Treatment efficacy with electrochemotherapy: A multi-institutional prospective observational study on 376 patients with superficial tumors

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Abstract

Background: Cutaneous metastases represent a therapeutic challenge. An increasing body of experience suggests that electrochemotherapy (ECT) provides effective tumor control, although its evidence basis should be strengthened.

Methods: This prospective, multicenter, observational study enrolled patients with superficial metastases, who underwent ECT at 10 centers between 2008 and 2013. Outcomes included adherence to European Standard Operating Procedures of ECT (ESOPE), tumor response, local progression-free survival (LPFS), toxicity and patient-reported outcomes (PROs, EORTC QLQ-C30 plus an 8-item questionnaire).

Results: We enrolled 376 eligible patients. Tumor histotype distribution was as follows: melanoma, 56%; squamous cell carcinoma, 11%; Kaposi sarcoma, 11%; breast carcinoma, 8%; basal cell carcinoma, 6%; soft tissue sarcomas, 3%; others, 5%. We registered 1304 target tumors (median size 1 cm). Treatment adhered to ESOPE in 88% of patients as to the route of drug administration, and in 70% as to electrode application. The procedure was mainly performed under sedation (64.6%) and by using intravenous chemotherapy (93.4%). Tumor response rate at 60 days was 88% (complete, 50%). Small tumor size predicted complete response achievement (OR 2.24, $p = 0.003$), higher LPFS (HR 0.68, $p = 0.004$) and improved PROs (Global Health Status, $p < 0.001$; wound bleeding, $p < 0.001$; healing, $p = 0.002$; and aesthetics, $p < 0.001$). Skin toxicity (grade $\geq$3, 7.8%) was lower in patients with tumors <2 cm ($p \leq 0.001$). One-year LPFS was 73.7% (95%CI 68.4–78.3).

Conclusions: ECT represents a valuable skin-directed therapy across a range of malignancies. The most frequently applied treatment modality is intravenous chemotherapy under sedation. Small tumor size predicts durable tumor control, fewer side-effects and better PROs.
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Keywords: Electrochemotherapy; Cutaneous metastases; Melanoma; Breast cancer; Squamous cell carcinoma; Basal cell carcinoma

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Introduction

Skin metastases are a relatively uncommon (0.6%–10.4%) though distressing problem in cancer patients.[1] They occur in up to 20% of melanoma patients, and, in half cases, represent the first site of progression.[2] Noncutaneous malignancies account for 10% of skin metastases, and are most commonly observed in breast cancer patients.[3] This condition can be highly symptomatic, due to necrotic evolution and ulceration, which may cause both physical and psychological discomfort.[4] Systemic and locoregional therapies or radiation represent the mainstay of treatment, nevertheless these options are often unfeasible, due to development of tumor resistance or deterioration of patient performance status (PS). Alternatives include photodynamic, intralesional and topical therapies, all of which have shown a variable degree of efficacy, although standardized protocols for optimizing their application are still lacking.[5–7] During the last two decades, a new treatment modality has been developed, combining transient tumor permeabilization (i.e. reversible electroporation) – obtained by means of properly tuned electric pulses – combined with cytotoxic agents (electrochemotherapy, ECT).[8,9] In ECT, electric pulses open transient pores on the cell membrane and propel drug molecules into the cytosol. Its principal advantage is local dose intensity, in fact high intratumoral drug concentration is achieved and cytotoxicity is increased by ∼8000 fold for bleomycin and by ∼80 fold for cisplatin.[10–12] Since early 90s, ECT emerged as a local treatment for superficial tumors.[13] There is now an increasing wealth of evidence that ECT, with either bleomycin or cisplatin, is efficacious across malignancies.[14–16] However, the procedure was standardized only in 2006, based on a multicenter European study on 61 patients,[10] whose clinical protocol has been subsequently adopted as the European Standard Operative Procedures of Electrochemotherapy (ESOPE).[17] Two meta-analyses have confirmed sustained antitumor activity for ECT.[5,18] Compared with conventional options, ECT has some advantages. It can be administered in one day; it is well tolerated and can be repeated; the majority of subjects have their tumor controlled locally. On this basis, the National Institute for Health and Care Excellence (NICE) has recently incorporated ECT into the multidisciplinary management of patients with skin metastases (interventional procedure guidance IPG446 – "Electrochemotherapy for metastases in the skin from tumors of non-skin origin and melanoma"), although supporting literature has weaknesses in both methodology and reporting.[19–21] Such conflicting considerations prompted us to launch the present multi-institutional study. After the ESOPE experience, no other multicenter study has been performed. Thus, the main goal was to confirm the ESOPE results, in a large real-world series and in a prospective setting, as well as to identify factors affecting patient outcome. Secondary aims were to describe the applied treatment modalities and to assess adherence to ESOPE. Finally, we collected data on tumor control and patient reported outcomes (PROs).

Patients and methods

Study management

This was a prospective, multicenter, single-arm, investigator-led observational cohort study promoted by the Italian Melanoma Intergroup (IMI) and the Italian Group of Dermato-Oncology (GIDO), and supported by Igea Spa, Carpi, Modena, Italy. Study supervision was directed by a steering committee of clinical investigators. The sponsor had no access to the data and no role in the preparation of this report. The institutional review board of each center approved the study and patient management conformed the rules of Good Clinical Practice.

Study population

We prospectively enrolled all the consecutive patients who underwent ECT from October 2008 through March 2013 at ten Italian centers (Fig. 1). Study follow-up was concluded on August 2014. Eligible patients were at least 18 years of age, had cutaneous/subcutaneous histologically confirmed metastases from cancer of any histotype, primary or recurrent basal cell carcinoma (BCC) or squamous cell carcinoma (SCC), had measurable disease, were unresponsive to or unsuitable for conventional treatments, had tumor nodule(s) smaller than 3 cm in thickness and not deeper than 3 cm. Additional inclusion criteria were: no concomitant treatments one month before and two months following ECT, a 0–2 Eastern Cooperative Oncology Group (ECOG) PS score, a life expectancy of at least three months, normal hematologic, hepatic and renal function. Patients were excluded if they had abnormal respiratory function, a cardiac pacemaker or arrhythmias, previous maximal exposure to bleomycin, or history of seizures.

Tumor registration

For each patient, a maximum of seven tumors were registered as target lesions and the sum of their largest diameters was used as a baseline value for subsequent response assessment.

Procedure

ECT was planned as a day-case procedure, unless patient comorbidities indicated otherwise. The anesthesiology technique was derived from the ESOPE, but adaptations were allowed according to local protocols. The ESOPE was strictly recommended for ECT treatment and its adherence was defined as the rate of patients in whom the recommended route of drug administration and electrode type were used (Supplementary Table 1); recommendations
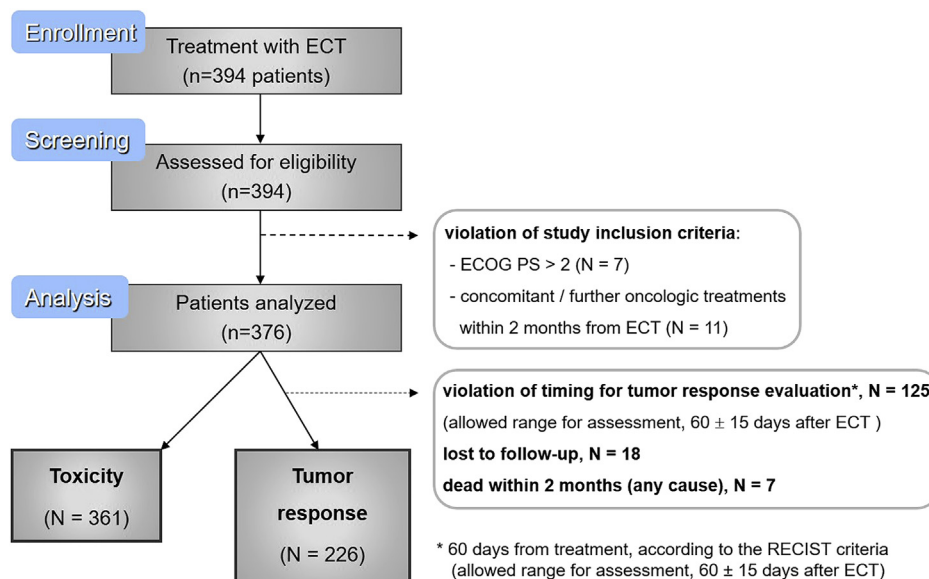
Figure 1. Study flow chart.

were extrapolated from the flow chart of the original ESOPE publication.[17] The patients received intravenous or intratumoral chemotherapy, followed by the application of electric pulses by means of a suitable electrode,[22] connected to a Cliniporator™ device. The choice between intravenous vs intratumoral chemotherapy was based on the number and size of tumor nodules. Indicatively, less than 20 small (i.e., <0.8 cm), not scattered tumor nodules, or less than 7 tumor nodules between 0.8 and 2 cm in size were indication of intratumoral drug (bleomycin or cisplatin) injection. The remaining patients were given intravenous bleomycin. The four *operating modalities* were defined by combining the type of anesthesia and the route of drug administration.[17]

Patient follow-up and assessment

After treatment, follow-up visits were planned at two weeks and then at 1, 2, 3, 6 and 12 months. At each visit, data were collected on local response, treatment failure, toxicity and PROs. Tumor response was clinically assessed according to the Response Evaluation Criteria in solid Tumors,[23] adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0). Accordingly, complete response (CR) was the disappearance of all target lesions, partial response (PR) a decrease of at least 30% in the sum of the longest diameters of target lesions, progressive disease (PD) was an increase of at least 20% in the sum of the longest diameters of target lesions; finally, stable disease (SD) was neither sufficient tumor shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Additional ECT and oncological treatments were allowed after two months. PROs were assessed by means of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 and an 8-item, self-compiled, disease-specific questionnaire, described in detail elsewhere.[24]

Statistical analysis

The Clinical Trials and Biostatistics Unit at Veneto Institute of Oncology managed data collection. Site monitoring visits were conducted to verify case report forms and source data. Two of the authors (LGC, PQ) and three external collaborators reviewed patient files. In case of controversies, supplemental information was gained from the referring center. Patient data were transcribed into an online, encrypted database. The relationship between variables was assessed with χ^2 or Fisher's exact test, as appropriate. Local progression-free survival (LPFS) was the interval between ECT and in-field tumor relapse or progression. LPFS estimates were calculated using the Kaplan−Meier method and compared with the log-rank test. Multivariable analysis was performed using the Cox proportional hazards regression method. A stepwise variable selection procedure was applied to identify a subset of covariates for the final model, considering all variables with a *p*-value ≤0.05 at univariate analysis and testing also the interaction terms. After checking the proportional hazards assumption, Hazard Ratios (HRs) with the 95% confidence intervals CIs, calculated according to the Wald method, were computed. To evaluate the impact of predictors of complete response, the odds ratios (ORs) and corresponding 95% CI were estimated through a multivariable logistic regression model. Patients' quality of life was examined by repeated measures ANOVAs with tumor size (≥2 cm vs <2 cm) as *between-subject* factor and time (before treatment and then 30 and 60 days after ECT) as *within-subject* factor and their interaction. The compound symmetry was

Table 1
Baseline demographics.

Characteristics	No.	%
Patients included	376	100
Age at first ECT (years)		
Median	71	
Range (min–max)	24–100	
Sex		
Male	164	43.6
Female	212	56.4
BMI		
Median	26	
Range (min–max)	17–46	
PS (ECOG)		
0	175	46.5
1	144	38.3
2	57	15.2
Histotype		
Melanoma	211	56.1
SCC	41	10.9
Kaposi	40	10.6
BC	31	8.2
BCC	24	6.4
STS	10	2.7
Other histotypes[a]	19	5.1
Distant metastases		
Yes	144	38.3
Visceral	98	68.1
Other sites[b]	46	31.9
Tumor location[c]		
Lower limb	168	44.7
Trunk	76	20.2
Head and neck	65	17.3
Upper limb	16	4.3
Multiple	51	13.6
No. of treated tumors[c]		
Median	3	
Interquartile range	1–5	
Tumor size (mm)[c,d]		
Median	10	
Interquartile range	6–20	
Tumor depth		
Hypodermis	349	92.8
Epidermis, dermis	27	7.2
Previous treatments[e]		
No	70	18.6
Yes	306	81.4
Type of previous treatment[f]		
Surgery	262	85.6
Chemotherapy	128	41.8
Radiotherapy	58	18.9
Immunotherapy/ILP	76	24.8

Legend: BMI, body mass index; PS, performance status; ECOG, Eastern Cooperative Oncology Group; SCC, squamous cell carcinoma; BC, breast cancer; BCC, basal cell carcinoma; STS, soft-tissue sarcomas; ILP, isolated limb perfusion.

[a] Other histotypes: other skin carcinoma (n = 4); sweat gland carcinoma (n = 3); gastric adenocarcinoma (n = 3); not specified (n = 3); lung adenocarcinoma (n = 2); metatypical carcinoma (n = 1); parotid gland adenocarcinoma (n = 1); endometrial adenocarcinoma (n = 1); bladder adenocarcinoma (n = 1).

[b] Lymph nodes, bone, soft tissue.

[c] Target lesion registered at baseline.

[d] Median tumor size considering all tumors treated (n = 1304) according to tumor histotypes was as follows: SCC, 30 mm (IQ range, 16–50);

chosen for the covariance structure. All statistical analyses were performed using the SAS statistical package (SAS, rel. 9.4; SAS Institute Inc., Cary, NC).

Results

Study population

We enrolled 394 patients (Fig. 1). This report includes 376 eligible patients fulfilling the inclusion criteria (Table 1). The median time from the diagnosis of primary tumor to ECT was 2 years (range, 0.5–52). Among melanoma and breast cancer patients, visceral metastases were present in 65/211 (30.8%) and 16/31 (51.6%), respectively. The total number of target lesions was 1304 (median 3 per patient, Interquartile (IQ) range, 1–5), median size being 10 mm (IQ range, 6–20).

Procedure

Two hundred eighty-seven (76.3%) patients underwent a single ECT (Table 2). The remaining 89 (23.7%) patients received from 2 up to 6 ECT courses on partially responding (n = 27) or newly occurred tumors (n = 62). Retreatment involved 124 of 1304 (9.6%) target lesions. As to the route of drug administration, adherence to ESOPE guidelines was 88% (range, 15.6–96.5% according to specific clinical scenarios), while as to the type of electrode adherence was 70% (range, 8.7–76.5%) (Supplementary Table 1). One-hundred seventy-seven (47.1%) subjects received further oncological treatments after ECT, including cytotoxic chemotherapy, immunotherapy and radiation.

Toxicity

Systemic

No treatment-related serious adverse events were reported during the procedure; during anesthesia monitoring, we observed grade 1 or 2 cardiac arrhythmia (atrial fibrillation or sinus bradycardia) in 15 patients. During the hospital stay, which lasted a median of 1 day (range, 1–4), 55/394 (13.9%) patients developed mild constitutional symptoms. One patient developed grade 3 thrombocytopenia, which was incidentally discovered and required no intervention.

Local

Distribution of dermatological toxicity was reported in 361 patients: grade 0, 150 patients (41.5%); grade 1, 118

STS, 15.5 mm (IQ range, 10–35); BC, 15 mm (IQ range, 10–35); BCC, 15 mm (IQ range, 10–30); Kaposi sarcoma, 10 mm (IQ range, 7–20); melanoma, 10 mm (IQ range 5–15).

[e] Since occurrence of skin metastases.

[f] Also more than one previous treatment per patients.

Table 2
Treatment details (N = 376 patients).

Characteristics	No.	%
Anesthesia		
Local	48	12.8
General sedation	243	64.6
General anesthesia[a]	77	20.5
Not known	8	2.1
Drug		
i.v. BLM	351	93.4
i.t. BLM	23	5.9
i.t. CDDP	2	0.5
Operating modality (ESOPE)		
A[b]	7	1.9
B[c]	41	10.9
C[d]	18	4.8
D[e]	302	82.7
Other[f]	8	2.1
Electrode type		
Needle, hexagonal array	284	75.5
Needle, linear array	72	19.1
Plate	13	3.5
Multiple electrodes	7	1.9
No of ECT cycles		
1	287	76.3
2	72	19.1
3	13	3.5
4	3	0.8
6	1	0.3

Legend: i.v., intravenous; i.t., intratumoral; BLM, bleomycin; CDDP, cisplatin; ESOPE, European Standard Operative Procedures of Electrochemotherapy — see Mir, 2006 [ref. 17].
[a] Twenty-three patients received ECT during surgical intervention.
[b] Local anesthesia and i.t. chemotherapy.
[c] Local anesthesia and i.v. chemotherapy.
[d] General sedation/anesthesia and i.t. chemotherapy.
[e] General sedation/anesthesia and i.v. chemotherapy.
[f] Anesthesia not known and i.v. chemotherapy.

patients (32.7%); grade 2, 65 patients (18.0%); grade 3, 23 patients (6.4%); grade 4, 5 patients (1.4%). The occurrence of toxicity was associated with tumor size >2 cm ($p < 0.001$) (Table 3). One hundred sixty-three patients (41.3%) reported skin pain, its severity being grade 2 or 3 in 12 (3%) and 4 (1%) cases, respectively. Five (1.3%) patients transiently required treatment with opioids. We did not find any association between post-ECT pain and patient characteristics or ECT parameters (data not shown). A female melanoma patient who received ECT in the axillary region, in the field of previous lymph node dissection and subsequent resections of soft tissue recurrences, developed a motor and sensory neuropathy shortly after the procedure. In particular, she reported paresthesias and pain in her upper extremity and weakness of shoulder abduction, which lasted six months and required treatment with opioids, pregabalin and tricyclic antidepressants. Intraprocedural electric current ranged from 1 to 3.5 A. Electrodiagnostic study, performed after 1 month, was suggestive for axillary neuropathy, while ulnar and radial sensory nerve conduction were normal.

Table 3
Skin toxicity after electrochemotherapy according to patient characteristics (n = 361).

Variable	No. of pts	Toxicity (NCI-CTCAE v3.0)				p-value[a]
		Grade 0—1		Grade 2—4		
		No	%	No	%	
Tumor Histotype						—
Melanoma	211	158	74.9	53	25.1	
Kaposi	40	37	92.5	3	7.5	
SCC	35	21	60.0	14	40.0	
BCC	17	17	100	0	—	
BC	31	15	48.4	16	51.6	
STS	10	7	70.0	3	30.0	
Other histotype	17	13	76.5	4	23.5	
Tumor Histotype						0.740
Melanoma	211	158	74.9	53	25.1	
Non-melanoma	150	110	73.3	40	26.7	
Tumor location						0.094
Head and neck	51	38	74.5	13	25.5	
Trunk	75	51	68.0	24	32.0	
Lower limb	168	124	73.8	44	26.2	
Upper limb	16	10	62.5	6	37.5	
Multiple	51	45	88.2	6	11.8	
Max tumor size						**<0.001**
<20 mm	155	130	83.9	25	16.1	
≥20 mm	206	139	67.5	67	32.5	

Legend: SCC, squamous cell carcinoma; BCC, basal cell carcinoma; BC, breast cancer; STS, soft tissue sarcomas.
[a] Chi-square test.

Tumor response

Efficacy data are presented in Table 4. The majority of complete responses were observed by the time of the second tumor assessment at 2 months (50.0% vs 30.1% at 1 month). Tumor size emerged as the exclusive predictor of response at univariate analysis (Supplementary Table 2). The rate of complete response was 62.1% in patients with small (<2 cm) tumors compared with 41.5% in patients with larger tumors (OR 2.31, 95% CI 1.34—3.96, $p = 0.002$). Although not significant at statistical analysis, tumor response rate (and CR rate) at 60 days according to histotype was as follows: breast cancer, 89.5% (36.8%); BCC, 88.9% (66.7%); Kaposi sarcoma, 88.9 (44.4%); SCC, 85.2% (40.7%); soft tissue sarcoma, 83.3% (83.3%); melanoma, 83.1% (53.7%); other histotypes, 60% (30%). We did not observe any regression on untreated tumors, consistent with lack of an abscopal effect.

Local control

The rate of LPFS at one year was 73.7% (95% CI, 68.4—78.3), median LPFS was 28.3 months (range, 23.0—37.6) (Table 4, Fig. 2a). While univariate analysis showed that PS, tumor histotype, tumor location, number of tumors and tumor size significantly affected LPFS, only PS ($p = 0.004$), tumor histotype ($p < 0.001$), location ($p < 0.001$) and size ($p = 0.004$) were significant

Table 4
Efficacy summary.

Local response	No.	%
At 30 days, *per-tumor* evaluation[a]		
CR	371	37.6
PR	291	29.5
SD	287	29.1
PD	37	3.8
At 60 days, *per-tumor* evaluation[b]		
CR	494	60.9
PR	141	17.4
SD	152	18.7
PD	24	3.0
At 30 days, *per-patient* evaluation[c]		
CR	88	30.1
PR	133	45.5
SD	62	21.2
PD	8	2.7
Not evaluable	1	0.3
At 60 days, *per-patient* evaluation[d]		
CR	113	50.0
PR	75	33.2
SD	30	13.3
PD	7	3.1
Not evaluable	1	0.4

End point	Value
Follow-up	
Median duration for alive patients − months (range)	13.9 (0.4−63.2)
Local (in-field) progression-free survival	
Median duration − months (95% CI)	28.3 (23.0−37.6)
1-year (95% CI)	73.7 (68.4−78.3)
Status at last f-up − No pts (%)	
Dead	140 (37.2)
Alive	236 (62.8)
Overall survival	
Median duration − months (95% CI)	34.6 (27.4−41.9)
1-year (95% CI)	80.0 (75.0−84.2)
Disease status at last follow-up − No pts (%)	
Disease free	81 (34.3)
Alive with skin metastases	58 (24.6)
Alive with skin and visceral metastases	31 (13.1)
Alive with visceral metastases	58 (24.6)
Unknown	8 (3.4)
Appearance of new lesions[e] − No pts (%)	
Yes	175 (46.5)
No	186 (49.5)
Unknown	15 (4.0)

[a] Assessed on 986/1304 (75.6%) of baseline tumors.
[b] Assessed on 811/1304 (62.2%) of baseline tumors.
[c] Assessed on 292/376 (77.7%) patients.
[d] Assessed on 226/376 (60.1%) patients.
[e] Metastases occurred outside ECT field.

predictors on multivariate analysis (Supplementary Table 3). LPFS of patients who received intravenous chemotherapy was comparable to that of patients who received intratumoral chemotherapy (Fig. 2b). Out-of-field metastases occurred in 175 (46.5%) patients. In the melanoma subgroup, there were 25 (11.8%) subjects (18 with lower limb tumors) who did not develop out-of-field recurrence. Overall, 156 (41.5%) patients developed distant, non-skin, disease progression.

Quality of life

Two hundreds and eleven patients (56%) compiled the EORTC QLQ-C30 (Table 5) at baseline, 30 and 60 days from ECT treatment. The *Global Health Status score* progressively increased from 59.6 (baseline) to 64.7 (1 month), up to 65.7 (2 months) ($p < 0.001$). We observed a lower score in patients with tumors ≥ 2 cm, compared with those with tumors <2 cm ($p = 0.018$); nonetheless, a significant increase after ECT was observed in both these groups ($p < 0.001$, Supplementary Table 4). The scores of the *five functional scales* did not changed after ECT as well as those of the symptom scales. Among the *six symptom single-item scales*, a statistically significant improvement was observed only in the *Constipation* scale ($p = 0.027$).

One hundred and seventy-nine patients (47.6%) compiled the 8-item questionnaire (Supplementary Table 5). Among the investigated items, the scores of wound bleeding ($p < 0.001$), healing ($p = 0.002$), and aesthetics ($p < 0.001$) showed a statistically significant improvement. The percentage of patients who stated that they would have accepted re-treatment, if required, was 79.3% (142/179) and 82.7% (148/179) at 1 and 2 months, respectively (Supplementary Table 6). The acceptance rate was higher in those with small tumors compared with those with larger tumors at one-month assessment (89.2% vs 72.4%, $p = 0.006$), but rates were similar at two-month evaluation (86.5 vs 80.0%, $p = 0.259$).

Discussion

This multicentric study, which is based on the largest prospective series published so far, strongly supports the efficacy of ECT in patients with superficial metastases from any histotype and skin cancers. ECT yielded sustained and durable response, with contained toxicity; furthermore, it appeared to preserve and, in some cases, positively influence health-related quality of life outcomes. Ultimately, this turned into a high acceptance rate by patients. As the number of involved centers increases, and multicenter trials are advocated to support ECT evidence basis, it is crucial to reach a consensus on patient selection, treatment application as well as to collect reliable outcome data in order to inform patients.[19]

Overall, despite some discrepancies, clinicians had a high level of adherence to the ESOPE protocol. In particular, in patients with more than 5 tumors (in whom intravenous chemotherapy is recommended) and in those with tumors ≥ 0.8 cm (in whom the hexagonal needle electrode is recommended), the adherence rate was 76.5% and 96.6%, respectively. According to our experience, the majority of ECT candidates can safely undergo the procedure under general sedation, thus confirming that this treatment is well tolerated and easily manageable from the anesthesiology point of view. In 20% of cases, ECT was carried out under general anesthesia, since treatment was applied intraoperatively, i.e., during major surgical procedures.
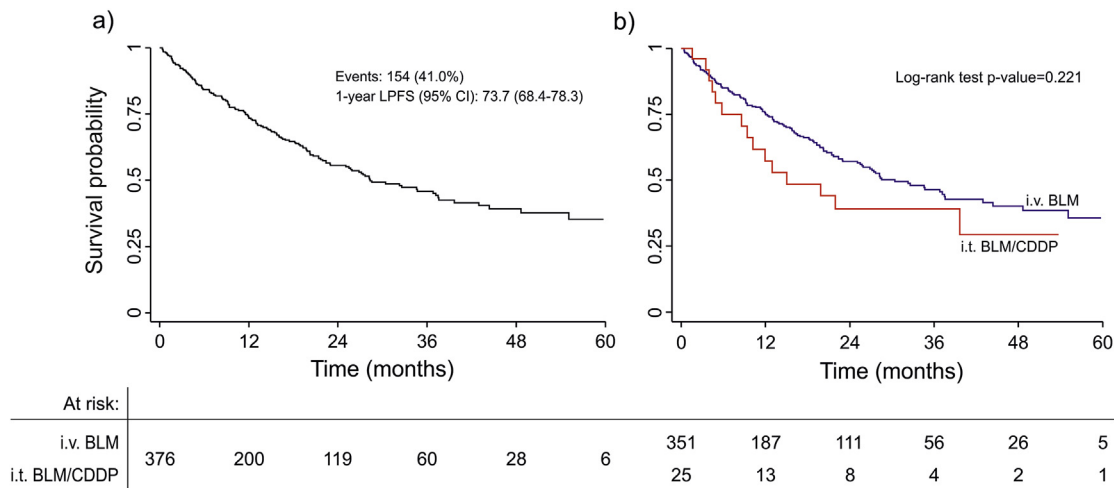
Figure 2. Local progression-free survival (LPFS) of patient with cutaneous metastases or skin cancers after electrochemotherapy. (a) LPFS of the entire study cohort. (b) LPFS according to the route of drug administration. *Legend:* BLM, bleomycin; CDDP, cisplatin; i.v., intravenous; i.t., intratumoral.

ECT side-effects were mainly confined to skin, with grade ≥3 adverse events being under 8%. These outcomes compare well with previous reports on ECT in melanoma[25,26] and breast cancer,[20] and also with other skin-directed treatments (e.g., photodynamic, intralesional and topical therapies), which are associated with grade ≥3 toxicity in less than 6% of patients.[5–7]

Although in small number, we observed that breast cancer histotype and in particular tumor size >2 cm were associated with higher rates of skin toxicity (Table 3). Breast

Table 5
Quality of life outcomes after electrochemotherapy (EORTC QLQ-C30[a]).

Electrochemotherapy (N = 211 patients)				
Scale	Baseline mean ± SD	30 days mean ± SD	60 days mean ± SD	p^{*}
Global health status				
Global health status	59.56 ± 22.83	64.73 ± 21.27	65.67 ± 22.87	**<0.0001**
Functional scales				
Physical functioning	75.38 ± 22.04	76.34 ± 20.92	75.22 ± 23.89	0.4541
Role functioning	78.04 ± 25.29	78.04 ± 24.82	78.20 ± 26.45	0.9833
Emotional functioning	76.59 ± 21.71	78.37 ± 21.98	78.81 ± 22.56	0.0770
Cognitive functioning	90.32 ± 16.67	90.92 ± 17.07	91.59 ± 14.79	0.3793
Social functioning	85.48 ± 22.40	87.04 ± 21.72	87.46 ± 21.48	0.1715
Symptom scales				
Fatigue	20.01 ± 20.37	21.85 ± 20.75	21.87 ± 22.34	0.1695
Nausea/vomiting	3.00 ± 8.99	1.89 ± 6.63	2.45 ± 8.49	0.2441
Pain	22.75 ± 24.37	22.04 ± 23.35	20.06 ± 24.29	0.1582
Dyspnea	10.21 ± 18.55	10.00 ± 18.74	10.27 ± 17.96	0.9511
Insomnia	21.17 ± 24.66	19.77 ± 24.33	19.68 ± 25.55	0.5135
Appetite loss	9.05 ± 17.18	9.05 ± 17.79	8.57 ± 17.58	0.9143
Constipation	11.59 ± 21.83	8.73 ± 17.95	9.21 ± 19.29	**0.0269**
Diarrhea	2.07 ± 9.86	1.26 ± 8.51	1.90 ± 10.13	0.4527
Financial problems	6.67 ± 15.57	6.51 ± 14.76	6.89 ± 17.66	0.7205

* *p*-value for ANOVA with Greenhouse-Geisser correction.
Comparison on each measure were made at three time points, using repeated measures analysis of variance (ANOVA) with time point as within-subject factor. Mauchly's test was executed to verify the assumption of sphericity and adjusted F test proposed by Greenhouse-Geisser was considered when sphericity did not meet.
Bonferroni's test for multiple comparison was used to test for significant differences in QOL scores over time since the sphericity condition is not met (the Bonferroni procedures is the best one to use in terms of type I error control).
^{a} The EORTC QLQ-C30 is a cancer-specific, self-administered 30-question instrument for evaluating the QoL in cancer patients. The questionnaire items are grouped into five functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning); three symptom scales (fatigue, nausea and vomiting, and pain); six symptom single-item scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and one global health status (GHS)/QoL scale. Of the 30 items, 28 are scored on four-point Likert scales and the remaining two items (29 and 30, for global health status) are scored on modified seven-point linear analog scales. Scores were derived from mutually exclusive sets of items, with scale scores ranging from 0 to 100 after linear transformation. Higher scores for the functioning and GHS/QoL scales indicated a higher level of functioning and a better QoL, respectively, whereas higher scores in symptom scales represented a higher level of symptom.

cancer patients generally undergo ECT after several lines of treatment, also including radiation, which may increase the risk of toxicity, as suggested by a phase II study in women with chest wall recurrence who were previously irradiated.[20] Large/widespread tumors are managed by means of the hexagonal electrode, which allows treatment of extensive skin surfaces; this, in turn, may induce tissue ischemia, due to the strong vascular disrupting effect of ECT.[27] It is advisable that clinicians are aware of these eventualities, since, when tumor necrosis and/or skin ulceration occur, timely surgical debridement and appropriate wound dressing is required.[20]

Pain control represent another relevant aspect of post-ECT management. In our study, 41% of patients reported pain, even though it was judged moderate or severe only in 3% and 1%, respectively. In the retrospective analysis of 121 ECT patients treated at seven European centers, moderate and severe pain were each reported by 13% of subjects.[28] This could be explained by the higher percentage (30%) of tumors in the head and neck region, the larger tumor size (median, 2.3 cm) and the more frequent application of local anesthesia (40% of patients), compared with the present study. On a multivariate analysis, pretreatment pain, high electric current intensity and diagnosis of melanoma or breast cancer were predictors of severe post-procedural pain.[28] We were not able to confirm these findings on our data. Of note, a melanoma patient who underwent ECT in the axillary region, in the field of previous multiple surgeries, reported relevant motor and sensor neuropathy. We hypothesize that extensive scarring may have altered local anatomy and possibly entrapped nerve fibers, thus making them vulnerable to injury by needle electrodes.

We observed an 80% overall response rate, with nearly half of patients achieving tumor regression after a single application. These findings confirm the ESOPE experience—where response rate also exceeded 80%, and results of more recent reports.[5,10,18,20—22,24,25,29—32] A comprehensive meta-analysis including both pre- and post-ESOPE studies indicates an 84.1% response rate, with 59.4% of complete responses.[18] Histotype-oriented studies, although not comparative,[19] indicate variable, but generally sustained response rates: up to 90% in melanoma,[25,26] ranging from 17% to 90% in breast cancer,[20,21,31] around 90% in soft tissue sarcomas and up to 100% in Kaposi sarcoma.[29,33] In the latter tumor type, the introduction of ECT (which yielded an 88.9% response rate with a 44.4% CR response rate in our study) seems particularly welcome since there is no standard therapy policy and conventional treatment options (i.e., radiation, intralesional therapies, cytotoxic chemotherapy) have specific limitations related to disease extension, number of skin metastases and myelotoxicity, respectively.[33]

Tumor size stood out as the exclusive predictor of tumor shrinkage. The patients with tumors smaller than 2 cm were 2.3 times more likely to achieve complete tumor regression compared with patients with larger tumors. This observation is in line with previous reports[25,26,34] and may have implications for patient selection and their management (i.e., need for additional ECT cycles). While incipient reports on ECT have focused on local response, more recent experiences highlight that durable tumor control can also be achieved.[20,24—26,29,33] Accordingly, 1-year LPFS in our study was 73.7% (Table 4, Fig. 2a), which compares well with the 73—88% control rate reported in the ESOPE trial.[10] However, the cumulative incidence of out-of-field recurrences was nearly 50%. These recurrences were managed with additional ECT cycles, nonetheless two different strategies could be pursued: the inclusion of treatment safety margins around tumors,[19] and the combination of ECT with immune modulating agents.[35,36] Interestingly, a subgroup (∼12%) of patients with lower limb melanomas remained free from new metastases and exclusive treatment with ECT ensured tumor control. This observation supports our previous experience, suggesting that patients with lower limbs in-transit metastases, particularly when small and limited in number, represent suitable candidates for treatment with ECT.[25]

Since cutaneous metastases generally portend a dismal prognosis, it is crucial that applied treatments preserve quality of life. According to the EORTC-QLQ C30, the *Global Health Status* showed a statistically significant improvement, while a collateral observation was the improvement of the *Constipation scale* score (Table 5). Interestingly, the 8-item questionnaire indicated a benefit in the items exploring skin metastases-associated complaints. Patient satisfaction was also confirmed by the high acceptance rate for retreatment, which ranged to 80%. We are aware that statistical differences cannot be automatically considered as clinically meaningful, nevertheless our results suggest that ECT does not deteriorate patient quality of life and that PROs deserve further investigation. A single study explored PROs after ECT so far. By administering the 8-item questionnaire to 35 melanoma patients, we found an improvement in wound healing, bleeding, esthetic impairment, and also in related aspects, such as activities of daily living and social relations.[24]

Our study has certain limitations. First, we included patients with heterogeneous malignancies and did not address the issue of which tumors might be most sensitive or resistant to ECT. Second, efficacy evaluation was focused on target lesions and on first ECT cycle, while in recent years evidence has accumulated that retreatment is beneficial in partial responders and in out-of-field relapses.[24,26] This is usually the case of melanoma patients with in-transit metastases, sarcoma patients with satellites, or breast cancer patients with lymphangitic tumor spread.[1] Therefore, it would be advisable that future studies include more details, such as out-of-field failure rate, efficacy of retreatment, and the effective number of ECT cycles required to achieve tumor control.[19] Another weakness was that tumor response was

clinically assessed, and thus possibly overestimated. Finally, it seems important to acknowledge that LPFS could have been influenced by further oncologic treatments and that PROs were partially investigated by means of a non-validated instrument.

In conclusion, the clinical experience with ECT is growing and the results are promising. However, due to the lack of high quality supporting evidence, the role of this treatment modality is yet to be fully defined. This multi-institutional real-world study adds on the evidence supporting skin-directed treatment with ECT in patients with superficial metastases and should foster the planning of well-designed (possibly comparative) trials.

Conflict of interest

Role of the funding source

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejso.2016.06.399.

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