data suggest that despite the many parameters that can influence the response, the differences in ORR are relatively small [13].

In general, studies see a higher response in smaller tumours (<3cm), independent of diagnosis. This can be explained by the insufficient coverage of the electric fields in larger tumours and the reach of applied electrodes, as well as differences in drug distribution within the tumour [47]. Size of tumours may also be indicative of tumour aggressiveness. Additionally, it is thought that previous treatment (such as radiotherapy) can disrupt the vasculature and the tissue can therefore have an impaired blood supply reducing the drug delivery to the tumour [49,82]. Studies mention that irradiated skin can appear hard and fibrotic, making it difficult to insert electrode needles and to reach a deep margin. The measured delivered current is thus seen lower in irradiated tumours compared to non-irradiated, possibly because of difficulties with needle insertion, resulting in a lower response [82].

Compared to other local treatments ECT is a relatively simple procedure that can be performed on any part of the body. ECT is particularly beneficial in cases, where standard treatments are not possible. For example in previously irradiated patients or patients with low performance status and comorbidities. This indicates that patients with SCC or BCC are especially suitable for ECT, since this group includes

patients that are immunosuppressed and are therefore not suitable for other treatments e.g., immune checkpoint inhibitors.

Over the past ten years there have been great advances in oncologic treatment with e.g., immune checkpoint inhibitors [25], BRAF/MEK inhibitors [23] and hedgehog inhibitors [24]. These treatments can in combination with ECT give a synergistic response [83]. Hedgehog pathway inhibitors are especially useful for treating BCC, whereas immune checkpoint inhibitors are indicated for treating SCC and MM [84]. Studies have investigated ECT in combination with immune checkpoint inhibitors (e.g., PD-1 inhibitors) or BRAF/MEK inhibitors for patients with MM [83,85,86]. As mentioned in our editorial the use of ECT for limiting surgical resections that require amputation may allow limb-sparing surgery for MM patients and new opportunities for disease management in complex patients [87]. ECT has thus potential both as treatment alone and in combination with other treatments.

ECT is mostly used as a palliative treatment and careful evaluation of patients' symptoms, patients' priorities as well as life expectancy must be balanced. Altogether, ECT is a simple procedure, which is reliable and quick to perform. The possibilities of using ECT in other settings are therefore being investigated, e.g., for calcium electroporation [88], endoscopic ECT [89] and as neoadjuvant treatment before conventional treatment [72]. These treatments could expand the therapeutic indications of ECT and possibly increase the overall survival. A study from 2008 published a cost-effective analysis of ECT, confirming a favourable cost-effectiveness ratio, compared to radiotherapy among others [90]. A study published later, suggests however that the electrode price should be reduced for successful implementation of ECT into clinical practice and in order for the treatment to be cost-effective [71].

Since 1993 most studies have used the standard bleomycin dose of 15.000 IU/m² (see Table 1), with a few exceptions. The first four studies used bleomycin doses of 10 mg/m² and 15 mg/m² (corresponding to approximately 15.000 IU/m² and 22.700 IU/m²) [14,26,28,31]. One of these is Domenge and colleagues from 1996, who conclude that decreasing the dose of bleomycin seems possible, but requires further studies [28]. The standard dose of 15.000 IU/m² used today, was introduced in the ESOPE study in 2006 [5] and published in the SOP in 2006 [4]. This dose has been used since.

In 2016, Groselj and colleagues investigated the pharmacokinetics of bleomycin in older patients and found a longer therapeutic window for bleomycin injection given in ECT. Based on the pharmacological parameters, they suggest that reducing the dose of bleomycin to 10.000 IU/m² would give an equally good anti-tumour effect in these patients [58]. Jamsek and colleagues state that the use of standard bleomycin dose in older patients, may lead to prolonged healing time and a more prominent inflammatory response, as a result of exceeded optimal bleomycin concentrations [17]. This study also concludes that a long-term tumour control could be achieved with a lower dose of bleomycin. A single study including six patients receiving a bleomycin dose of

10.000 IU/m², also concludes that this is an effective treatment [74]. In 2018, Rotunno and colleagues retrieved and analysed data from the InspECT database, examining ECT with reduced bleomycin from 2013 to 2016. The study states that some ECT centres already have adopted the use of a reduced bleomycin dose in patients with impaired renal function or when patients are scheduled for multiple ECT cycles, with the aim to reduce the cumulative dose of bleomycin and associated side effects [29]. The lifetime dose of bleomycin should not exceed 400.000 IU [9], so reducing the dose opens the possibility of giving multiple treatments if necessary. Some clinicians have gone as far as to reduce the dose with 50%. When analysing the different doses of 7.500 IU/m², 10.000 IU/m² or 13.500 IU/m², corresponding to a reduction of 50%, 30% and 10% respectively, a similar ORR is observed (91, 84 and 89%) compared to studies using the standard dose. It is however important to note, that this study only includes 57 patients [29]. It should also be noted that this review includes a total of four studies using a reduced dose of bleomycin. Compared to 50 studies using the standard dose, this results in a much lower power.

Groselj and colleagues suggest that lowering the dose might not be recommended, based on their studies in 2018 and 2021 [16,19]. This is due to differences in plasma concentration and the elimination rate of bleomycin, which are both important parameters. The results indicate that the physiological parameters related to patient age, need to be considered to ensure safe and effective treatment of ECT using intravenous bleomycin [16]. However, it is not possible to give a definite conclusion, since a correlation between the plasma bleomycin and pharmacokinetics of bleomycin in different age groups is needed to confirm this.

In summary, a reduction of the bleomycin dose may benefit the patient by causing fewer side effects and perhaps opening the possibility of treating more patient groups, e.g., patients with comorbidities. Randomised studies with a larger cohort of patients, treated with a reduced dose of bleomycin, have not yet been utilised and are required to evaluate the appropriate indications and clinical significance of reduced bleomycin doses in the use of ECT.

Conclusion

ECT is well established as a treatment for primary and secondary cutaneous malignancies and has been used for the past 30 years. It is a safe and simple palliative procedure with a satisfying response, which is essential for cutaneous malignancies that can be difficult to manage and affect patients QOL. Studies published from 1993 to 2021 investigating the effect of ECT indicate a consistent and high response rate with a mean ORR of 81.5%. However, side effects may be observed, which can be connected to the dose of bleomycin and some patient groups are precluded from treatment due to perceived risks. The few studies that have investigated lowering the bleomycin dose find a similar ORR (85.5%), thus opening the possibility of a non-inferior effect. It will be necessary to conduct a randomised controlled trial, with two groups receiving ECT with different doses of bleomycin, in

order to investigate the possibility of reducing the dose whilst retaining efficacy.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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