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Electrochemotherapy – A locoregional therapy with well-established palliative effect in patient with large recurrent lesion of head and neck

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ABSTRACT

Background: Electrochemotherapy (ECT) is a well established treatment strategy for skin tumors of different histology. The aim of this study was to evaluate the feasibility and efficacy of electrochemotherapy in the palliative setting in patients with head and neck malignancies, already treated with surgery and/or radio-chemotherapy with no other therapeutic option.

Methods: Thirty-six patients with a loco-regional M0/M1 relapse with no other therapeutic option not suitable for a cure with a radical intent by surgery or RT and not suitable for systemic therapy and/or already treated with it, were admitted to electrochemotherapy (ECT) protocol treatment. ECT was performed according ESOPE guidelines. Clinical features, treatment response, and adverse effects were evaluated 15, 30 days and then every months after the treatment.

Results: An overall response of 100% was observed. Only 3 patients out 36 showed a CR. Overall survival probability at 12 months was 41.6% (median OS: 9 months). In all patient, an improvement of quality of life in terms of pain, bleeding events were observed, while need for medical assistance or dressing was significantly reduced 1 month after electrochemotherapy ($p < 0.001$).

Conclusions: Electrochemotherapy is an effective palliative treatment of non-resectable head and neck malignancies able. Due to the ECT limited side effects, its early use would be desirable to obtain a better local control of the disease and improve quality of life of patients.

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1. Introduction

Electrochemotherapy (ECT) is a well-established treatment for cutaneous tumors consisting in the combination of electroporation and chemotherapy. Electroporation has been studied for approximately 20 years as a means of facilitating the transport of normally non-permeant molecules into cells. By applying an electric field to the cells, the membrane become permeable, allowing chemotherapeutic agents such as bleomycin to enter the cell-increasing its toxicity (Mir et al., 1991).

Worldwide, carcinomas of the head and neck (H&N) account for more than 5% of all malignancies, which are squamous cell carcinomas in 90% of cases (Shield et al., 2017). Despite multimodal treatment, 50–60% of patients with stage III or IV disease relapse locoregionally. Recurrent or locally advanced cancers are a

challenge for clinicians and very debilitating for patients. The interest for ECT use in treatment of the tumours in the H&N area has increased because specific clinical problems may arise due to failure of or expected disfigurement from standard treatments. Of these, most patients are not suitable for salvage treatment and eventually became candidates for palliation (Iocca et al., 2018). Many clinical reports have described the results of ECT in treatment of H&N tumours (Gargiulo et al., 2012; Scelsi et al., 2013; Mevio et al., 2012; Campana et al., 2014a), and encouraging results have been obtained.

In this prospective study, we evaluate the feasibility and efficacy of ECT in the palliative setting in patients with recurrent inoperable H&N malignancies not suitable for standard palliation by systemic chemotherapy. Quality of life in terms of bleeding, pain and reduction of costs are discussed.

2. Materials and Methods

A total of 36 patients with recurrent inoperable H&N malignancies observed from April 2012 to November 2017 at the

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Department of Otolaryngology Head and Neck Surgery of the National Cancer Institute Regina Elena, Rome, Italy (28 males, 8 females, age 37–94 years; mean: 65.5 years; median 75 years) underwent ECT treatment. All patients were already treated by multimodal therapy and, at the time of inclusion, presented with a locoregional M0 or M1 relapse not suitable for a cure with a radical intent by surgery or RT and not suitable for systemic therapy and/or already treated with it. Patient demographic and staging characteristics are shown in Table 1. Histological and clinical characteristics of tumor are also indicated in Table 1.

Eligible were all patients affected by recurrent, metastatic, or primary cancer of the H&N area not suitable for surgery or chemo-

radiotherapy on the basis of poor general condition, age, cardiac deficit not related to electrical malfunction, reduced lung performance, comorbidities, high risk of major intra-postoperative complications, risk of anaesthesia, or previous treatments, or when the surgery would be too destructive to resolve the problem. Only palpable lymph nodes were treated, as evidenced by the staging. Cervical node metastases were all voluminous and palpable. Most cancer lesions were >6 cm in diameter and were often painful, bloody and ulcerated.

The technical procedure and patient selection were based on the ESOPE guidelines (Mir et al., 2006; Marty et al., 2006). Inclusion criteria were life expectancy >6 months and measurable

Table 1
Demographics and staging.

Pts	Gender	Age	ECOG PS	Histology and T site	TNM (ryc)	Application site	Response	Porations	Electrode	Treatment No.	Adjunctive treatment
1	M	52	4	Larynx SCC	T4aN2cM0	Tongue + LN	PR	20	exagonal	1	None
2	M	67	2	Larynx SCC	T4aN0M0	Peristomal recurrence	PR	67–50	exagonal	2	None
3	M	79	3	Ear melanoma	T4bN0M1	Retroauricular skin	PR	40	exagonal	1	None
4	M	88	2	Recurrence from Melanoma	pT4N2aM0	Latero cervical LN	PR	46	linear	1	None
5	M	59	2	Oral cavity SCC	T0N2cM0	LN	PR	31–50–57–90	exagonal	4	None
6	M	83	3	Oral cavity SCC	T0N2bM0	LN	PR	14	exagonal	1	None
7	M	71	2	Oral cavity SCC	T0N2bM0	LN	PR	20–20	exagonal	2	Cetuximab
8	F	83	3	Oral cavity SCC	T4aN0M0	Buccal mucosa	PR	35	exagonal	1	None
9	M	69	2	Oral cavity SCC	T0N2cM0	LN	PR	36	exagonal	1	None
10	F	62	3	Oral cavity SCC	T4aN0M0	1/3 posterior tongue	PR	13	finger	1	None
11	M	74	3	Oral cavity SCC	T4aN0M0	Chin skin/oral cavity	PR	22	exagonal	1	None
12	M	69	2	Oral cavity SCC	T4aN2bM0	Oral cavity + LN	CR	45	finger	3	Methotrexate
13	M	87	3	Oral cavity SCC	T0N3M0	LN	PR	21	exagonal	1	None
14	M	68	3	Oral cavity SCC	T4aN0M0	Floor of the mouth + lips	PR	52	finger	2	PDT
15	M	75	3	Oral cavity SCC	T4aN0M0	Oral cavity mucosa	PR	35	finger	1	None
16	M	53	2	Oral cavity SCC	T4aN0M0	Buccal mucosa	CR	16	exagonal	1	None
17	M	74	2	K tongue	cT4aN2c	Tongue	PR	60	linear	1	None
18	F	57	1	Oral cavity SCC	rN3M0	Retro and submandibular LN	PR	33	linear	1	Methotrexate
19	F	62	3	Oral cavity SCC	rT0N3M0	Latero cervical LN	PR	70	Linear	1	None
20	M	75	3	Oropharynx SCC	T0N2bM0	LN	PR	30–32	exagonal	2	None
21	M	94	2	SCC left skin cheek	cT4aN0M0	Left Cheek	CR	10–73	Linear	2	None
22	F	82	3	SCC left skin cheek	cT4aN2bM0	Left cheek and sottomandibular LN	PR	74–52	Linear	2	None
23	F	87	3	SCC mucosal right cheek	cT4aN2bM0	Right cheek	PR	12	Finger	1 (4 previous cycles in other hospital)	None
24	M	90	2	SCC right cheek	rcT4N0M0	Right latero- cervical and supraclavicular region	PR	86	Linear	1	None
25	M	93	2	SCC left cheek	rcT4N0M0	Left cheekbone and prauricular skin	PR	25	Linear	1	None
26	M	62	4	SCC Chin skin	T4aN0M0	Chin skin	PR	96	exagonal	1	None
27	M	62	1	Frontal area skin SCC	T0N3M0	LN	PR	53	exagonal	1	Extreme
28	M	85	2	Frontal area skin SCC	T0N2M0	Preauricular area	PR	25	exagonal	2	None
29	F	85	2	Frontal area skin SCC	cT4aN0M0	Zygomatic temporal frontal region	PR	98–70–74–38	Linear	4	None
30	M	88	4	External ear SCC	T0aN3M0	External ear	PR	52	exagonal	1	None
31	M	75	2	Preauricular skin SCC	T1N2M1	LN + preauricular area	PR	48–59–50	exagonal	3	None
32	F	37	1	Maxillary sinovial sarcoma	T4aN0M1	Maxillary area	PR	74–55–10	exagonal	3	None
33	M	79	2	Parotid mucoepidermoid carcinoma	T4aN0M0	Preauricular area	PR	65–82	exagonal	2	None
34	M	64	2	Parotid adenocarcinoma	T4aN0M1	Preauricular area	PR	13	exagonal	1	None
35	M	86	2	SCC left parotid and left hallway hall	cT4aN0M0	Left Parotid + hallway hall	PR	51	Linear	1	None
36	M	78	2	SCC	rcT4N1M0	Peristomal and submandibular region	PR	35	Linear	1	None

SCC: squamous cell carcinoma; LN: laterocervical lymph nodes; PR: partial response; CR: complete response; PDT photodynamic therapy.

cutaneous or mucosal tumor lesions. Exclusion criteria were as follows: clinically manifest arrhythmia, interstitial lung fibrosis, epilepsy, active infection, known allergy to bleomycin, kidney failure, previous treatment with bleomycin at the maximum cumulative dosage, and different anticancer therapies administered within 2 weeks of the ECT. Before treatment, all the patients underwent radiologic evaluation with computed tomography (CT) and/or magnetic resonance imaging (MRI) in order to define the widest diameter of the lesion. Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST) criteria were utilized for evaluation of the results after ECT.

All the lesions were documented by photographs in order to evaluate aesthetic and functional results after treatment. The clinical trial was approved by the institutional ethics committee and ECT indication was agreed by a multi-disciplinary tumour board for each patient (registration code RS 362/13). Each patient was asked to give a written informed consent to participate to the study.

2.1. ECT protocol

The procedure was performed with local anaesthesia consisting of tissue infiltration with 2% lidocaine or under mild sedation. One patient with total laryngectomy was treated on the posterior part of the tongue and, because of specifically request, received general anaesthesia.

All the patients received an intravenous bolus injection of 15,000 IU/m² of bleomycin. Eight minutes after the infusion, the electric pulses were delivered by means of different types of needle electrodes (hexagonal, or finger) chosen according to the site, volume and shape of the lesions to be treated, and generated by a Cliniporator™ (IGEA srl, Carpi, Italy).

2.2. Postoperative evaluation

Patients were evaluated 1 month after the treatment and every 3 months until 24 months. Tumor response was evaluated according to RECIST criteria (Eisenhauer et al., 2009) (Table 1). Pain was evaluated using a visual analogue scale (VAS) (Carlsson, 1983) varying from 0 (no pain) to 10 (extreme pain), both before ECT and 1 month after ECT. At each visit, the same examinations as during pre-operative evaluation (clinical and radiological, photographic) were performed. Furthermore the hospitalization time, the number of dressings performed by medical staff and the bleeding events 1 month before and after ECT were analysed. A single ECT treatment was delivered as treatment in 23 patients, 2 in 8 patients, 3 in 3 patients, and 4 in 2 patient (Table 1). The poration column of Table 1 also indicates the number of electrodes inserted for each treatment. A new ECT treatment was planned at each follow-up visit, in case of evident and symptomatic persistence in terms of pain and/or bleeding.

2.3. Statistical considerations

Endpoints include overall survival (OS), disease-specific survival (DSS), safety, tolerability pain control and post-operative care that impact on quality of life. Disease-specific survival (DSS) and overall survival (OS) were measured from the time of treatment until death and analysed using the Kaplan–Meier method. The Wilcoxon test was used where appropriate for continuous variables. A multivariate analysis was performed using the Cox proportional hazards model. Statistical significance was considered at the level of $p < 0.05$. Matlab software was used for the statistical analyses (Matlab R2007a; MathWorks, Natick, MA).

3. Results

ECT was completed successfully in all patients. The mean follow up time was 7.6 months (range 2–18 months). Complete response (CR) and partial response (PR) are shown in Table 1. OS probability at 12 months was 46.5% (Fig. 1a), while the median OS was 9 months. DSS probability at 12 months was 48.4% (Fig. 1b). In 3 of 36 (8.3%) patients, a CR was observed, while a PR was obtained in 33 patients (91.6%). In all, 31 of 36 patients were histologically classified as SCC, 2 as melanoma and 3 as of other types. Repeat treatment was planned at each follow-up visit in case of evident and symptomatic persistence and was necessary in 14 of 36 (38.8%) patients because pain and bleeding was still present. Eleven patients were treated with linear electrodes, 5 with finger and the other 20 with hexagonal ones. Linear electrodes have a gap between needles of 2.5 mm and multiple insertions are need to completely cover the lesion but are less painful for patients with less muscle contraction. In the hexagonal one, the needle separation is 7.3 mm and less insertion could be enough to cover the entire lesion, but this option is more painful for patients.

Univariate and multivariate analysis were performed considering as prognostic factors age, gender, ECOG performance status, histology, TNM, type of electrodes, number of treatments received, and the use of adjunctive treatment. No factor was significant at univariate and multivariate analysis (Table 2, A and B).

All patients were discharged within 24 h from the admission. No post-operative bleeding events occurred. We did not experience any major complications. Post-operative fever was observed in 1 patient (patient 6) and was successfully managed using paracetamol. Post-operative pain was successfully managed at home using paracetamol *per os* in 35 patients (1 g every 8 h) for at least 5 days. Only in 1 patient were opioid medications required for pain control.

Pain evaluation by means of the VAS resulted in a significant pain reduction after ECT. The mean VAS score before treatment was 6.08 and 1.25 1 month after ECT ($p < 0.001$, Table 3).

Before treatment, patients were referred to our center on average 6.8 times in the last month for the local management (dressings). After treatment, patients were referred to our center on average for 1.29 times per month. The difference was statistically significant ($p < 0.001$, Table 3). Before ECT, 15 patients (41.6%) experienced local bleeding at least once per week. One month after treatment only 2 patients (5%) complained of occasional bleeding ($p < 0.001$).

4. Discussion

Despite the fact that the majority of patients presenting with an early H&N cancer will remain disease free after single-modality treatment, many patients presenting with an advanced H&N cancer relapse locoregionally only, at distant sites only or both. A few patients with a locoregional recurrence can be salvaged by surgery or reirradiation while most patients with recurrent or metastatic disease qualify only for palliative treatment (Vermorken and Specenier, 2010).

Goals of treatments in these circumstances are mainly symptom control, prevention of new cancer-related symptoms, improvement in quality of life, disease stabilization and possibly prolongation of OS. Often it is necessary to combine local and systemic treatments to achieve the objective of yielding higher cure rates and lower toxicities in H&N cancers (Bernier, 2016).

In case of unresectable recurrent or persistent disease, Head and Neck 2015 NCCN guidelines recommend reirradiation with or without systemic therapy, systemic therapy, clinical trial or best supportive care (Pfister et al., 2015). These treatment options

Patient A

1. Pre-op



2. 90 days post-op



Patient B

1. Pre-op



2. 90 days post-op



Fig. 1. Patient A–B. Intraparotidial metastases from skin cancer.

should be evaluated considering the patient's performance status (PS) and life expectancy. Reirradiation is characterized by a high chance to experience acute and long term toxicities and should be reserved for highly selected patients.

In this setting, systemic chemotherapy remains a palliative alternative to the best supportive care. Only the cisplatin/5-fluorouracil regimen (PF) and more recently the EXTREME trial (cetuximab + PF regimen, then followed by cetuximab as maintenance therapy) have been demonstrated to improve the overall survival rate (Vermoken et al., 2008; Forastiere et al., 1992). According to the NCCN guidelines, a single chemotherapy agent regimen should be considered for PS > 1 (Pfister et al., 2015) and could be used in association only in cases of good PS (0–1) (Oken et al., 1983) (e.g. EXTREME (Vermoken et al., 2008)). A main limitation of systemic therapy is its toxicity. Those patients not suitable for salvage treatment are eventually candidates for palliation (Iocca et al., 2018).

Tumors of the head and neck are hard to manage (Mevio et al., 2012; Burian et al., 2003; Landström et al., 2010; Landstrom et al., 2011; Allegritti and Panje, 2001; Campana et al., 2014b) because this is a particularly complex anatomical region, with the presence of critical structures, such as carotid and cranial nerves, compacted in a small space. ECT results in a minimal or nil function impact and

leads to healing of treated tumor lesions without damage to the healthy tissues. For these reasons, ECT is proposed as an alternative to palliative chemo- or radiotherapy, and partial and complete remission rates have been reported in various clinical trials. No serious side effects have been reported (Gargiulo et al., 2012; Mevio et al., 2012; Sersa et al., 2000).

An early application of ECT followed by adjuvant radiation therapy was described by Landstrom et al. in a phase II trial enrolling patients with early stage (T1-2) oral and base-of-tongue carcinomas. No recurrences were observed during the entire follow-up period, and all the patients were alive at 5 years and reported only mild local toxicity (Landström et al., 2015).

According to Bertino et al. (2016), better responses to ECT treatment are obtained with small lesions (≤ 3 cm), primary tumours responded better than secondary (recurrent or metastatic) tumours, and treatment of naïve lesions responded better than pre-treated lesions (Bertino et al., 2016). In a prospective trial, six European institutions investigated electrochemotherapy in recurrent, mucosal H&N tumours. Intention-to-treat analysis in 36 evaluable patients revealed an objective response of 56% [complete response 8 (19%), partial response 16 (37%), stable disease 10 (23%), progressive disease 3 (7%), and not evaluable 6 (14%)]. Three patients (7%) remained in complete response at 30, 34, and 84 months post-

Table 2
Univariate (A) and multivariate (B) analysis of prognostic covariates.

A	Univariate Analysis		
	P value	95% CI Inferior Buond	95% CI Superior Buond
Gender	0.35	−0.12	0.34
Age	0.82	−0.01	0.01
ECOG PS	0.33	−0.06	0.19
Histology	0.54	−0.08	0.14
T	0.21	−0.08	0.02
N	0.45	−0.05	0.11
M	0.54	−0.21	0.40
Treatment No.	0.57	−0.12	0.07
Electrode Type	0.31	−0.20	0.06
Adjunctive treatment	0.32	−0.41	0.14
B	Multivariate Analysis		
	P value	95% CI Inferior Buond	95% CI Superior Buond
Gender	0.18	−0.10	0.49
Age	0.48	−0.01	0.01
ECOG PS	0.52	−0.11	0.22
Histology	0.39	−0.08	0.21
T	0.23	−0.19	0.05
N	0.68	−0.19	0.13
M	0.59	−0.30	0.51
Treatment No.	0.47	−0.15	0.07
Electrode Type	0.93	−0.21	0.23
Adjunctive treatment	0.71	−0.45	0.31

CI: confidence interval; ECOG PS: performance status.

treatment. The treatment procedure was generally well tolerated (Plaschke et al., 2017). Di Monta et al. confirmed that ECT displayed more effectiveness of other therapeutic options in locally advanced cSCC treatment (Di Monta et al., 2017).

In our previous study in 24 patients with recurrent H&N tumors, we showed ECT usefulness in terms of significant of medical assistance. ECT has proved to be not too stressful or painful a procedure; in fact, among the interviewed patients, 20 out of 24 (83.3%) stated that they would be willing to accept the treatment next time if it were indicated (Pichi et al., 2017).

In this study, a PR rate of 94.4% was observed while only 3 patients (8%) presented a CR. Thirty-one patients (86.1%) were affected by SCC, and in this group of patients we observed 10% of CR and 100% of PR. The minor CR observed in comparison to the literature data were not surprising and might be due to heterogeneity of our series, including cutaneous or mucosal tumor localization, and for this reason not perfectly comparable to other studies. The lesions treated were of a very large size and the patients were generally physically debilitated with PS 3 or 4. In some cases, ECT was performed with the sole purpose of stopping bleeding and relieving the pain, and despite the condition of the lesions, it has been able to provide patients with a better life course. In our study, we performed a univariate/multivariate analysis (Table 2, A and B) considering as prognostic factors age, gender, ECOG performance status, histology, TNM, type of electrodes, number of treatments received, and use of adjunctive treatment. No factors were

Table 3
Pain and post-treatment management.

	Mean	Standard Deviation	p Value
VAS_preT	6.08	1.38	<0.001
VAS_postT	1.25	0.91	
Delta_VAS	4.83	1.34	<0.001
Dressings/months preT	6.83	1.16	
Dressings/months postT	1.29	0.55	
Dressings/months Delta	5.54	1.17	

VAS: visual-analogue scale; PreT: pre-treatment; PostT: post treatment; SD: standard deviation.

significant. This result is not surprising, because only 2 out 36 patients were in complete remission. To better investigate the impact of the considered prognostic covariates, probably a more numerous sample is needed, and palliative ECT treatment should be performed early even in association with other therapy in order to obtain a better local disease control of the disease and with a higher probability to achieve a complete response.

There are many potential benefits with the use of ECT, the most important of which is its reliability and versatility. The treatment can be performed virtually in every patient independently from the performance status. In fact we performed one treatment with general anaesthesia and all other procedures with local or mild sedation, in an office-based setting, without performing a tracheostomy, even in patient with PS 4. The avoidance of intubation allowed us to better manage patients suffering from microstomia, oral cavity oedema, pain and trismus. ECT is very simple to be performed, and is repeatable every 30 days. ECT treatment is completed in less than 25 min because after a single dose of intravenous bleomycin administration, the maximal plasmatic concentration is reached in 8 min and it is maintained for about 20 min, then is gradually reduced. Electrochemotherapy is a well-accepted palliative treatment by patients with H&N tumor (Pichi et al., 2017). Among the interviewed patients, 30 out of 36 (83.3%) would be willing to accept the treatment next time if it were indicated. From the first case, we were able to efficaciously complete every treatment without delays or complications.

In our study, we did not experience any major complications and prolonged hospitalizations. This means that ECT could be performed safely even in PS 3–4 without deterioration of quality of life. All patients had arterial blood gas analysis the day before the application to avoid lung fibrosis, which could be exacerbated by bleomycin injection. Even in cases of partial response, ECT resulted in a sensible improvement, especially in terms of pain and bleeding reduction, and need for medical/paramedical care.

ECT by itself is responsible for a certain degree of post-operative pain, which was successfully managed using oral paracetamol at home. Only in one patient were opioid medications required for pain control. Pain evaluation by means of the VAS resulted in a significant pain reduction after ECT ($p < 0.001$, Table 3). This results in a sensible reduction in the administration of pain medications which are considerably used and often abused by advanced-stage HNC patients. With knowledge of the risk factors, pain treatment can be better planned in advance (Quaglino et al., 2015).

The usefulness of ECT also extends to the reduction in terms of medical assistance with a need for dressing that ranging from the 5–7 monthly in the pre-ECT period to 1 monthly after treatment (dressings, Table 3). Patients themselves were able to take care of the treated area by simple disinfection and dressings. These results depend partially on the significant reduction of bleeding events after ECT that represented one the main reason for requesting medical assistance. One month after treatment, only 2 patients (8%) complained of occasional bleeding.

ECT peculiar cicatrization and pain/bleeding reduction could be explained with the 'vascular lock phenomenon'. In fact, blood flow changes occur after the delivery of electric pulses in vivo (Sersa et al., 1999), and restoration of the initial blood flow levels may take hours. The mid-term and long-term antivasular effects of the ECT could thus result from the killing of the tumour endothelial cells, which would prevent the rapid reorganisation of the tumour vasculature. Consequently, an almost permanent, extremely hypoxic situation is created after ECT (Cemazar et al., 2001).

According to Parikh et al. (2013), to ensure that patients receive the best care throughout their disease, palliative care should be started along with standard medical therapy for patients with serious illness because it is indicated at any age and at any stage,

specially in cancer patients, and can be provided at some time of curative treatment. Early palliative care might produce a better symptom control with significant improvement of quality of life.

A limitation of our study is the relatively small sample size, and the patients' heterogeneity in terms of clinical features and treatment. Our study includes patients with both primary and lymph node recurrences and patients who received concomitant palliative systemic chemotherapy. Reducing the need for the medical support results undoubtedly in an improved quality of life, from the psychological point of view; in fact, the patients are able to care for themselves and were less depressed. From the practical point of view, ECT treatment reduces hospital travel, which is an advantage for patients and at the same time reduces costs for the hospital in terms of the commitment of medical and nursing personnel. Our investigation of ECT is still ongoing, and we hope to publish more data in the future with more representative samples, stratified by histology, recurrence site, and concomitant treatments.

5. Conclusion

In conclusion, ECT has proved to be effective in the palliative treatment of non-resectable HNC, and its use is suggested especially in patients with unfavorable PS. ECT is able to ameliorate patients' quality of life and to achieve local tumor control without damage to healthy tissue and with limited side effects. Reduction of costs are also obtained. There is no evidence for improved survival using ECT.

Conflicts of interest

The authors declare no conflict of interest. The authors do not have any relevant financial activities outside the submitted work. (Campana et al., 2009).

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