European Journal of Cancer 63 (2016) 41–52

Available online at www.sciencedirect.com

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Original Research

European Research on Electrochemotherapy in Head and Neck Cancer (EURECA) project: Results of the treatment of skin cancer

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Received 5 February 2016; received in revised form 15 April 2016; accepted 2 May 2016
Available online 4 June 2016

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http://dx.doi.org/10.1016/j.ejca.2016.05.001

KEYWORDS
Electrochemotherapy;
Basal cell carcinoma;
Squamous cell carcinoma;
Malignant melanoma;
Head and neck;
Quality of life

Abstract Electrochemotherapy is an effective and safe method for local treatment of cutaneous and subcutaneous tumours, where electric pulses cause increased permeability of cell membranes in the tumour mass, enabling dramatically enhanced effectiveness of bleomycin and other hydrophilic drugs. Here, we report results of a European multi-institutional prospective study of the effectiveness of electrochemotherapy in the treatment of skin cancer of the head and neck (HN) area, where standard treatments had either failed or were not deemed suitable or declined by the patient. A total of 105 patients affected by primary or recurrent skin cancer of the HN area were enrolled; of these, 99 were eligible for evaluation of tumour response. By far, the majority (82%) were treated only once, and 18% of patients had a second treatment. The objective response was highest for basal cell carcinoma (97%) and for other histologies was 74%. Small, primary, and treatment-naive carcinomas responded significantly better ($p < 0.05$), as investigated by univariate analysis. Electrochemotherapy was well tolerated and led to a significant improvement of quality of life, estimated by the European Organisation for Research and Treatment of Cancer quality of life questionnaires. At 1-year follow-up, the percentages of overall and disease-free survival were 76% and 89%, respectively. Electrochemotherapy is an effective option for skin cancers of the HN area and can be considered a feasible alternative to standard treatments when such an alternative is appropriate. The precise role for electrochemotherapy in the treatment algorithm for non-melanoma skin cancer of the HN region requires data from future randomised controlled studies.
(ISRCTN registry N. 30427)

1. Introduction

Recurrent or locally advanced neoplasms of the head and neck (HN) area can be a considerable challenge for clinicians and debilitating for the patient, especially when important anatomical structures are involved.

Electrochemotherapy is a relatively new local ablative technique that utilises electroporation for enhanced drug (bleomycin or cisplatin) delivery to cells by generating transient permeation structures in the cell membrane [1–4]. Over the past 20 years, electrochemotherapy has been shown to have proved effectiveness in the treatment of cutaneous, subcutaneous, mucosal, or deep seated tumours of various histologies and in different body sites. It is also effective in controlling of bleeding from metastatic tumour deposits and mass-related symptoms [5–12]. Standard operating procedures for tumour management with electrochemotherapy were published in 2006 [13].

The main advantages of electrochemotherapy are high local tumour control with minimal damage to normal tissue, limited side-effects, and good cost/benefit ratio [10]. The objective response (OR) rate of skin tumours is achieved in 70–80% with good cosmetic results [12,14]. Recently, interest has increased for its use in treatment of the tumours in the HN area where specific clinical problems may arise due to failure or expected disfigurement of standard treatments. Clinical reports are now beginning to emerge describing electrochemotherapy in treatment of HN tumours [15–18].

With the aim of evaluating the acceptability and effectiveness of electrochemotherapy in treatment of cutaneous and mucosal cancer of HN area, a European multi-institutional co-operation was developed for the European Research on Electrochemotherapy in Head and Neck Cancer (EURECA) trial. We now report outcome data for electrochemotherapy treatment for cutaneous tumours in the HN area.

2. Patients and methods

Patients were enrolled and treated at six European institutions (Pavia, Ljubljana, Barcelona, Bradford, Amsterdam, and Copenhagen) participating in the EURECA project and working as part of the International Network for Sharing Practice in Electrochemotherapy (INSPECT) Network database (ISRCTN registry N. 30427). This European multi-institutional observational prospective longitudinal study was designed to evaluate the efficacy of electrochemotherapy in local tumour control as primary outcome measure. Secondary outcome measures were safety, overall and disease-free survival (DFS), and the quality of life for cancer patients with tumours in HN area. Each participating institution obtained institutional and/or ethical approval for the study with their respective bodies. Participating centres uploaded patient demographics, type of tumour, size and site of the target nodule (in case of multiple nodules of the largest one), previous treatments information, treatment sessions (no

more than two), tumour response, side-effects, evaluation of pain and quality of life, and follow-up data to the INSPECT database.

Eligible patients for the study were all patients affected by recurrent, metastatic, or primary cancer of the HN area not suitable for surgery or chemo/radiotherapy because of patient co-morbidity, anticipated negative outcome of major surgical intervention (high risk of major intra-postoperative complications, functional sequelae or poor cosmetic result, risk of prolonged anaesthesia, etc.), previous treatments or patient preference. The study also included patients with primary tumours who refused any other standard treatment. The treatment decision was taken at the level of a multidisciplinary board after thorough consultation which included surgeon, radiation and medical oncologist and the patient. Detailed inclusion and exclusion criteria are listed in Table 1.

2.1. Pre-operative evaluation

Selection of the target nodule was performed according to the RECIST criteria (version 1.1). The minimum tumour size for the application of electrochemotherapy was 1 cm in the longest diameter measured by caliper on clinical examination or by computed tomography/magnetic resonance imaging. All nodules were photographically documented.

Table 1
Inclusion and exclusion criteria for the application of electrochemotherapy.

Inclusion criteria	Exclusion criteria
1. Histologically verified cancer of any type	1. Other symptomatic lesions not under control
2. Progressive and/or metastatic disease	2. Lesions not suitable for electrochemotherapy (bone invasion, large vessels infiltration, etc.)
3. Primary disease not eligible for surgery for patient's general conditions or for the need of extensive surgery	3. Acute lung infection
4. Patients must have been offered standard treatments	4. Symptoms of poor lung function necessitates DLCO and patient cannot be treated if this is abnormal
5. Measurable lesions suitable for application of electric pulses	5. Severe coagulation disorders not correctable
6. Age > 18 years	6. Previous allergic reactions to bleomycin
7. Performance status (Karnofsky ≥70; WHO ≤2)	7. If cumulative dose of 240,000 IU BLM/m^2 was previously exceeded
8. Life expectancy >3 months	8. Chronic renal dysfunction (creatinine> 150 μmol/L)
9. Treatment free interval of at least 4 weeks after previously applied chemo- or radiotherapy to the target lesions	9. Pregnancy or lactation
10. Patients must be mentally capable of understanding the information given and sign informed consent	

WHO = World Health Organisation.

Pain intensity was evaluated using the Numeric Rating Scale (NRS) for pain [19]. NRS is a unidimensional 11-point numeric scale between '0' as 'no pain' and '10' as 'worst pain'. We used a previously published cutoff on NRS score [20]: 0–2 mild pain, 3–4 moderate pain, and 5–10 severe pain. Pain medication was registered as 'none', 'sometimes', 'controlled by non-opioids', 'controlled by opioids', 'uncontrolled', or 'unknown'.

Quality of life (QoL) was evaluated with three QoL questionnaires (EQ-5D, European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30, and EORTC QLQ-H&N35) [21–23].

2.2. Procedure

Electrochemotherapy was performed according to the standard operating procedures published in 2006 [13]. Bleomycin was administrated either intravenously (i.v.) or intratumourally (i.t.), depending on the site, size, number of skin nodules, and risk of pulmonary fibrosis. Local anaesthesia (in some centres with sedation) was generally used for treatment of <3 nodules, <2 cm in diameter located on the head or face, while general anaesthesia was preferred in cases with more than three nodules or when tumours were larger than 2 cm, or located on the lip, chin, cheek or neck. Electric pulses (eight pulses of 100 μs duration, amplitude of 1000 V/cm for needle electrodes or 1300 V/cm for plate electrodes) were delivered with an electroporator (IGEA srl, Carpi, Italy) immediately after the i.t. injection or 8 min after the i.v. injection of bleomycin. The type of the electrode (plate, row-needle, hexagonal or finger) (IGEA srl) was chosen according to site, size and shape of the nodule.

2.3. Postoperative evaluation

NRS for pain and QoL questionnaires were collected every day during inpatient stay and at each follow-up visit, respectively.

The first two follow-up visits were planned at 1 and 2 months after electrochemotherapy. The cutoff point for tumour response evaluation was fixed at 2 months. Tumour response of target lesions was made according to the RECIST criteria (version 1.1). Biopsies for verification of tumour response were performed only in case of unclear clinical and/or radiological evidences.

At each visit, patients were submitted to the same examinations as during pre-operative evaluation (clinical and radiological, photographic, QoL questionnaires). Adverse events and side-effects were rated according to the CTCAE, version 4.02.

In cases with partial response (PR) at 2 months follow-up, a second electrochemotherapy treatment was considered. In cases with stable disease (SD) or

progressive disease (PD), or stable response or PR after the second electrochemotherapy, other treatment options were considered and applied.

All complete responders were followed up at 4, 8, and 12 months after the treatment. At each follow-up visit, the same examinations as applied in pre-operative evaluation were performed.

2.4. Statistics

SPSS (15.0; Statistical Packages for Social Sciences, Chicago, IL, USA) was used for statistical analysis. In descriptive analysis, categoric variables have been reported as absolute frequency numbers and percentages; continuous variables have been reported in terms of median value and range (minimum–maximum). Response to treatment was analysed in terms of rate and compared among groups by the chi-square test. In follow-up analysis versus baseline, Wilcoxon paired rank test of sign was used for ordinal data and McNemar's test for nominal data. Analysis of variance test for repeated measurements was used to test the hypothesis controlling for influence of covariates. For survival analysis, Kaplan–Meier analysis was applied. This analysis was also used to determine 1-year survival, together with 95% confidence interval. Local DFS was calculated among patients who reached a complete response (CR), and progression was defined as appearance of new nodules/recurrences in the treated area. The analysis of local DFS was performed also on the whole population, by adapting the survival data on CR patients with the percentage of CR in the whole population.

3. Results

3.1. Patients

Between November 2011 and January 2015, 105 patients with tumours of the skin in the HN area were consecutively included. Patient demography is listed in Table 2.

3.2. Tumour histology

According to the protocol, only one target lesion was taken into consideration for the evaluation of tumour response to electrochemotherapy (Table 3). Among the 105 electrochemotherapy treated nodules, 50 were squamous cell carcinoma (SCC), followed by 34 basal cell carcinoma (BCC), 10 melanoma metastases, and 11 nodules of other histology (3 undifferentiated carcinoma, 3 adenocarcinoma, 1 renal carcinoma, 1 leiomyosarcoma, 1 lentigo maligna, 1 syringoma, and 1 sarcomatous tumour). Fig. 1 illustrates the distribution of the tumour nodules according to anatomical subsites.

Tumours were segregated into smaller and larger than 3 cm in diameter (overall the tumours ranged from 0.2 to 14.5 cm; median 2 cm), the larger lesions comprising 34% of all the treated nodules (Table 3).

All target tumours were submitted to an initial electrochemotherapy session, while 19 (18%) were re-treated with a second electrochemotherapy session after a median time of 114 d (range 21–280 d), to treat residual tumour (Table 4).

Table 2
Patient demography and treatment choices.

Pre-treatment visit (105 patients)	N	%
Gender		
- Male	75	71
- Female	30	29
Age (years)		
- Median	77	
- Range	39–96	
- <70	26	25
- 70–80	41	39
- >80	38	36
Diagnosis		
BCC	34	32
SCC	50	48
MM	10	9
Other	11	11
Primary disease		
- Stage I–II	43	81
- Stage III–IV	10	19
Recurrent/metastatic disease		
- Stage I–II	45	87
- Stage III–IV	7	13
Previous treatments		
- Surgery only	33	31
- CT/RT	10	9
- Surgery + CT/RT	32	31
- No treatment	28	27
- Unknown	2	2
Bleomycin administration		
- Local	8	8
- Systemic	97	92
Anaesthesia		
- Local	46	44
- General	59	56
Electrodes used		
- Plate	4	4
- Row needle	46	44
- Hexagonal	51	49
- Combination	4	4

BCC = basal cell carcinoma; CT = chemotherapy; MM = malignant melanoma; RT = radiotherapy; SCC = squamous cell carcinoma.

Table 3
Size of the treated nodules according to the different histologies.

Histology	≤3 cm	>3 cm	Total (%)
BCC	31	3	34 (32)
SCC	26	24	50 (48)
MM	8	2	10 (9)
Other	4	7	11 (11)
Total	69 (66%)	36 (34%)	105 (100)

BCC = basal cell carcinoma; MM = malignant melanoma; SCC = squamous cell carcinoma.

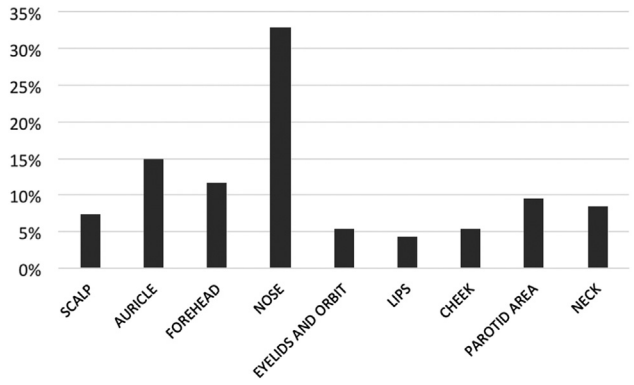

Fig. 1. Distribution of the tumour nodules according to the different anatomical subsites.

Of these 105 patients, six were not considered in the outcome analysis because the required follow-up of 60 d was not possible. Four had died due to systemic progression of the disease not related to the procedure, one was lost to follow-up, and one patient suffered a serious adverse event (sepsis-related death post-treatment; see below). Ninety-nine patients (94%) were finally eligible for evaluation of tumour response.

3.3. Tumour response

The highest response rate was observed with BCC (Table 5). Tumours were 20 primary and 14 recurrent BCC. Thirty-three of 34 (97%) BCC responded with OR, and of these 91% were CR (Figs 2 and 3). The treatment was successful also in two of the three tumours that were larger than 3 cm. The only patient with SD had extensive recurrent lesion of the left orbit and was not re-treated. Of the two partial responders, one was re-treated with further PR, and the other was not re-treated but showed regression of the lesion over the time.

Overall, 48 (74%) of the 65 other tumour types showed a response to treatment. Among these, 48% were CR, 26% PR, and 19% were SD, 4 (6%) PD, and 1 (1%) was not evaluable (NA) due to crust formation and ulceration at the cutoff point of 2 months (Table 5). Among this group of other histological tumour types, the higher percentages of OR were observed for SCC (Figs 4 and 5) and MM (79% and 77%, respectively).

Univariate analysis of factors influencing tumour response revealed that it was independent of the different methods of bleomycin administration, while tumour characteristics and previous treatments showed significant correlations, as reported in detail here below.

Tumour size in all the tumours (BCC and all other histologies) significantly affected the response to electrochemotherapy, i.e. smaller tumours had a higher response rate (chi-square test $p = 0.0299$). In more detail, tumours ≤ 3 cm in diameter showed OR of 88%, whereas for tumours >3 cm in diameter OR was 68%.

Primary tumours responded better than secondary (recurrent/metastatic) tumours (chi-square test $p = 0.0330$). In fact, for the 50 primary tumours, the percentage of CR was 70%, PR 20%, SD 8%, and PD 2%. In 49 secondary tumours, the percentage for CR was 55%, PR 18.5%, SD 18.5%, and PD 6%, and 2% of treated tumours were not evaluable for response.

Tumours which were not treatment naive showed reduced effectiveness of electrochemotherapy (no treatment versus previous treatments, chi-square test $p = 0.0269$). Interestingly, for recurrent tumour nodules, previous surgery least affected the outcome compared to (chemo) radiotherapy or multiple treatments. Among the 49 patients with secondary tumours, 23 had received only surgery as previous treatment, while 21 had received surgery plus radiotherapy or chemotherapy (or both) and four had received radiotherapy or chemotherapy (or both). For one patient, previous treatments were not reported. The response of these tumours in patients previously treated with surgery was 78% CR, 9% PR, and 13% SD. In patients receiving surgery plus chemotherapy or radiotherapy, 43% had CR, 24% PR, 19% SD, 9% PD, and 5% NA. Finally, among the four patients receiving only chemotherapy or radiotherapy, we observed 1 CR (25%), 2 PR (50%), and 1 PD (25%). The trend from CR in patients previously treated with surgery shifted towards PR with chemotherapy and/or radiotherapy and analysis with the chi-square test demonstrated a significant difference in outcome among these groups (surgery only versus other treatments [$p = 0.0394$]).

3.4. Safety of the procedure and side-effects

Crust formation over the treatment was considered part of the healing process. Minor side-effects included: actual skin ulceration (14 patients, 5 of grade III), skin hyperpigmentation (7 patients, grade I/II), suppuration (4 patients, grade I/II), headache (1 patient, grade I), nausea (1 patient, grade II), skin odour (2 patients, grade I/II), dysphagia (1 patient, grade II), and maculopapular rash (1 patient, grade II).

There was only one major adverse event. A patient with a large ulcerated tumour died with symptoms attributable to septic shock on the second day after the procedure, despite the intra- and postoperative antibiotic administration and best supportive care.

In cases of extensive full thickness lesions of cheek, chin and lips, we observed massive tumour necrosis with the appearance of loss of oral competence and salivary fistula formation (four patients). In these cases, no surgical intervention was performed due to the advanced and local PD; only local medications, feeding tubes or percutaneous endoscopic gastrostomy (PEG) were used when necessary.

Moreover, recurrent lesions of the scalp with bone exposure did not undergo, even in case of CR, closure of

Table 4
Sessions of electrochemotherapy.

Sessions	N. (%)	Primary	Recurrence	≤3 cm	>3 cm
I Electrochemo therapy	86 (82%)	43	43	53	33
II Electrochemo therapies	19 (18%)	10	9	16	3
Total	105 (100%)	53	52	69	36

the skin defect. All the other cases with CR to treatment healed well with no or only minor tissue defects.

3.5. Pain

Electrochemotherapy did not significantly affect pain levels in patients with no or only mild pain reported before the treatment. It did not relieve pain in patients with pain before treatment. However, during follow-up, the percentage of patients with no pain significantly increased (70–90% at 3 months), and incidence of severe pain significantly decreased (19–3% at 3 months).

Univariate analysis of factors influencing the post-operative pain score revealed that pain in the first month after treatment was significantly higher in patients with larger lesion size ($p < 0.0001$), lesions in previously irradiated areas ($p = 0.0005$), and SCC ($p = 0.009$).

The percentage of patients not taking pain medication (70% before treatment) increased after treatment up to 82% at 3 months after electrochemotherapy, and it is noteworthy that only few patients took opioids at baseline (11%), falling to 2% after treatment.

3.6. Quality of life

The analysis of QoL showed a significant progressive positive perception of well-being for the EQ-5D (Fig. 6), a significant improvement of physical functioning, role functioning and decrease of fatigue and pain for QLQ-C30 (Fig. 7). There was a general improvement in all domains of the QLQ-H&N35, with perception of feeling ill, pain and use of analgesics, and mouth opening being the most significant (Fig. 8).

3.7. Survival

During 1-year follow-up (median 6 months; range 15 d – 12 months), 10 of the 62 patients with CR (16%) had a recurrence in the treated area after a mean period of 8.3 ± 3.5 months (median 8.1, range 2.6–13.6) after the first electrochemotherapy. Of these, four were BCC and six were SCC. The dimensions of the original lesions in these cases were 25, 10, 8, and 5 mm and 50, 24, 17, 15, 15, and 7 mm, respectively.

Further analysis of these ten patients showed that four were treated only once and then went off study; three patients had already received two cycles of electrochemotherapy when they had recurrences and went off study for other treatments and three patients were retreated immediately after recurrence (two of these had CR, the last went off study because unwilling to follow-up).

Kaplan–Meier overall survival curves for the whole group of patients and for the different histologies are shown in Figs. 8 and 9. At 12 months of follow-up, the overall survival rate was 76% (confidence interval [CI] 66–85%). All BCC patients survived during the follow-up period, survival rate at 12 months for SCC patients was 64% (CI 49–78%); for MM 89% (CI 68–100%) and for the other histologies 46% (CI 4–88%).

Analysis of the 1-year local DFS made on the whole cohort of patients as well as for the subgroup of patients with CR and for their different histologies are illustrated in Figs. 10 and 11. Among CR patients, we observed an overall DFS of 89% (CI 69–97%) with the following differences for the different histologies: MM 100% (only four cases reached 1-year follow-up), BCC 89% (CI 75–100%), and SCC 87% (CI 72–100%).

Table 5
Response of skin cancer evaluated at 2 months follow-up.

Response/histology	No. of lesions (%)	≤3 cm	>3 cm
BCC			
CR	31/34 (91%)	29/34 (85%)	2/34 (6%)
PR	2/34 (6%)	2/34 (6%)	0/34 (0%)
SD	1/34 (3%)	0/34 (0%)	1/34 (3%)
PD	0/34 (0%)	0/34 (0%)	0/34 (0%)
NA	0/34 (0%)	0/34 (0%)	0/34 (0%)
Subtotal	34/34 (100%)	31/34 (91%)	3/34 (9%)
SCC			
CR	26/47 (55%)	20/47 (43%)	6/47 (12%)
PR	11/47 (24%)	2/47 (4%)	9/47 (20%)
SD	7/47 (15%)	4/47 (8%)	3/47 (7%)
PD	2/47 (4%)	0/47 (0%)	2/47 (4%)
NA	1/47 (2%)	0/47 (0%)	1/47 (2%)
Subtotal	47/47 (100%)	26/47 (55%)	21/47 (45%)
MM			
CR	5/9 (55%)	4/9 (44%)	1/9 (11%)
PR	2/9 (22%)	2/9 (22%)	0/9 (0%)
SD	1/9 (11%)	1/9 (11%)	0/9 (0%)
PD	1/9 (11%)	0/9 (0%)	1/9 (11%)
NA	0/9 (0%)	0/9 (0%)	0/9 (0%)
Subtotal	9/9 (100%)	7/9 (78%)	2/9 (22%)
Other			
CR	0/9 (0%)	0/9 (0%)	0/9 (0%)
PR	4/9 (44%)	1/9 (11%)	3/9 (33%)
SD	4/9 (44%)	3/9 (33%)	1/9 (11%)
PD	1/9 (11%)	0/9 (0%)	1/9 (11%)
NA	0/9 (0%)	0/9 (0%)	0/9 (0%)
Subtotal	9/9 (100%)	4/9 (44%)	5/9 (56%)
Total	**99/99 (100%)**	**68/99 (69%)**	**31/99 (31%)**

BCC = basal cell carcinoma; CR = complete response; MM = malignant melanoma; NA = not available for crusts or ulceration; Other = other skin malignancies; PR = partial response; PD = progressive disease; SCC = squamous cell carcinoma; SD = stable disease.
≤3 cm = maximum diameter of the target lesion less or equal to 3 cm; >3 cm = maximum diameter of the target lesion greater than 3 cm.

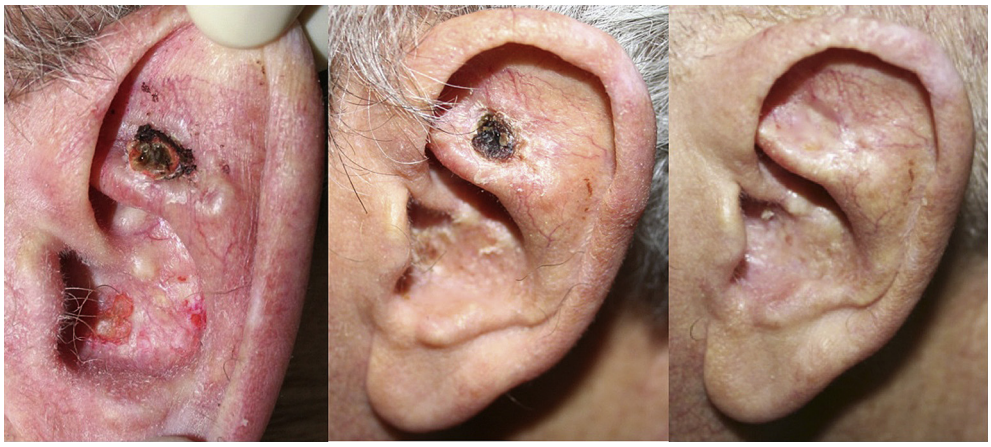

Fig. 2. Primary BCC: baseline (left), 2 months after ECT (center), and 1 year after ECT (right) (finger electrode 10 mm, local anaesthesia, i.v. bleomycin 15,000 IU/m^2, 3 pulses). The patient was offered surgery and radiotherapy but refused both due to respectively cosmetical and functional outcome (surgery), and long duration treatment (radiotherapy). The patient explained that he would prefer to try ECT reserving surgery or radiotherapy for possible recurrence.

4. Discussion

This study describes the largest clinical trial of melanoma and non-melanoma skin cancers of the HN area treated with bleomycin electrochemotherapy. This modality is shown to be effective with OR rates in accordance with previous papers ranging from 59% to 100% [15,17,18]. The response rates here reported must be seen in the light of this study reporting results of electrochemotherapy in patients with tumours recurrent after other treatments (71%) and also with a high percentage of tumours over 3 cm in diameter (34%). In addition, 1-year overall survival and local DFS rates (76% and 89%, respectively) were favourable, further confirming the effectiveness of this treatment in skin tumours of the HN area. We also demonstrate for the first time that quality of life was improved after electrochemotherapy with long-lasting positive effects on pain control, perception of well-being, physical functioning, and role functioning, as demonstrated by the results of the three QoL questionnaires.

The success of this treatment was dependent on tumour type and was most effective in BCC, in agreement with other studies [5,15,24–26]. Our findings also suggest that the use of electrochemotherapy should be as early as possible in disease progression in selected cases, such as the elderly or patients with multifocal disease to avoid disfiguring treatment outcomes.

Unfortunately, our data do not provide information about tumour response with different subtypes of BCC (nodular versus morphemic) due to histopathological details not being recorded. Our data suggest that a margin of normal-appearing tissue surrounding the lesion of at least 5–10 mm, adapted to the shape and size of the lesion, must be treated to maximise tumour response. This is similar to guidelines for surgical treatment and radiotherapy planning [27].

The high response rates seen in this study appears to be influenced by several factors, which should be taken into consideration when deciding on the best treatment option for individual patient.

The response to electrochemotherapy is significantly correlated with tumour size, as has previously been demonstrated [10]. These studies demonstrated that electrochemotherapy is more effective in small tumour nodules (<3 cm) and in sarcoma compared with carcinoma tumour nodules. This previous work could not evaluate differences in time to response by differing tumour types and this is a novel finding in our work.

Response rate was also dependent on previous treatment. The most responsive cases were treatment-naive patients with primary tumours, whereas previous chemotherapy and/or (chemo)radiotherapy significantly decreased tumour response rate. These data lead us to similar conclusions to those of Campana et al. [18] in a retrospective series of non-melanoma HN cancers. These investigators stated that chemotherapy resistance and changes in tissue produced by previous treatments, such as disruption of the vasculature, scarring or necrosis, can impair blood supply thus impairing drug distribution.

This study has also confirmed that electrochemotherapy is in general a safe procedure, with only minimal side-effects, in line with previous reports [8,17].

Regarding the ulceration and healing time, an important issue is dose of the drug. In some earlier studies [2], an i.t. dose of bleomycin 5 times larger than the one used in the current study (which results from the Standard operating procedures [SOP] of the ESOPE study [13]) and a voltage of 1.3 kV/cm were used, whereas in the current study, in accordance with the SOP published from the ESOPE group [13], only 1 kV/cm was used for the needle electrodes. The higher dose of bleomycin (fivefold greater), combined with almost

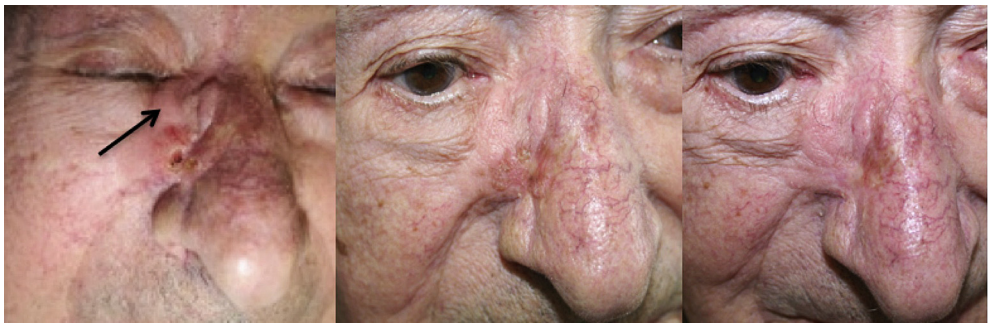

Fig. 3. Recurrent BCC: baseline (left), 2 months after ECT (center), 1 year after ECT (right) (row-needle electrode 10 mm; local anaesthesia + sedation; i.v. bleomycin 15,000 IU/m^2, 4 pulses) The patient was previously submitted to surgery (three times) and refused another operation. Radiotherapy was deemed less optimal due to extension over both the nose, cheek, and up to the medial cantus (arrow).

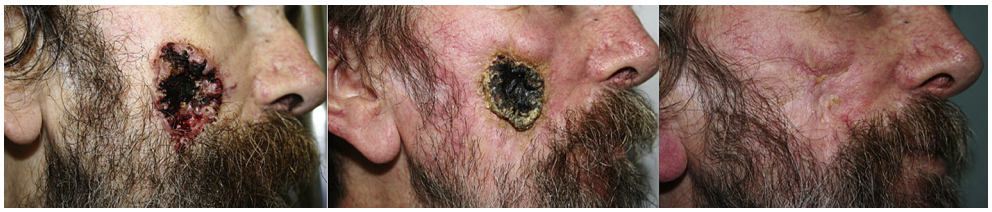

Fig. 4. Primary SCC in a patient with concomitant lung metastases from colorectal carcinoma: baseline (left), 2 months after ECT (center), and 7 months after ECT (right) (exagonal electrode 30 mm, general anaesthesia, i.v. bleomycin 15,000 IU/m^2, 6 pulses). Due to advanced stage of the patients colorectal carcinoma, life expectancy was limited and major surgery was deemed to be an unreasonable intervention for this patient, likewise a long treatment course of radiotherapy was discouraged. At the same time, the patient had symptoms and so a short intervention as ECT was chosen.

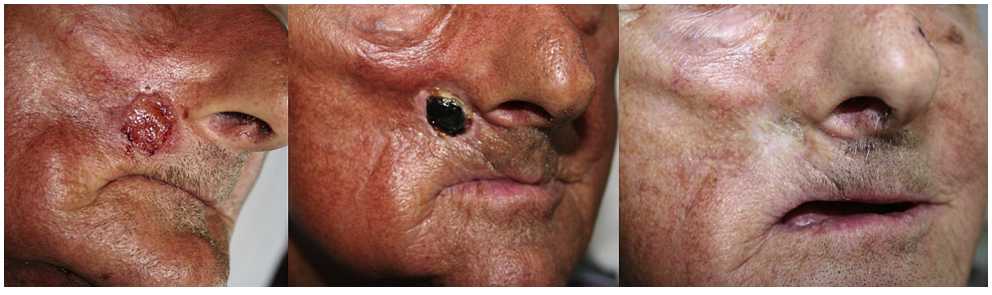

Fig. 5. Recurrent SCC: baseline (left), 2 months after ECT (center), 1 year after ECT (right) (exagonal electrode 10 mm, general anaesthesia, i.v. bleomycin 15000 IU/m^2, 3 pulses) The patient was previously submitted to partial maxillectomy and refused another major operation with reconstruction. Furthermore, the patient suffered from rapidly progressing Parkinson's disease. Radiotherapy was suggested, but refused by the patient due to the long duration of treatment. Thus he preferred to try ECT.

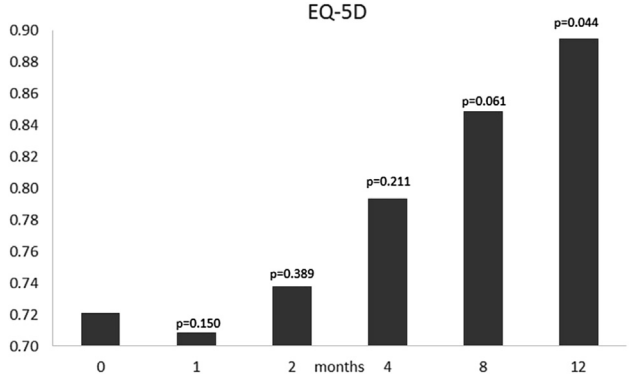

Fig 6. EQ-5D mean values at baseline and at each follow-up visit.

30% increase in voltage have been shown to produce a much higher risk of ulceration. Following the SOP [13] has in this and other studies resulted in a low level of normal tissue damage. In this study, 92% of patients received chemotherapy i.v. and only 8% had drug injected directly i.t; i.t. injection was used only where patients had documented chronic obstructive pulmonary disease at risk for pulmonary fibrosis [28].

In cases with extensive, necrotic skin lesions, we consider it mandatory to administer perioperative systemic antibiotic therapy in order to reduce the risk of sepsis due to systemic release of bacteria and bacterial products from the microflora colonising the tumour

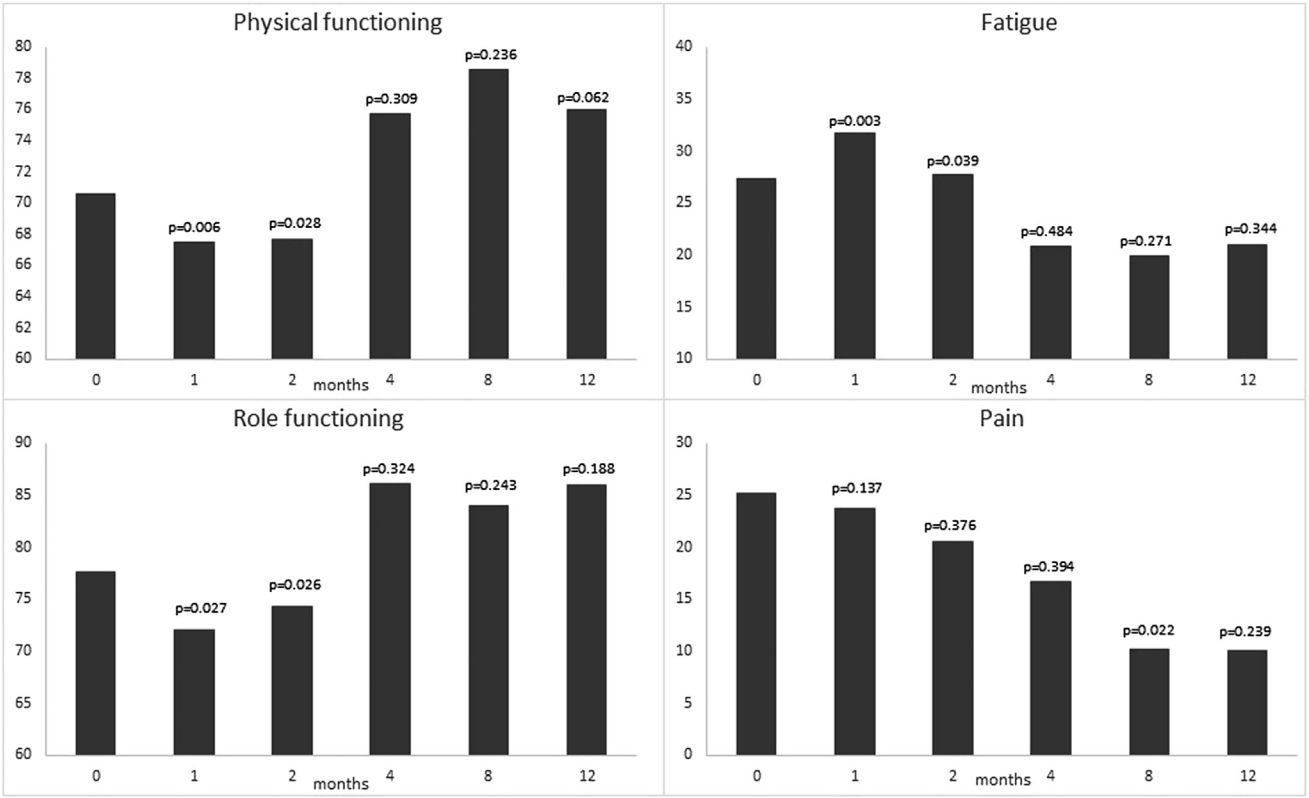

Fig. 7. QLQ-C30 mean values at baseline and at each follow-up visit.

nodule, as happened in one case in this trial. Further, in patients with lesions infiltrating full thickness of skin coverage on the cheek, chin or lips, wide loss of tissue with fistula formation or labial incompetence must be anticipated and considered in the pre-treatment decision process. Patients must then be thoroughly informed of these potential complications, which will negatively impact quality of life if reconstruction is not possible.

Our data on pain confirmed the findings recently published by the INSPECT group [29]. In general, electrochemotherapy does not result in increased pain immediately after treatment and this was observed both for patients with pre-existing none or mild pain and for patients with pre-existing severe pain. However, pain was usually observed to increase in the following 45 d after treatment and then decrease [29].

Of note also is that electrochemotherapy did not require increased dosage of drugs for pain relief and the percentage of patients taking opioids, although low before treatment, significantly dropped after, in agreement with the findings of Quaglino et al. [29] who demonstrated that patients need significantly less analgesic medication after treatment. Analysis of factors influencing the baseline pain score and the level of pain after treatment revealed that the most significant determinants were tumour size, previous treatments and SCC histology. Once again, this evidence is consistent with Quaglino et al. [29] who hypothesised that large lesions or pre-treated areas, especially pre-irradiated ones, can lead to a more severe tumour necrosis and inflammation, resulting in more severe pain. Taking this information into account, it is possible to identify a specific population of patients who may be at risk of severe pain after electrochemotherapy and, therefore, are candidates for specific pain-relief treatment protocols.

Interestingly, quality of life improved after ECT with long-lasting positive effects on pain control, perception of well-being, physical functioning and role functioning, as demonstrated by the results of the three QoL questionnaires in our study.

This is the first prospectively designed study focused on HN non-melanoma skin cancer that has evaluated overall and local DFS of patients submitted to electrochemotherapy. The observed 12-month overall survival and DFS rates of 76% and 89%, respectively, are high, even in view of rather short follow-up time (median 6 months).

Furthermore, in this study histologic confirmation of treatment response was not an end-point, although the biopsy was performed upon clinical suspicion of either remaining tumour or recurrence.

The purpose of this study has been to investigate ECT as an option in patients where standard treatment modalities have been deemed not indicated due to expected increase in the risk of serious morbidity or of unacceptable functional outcome. Further, where

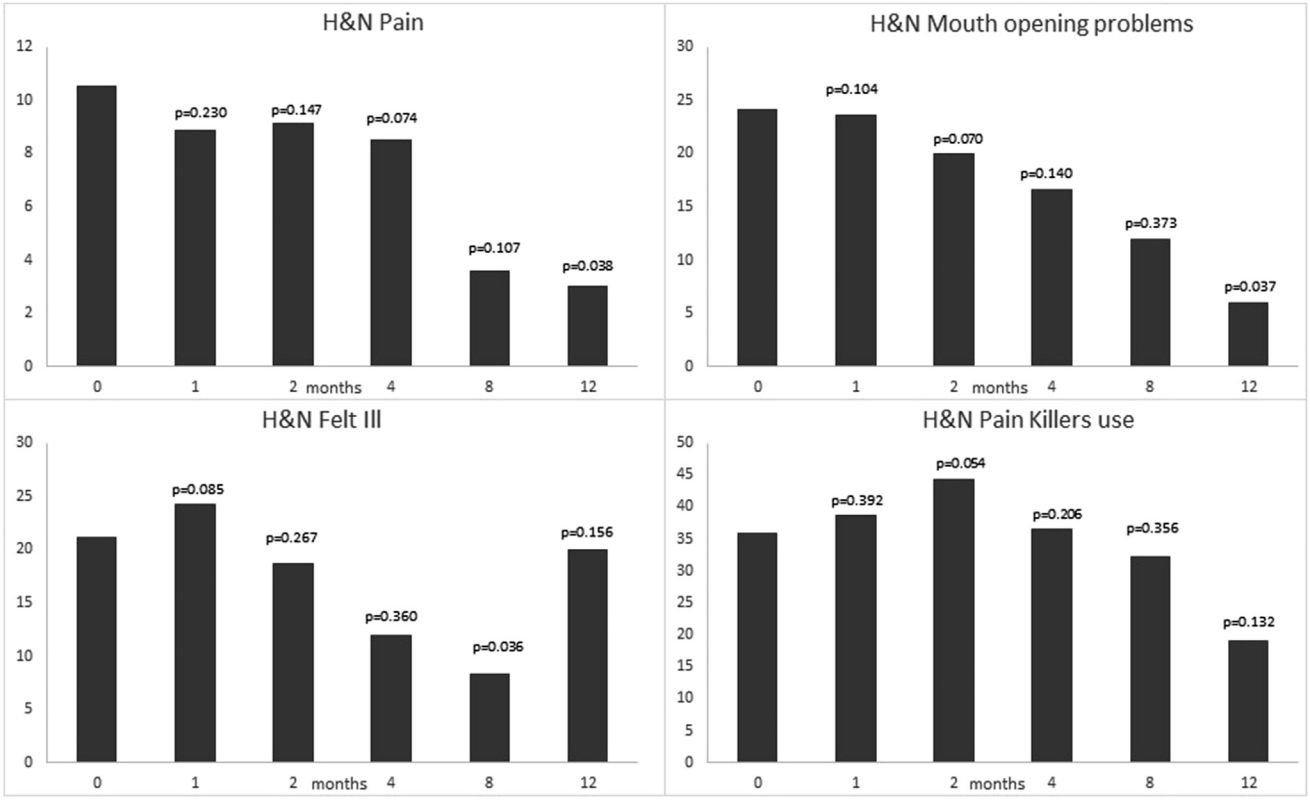

Fig. 8. QLQ-H&N35 mean values at baseline and at each follow-up visit.

patients declined proposed surgery or radiotherapy, or where co-morbidities played an important role in treatment decision-making process. Certainly, the majority of patients with HN skin cancer can be adequately treated using dermatological treatments, surgery or radiotherapy; however, this does not mean that further alternatives are not necessary. Whether electrochemotherapy could play a role in primary treatment of these cancers requires to be investigated in future randomised controlled trials.

5. Conclusions

Electrochemotherapy is an effective treatment option for skin tumours of the HN area and in particular for BCC. The response rate in small, primary, and treatment-naive tumours is high and the functional, anatomical, and aesthetic preservation of the HN structures can be excellent in such cases. Randomised trials will be needed to evaluate a possible role for electrochemotherapy as a first-line curative treatment.

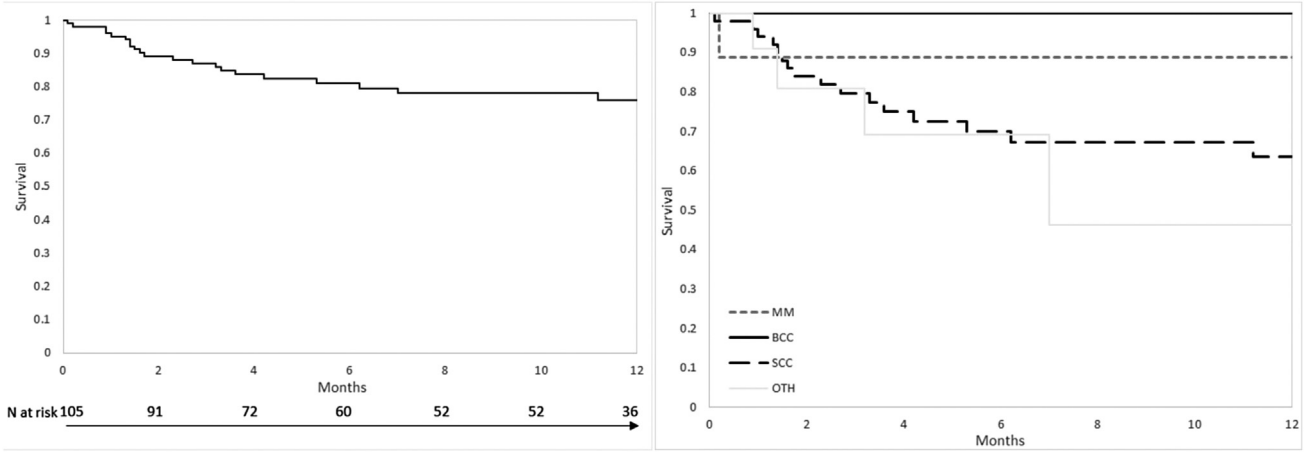

Fig. 9. Overall survival in total cohort and in subgroups per diagnosis. BCC = basal cell carcinoma; MM = malignant melanoma; SCC = squamous cell carcinoma; OTH = other histologies.

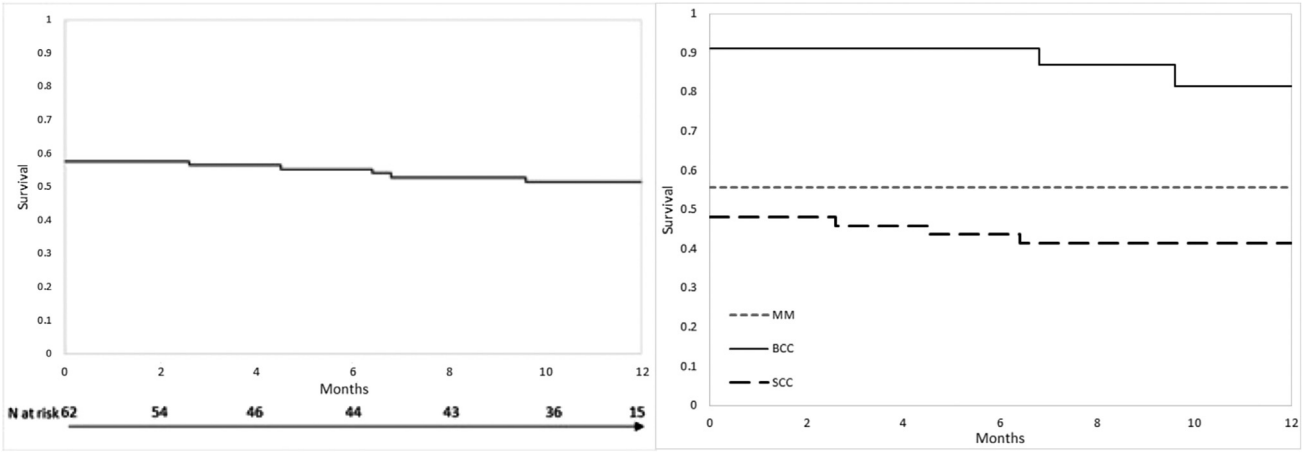

Fig. 10. Local disease-free survival in the total cohort and in subgroups per diagnosis. BCC = basal cell carcinoma; MM = malignant melanoma; SCC = squamous cell carcinoma.

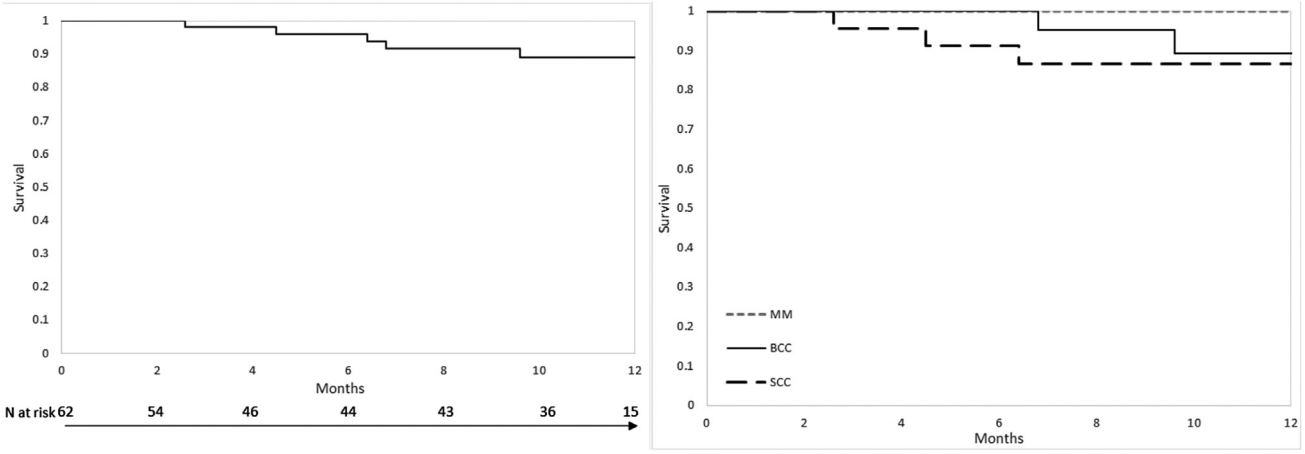

Fig. 11. Local disease-free survival in CR patients observed in the total cohort and in subgroups per diagnosis. BCC = basal cell carcinoma; MM = malignant melanoma; SCC = squamous cell carcinoma.

Conflict of interest statement

IGEA (Carpi, Italy) hosts the INSPECT database, but the database is controlled by an independent board, and the uploaded data are contractually belonging to the investigators involved. Francesca de Terlizzi is an IGEA employee. All the authors were invited to meetings on electrochemotherapy by IGEA.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2016.05.001.

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