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Original Research

Electrochemotherapy for advanced cutaneous angiosarcoma: A European register-based cohort study from the International Network for Sharing Practices of electrochemotherapy (InspECT)

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ABSTRACT

Background: Cutaneous angiosarcoma (cAS) is a highly aggressive malignancy that challenges the radicality of surgical treatment. Electrochemotherapy (ECT), a skin-directed treatment based on cytotoxic chemotherapy combined with local electric pulses, may be an intraoperative adjunct and a new opportunity in the therapeutic strategy. This cohort study reports the experience with ECT as an option.

Methods: Data on patients with locally-advanced/metastatic cAS who underwent ECT between October 2013 and October 2018 at eight European centres were prospectively submitted to the InspECT (International network for sharing practices of ECT) register. Patients received therapy according to the European Standard Operating Procedures of ECT (ESOPE). Treatment feasibility was assessed based on tumour coverage with electrodes and recorded tissue current; treatment toxicity and tumour response were graded according to CTCAE v5.0 and RECIST v1.1 criteria, respectively; patient-reported outcomes (PRO) were evaluated using a visual analogue score (VAS) for pain, acceptance of retreatment and the EQ-5D questionnaire.

Results: We enrolled 20 patients with advanced cAS in the scalp/face (n = 7), breast/trunk (n = 10) or limbs (n = 3). Target tumours (n = 51) had a median size of 2.3 cm (range, 1–20). We administered 24 ECT courses using 1–4 cm treatment safety margin around tumours. In five patients, ECT was combined/sequenced with surgery. Median tissue current was 3 A (range, 1.5–10), tumour margins coverage rate was 75% (15/20 patients). The objective response rate (ORR) was 80% (complete, 40%). Grade-3 toxicity included skin ulceration (15%) and pain (10%), with no significant change of PRO scores. Bleeding control was achieved in 13/14 patients with ulcerated tumours. With a median overall survival of 12.5 months, the local progression-free survival (LPFS) was 10.9 months.

Conclusion: ECT produces sustained response rate with minimal side effects and should be considered an option for advanced cAS. Palliative benefits include patient tolerability, local haemostasis and durable local control. Definition of optimal timing, treatment safety margins and combination with surgery need further investigation.

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Abbreviations

cAS	cutaneous angiosarcoma
CR	complete response
ECT	Electrochemotherapy
ESOPE	European standard operating procedures of electrochemotherapy
InspECT	International network for sharing practices of electrochemotherapy
LPFS	local progression-free survival
QoL	quality of life
PD	progressive disease
PR	partial response
PRO	patient-reported outcomes
SD	stable disease

1. Introduction

The surgical management of patients with advanced cutaneous angiosarcoma (cAS) is particularly challenging because of high-grade tumour histology, multifocality and widespread proliferation, which invariably result in high rates of recurrence [1,2]. Despite multimodal treatment, in fact, cAS represents an incurable disease for most patients and a cause of substantial deterioration of their quality of life (QoL) due to extensive skin tumour involvement. In this context, surgical treatment should be aimed at achieving wide resection margins but should also allow prompt administration of adjuvant/maintenance therapy [3,4], while in most advanced cases, local tumour control and preservation of patient QoL should be prioritized. In order to manage these uncommon and complex situations, it is important that surgical oncologists be aware of the most recent technologies capable of providing the best possible results in term of the oncological outcome, with concern on the quality of life and economic issues.

Electrochemotherapy (ECT) has demonstrated clinical utility across a variety of superficial cancers not amenable to surgical resection and has been associated with prolonged tumour control and positive patient-reported outcomes (PRO) in several studies [5–7]. The key-mechanism of ECT consists of two stages, the administration of a cytotoxic drug (i.e., bleomycin or cisplatin) followed by the application of short, high-voltage electric pulses to the tumour. Irrespective of tumour histotype, these pulses determine the opening of aqueous pores through the cell membrane and temporarily increase its permeability (reversible electroporation) to chemotherapy, thus leading to cell death [8].

These favourable results have prompted researchers to investigate this treatment modality also in other, more challenging histotypes, including bone metastases, visceral tumours and also soft tissue malignancies [8,9]. Due to the rarity and heterogeneity of these neoplasms, the experience accumulated so far mainly refers to the patients with Kaposi's sarcoma, in whom ECT ensures prolonged disease control with minimal side effects [10]. Interestingly, initial clinical experiences are indicating that ECT may be effective also in angiosarcoma [11–15]. According to an Italian retrospective multicenter study including 19 patients with superficially metastatic cAS treated by ECT between 2007 and 2014, the objective response rate was 63% and one-year local progression-free survival (LPFS) was 68% [12]. Additionally, palliation of tumour bleeding and pain relief were reported in five and six patients, respectively.

In 2013, the National Institute for Health and Care Excellence (NICE) has endorsed the submission of data on all patients undergoing ECT to the InspECT (International Network for Sharing Practices of ECT) register [16] and in 2016, ECT has been included in the UK sarcomas guidelines as a treatment option for patients with oligometastatic disease [17]. The InspECT group has conducted this study to investigate the feasibility and efficacy of ECT in cAS and to explore the modality of its application along with PRO.

2. Methods

2.1. Participating centres

The present multi-institutional prospective cohort study is part of larger research conducted at InspECT centres on patients treated with ECT with the approval of the local ethics committees and in accordance with the standards of the Good Clinical Practice (http://www.insp-ect.org). InspECT is an open, independent network of 25 ECT centres from nine European countries founded in 2008, which adopt a common clinical protocol, share clinical experiences and promote collaborative research [18]. The present study was conducted at eight sarcoma referral centres and has been retrospectively registered (Research Registry ID:5055). An investigator meeting was held during the annual InspECT meeting in Rome (2013), Munich (2014), Ljubljana (2015), Bristol (2016), Pavia (2017) and Budapest (2018).

2.2. Study population

Patients with locally advanced or metastatic cAS not amenable to surgical treatment who underwent ECT from October 2013 to May 2019 were identified. Patient selection for ECT was in accordance with the inclusion/exclusion criteria indicated in the European Standard Operating Procedures of ECT (ESOPE) [19]. The treatment plan was agreed at the local multidisciplinary team (MDT) meeting. Each patient underwent an anesthesiological evaluation and gave written informed consent.

2.3. Treatment

ECT was performed according to the ESOPE [20] and was carried out by a physician acquainted with the procedure (at least 5 ECTs/year). Bleomycin was administered intratumorally (250–1000 IU/cm^3 depending on tumour volume) or intravenously (15,000 IU/m^2); after one or 8 min, respectively, patients received electric pulses delivered to all known superficial cancer lesions by means of a 2-cm long, linear- or hexagonal-array needle electrode connected to a CE-certified pulse generator (Cliniporator™, model EPS-01 or EPS-02; IGEA, Carpi, Italy). The electric pulses consisted of a train of eight square wave pulses of 400–960 V, 100 ms duration and 5000 Hz repetition frequency. Further ECT courses were scheduled in case of partial response (PR) or stable disease (SD), or in-field/out-of-field recurrence.

2.4. Outcome assessment

Tumour response was clinically evaluated and graded with the adapted Response Evaluation Criteria in Solid Tumours (RECIST v1.1) [21,22]. In each patient, we performed a unidimensional measurement by means of a calliper on up to seven measurable lesions (target lesions) at baseline and at each follow-up visit (at 1, 2 and three months and every four/six months thereafter). Treatment outcome was categorized as complete response (CR), PR, SD, or progressive disease (PD). Toxicity was graded according to the Common Toxicity Criteria for Adverse Events (CTCAE v5.0). PRO measure was performed by means of a numeric visual analogue scale (VAS) for pain, acceptance of retreatment, and health-related QoL evaluation with the EQ-5D-3L questionnaire (https://euroqol.org/eq-5d-instruments/eq-5d-3l-about/).

2.5. Data collection

Clinical information and ECT parameters (retrieved from the software of the pulse generator) were prospectively uploaded in the InspECT register (https://insp-ect.eu). These included patient demographics and medical history, characteristics of skin metastases, ECT modalities, treatment outcome and toxicity, patient follow-up and PRO. An internal quality assurance group verified the accuracy of source data in the frame of a general audit program.

2.6. Statistical considerations

In the descriptive analysis, continuous variables are presented as medians with range, and categorical variables are reported as absolute numbers with percentage. Statistical differences in the distribution of the examined factors across the groups were determined using the Chi-square or the Fisher exact test, as appropriate, and a two-sided P value ≤ 0.05 was considered statistically significant. Comparisons between pre- and post-treatment VAS and EQ-5D-3L scores were made by the Student t-test, and variables were tested for normal distribution by the skewness and kurtosis test. Patients' quality of life was examined by means of the analysis of variance (ANOVA) with repeated measures with time (baseline, 30 days, and 60 days after ECT) as within-subject factor. LPFS indicated the interval from ECT application to recurrence/progression within ECT field, while overall survival (OS) was the interval between ECT and disease-specific death. The Kaplan–Meier method was used to estimate LPFS and OS. All statistical analyses were performed using SPSS (15.0; Statistical Packages for Social Sciences, Chicago, IL, USA).

3. Results

3.1. Study population

Twenty patients with advanced cAS underwent ECT between October 2013 and October 2018 (Table 1). Tumour sites included the scalp/face (n = 7), trunk (secondary angiosarcoma of the breast, n = 10) and limbs (n = 3). Two patients (one with scalp and one with chest wall cAS) had epithelioid angiosarcoma. Fifty-one tumours were registered as target lesions (median 3/patient, range 3–7) with a median size of 2.3 cm (range, 1–20). Mild or moderate tumour bleeding was noted in 14 patients (70%) at baseline.

3.2. Electrochemotherapy

Patients received 24 ECT courses (median, 1/patient, range, 1–2; Table 2). The extension of ECT safety margins around tumours ranged from 1 to 4 cm, depending on treatment intent (Fig. 1). In 16/20 patients, there were no anatomical constraints to electrode application. In five patients, ECT was variably combined with surgical resection according to clinical judgement. The median duration of the procedure was 28 min (range, 15–40). Three patients (15%) were receiving concomitant systemic treatment at the time of ECT. Four patients (20%) underwent retreatment after a median interval of 3.1 months (range, 1.1–6.1).

3.3. Therapeutic outcomes

3.3.1. Tumour response

Tumour response was evaluable in all 20 patients and in 49 of 51 target lesions (Fig. 2). Per-tumour local response was as follows: CR, 61%; PR, 22%; SD, 18%; PD, 2%. Per-patient local response was as follows: CR, 40% (8/20); PR, 40% (8/20); SD, 15% (3/20); PD, 5% (1/20). The distribution of CRs according to the anatomical location was as follows: scalp, n = 3; trunk, n = 4; limb, n = 1. Tumour resolution was pathologically confirmed in 4 of 5 patients who underwent confirmatory biopsy (Fig. 3). Control of local bleeding was achieved in 13 of 14 patients (93%) with ulcerated tumours.

Overall, median response duration in patients with CR, PR or SD was 4.7 months (range, 0.6–36.1); in those with CR (n = 8), median response duration was 11.4 months (range, 3–36.1). We did not observe any significant correlations between tumour response and patient characteristics (sex, p = 0.85; age, p = 0.52), angiosarcoma features (anatomical location, p = 0.96; disease stage [locally advanced vs metastatic], p = 0.58; disease focality, p = 0.85; presence of lymphedema, p = 1.0; previous irradiation, p = 1.0; tumour size, p = 0.37; bleeding, p = 0.55) or ECT parameters (anaesthesia, p = 0.30; route of

Table 1
Study population (N = 20 patients).

Characteristics	Number (%) or median (range)
Sex	
Female/Male	13 (65)/7 (35)
Age	76 (61–84)
Charlson Comorbidity Index Score	6 (4–16)
Risk factors for angiosarcoma	
Previous irradiation[a]	10 (50)
Chronic lymphedema	4 (20)
Previous cancer (n = 15)	
Brest cancer	11 (55)
Cutaneous melanoma	1 (5)
Desmoid	1 (5)
Prostate cancer	1 (5)
Thyroid cancer	1 (5)
Previous treatment[b]	
Surgery	3 (15)
Surgery + RT	4 (20)
Surgery + Systemic treatment	8 (40)
Systemic treatment	1 (5)
Systemic treatment + RT	4 (20)
Surgery + RT + Systemic treatment	1 (5)
Radicality of resection (n = 16)	
R0/R1/R2	10 (63)/4 (25)/2 (13)
Disease presentation	
Primary	7 (35)
Recurrent	13 (65)
Disease extension[c]	
Locally advanced	17 (85)
Metastatic	3 (15)
Anatomical location	
Scalp/face	7 (35)
Breast/chest wall	10 (50)
Limbs	3 (15)
High-grade tumours	19 (95)
AJCC TNM staging	
IIA/IIB/III	1(5)/8 (40)/8 (40)
IV	3 (15)
Tumour burden (ECT target)	
Single/multifocal	6 (30)/14 (70)
Total number of treated tumours	164
Total number of target lesions[d]	51
No of target tumour per patient	3 (2–7)
Patients with non-target tumours[e]	7 (35)
Tumour size (cm)	2.3 (1–20)
Tumour bleeding	
Yes°/No	14 (70)/6 (30)

° Grading was as follows: G1, n = 5 patients; G2, n = 9 patients (RECIST criteria).

[a] Median interval from RT to angiosarcoma, 11.4 years (range, 5.3–34). No patient had immunosuppression or exposure to carcinogens.

[b] Previous treatment for angiosarcoma. The surgical procedures included the following: simple excision, n = 2; wide local excision (WLE), n = 3; WLE + flap reconstruction, n = 3; WLE + graft reconstruction, n = 2; mastectomy, n = 3; mastectomy + split skin grafting, n = 3.

[c] At the time of patient enrollment for ECT.

[d] Tumours registered to evaluate response to treatment (according to the RECIST criteria).

[e] These patients had non-measurable metastases in addition to the target lesions (median 3/patient, range 1–7).

Table 2
Electrochemotherapy (N = 20 patients).

Parameter	Number of pts (%) or Median (range)
Anaesthesia	
General[a]	19 (95)
Local	1 (5)
Route of bleomycin administration	
Intravenous bolus[b]	18 (90)
Intratumoral injection	2 (10)
Electrode type	
Needle hexagonal	17 (85)
Needle row	3 (15)
No of electrode applications	82 (7–248)
Tumour coverage with pulses[c]	
Deep margin	15 (75)
Lateral margins	15 (75)
Extension of lateral safety margins	
1 cm	8 (40)
2 cm	8 (40)
3 cm	3 (15)
4 cm	1 (5)
Anatomical constraints[d]	
No/Yes	17 (81)/4 (19)
Electric current (Ampere)	3 (1.5–10)
Combination of ECT with surgery	5 (25)
Debulking[e] + ECT[°]	2
Resection + ECT[°]	2
Neoadjuvant ECT → Resection[•]	1
Concomitant systemic treatment[◇]	3 (15)
Additional ECT cycles	5 (25)

[°] Within the same procedure.
[•] In a separate procedure.
[◇] Gemcitabine, n = 1; ifosfamide, n = 1; pazopanib, n = 1.
[a] Includes general anaesthesia and mild general sedation.
[b] Three patients received a de-escalated does (by 25%, 25% and 50%, respectively) due to impaired renal function.
[c] Per-tumour coverage rates: deep margin, 82%; lateral margins, 82%.
[d] Impediment to the application of electrodes. In order to achieve effective pulse delivery, all the needle electrodes of the pulse applicator must be inserted into tissue. This can be difficult on highly curved skin surfaces or due to the proximity of delicate anatomical structures or bone.
[e] Surgical resection of the exophytic portion of the tumour.

drug administration, p = 0.13; electrode type, p = 0.67; extension of treatment safety margins, p = 0.37; anatomical constraints, p = 0.65).

3.3.2. Tumour control

Median follow-up was 15 months. Seven patients (35%) experienced local recurrence, after a median interval of 3.4 months (range, 0.9–28). One-year LPFS was 68% (95% CI 47%–90%) (Fig. 4).

3.3.3. Toxicity

There were no treatment-related serious adverse events and the hospital stay was uneventful. Local and systemic toxicities observed during follow-up are reported in Table 3.

3.3.4. Pain

Six patients (30%) experienced various grades of treatment-induced pain, which was severe in two patients (10%) three months after ECT (Table 3). These included a patient with cAS of the face and a patient with a chest wall tumour and G2 local pain at baseline. There were no significant correlations between post-treatment pain and patient/tumour characteristics or ECT parameters (Suppl. Table 1).

3.3.5. Skin toxicity

Five patients (25%) developed various grades of skin ulceration, which was nonetheless reversible and manageable on an outpatient basis in all cases (Table 3). In the three patients with grade 3 toxicity, skin ulceration lasted two months (n = 1) and one month (n = 2). We did not observe any significant correlations with patient characteristics, tumour feature or treatment parameters (Suppl. Table 1).

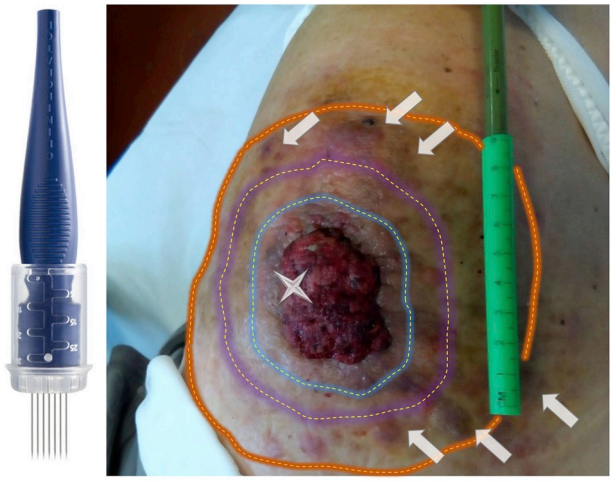

Fig. 1. Electrochemotherapy safety margins. Treatment of a locally advanced angiosarcoma of the lower limb by means of a hexagonal array needle electrode (left). The patient presented with a 5-cm, bleeding exophytic tumour (arrow) and multiple satellite nodules. The extent of treatment safety margins can vary depending on treatment intent and tumour location (due to possible anatomical constraints to electrode placement). If treatment intent is merely palliative (i.e. control of tumour bleeding), a 1-cm margin can be appropriate (inner dotted line); conversely, if electrochemotherapy is aimed at improving local control, possibly in the frame of a multimodal treatment strategy, wider (e.g. 2 or 4 cm) margins can be applied (outer dotted lines). In the latter case, increased inflammatory reaction, postoperative pain and skin toxicity should be considered (*Courtesy of the Department of Surgery Oncology and Gastroenterology of the University of Padova*).

3.4. Patient-reported outcomes

At the conclusion of the procedure, the median VAS score for pain was 2.5 (range, 0–8); after one month, it was 1.5 (range, 0–8; p = 0.20), and after two months it decreased to 1.0 (range, 0–3; p < 0.04). At the conclusion of the procedure, 18 of 20 patients (90%) stated that treatment was tolerable and that they would accept undergoing another session, if necessary (two patients did not answer); at one- and two-month follow-up, all patients stated that would accept eventual re-treatment. Pre- and post-ECT EQ-5D scores were comparable. In particular, there were no significant differences in either the five dimensions of mobility (p = 1.0), self-care (p = 0.67), usual activities (p = 0.41), pain/discomfort (p = 0.63) and anxiety/depression (p = 0.65) or the EQ-VAS score (p = 0.30) for overall health state. The median EQ-VAS score was 44 (range, 0–83) at baseline, 55 (range, 0–85) at one month, and 50 (range, 0–80) at 2 months. All the variables of the EQ-5D questionnaire were found to be stable over time by means of the ANOVA.

3.5. Clinical course

Thirteen patients (65%) developed new skin lesions after a median of 1.8 months (range, 0.7–10) and 7 (35%) experienced systemic recurrence/progression after a median of 6.4 months (range, 1.8–31). Five patients (25%) received further systemic treatment (gemcitabine, n = 1; ifosfamide, n = 1; paclitaxel, n = 1; pazopanib, n = 2). Median OS was 12.5 months (range, 6.1–53.5).

4. Discussion

Electrochemotherapy can provide a fundamental contribution to overcoming the limitations of the standard surgical approach in patients with cAS. Despite the introduction of new systemic agents, the

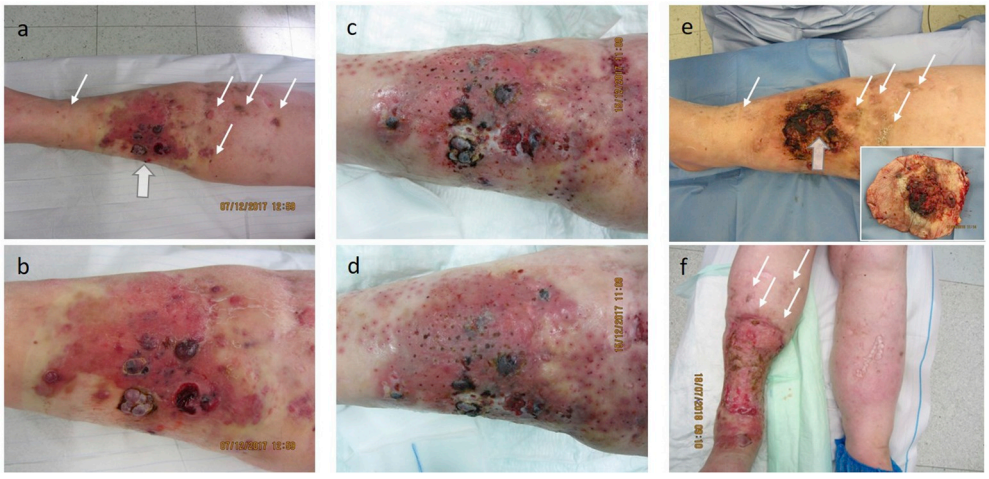

Fig. 2. Angiosarcoma of the lower limb. Baseline clinical presentation (a,b). The patient had a locally advanced lesion in the leg (arrow) and multiple satellite metastases (thin arrows). A single course of electrochemotherapy was performed with reduced bleomycin dose, due to compromised renal function. After one week, partial regression of the tumour nodules was observed, coupled with moderate inflammatory reaction and mild vascular congestion (c,d). After three months, tumour regrowth was observed within the treatment field (arrow), while the satellite nodules were completely resolved (thin arrows) (e). The patient underwent wide local resection with negative margins; the pathological examination was negative on random skin biopsies as well. Seven months after ECT the patient was maintaining local control (f) (*Courtesy of the Plastic Surgery Unit, University Medical Center, Mainz*).

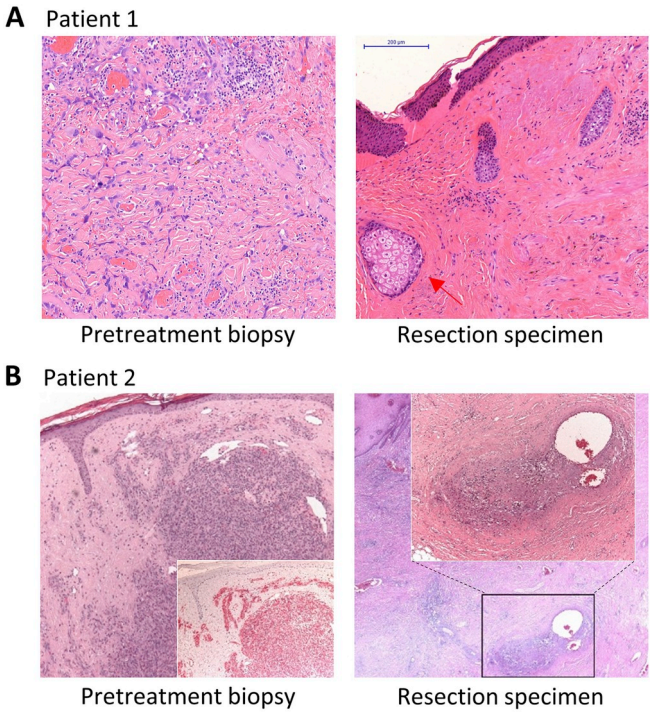

Fig. 3. Pathological response to electrochemotherapy in two patients with cutaneous angiosarcoma. Panel A shows representative sections of tumour specimens obtained from a patient with cutaneous angiosarcoma of the scalp at baseline (left) and after treatment (right) (haematoxylin and eosin staining). In this patient, despite complete clinical regression, residual tumour cells were present in the resection specimen (arrow). Panel B shows representative sections of tumour specimens obtained from a patient with lower limb angiosarcoma at baseline (left) (haematoxylin and eosin staining 50x and immunostaining for CD31 100x) and after electrochemotherapy (right) (haematoxylin and eosin staining 16x). Neoplastic cells are present throughout the pre-treatment specimen, whereas the post-treatment specimen confirms complete tumour regression. Post-electrochemotherapy histology demonstrates a broad dermal scar under epidermal hyperplasia with dying tumour cells. The insert shows shrinking neoplastic remains with siderosis in the deep dermis. (*Courtesy of the Department of Dermatology and Allergology, University of Szeged and the Department of Dermatology, Medical Center, Mainz*).

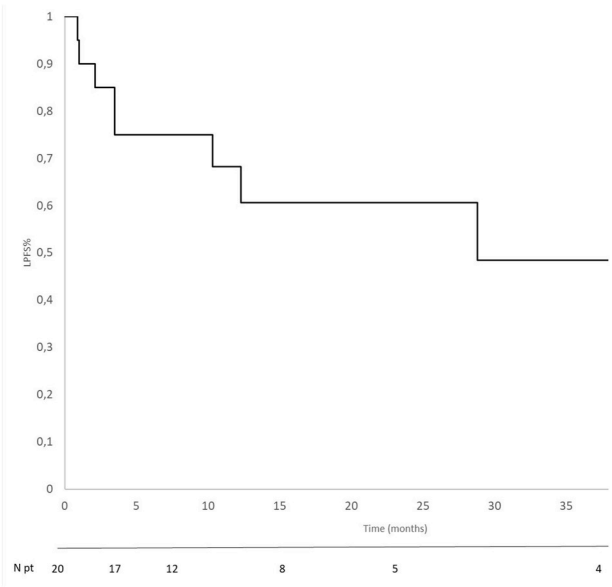

Fig. 4. Kapan-Meyer estimate of local progression-free survival in 20 patients with cutaneous angiosarcoma treated with electrochemotherapy.

prognosis of patients with cAS remains unsatisfactory and their patient QoL is often heavily compromised, as also indicated by the low EQ-VAS score in our population. In the advanced disease setting, the indication to surgical treatment should be cautious and should take into account patient age, the morbidity of wide resection margins, the need for prompt adjuvant/maintenance systemic treatment [3,4,23], along with the considerable risk of recurrence [1]. Following a single course of ECT, 8 of 20 patients (40%) in our cohort achieved CR with tolerable side effects. Importantly, this translated into durable tumour control (median LPFS was 10.9-month), which is a remarkable palliative achievement not only in view of the limited life expectancy of our patients (median OS, 12.5 months) but compared with the results reported with systemic treatment as well [24].

Although the small population prevents us from making general conclusions, we did not observe any serious complications; moreover, postoperative pain was mild in most cases and, importantly, the majority of patients would accept another course of treatment. Thanks to the flexibility of the procedure, high tolerability and favourable toxicity profile, ECT can be easily integrated into a multimodal therapeutic strategy for cAS. In particular, its safety is of critical importance for

Table 3
Toxicity (CTCAE v5.0).

Toxicity	Baseline	1 month	2 months	3 months
Local				
Bleeding				
G1	5 (25)	1 (5)	1 (5)	1 (5)
G2	9 (45)	0	0	0
Pain of skin				
G1	2 (10)	6 (30)	5 (25)	5 (25)
G2	3 (15)	3 (15)	1 (5)	1 (5)
G3	0	2 (10)	1 (5)	2 (10)
Hyperpigmentation				
G1	1 (5)	4 (20)	5 (25)	2 (10)
G2	1 (5)	2 (10)	1 (5)	0
Skin ulceration				
G1	2 (10)	4 (20)	2 (10)	0
G2	0	4 (20)	2 (10)	4 (20)
G3	0	1 (5)	3 (15)	0
Lymphedema				
G1	0	0	0	0
G2	2 (10)	0	0	0
G3	0	0	0	1 (5)
Skin infection				
G1	1 (5)	2 (10)	1 (5)	0
G2	0	1 (5)	0	0
Skin/soft tissue necrosis				
G2	0	2 (10)	1 (5)	1 (5)
Pruritus				
G1	0	0	0	0
G2	0	0	1 (5)	0
Odor				
G1	0	0	0	0
G2	0	1 (5)	2 (5)	0
Systemic				
Nausea/Vomiting				
G1	1 (5)		1 (5)	0
G2	0		0	0
G3	1 (5)		0	1 (5)
Vertigo				
G1	0	0	0	0
G2	1 (5)	1 (5)	1 (5)	1 (5)

patients, providing an opportunity for the administration, without delays, of systemic treatment, which remains fundamental and can contribute to preserving cosmetic outcome in cases with extensive skin infiltration [4,25].

Safety concern about ECT refers to the administration of electric pulses and chemotherapy. Although pulse delivery has the potential to induce epileptic seizures, cardiac arrhythmias and painful muscle contractions, a recent comprehensive review, including more than 60 clinical studies, indicates that these events are extremely rare [8]. Yet, meticulous patient selection and thoughtful ECT application are of critical importance [8]. On the other hand, it is worth noting that while locally injected bleomycin is generally safe [26,27], its systemic administration can produce a range of relatively common dermatologic toxicities and can lead, although very rarely, to potentially fatal lung complications [28,29]. Thus, careful consideration of risk factors for bleomycin-related lung toxicity is mandatory when screening patients for ECT [8].

Contrary to primary skin cancers, head and neck malignancies, Kaposi's sarcoma and breast cancer, the clinical experience with ECT in angiosarcoma is limited yet. In 2016, an Italian retrospective multicentre study with 19 cAS patients indicated a 63% objective response rate with 68% of patients maintaining local control one year after ECT. Additionally, palliation of tumour bleeding and pain relief were achieved in 5 and 6 patients, respectively [12]. In 2012, di Meo et al. documented the case of an 81-year-old cardiopathic woman with multifocal angiosarcoma in a lymphoedematous limb following lymph node dissection for melanoma. Due to disease extent and comorbidities, ECT was offered as a palliative measure. Although the patient died from an unrelated cause (stroke) before starting treatment, this report describes a suitable ECT candidate [30]. Importantly, since ECT is regarded as a low demanding procedure and is generally offered to frail patients, meticulous anesthesiological evaluation and a streamlined clinical pathway are fundamental to avoid complications and provide a meaningful clinical benefit [8]. Solari et al. included two cAS patients in a cohort of 39 individuals with skin metastases treated with ECT, but only one of them was responsive to treatment and no follow-up data were provided [31]. Finally, Guida et al. reported on a patient who underwent two ECT courses as the exclusive treatment for a 30-cm cAS of the shoulder and achieved CR. Remarkably, the patient remained disease-free after 17-months and no additional interventions [11].

Interestingly, there are some case reports suggesting the feasibility of ECT in the frame of a multimodal treatment strategy. Benevento et al. reported on a 76-year-old woman with locally advanced secondary cAS of the breast occurred after breast-conservative surgery, axillary dissection and radiotherapy for invasive ductal carcinoma. Combined treatment included wide local excision of the bulky tumour and two ECT cycles on isolated skin metastases on the abdominal wall, followed by chemotherapy. After 18 months, patient follow-up was uneventful [13]. Campana et al. reported on another breast cancer patient with Stewart-Treves Syndrome (angiosarcoma on lymphedema) of the upper limb who underwent successful limb-preserving treatment with hyperthermic isolated limb perfusion (HILP), isolated limb infusion (ILI) and ECT over a 12-year period [15]. In 2016, Mocerino et al. reported on a 77-year-old woman with a secondary angiosarcoma of the breast who underwent mastectomy, contralateral mastectomy combined with ECT on previous mastectomy scar, radiotherapy, additional ECT on the chest wall, and liposomal doxorubicin. At the time of publication, two years after chemotherapy, there was no evidence of recurrence [14].

Recently, Al-Hadithy et al. reported mixed results in three cAS patients who were included in a cohort of 48 individuals with skin metastases. These three elderly patients presented with primary or recurrent angiosarcoma of the medial canthus or of the nose/upper lip region. One patient was not evaluable for response and, in the other two, the treatment outcome was in the range of PR and SD. Unfortunately, both of them experienced complications (bruising, neuropathic pain and infection) and one required intensification of the wound dressing schedule [7]. In our opinion, this could be explained by the challenging anatomical location of the treated tumours. Despite ECT being repeatedly demonstrated safe in the periorbital region, particularly in patients with basal cell carcinoma [32,33], when dealing with an aggressive disease such as cAS, which presumably requires wider treatment fields, special care is advisable. This consideration is supported also by the poor control of pain reported in one of our patients with cAS of the face region. Nonetheless, multi-institutional studies and experience from referral centres suggest the tolerability, long-term efficacy and clinical benefit of ECT in tumours of the head and neck region [6,34].

Discerning the impact of any local therapies in patients with skin metastases remains a complex task, due to variation in treatment application, comorbidities, cumulative toxicities, and methods of assessment. A discrepancy between patient- and clinician-reported outcomes has been observed not only in our study (with regard to the grading of pain severity) but also in other experiences with ECT [7]. Further research is needed to validate dedicated instruments to assess the actual burden of skin metastases and the impact of skin-directed therapies, and to elucidate the not always obvious correlation between oncologic outcomes and patient perception [5]. In order to tackle this and other methodological issues, the recommendations for improving the quality of reporting of clinical ECT have been proposed in 2016 [35], in line with similar initiatives aimed at improving scholarly publishing in surgery [36].

Concerning the further development of ECT application, efforts are in place to consolidate its evidence basis. The National Institute for Health and Care Excellence (NICE) has recommended that data on all treated patients be submitted to the international InspECT register [16],

which the present study is based on. Moreover, the InspECT group offers the opportunity for multi-institutional collaboration [37]. Finally, ECT has recently gained more attention by the surgical community and the European Society of Surgical Oncology (ESSO) has recently introduced a dedicated course that provides an opportunity for specific training [37]. Hopefully, these efforts will promote the alignment of practice across centres and will allow researchers to rigorously investigating ECT in the context of high-quality clinical trials.

Due to the aggressive nature of the disease and the heterogeneity of clinical presentations, the management of patients with advanced cAS requires an individualized multimodal approach in the frame of a shared decision-making protocol [14,24]. Fujisawa et al., for instance, reported encouraging outcomes by combining chemoradiotherapy with taxane and maintenance chemotherapy [4]. In a multicentre retrospective study on 16 patients, the response rate was 94% (14 patients with CR) and local control ranged between 5 and 28 months, although half patients experienced grade 3/4 neutropenia. If optimal preoperative care is delivered, ECT is a flexible, safe and effective adjunct. Yet, it can be applied as a day case or one night-stay procedure, depending on disease extent, and patients retain their functional autonomy [8]. Interestingly, this can save resources in the current tight economic environment. Finally, ECT has the potential to be combined with radiotherapy. Although this strategy is still unexplored in the clinic, preclinical studies in murine tumour models have indicated that ECT has a radiosensitizing effect which is retained at low bleomycin dosages [38–40]. This observation is of particular interest since there is emerging clinical evidence supporting the efficacy of ECT with de-escalated bleomycin dosages [41].

ECT should not be considered a mere alternative to surgical treatment. Interestingly, we reported a range of possible applications (Table 2) that are in line with the recently updated standard operative procedures of ECT where tumour debulking followed by intraoperative ECT has been introduced as an option to reduce tumour burden and improve treatment application [20]. Each of these strategies has potential advantages and controversial aspects (Table 4), which require the coordination among surgeons, medical oncologists, radiation therapists and plastic surgeons to optimise patient outcome and further investigation to increase their evidence basis.

This study has limitations. First, the small sample size, which is almost inevitable when dealing with a rare disease such as sarcomas [23]. Therefore, we endorse sharing future clinical experiences with ECT to aid the surgical community in managing this rare condition. Second, the overestimation of tumour response, due to discrepancy between clinical and pathological assessment as demonstrated by one of our patients who had residual microscopic disease in the resection specimen despite complete response at clinical evaluation (Fig. 3). However, even though post-ECT biopsies were on occasion available, their feasibility is questionable in most cases, due to concerns around an invasive diagnostic procedure in a palliative setting. Third, despite a consistent approach across centres, still, there was some variation in the use of ECT concerning the extension of treatment safety margins, the timing of retreatment, and the combination/sequencing with surgery.

Table 4
Local treatment modalities for cutaneous angiosarcoma.

Treatment strategy	Indications	Advantages	Open issues
Surgery	•Patients with few and small tumours that are easily resectable •Locally advanced tumours, well-demarcated (R0 resection likely)	Definitive treatment in case of R0 resection	Patient selection High risk of new lesions High risk of local recurrence
Radiotherapy	•Surgery not practicable •Symptomatic tumours	No-touch technique Consolidated experience	Tissue tolerance (especially in case of re-irradiation) Feasibility in patients with multifocal disease
ECT	•Surgical resection contraindicated due extensive local infiltration •Surgical resection practicable but inappropriate (e.g. multifocal tumours) •Patient performance status or disease behaviour mandate palliative treatment only	Avoid the morbidity associated with surgical resection Rapid palliation on mildly bleeding tumours where resection would be disproportioned Continuation of concomitant systemic treatment	Optimal number and frequency of ECT cycles are unknown No comparative data with surgery
Debulking + ECT(within the same procedure)	•Fungating tumours (when complete resection causes extensive tissue loss) •Moderate tumour bleeding better controlled by means of surgical resection and cauterization	Immediate resolution of the exophytic portion of the tumour while avoiding complex resections Avoidance of postoperative complication linked to ECT-induced tumour necrosis	Optimal tumour size Palliation benefit needs to be demonstrated
Resection + adjuvant ECT (in the same procedure)	•Tumours of any size where infiltration of resection margins is likely	Simultaneous treatment of tumours with different size and extension Reduction of risk of local recurrence	Extension of ECT safety margins unknown ECT effect on wound healing unknown
Resection + adjuvant ECT (in a separate procedure)	•Previous resection with R1 margins and further surgery not practicable/refused	Tissue preservation	Extension of ECT safety margins unknown
Neoadjuvant ECT followed by resection (in a separate procedure)	•Multifocal tumours with different size •Benefit of surgery uncertain •Mixed response after ECT	Neoadjuvant ECT may create a surgical option Improved patient selection (avoidance of surgical resection in complete responders or in those with rapid progression	Number and frequency of ECT cycles before surgery unknown ECT effect on wound healing unknown
Neoadjuvant ECT followed by RT	•Aggressive, locally-advanced tumours	Exploitation of the radiosensitizing effect of bleomycin and cisplatin[a]	This therapeutic strategy has not yet been explored in the clinic
Photodynamic therapy (PDT)	•Thin lesions	Repeatability No scar formation Combination with surgery Possible immunological effect	Limited clinical experience[b]

[a] Supporting preclinical studies: Sersa 2000 [38], Kranjc 2009 [39], Rezaee 2017 [40].
[b] Published case reports: Liu D, Photodiagnosis Photodyn Ther. 2019; 25:317–318. Gao Y, Photodiagnosis Photodyn Ther. 2017; 19:153–155. Thong PS, Lancet Oncol. 2007; 8:950–2.

Unfortunately, small numbers prevented us from detecting meaningful correlations, nonetheless, these controversial aspects represent the basis on which to start a discussion and plan future investigations.

5. Conclusions

This study indicates that ECT is practicable locoregional treatment in patients with advanced cAS when an MDT performs patient selection and treatment indication is part of a multimodal therapeutic strategy. The procedure can be variably combined with surgical treatment and leads to high response rates, with low morbidity. Treatment application to cAS of the face or in patients with poor pain control at baseline warrants special caution due to possible intensification of local discomfort. In well-selected cases, ECT palliative benefit includes optimal patient tolerability, local haemostasis and durable tumour control. Our findings set the stage for future collaborative studies aimed at establishing the optimal timing, the extension of treatment safety margins and the most appropriate combination with surgery.

Ethical approval

Not required. The present study is based on the partial analysis of the international InspECT (https://insp-ect.eu) in accordance with the NICE guidance IPG 446 (NICE National Institute for Health and Care Excellence, Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma). Nice. org.uk/guidance/ipg446).

Author contribution

LGC, SV, PQ and DM planned the study. LGC, AO, HS, GM, PC, MS, PQ, DM and EK treated patients. KB, FdT, HS, GM, RC, PC, GS, DM, MB collected data. LGC and FdT managed the database. FdT and SV performed statistical analyses. LGC prepared the first draft of the paper. HS, PC, GS, SV, PQ and DM revised the draft. All authors revised the final version of the manuscript and approved the submission.

Research registration number

1. Name of the registry: **Research Registry**
2. Unique Identifying number or registration ID: **researchregistry5055**
3. Hyperlink to the registration (must be publicly accessible): https://www.researchregistry.com/register-now#home/registrationdetails/5d422e76dc22710011252b0e/

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Data statement

The dataset generated and analysed during the current study is not publicly available due to patient privacy restrictions and ongoing data collection for research purposes but are available from the corresponding author on reasonable request and upon previous agreement of the InspECT centres.

Declaration of competing interest

LGC, AO, HS, GM, PC, RC, GS, PQ, DM, MB and EK received travel grants from IGEA S. p.A. (Carpi, Italy) to attend the annual InspECT meeting. FdT is IGEA S. p.A. employee. IGEA S. p.A. hosts the InspECT database, which is administered by an independent board. KB, MS and SV have no competing interests to declare.

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In the preparation of this manuscript, the authors followed the S-PRINT (Sustainable Paperless Reference Initiative Nourishes Trees) recommendation and printed only 4 papers out of 40 included in the reference list (S-PRINT score: 10%) (https://twitter.com/LucaCampana_611/status/1140741813277483008).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.10.013.

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