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Electrochemotherapy (ECT) in treatment of mucosal head and neck tumors. An international network for sharing practices on ECT (InspECT) study group report

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ABSTRACT

The aim of this multicenter study was to evaluate the effectiveness and safety of electrochemotherapy (ECT) for the treatment of mucosal tumors in the head and neck.

A total of 71 patients with 84 nodules of different histologies in the oral cavity, pharynx and larynx treated by ECT were evaluated. The data were collected from the InspECT database from 10 participating centers throughout Europe.

Primary and recurrent/secondary tumors of different histologies were treated. The overall response rate was 65 %, with a 33 % complete response rate with limited side effects. The response rates of the primary and secondary tumors were not different. However, smaller tumors responded better than tumors larger than 3 cm in diameter. Furthermore, the tumors that were treated with curative intent responded significantly better than those treated with palliative intent.

This study demonstrated the feasibility, safety and effectiveness of ECT in a larger cohort of patients with mucosal lesions in the head and neck region. Based on the available data, ECT can be used for the treatment of recurrent and, in some cases, primary mucosal tumors located in the oral cavity, larynx, and pharynx. A better response was obtained in patients with smaller primary tumors treated with curative intent.

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1. Introduction

Head and neck cancer is one of the most common and deadliest cancers worldwide [1,2]. In particular, Current estimates suggest that the incidence of head and neck cancer (HNC; including lip/oral cavity, oesophagus, larynx, oropharynx, hypopharynx, salivary glands and nasopharynx) in Europe is approximately 21.8 per 100,000, with mortality rates approximately 15.6 per 100,000 [3]. In Europe, quite half of the newly diagnosed patients with head and neck (H and N) cancers are older than 65 years of age [1]. Due to their location and proximity to critical structures, these tumors pose a particular treatment problem if they are to be removed by surgery or irradiation. Special consideration should be given to the possible detrimental effects of radiotherapy treatment to adjacent critical normal tissues-such as cranial nerves, brainstem, and brain-as may occur in lesions of the nasal fossa [4,5]. Furthermore, it is extremely difficult for surgery to achieve wide negative margins, which leads to a high local relapse rate up to 30 % for squamous cell carcinoma [6], and 50%–90 % for mucosal melanoma [7]. Despite the refinement of these two common treatment approaches, new systemic drugs have recently been introduced to improve the efficacy of treatment [8].

Recurrent mucosal tumors pose an even greater challenge to effective treatment. When surgery and radiotherapy are not possible, the curative intent of treatment is usually not obtainable. Elderly patients or patients with comorbidities may be excluded from alternative palliative systemic treatments and the recurrent tumor leads to further deterioration of existing functions, disfigurement, further impairment of quality of life, and eventually death. New treatment approaches with good efficacy and quality of life criteria are therefore needed [9–11].

Electrochemotherapy (ECT) is a local ablative technique based on the increased cytotoxicity of bleomycin or cisplatin, as these two drugs reach tumor cells to a greater extent by applying electrical pulses to tumors [12]. In fact, when applied to tissue cells, electrical pulses trigger the electroporation phenomenon, described as the temporary formation of permeable structures called electropores at the level of cell membrane. These electropores last for a period of time in the order of minutes and allow the introduction of the drug inside the cell at a concentration sufficient to kill the cell by a mitotic death. ECT has a good toxicity profile and high local efficacy. The objective response rate of cutaneous tumors treated with ECT is 85 % across different tumor histologies [13]. Currently, this treatment has also been adapted for the treatment of deep-seated tumors, such as those in the liver, pancreas, colon and bones [14–17].

The technological refinement of the treatment has also made it easier to treat oral mucosal tumors. The electrodes attached to the finger enable the treatment of tumors in the oral cavity, and the so-called Stinger electrodes also enable the treatment through an endoscopic approach [18].

To date, there have not been many clinical studies on the treatment of mucosal tumors in the head and neck area, particularly in the oral cavity. The most recent systematic review by Strojan et al. (2021) [19] analyzed studies published between 1998 and 2020. They identified 16 studies with 164 patients. The complete response rate for patients who underwent ECT with curative intent (36 patients) was 80 %, while the complete response rate for patients with palliative intent (128 patients) was only 31 %. This indicates a relatively low response rate of mucosal tumors to ECT compared to other tumor types. Although the treatment is quite demanding, these studies have shown that ECT does not worsen quality of life, and no serious adverse effects have been reported, suggesting a good safety profile of the treatment [9,10,20–23].

In this cohort study, we report the outcomes and safety profiles of patients with mucosal tumors of the oral cavity, pharynx and larynx included in the InspECT database from 10 cancer centers across Europe. In addition, the study compared the treatment outcomes of primary and recurrent (secondary) tumors, which were well balanced. This comparison is important for the acceptance of this therapy as a first-line treatment, palliative care or debulking. The role of ECT in recurrent tumors with curative intent is also discussed.

2. Patients and methods

2.1. Patients

Data on 71 patients and 84 nodules were retrieved from the InspECT database for patients treated with ECT for mucosal lesions of the head and neck region. Patients were treated at 10 InspECT centers: Pavia, Copenhagen, Torino, Ljubljana, Rome, Mirano (Venice), Castle Hill, Middlesbrough, Genova and Munich.

The InspECT group is a European collaborative including 41 clinical centers applying ECT. The registry collects baseline patient and tumor characteristics, ECT modalities, treatment toxicity, and patient outcome. Ethics approval was sought by each institution individually. Participation in the database collaboration was by signed agreement [24]. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki.

According to country-specific guidelines, patient selection was based on institutional preferences, including referral after multidisciplinary discussion for patients with symptomatic metastases at the mucosa and primary persistent/recurrent mucosal lesions. In particular, ECT treatment was considered in (a) carefully selected patients with locally advanced disease, with persistent or recurrent primary mucosal tumor when all other treatment options, including surgery and radiotherapy, were not feasible; (b) with primary naïve cSCC lesions when every other therapeutic option was contraindicated because of radically unresectable disease, at high risk of functional organ damage or because of a precarious physical condition of the patient due to comorbidities; and (c) when the patient, after being exhaustively informed, refused any other treatment option.

Patients with primary tumors were treated with curative intent, whilst patients with primary persistent or recurrent tumors as well as metastatic lesions were treated with palliative intent.

2.2. Procedure

ECT was performed according to the European Standard Operating Procedures on ECT [25,26]. Briefly, bleomycin was administered either intratumorally (1000 IU/m^2) or intravenously (15,000 IU/m^2), depending on the number and size of the lesions. One of the following electrodes was used: (1) type I: two plates with a 6-mm gap; (2) type II: two parallel rows of needles with a 4 mm gap; and (3) type III: a hexagonal array with a 7.3 mm gap. Eight electrical pulses 100 msec in duration were delivered using a square-wave electric pulse generator (IGEA, Carpi, Italy) and standard electrodes. For use inside the mouth, larynx, and pharynx, a specific set of type II electrodes, called “finger electrodes”, have been applied. These electrodes have the advantage of being worn on a finger so that the clinician can position the active part of the electrode, the needles, directly in the mucosal lesion by using his or her finger (see Fig. 1A). In some cases, the new “Stinger” electrode, recently introduced in clinical practice, was applied to treat deep lesions in the pharynx/larynx cavity that were not treatable with finger electrodes. This electrode is equipped with a long connector cable (20 cm) and 5 expandable needles positioned at a fixed distance of 0.4 cm in a square geometry. The total needle length is 4 cm, with an active part at the 2 cm extremity. Before positioning in the pharynx/larynx, the needles are inside the probe in the cable, while once positioned, the 5 expandable electrodes are extruded and penetrate the lesion so that the electric field can cover the entire volume of interest during ECT (Fig. 1B).

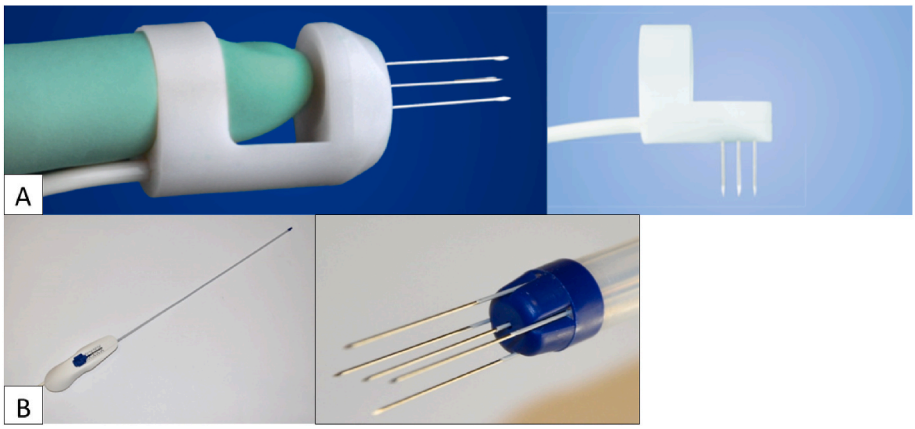

Fig. 1. Electrodes for ECT in mucosal oral cavity lesions and pharynx/larynx lesions. **1A.** Finger electrode. Position of the finger into the electrode. Two configurations of the electrode for use: needles parallel to the finger and needles perpendicular to the finger. **1B.** Stinger electrode. The 20 cm insertion cable with the probe on the top. From the probe, the electrodes are extruded once the probe is positioned near the lesion.

2.3. Response evaluation

Locoregional tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1), modified to include the response of the treated mucosal metastases [27]. Tumor response was evaluated by measuring the maximum size of the treated metastases and documented using digital photography, echography or radiologic imaging. The response was registered for each target lesion at follow-up 1–2 months after ECT.

Tumor-related symptoms were registered following the CTCAE v5.0 criteria [28]. The specific analysis was concentrated on ulceration, suppuration, nausea, odor, dysphagia, swelling and bleeding of tumor lesions.

2.4. Statistical analysis

The descriptive statistics entailed the median and range for continuous variables and absolute counts and percentages for categorical variables. Comparisons between groups were performed by 2-tailed heteroscedastic uncoupled t-tests, while comparisons of repeated measurements on the same group over time were performed by 2-tailed coupled Student's t-test for continuous variables. Comparisons between categorical variables were performed by contingency table analysis and the Chi-square test with correction for repeated measurements. Univariate analysis for objective response was performed by a logistic model with the evaluation of relative risk (RR) and 95 % confidence interval (% C.I.). Survival analysis was performed by calculating Kaplan–Meier survival curves and 1-year survival percentages. NCSS 9 (NCSS, LLC. Kaysville, Utah, USA; www.ncss.com) software was used for the analysis.

3. Results

3.1. Patient and tumor characteristics

Between January 2012 and July 2022, a total of 71 patients (84 mucosal lesions) with a median age of 72 years (range 39–97) who underwent ECT and were followed up at a minimum of 45 days were included. In Fig. 2 three cases of patients treated by ECT.

Table 1 shows the patient characteristics. The vast majority of patients were affected by squamous cell carcinoma (SCC) (82 %), and almost half of them (48 %) had a primary mucosal lesion. The remaining patients had malignant melanoma and other tumor types. Most of the patients had sustained previous treatments, i.e., 24 % had surgery + chemotherapy + radiotherapy, 17 % surgery, and 17 % surgery + radiotherapy. Twenty-three percent were treatment naive. The lesions were divided into oral cavity and pharynx/larynx. The majority of lesions were located in the oral cavity (73 %).

3.2. Treatment and response to treatment

The median lesion size was 30 mm (range 8–153 mm). Regarding ECT, 89 % of patients were treated with intravenous bleomycin injection, and only 11 % were treated with intratumoral administration of the drug. The majority of the patients were treated under general anesthesia (83 %). In terms of treatment, different types of electrodes were used: type I (plate) in 8 % of the tumors, type II (row needles: linear, finger, stinger) in 50 % and type III (hexagonal needles) in 42 %. Coverage of the lateral margins during ECT was obtained for 69 % of the lesions, and deep margin coverage was obtained for 51 % of the lesions. Preirradiated lesions composed 49 % of the total lesions. No differences were observed between oral cavity lesions and pharynx/larynx lesions in terms of size, drug administration, analgesia, electrode type, covered margins, or preirradiation (p = not significant). However, the OR rate varied depending on the location in the oral cavity, as well as in the pharynx. The best results were obtained for lesions on the lip (90 %), gingiva (80 %), floor of the mouth (75 %) and mobile tongue (73 %); the worst were obtained for lesions on the hard palate (53 %), retromolar trigone (57 %), oropharynx (57 %) and rhinopharynx (60 %).

The response to treatment is reported in Fig. 3 for the overall cohort was: 33 % CR, 32 % PR, 20 % SD, 14% PD. In the subgroup of oral cavity lesions was: 34 % CR, 34 % PR, 17 % SD, 15 % PD, and in pharynx/larynx lesions subgroup was: 30 % CR, 27 % PR, 30 % SD, 13 % PD. No differences in the response rate were observed between the two tumor locations ($p = 0.6458$).

Factors potentially related to an objective response were tested by univariate analysis, and the results are reported in Table 2. Small lesion size (≤3 cm) was significantly related to a better OR ($p = 0.0463$), and preirradiation and heavy prior treatment (surgery + chemotherapy + radiotherapy) were associated with a worse OR ($p = 0.0050$ and $p = 0.0240$, respectively). Patients treated with curative intent had significantly better results than patients treated with palliative intent ($p = 0.0089$).

We observed 21 deaths among our cohort of patients. Eight of them were due to systemic progression of disease (38 %), 8 patients died for tumor progression (38 %), 3 patients died for declined conditions (14 %), 1 (5 %) for infection, 1 (5 %) for cranial trauma. Mean time to progression in the whole cohort of patients was 5.9 ± 11.1 months; mean time to progression in patients treated for curative intent is 12.2 ± 18.1 whilst in patients treated with palliative intent is 3.1 ± 2.9 ($p = 0.0170$). Survival analysis resulting in Kaplan–Meier curves for local progression-free survival and overall survival are reported in Fig. 3. The

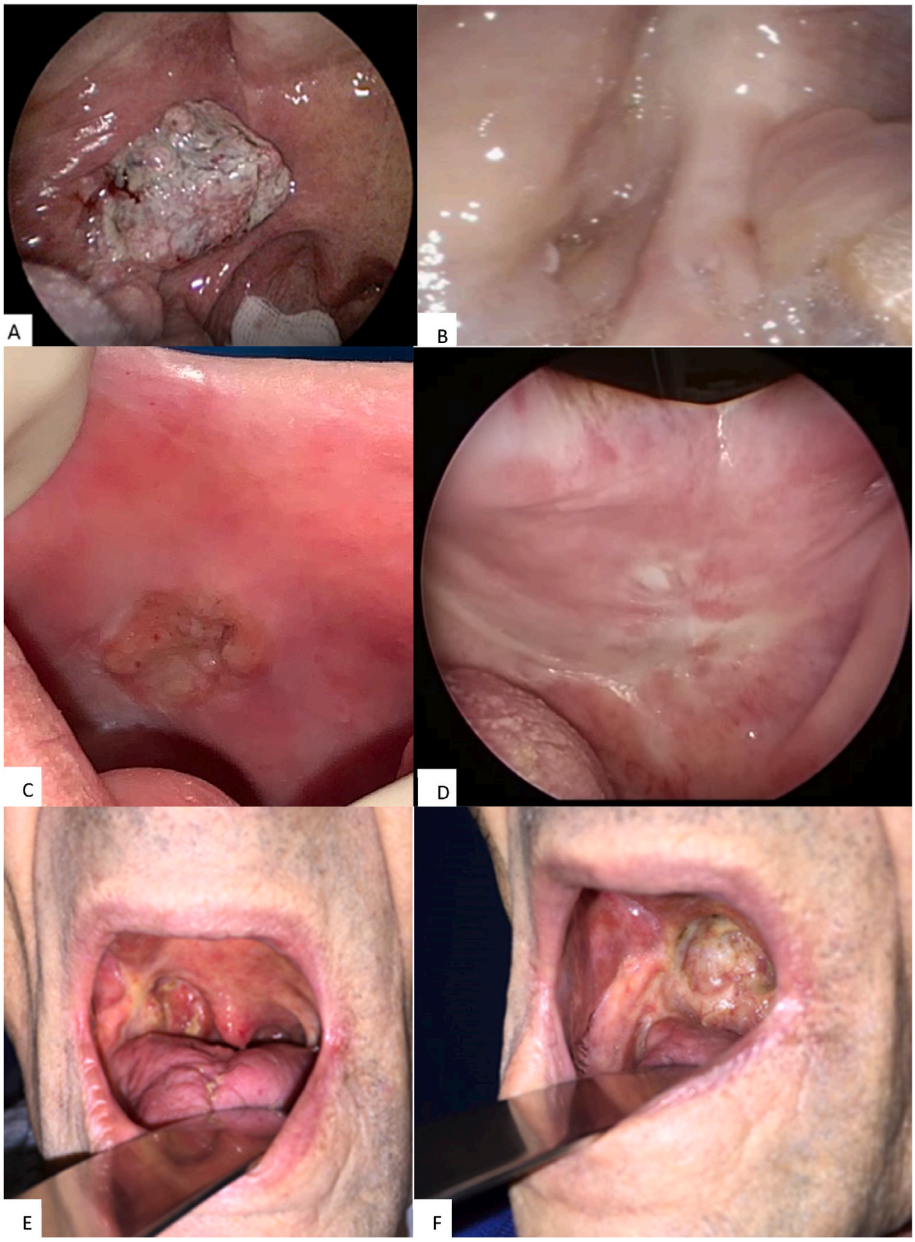

Fig. 2. Three cases of patients treated by ECT. Patient treated at the right retromolar trigone. 2A. Before ECT. 2B. After 3 months from ECT. Patient treated at the right cheek intraoral. 2C. Before ECT. 2D After 12 months from ECT. Patient treated at the hard palate. 2E. Before ECT. 2F. After 16 months from ECT.

one-year local progression-free survival rate was 42 % (95 % CI 25%–59 %) (Fig. 3A), and the 1-year overall survival rate was 44 % (95 % CI 26%–63 %) (Fig. 3G). An in-depth analysis of local progression-free survival revealed that primary vs secondary lesions (Fig. 3B), oral cavity lesions vs pharynx/larynx lesions (Fig. 3C), prior irradiated vs not prior irradiated lesions (Fig. 3D), and small vs large lesions (Fig. 3E) did not significantly differ in the time to progression ($p = 0.3763$, $p = 0.7453$, $p = 0.1853$, $p = 0.2101$, respectively), while lesions treated with curative intent vs palliative therapy had a significantly shorter time to progression and overall survival, as shown by Kaplan–Meier survival curve analysis ($p = 0.0125$ and $p = 0.0018$, respectively) (Fig. 3F and H).

3.3. Toxicity

The toxicity of the treatment was generally mild/moderate, except for 10 % (7 patients) of the patients who had grade III/IV ulceration. Of these 7 patients, 4 already had grade III/IV ulcers before the ECT session. The severity of pain was not extremely high, with a mean value before ECT of 2.6 ± 3.0 VNS, with 57 % of patients experiencing mild pain (0–2). Immediately after ECT, the mean score was 1.9 ± 2.3, with 62 % of patients experiencing mild pain. At the 30-day follow-up, the mean pain value was 1.8 ± 1.6 (74 % mild), 3.0 ± 2.0 (mild pain in 55 % of patients during follow-up) at 60 days and 1.0 ± 2.0 (mild pain in 78 % of patients) at 120 days. The difference in mean pain severity over time was not statistically significant according to 2-tailed paired Student's *t*-test ($p = 0.1149$, 0.2230, 0.2641, 0.6772 vs pre-ECT values).

4. Discussion

This study demonstrated the feasibility, safety and effectiveness of ECT in a larger cohort of patients with mucosal lesions in the head and neck region. The tumor response of patients with various tumor histologies in the oral cavity, pharynx and larynx showed a high objective

Table 1
Descriptive statistics.

		N	%			N	%
GENDER	M	46	65 %	**TUMOR**	Primary	34	48 %
	F	25	35 %		Secondary	37	52 %
AGE	Median	72		**STAGE**	T1/T2	44	62 %
	Range	39–97			T3/T4	24	34 %
	<70 yrs	28	39 %		unknown	3	4 %
	71–80 yrs	22	31 %	**ECT INTENT**	Curative	24	34 %
	>80 yrs	21	30 %		Palliative	47	66 %
DIAGNOSIS	SCC	58	82 %	**PREVIOUS TR**	Surg + CT + RT	17	24 %
	MM	4	7 %		NO	16	23 %
	Adenoidocystic ca	3	4 %		Surgery	12	17 %
	Oropharynx ca	2	3 %		Surg + RT	12	17 %
	Undifferentiated ca	1	1 %		RT	7	9 %
	TCC	1	1 %		CT + RT	5	7 %
	Salivary gland ca	1	1 %		CT	2	3 %
	Mucoepidermoid ca	1	1 %				
NODULES' SITE	Oral cavity	61	73 %	**LOCALISATION**	Hard palate	17	20 %
	Pharynx/Larynx	23	27 %		Mobile tongue	12	14 %
					Lip	9	11 %
					Floor of mouth	8	10 %
					Retromolar trigone	7	9 %
					Gingiva	5	6 %
					Internal cheek	2	2 %
					Mandible	1	1 %
					Pharynx	9	11 %
					Rhinopharynx	5	6 %
					Tongue base	3	3.5 %
					Soft palate	3	3.5 %
					Supraglottis	2	2 %
					Larynx	1	1 %

SCC = squamous cell carcinoma, MM = malignant melanoma, TCC = transitional cell cancer; Surg = surgery, CT = chemotherapy, RT = radiotherapy.

response rate of 65 %. A better response was obtained in patients with smaller primary tumors treated with curative intent.

The studies that evaluated ECT in head and neck cancers strictly delineated between skin lesions and mucosal lesions [10,29]. Predominantly, they evaluated recurrent lesions in the oral cavity that were treated with palliative intent. Therefore, the results of these studies yield an approximately 50 % objective response rate [9–11]. Due to the presence in these studies of heavily pretreated lesions, without any other option except for ECT, authors evaluated this treatment outcome as good, with positive outcomes in quality of life and safety, because for these patients the alternative was best supportive care only [11,20]. Our study has better treatment outcomes than most of the other studies, most likely because the tumors included in the study were smaller tumors (<3 cm in diameter) and primary tumors that had not received any prior treatment and underwent ECT with curative intent. The complete response rate in our study was approximately 33 %, with no difference between tumors located in the oral cavity and in the pharynx or larynx. A better response was found in tumors that were more amenable to the application of electric pulses, such as on the lips, compared to rhino and oropharynx regions.

This led us to discuss the accessibility and possibility of treating the whole tumor mass. It is well known that for good treatment outcomes, drug must be available in the tumors at the time of application of electric pulses. Therefore, most of the patients were given the drug intravenously since intratumoral drug administration would likely not enable adequate drug distribution in tumors located in the oral cavity, pharynx or larynx. The other aspect that was not intensively discussed in other studies was the coverage of the tumors with the electric field [30]. If the tumor is inadequately covered with electric pulses, a complete response cannot be expected. In our study, the margins were not sufficiently covered in a high percentage of the treated tumors. Interestingly, we found that the objective response rate was the same in either situation. This is unexpected but could be due to unintentionally incorrect reporting due to the foul estimation of tumor size and thus margins resulting in conceivably sufficiently treated margins.

The safety of ECT was evaluated by monitoring adverse events. Very few grade III/IV toxic side effects were reported. As in other studies, the predominant side effects were ulceration, suppuration, odor and, in some cases, nausea. All these side effects were mild and predominantly grade I/II, therefore, this treatment procedure is considered relatively safe. Similar positive results have been observed by Riva et al. in a study on quality of life profile in patients treated with ECT for cutaneous and mucosal lesions of the head and neck [20].

It is of interest to outline that 30 % of the cohort of patients was over 80 years older (75 % were over 65 years) and was efficiently treated with ECT, showing that electrochemotherapy could be a valid option in deciding treatment for very elderly patients, even when comorbidities prevent the use of other more aggressive therapeutic strategies [31].

The relatively better treatment response may also be due to the use of finger electrodes, which enable the surgeon to reach most of the locations in the mouth [20,23]. However, the use of this electrode requires multiple applications of electric pulses to tumors that are 3 cm in diameter, due to its limited size.

A step forward was made with the development of the stinger electrode, recently introduced in the market, which also enabled the treatment of the pharynx and larynx as well as other sites only reachable with an endoscopic approach [18]. The long holder ambles the accessibility of deeper structures, and when the tumor site is reached, the electrodes can be extruded from the cable, deployed, and fixed to the tumor. In our study, three patients were treated with this type of electrodes and all experienced good responses. Especially when treating difficult available tumors sites with this specific ECT procedure, we advise new treating physicians to seek advice from experienced doctors.

The therapy was proposed with a curative intent in 24 patients, nine of which obtained a complete response (38 %) and overall, 20 (83 %) a local disease control, with an overall 1 year local progression free survival of 66 % (C.I. 43%–89 %) and overall survival of 74 % (C.I. 50%–98 %).

Interestingly, among the 37 patients with recurrent tumors, 9 have been cured (24 %), achieving a complete response. They were free from

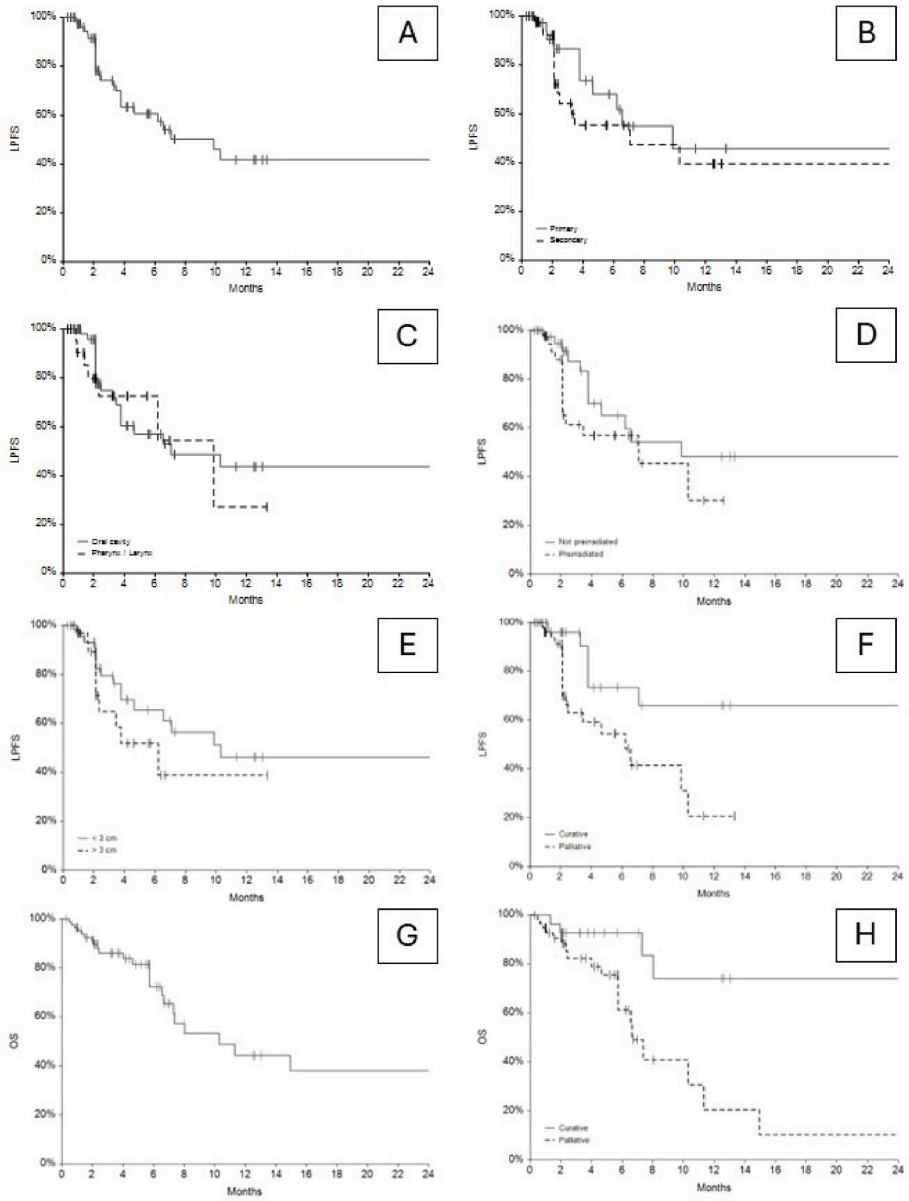

Fig. 3. Local progression-free survival (LPFS) and overall survival (OS) curves. **3A.** LPFS Entire population. **3B.** LPFS in patients with primary vs secondary tumors treated. **3C.** LPFS in patients with oral cavity vs pharynx/larynx tumors. **3D.** LPFS in patients with preirradiated vs non preirradiated tumors. **3E.** LPFS in patients with small tumors ($\leq$3 cm) vs large tumors (>3 cm). **3F.** LPFS in patients treated with curative vs palliative intent. **3G.** OS in the entire population. **3H.** OS in patients treated with curative vs palliative intent.

disease with a median time of 6.7 months and only 2 recurred after 7 and 10 months respectively. These patients had not alternatives at the moment of ECT and were cured, despite their condition. To the best of our knowledge, this has not been reported with any other treatment. This result is encouraging and puts ECT among other local treatment modalities or even better, more effective, even when the standard treatments have failed. This finding underlines the effectiveness of ECT in palliative situations. Furthermore, since ECT rarely causes severe side effects, it can also be employed in debulking processes, either as a first-line treatment or after progression of the disease. If ECT is considered as first-line treatment, should be considered cautiously. It could be considered for smaller tumors and in specific locations where complete coverage of the tumors with an electric field can be achieved. It could also be considered in patients with severe comorbidities when systemic therapies (i.e. immunotherapies) are not commendable, surgery is too risky due to of location of the lesion or due to patient's general health status. The new recently developed electrode has widened the range of applicability of ECT in clinical situations from simple easy access tumor sites to now include more challenging locations increasing the possibility of usage when mucosal lesions are inaccessible to standard treatments, i.e. surgery or radiotherapy.

It is difficult to make a direct comparison with other patients which received only best supportive care because most of these patients would have received only palliative care for symptoms alleviation, as no other therapeutic options are available. Furthermore, 75 % of the cohort of patients is older than 65 years, and there are no standards of treatment for head and neck cancer elderly patients because of their underrepresentation in clinical trials [32]. It is therefore proposed to such patients a treatment optimized to control the disease while avoiding alteration of quality of life. It has been shown that compliance to standard radiotherapy is poor in elderly patients, because of radiotherapy's acute toxicity, with functional mucosal reaction which is increasing with age [32]. Concomitant chemoradiotherapy is even worse because of an increased toxicity compared to radiotherapy alone, and this

Table 2
Univariate analysis for objective response (OR).

VARIABLE		OR%	NON OR%	RR	C.I.95 %	P VALUE
SIZE	≤3 cm	74 %	26 %	2.69	1.08–6.72	0.0463
	>3 cm	53 %	47 %			
LOCALISATION	Oral cavity	68 %	32 %	1.62	0.61–4.31	0.3362
	Pharynx/larynx	57 %	43 %			
TUMOUR TYPE	Primary	76 %	24 %	2.42	0.94–6.21	0.0632
	Secondary	56 %	44 %			
DIAGNOSIS	SCC	63 %	37 %	1.40	0.44–4.42	0.5704
	Other	71 %	29 %			
MARGINS COVERED	Yes no	64 %	36 %	1.10	0.45–2.69	0.8307
		66 %	34 %			
PREIRRADIATED	Yes no	50 %	50 %	3.78	1.46–9.78	0.0050
		79 %	21 %			
ELECTRODE	Linear/finger/stinger	65 %	35 %	1.10	0.44–2.79	0.8361
	Hexagonal	63 %	37 %			
DRUG ADMIN	I.V.	68 %	32 %	2.50	0.69–9.02	0.1522
	I.T.	45 %	55 %			
ANALGESIA	General	68 %	32 %	2.14	0.71–6.44	0.1719
	Local	50 %	50 %			
# APPLICATIONS	≤20	75 %	25 %	2.63	0.95–7.23	0.0588
	>20	53 %	47 %			
T stage	T1/T2	63 %	37 %			
	T3/T4	64 %	36 %	0.96	0.36–2.56	0.9419
PREVIOUS TREATMENTS	No (ref)	81 %	19 %			
	Surgery	79 %	21 %	0.84	0.14–5.07	0.8549
	Surgery + radio	90 %	10 %	2.08	0.19–23.30	0.5535
	Surgery + chemo + radio	56 %	44 %	0.18	0.04–0.80	0.0240
INTENT	Curative	85 %	15 %	4.49	1.38–14.67	0.0089
	Palliative	44 %	56 %			

intensification seems to benefit only to patients less than 65 years old [33]; finally, the standard concomitant chemoradiotherapy foresees cisplatin at a dose of 100 mg/m^2, which is not suitable for frail patients. The cetuximab-radiotherapy combination produces a significant locoregional and survival benefit in moderately advanced head and neck cancer, but did not show a benefit for elderly patients, with a median progression free survival of 2.3–4.2 months [33]. We found in the literature a paper on advanced mucosal melanoma treated with immunotherapy: a median progression free survival of 3 months was observed in patients treated with nivolumab monotherapy and 5.9 months for patients treated with a combination of nivolumab-ipilimumab therapy. One-year progression free survival in patients with combined treatment was 36 % [34], in our cohort of patients one-year local progression free survival was 42 %.

In conclusion, this study is the first multicenter study with a large cohort of patients treated with ECT for mucosal cancer in the head and neck. Primary and recurrent/secondary tumors of different histologies were treated. The overall response rate was 65 %, with a 33 % complete response rate with limited side effects. The response rate of the primary tumors was not different from the response rate of the secondary and recurrent tumors. Interestingly, the tumors that were treated with curative intent, as well as treatment naïve and smaller lesions had significantly better outcomes. Based on the available data, ECT can be used for the treatment of recurrent and, in some cases, primary mucosal tumors located in the oral cavity, pharynx, and larynx.

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CRediT authorship contribution statement

Giulia Bertino: Conceptualization, Methodology, Investigation, Data curation, Writing – review & editing, Visualization, Supervision. **Marta Minuti:** Data curation. **Ales Groselj:** Conceptualization, Methodology, Investigation, Data curation, Visualization. **Crt Jamsek:** Data curation. **Barbara Silvestri:** Writing – review & editing, Investigation. **Silvia Carpene:** Data curation. **Paolo Matteucci:** Writing – review & editing, Investigation. **Giuseppe Riva:** Writing – review & editing, Investigation. **Giancarlo Pacorari:** Data curation. **Matteo Mascherini:** Data curation. **Camilla Kjaer Lonkvist:** Data curation. **Tobian Muir:** Data curation.**Christian Kunte:** Data curation.**Francesca de Terlizzi:** Methodology, Formal analysis, Data curation, Investigation. **Gregor Sersa:** Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization.

Declaration of competing interest

Francesca de Terlizzi is an IGEA employer. No other authors have conflicts of interest.

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