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Electrochemotherapy as palliative treatment in patients with recurrent and/or metastatic head and neck tumours: features analysis for an early determination of the partial responsive patients

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Abstract. – OBJECTIVE: The aim of this study was to identify features mainly involved in determining the partial response (PR) to the Electrochemotherapy (ECT) in patients with recurrent and/or metastatic head and neck (H&N) tumor; the identified features were also used in a decision chart in order to provide the clinician with a support tool in deciding further therapies.

PATIENTS AND METHODS: 131 patients (186 treatment sessions) with recurrent and/or metastatic H&N neoplasm were subjected to ECT. Treatment response was evaluated based on Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1 two months after the ECT. The grade of bleeding and pain before, at the end and one week after ECT treatment were evaluated. Univariate and multivariate analysis were performed to identify features involved in determining the patient PR.

RESULTS: In the context of the univariate analysis, tumor size significantly influenced the response to ECT, with higher PR rate of 58.3%: 28 among 48 patients with lesion size ≤ 3 centimeters (p-value < 0.001 at Chi-square test). Pain and bleeding pre-treatment were positively correlated to PR (p-value < 0.001 at Chi-square test). A difference in the current flowing in the tissue during treatment was also observed in partially responsive patients, where the median current value (6.6 A) was higher than that achieved in patients that did not show PR (3.3 A). In the context of the multivariate analysis, the best performances are achieved with the BART method (accuracy of 84%). The main clinical factors to predict the partial response, among investigated features, that have shown to be considered were the pain value felt before performing the treatment and the median current delivered during the ECT treatment. A decision-making support tool to predict the patient prognosis in terms of response rate could be represented by the decision tree obtained with CART algorithm, where a pain pre-treatment more than 5 and a median delivered current not less than 2.8 A led to the prediction a partial responsive patient with an accuracy of 75%.

CONCLUSIONS: The study confirmed that ECT is an interesting antitumoral therapy in advanced chemo- and radio-refractory H&N neoplasms, able to reduce frequent symptoms and to improve the quality of life. Pain pre-treatment and delivered current are the most important variables when predicting the partial response of patients.

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Key Words:
Electrochemotherapy, Advanced head and neck cancer, Tree-based approach, RECIST, Partial response.

Introduction

More than 5% of the carcinomas worldwide are carcinomas of the head and neck (H&N) account for more than 5% of all malignancies, and in 90% of cases are squamous cell carcinomas (SCC)[1]. Despite aggressive and site-specific therapies, a great number of patients develops disease recurrence: until 60% of local failure risk and until the 30% of distant failure risk[2,3]. Many patients with recurrent and/or metastatic (R/M) HNSCC have a poor survival with a disease that is no longer suitable to curative therapy, and they are often referred to palliative therapies[4-9]. At present, a targeted therapy added to cytotoxic chemotherapy results in a significantly prolonged survival from a median of 7.4 months to 10.1 months[10]. Long-term survival is possible only in a minority of patients with locally recurrent, non-metastatic HNSCC that is amenable to salvage surgery and/or re-irradiation[11-17]. Recent evidence[18] indicates that preirradiated tumors have a significantly lower response rate to ECT.

Prolonged disease-free survival seems possible also in patients with locally recurrent disease undergoing palliative systemic therapy compared with patients with metastatic disease[14].

Electrochemotherapy (ECT) is a well-established antitumor strategy for cutaneous tumors. Specifically, through the electroporation of tumor cells, ECT enhances the antitumor activity of poorly or non-permeating cell-membrane chemotherapeutics[18-21]. Moreover, the vascular effect commonly referred to as "vascular lock" supports ECT potential to lesions bleeding control[21-26].

Many clinical reports[27-30] described results of ECT in treatment of H&N tumors. Longo et al[31] confirmed that ECT is an interesting antitumoral therapy in advanced chemo and radio-refractory H&N neoplasms, able to reduce frequent symptoms and improve the quality of life in a study with 93 patients with advanced carcinoma of H&N.

In the present study we aim to identify those features that are mainly involved in determining the partial response to the ECT in patients with R/M HNSCC; furthermore, to use the most important features into an evaluation chart that the clinician could use to predict patient prognosis.

Patients and Methods

Patients Characteristics

Between May 2011 and May 2021, 101 patients (82 male and 49 females, with a median age of 77 years [range 21-98]) with a diagnosis of recurrent and/or metastatic neoplasm of the head and neck, treated with at least two chemotherapy lines and/or with radiation therapy were recruited. Of these, 46 patients were treated twice and 3 of them four times, for a total of 186 ECT sessions.

Local Ethical Committee approved the clinical trial. Pre-, intra-, and post-ECT outcomes were stored in an electronic database and retrospectively collected. Written informed consent was signed by each patient included in the study. Inclusion and exclusion criteria were reported in our previous publication[31]. Table I reports the patient's characteristics.

Surgery and ECT Protocol

ECT procedure and the patient selection were performed according to the ESOPE (European Standard Operating procedure of Electrochemotherapy) guidelines[32,33]. All patients were treated under general anesthesia and a specific pain management protocol was employed[31]. ECT was performed administering bleomycin intravenously (15.000 IU/m^2) 8 minutes before the application of electrical pulses delivering using electrodes with linear, hexagonal or finger configuration (IGEA S.p.A., Carpi, Italy) depending on the size and localization of the tumor[31]. Multiple insertions (20 on average, range 1-105) of the electrode in the target lesions to obtain complete tumor coverage and a margin area of free tissue growths of 3-5 mm (overtreatment) were performed.

Electric protocol was delivered by Cliniporator™ device (IGEA S.p.A., Italy) with the following parameters: 8-96 pulses with an amplitude of 400-730 V (electric field intensity between 910-1000 V/cm), a duration of 100 µs and with a repetition frequency of 5000 Hz.

Treatment was completed within 8 to 40 minutes after the bleomycin injection[32,33].

Treatment Response Assessment

Treatment response was assessed two months after the ECT according to Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1.

Pain and bleeding control was assessed for all patients before and one week after the ECT. The visual analogue scale (VAS) was employed to grade the pain. The bleeding was scored on a

Table I. Dataset description. Patients with PR equals to 0 have progressive/stable disease or completely responded, while partially responsive patients have a PR equal to 1.

				Distribution			
Feature	**Type of variable**	**Description**		**All (n. 131)**	**PR (n. 48)**	**Non-PR (n. 83)**	***p*-value***
Sex	Categorical	Patient gender.	F:	49	18	31	
			M:	82	30	52	0.86
Age	Continuous	Patient age.	Min:	25	25	25	
			1st Qu:	67.5	67.5	67.5	
			Median:	77	77	80	0.59
			Mean:	75.53	74.5	76.12	
			3rd Qu:	86.5	85	87.5	
			Max:	98	25	98	
Localization	Categorical	Tumor localization.	Head:		37	56	
			Lip:	93	1	2	
			Neck:	3	0	1	0.78
			Oral cavity:	1	5	5	
			Ph/l:	10	2	10	
			Tongue:	12	3	9	
Diagnosis	Categorical	Tumor histotype of the target lesion.	Adenoca:	33	11	22	
			BCC:	20	13	7	
			Epidermoid:	6	0	6	0.04
			SCC:	72	24	48	
Prev_treat	Categorical	Other treatments the patient has undergone previously to ECT.	CT:	5	0	5	
			RT:	50	16	34	0.28
			CT+RT:	76	32	44	
Size	Categorical	Tumor size before treatment.	< 2:	7	6	1	
			≥ 2, < 3:	50	22	28	
			≥ 3, < 4:	41	19	22	
			≥ 4, < 5:	24	1	23	<0.001
			> 5:	9	0	9	
Electrode	Categorical	Type of electrode used.	Finger:	12	4	8	
			Hexagonal:	115	42	73	
			Linear:	4	2	2	0.99
N_ECT	Continuous	Number of ECT applications.	Min:	6	6	7	
			1st Qu:	15	12	16	
			Median:	21	17.5	23	
			Mean:	24.58	20.5	26.94	0.05
			3rd Qu:	30	26.25	31	
			Max:	105	49	105	
Curr_ECT	Continuous	Median value of current delivered during the ECT treatment.	Min:	0.62	1.3	0.62	
			1st Qu:	2.4	4.975	2	
			Median:	4.9	6.6	3.3	
			Mean:	5.279	6.459	4.597	<0.001
			3rd Qu:	7.95	8.625	7.25	
			Max:	14.1	10	14.1	
Pain_pre	Ordinal	Pain felt before the ECT treatment.	6:	28	18	10	
			2:	25	1	24	
			4:	14	3	11	<0.001
			10:	13	9	4	
			8:	12	7	5	
			5:	10	3	7	
			Other:	29	7	22	
Bleed_pre	Ordinal	Bleeding observed before the ECT treatment.	1:	66	7	59	
			2:	39	24	15	<0.001
			3:	26	17	9	
PR (response)	Categorical (Binary)	Partial response.	0:	83			
			1:	48	-	-	

The following abbreviations are used: Pharyngeal/laryngeal (Ph/l), Adenocarcinoma (Adenoca), Chemotherapy (CT), Radiotherapy (RT). **p*-value at Chi square test for categorical/ordinal variables and at Kruskal-Wallis test for continuous ones.

scale with three values: 1 for no bleeding; 2 for moderate bleeding and 3 for severe bleeding. The bleeding is considered "moderate" when it is not fast and under control and slows or stops with pressure. Medical assistance once a week is sufficient. By "severe" we mean bleeding that does not stop or slow with pressure, which pumps quickly from the wound by wetting many dressings. In this case, at least twice a week, medical assistance is required.

Statistical Univariate and Multivariate Analysis

For each sample (patient), 11 predictors (Table I) were collected in order to describe it with both diagnostic- and treatment-related variables. Furthermore, an additional variable, i.e., partial response (PR), was considered as response variable.

In the context of univariate analysis, the Chi square test for categorical/ordinal variables and Kruskal-Wallis non-parametric test for continuous variables were performed to assess the significant difference between percentage values and between median values, respectively, in different population subgroups.

In the multivariate analysis, a (decision) tree-based approach has been carried out. Following an appropriate data manipulation, several standard tree-based algorithms were run with the aim of comparing their performance and for the purpose of a more robust evaluation of the results (i.e., less susceptible to overfitting). The setting of the tuning parameters of each algorithm has been performed through a repeated 10-folds cross validation (CV), using a repetition number equals to 10.

Boruta and Bayesian Additive Regression Trees (BART) algorithms have also been used to confirm the variable importance observed in the tree-based algorithms. Moreover, a Generalized Linear Model (GLM) has been run to provide a baseline reference result.

Performances were compared in terms of accuracy.

While tree-based algorithms do not need any data preparation and preprocessing activities, in order to correctly execute the GLM algorithm, some manipulations were deemed indispensable. Particularly, ordinal and categorical data were converted into cardinal and dummy variables, respectively. Furthermore, data centering and scaling of all continuous variables was used in order to prevent variables with higher magnitude from being (erroneously) considered as more important.

A p-value <0.05 was considered significant for all tests. All analyses were performed using RStudio software [34].

Algorithms Details

In order to obtain comparable results, all the tree-based algorithms and the GLM one was run using the train function in the caret package. The Boruta and BART algorithms were executed, respectively, with the Boruta and bartMachine functions in the in homonymous packages.

Generalized Linear Model (GLM) algorithm

GLM algorithm was run setting the *method* argument to 'glm' in the train function. The data had previously been appropriately manipulated, centered, and scaled. All the predictors were considered in the analysis, while the PR variable was used as response. The importance of the variables, the model accuracy and the model coefficients were extracted when analyzing the final model. Since the model does not require tuning parameters, CV has not been necessary.

Classification and Regression Trees (CART) algorithm

Classification and regression trees are machine learning methods that recursively partition the data space considering each predictor at time[35]. The partition is binary, and the algorithm determines the optimal sub-partition for prediction choosing the predictor that allows achieving the best split[36]. CART method has two main limitations; firstly, it tends to overfit the data, that is the model is much more susceptible to noise; secondly, it suffers of variable selection bias, i.e., for variables that have more splits, there is a high probability that they will be chosen to split the top nodes of the tree, even if they are less informative than others[37]. In our work, CART algorithm was run setting the *method* argument to 'rpart' in the train function. All the predictors were considered in the analysis, while the PR variable was used as response. '*cp*' (complexity parameter) is the tuning parameter of the algorithm, and has been chosen through the repeated 10-folds CV. The importance of the variables, the model accuracy and the tree representation were obtained when analyzing the best-tune model (i.e., the model with the best cross-validated performance).

Random Forests (RF) algorithm

Random forests are a machine learning approach that has the goal of improving prediction

performance and reduce instability of CART by averaging multiple decision trees (a forest of trees constructed with randomness)[36,38]. The process generates many decision trees in which randomness is induced through bootstrap or bagging; the classification obtained from the forest is then obtained averaging that achieved results from each tree. While the RF improve the performance of a single tree, the main disadvantage of this algorithm is that the interpretability (i.e., the graphical decision tree) is lost. We run the RF algorithm setting the *method* argument to 'rf' in the train function and using the default number of trees in the forest (i.e., 500). All the predictors were considered in the analysis, while the PR variable was used as response. '*mtry*' (i.e., the number of predictors selected at each node) is the tuning parameter of the algorithm, and has been chosen through the repeated 10-folds CV. The importance of the variables, the model accuracy and the evolution of the error were obtained when analyzing the best-tune model.

Boruta algorithm

Boruta method is based on the idea that, by adding randomness to the system and collecting results from the ensemble of randomized samples, one can reduce the misleading impact of random fluctuations and correlations[39]. Specifically, this extra randomness shall provide us with a clearer view of which predictors are really important, compering each predictor with the so-called shadow attributes. While on the one hand its purpose is also its main advantage, the algorithm, being a humble heuristic approximation, has the limit of requiring a practically infinite number of samples to be solved exactly[39]. In the contest of this study, the Boruta function was used with default parameters and the variable importance plot was obtained. All the predictors were considered in the analysis, while the PR variable was used as response.

Bayesian Additive Regression Trees algorithm

BART method provides a flexible approach to fitting a variety of regression models by embedding the concept of *sum-of-trees model* in a Bayesian inferential framework to support uncertainty quantification[40]. Thanks to the idea of using a regularization prior distribution, the risk of overfitting is avoided, allowing the BART algorithm to fit highly non-linear response surfaces, even with a large number of predictors, without requiring specifying the functional form of the relationship between predictors and the response.

In the contest of this study, the bartMachine function was used with default parameters and the variable importance plot and the model accuracy were obtained. All the predictors were considered in the analysis, while the PR variable was used as response.

Results

Univariate Analysis

Two months after the ECT, 5 (4%) cases, showed a complete response (CR) and 47 (36%) cases a partial response (PR), respectively. After the first ECT procedure, 19 (14%) patients experienced a progressive disease (PD) while the remaining 60 (46%) patients in stable disease (SD). The higher PR rate was observed in 28/48 (58.3%) of patients with lesion smaller than 3 centimeters (p-value < 0.001, Table I) confirming that tumor size influences the overall response according to previous clinical experiences where the cutoff of 3 cm was selected[17].

Other variables with statistically significant relationship with the outcome were found to the: diagnosis, pain felt, and bleeding observed pre-treatment and the median current delivered during the ECT treatment. Higher pain (>5) and bleeding (≥ 2) values determined a major PR rate (83.3% (40/48) and 85.4% (41/48) respectively). Moreover, SCC lesions had a higher PR rate (24/48) compared to BCC (13/48) or adenocarcinoma (11/48) diagnosis.

As shown in boxplots of Figure 1, the median current delivered during the ECT treatment has a different distribution in partially responsive patients compared to patients other than partially responsive (Figure 1A); a comparable result was observed when analyzing the distribution of delivered current when splitting patients in terms of pain pre-treatment (higher or lower than 5 – Figure 1B) and in terms of bleeding pre-treatment (higher or lower than 2 – Figure 1C). Current distribution had a higher median value in patients with PR (Curr_ECT median value = 6.6 A) compared to patients with other than PR (Curr_ECT median value = 3.3 A). The p-value at Kruskal-Wallis test was <0.001. Furthermore, current distribution had a higher median value in patients with pain pre-treatment > 5 (Curr_ECT median value = 6.3 A) compared to patients with pain pre-treatment ≤ 5 (Curr_ECT median value

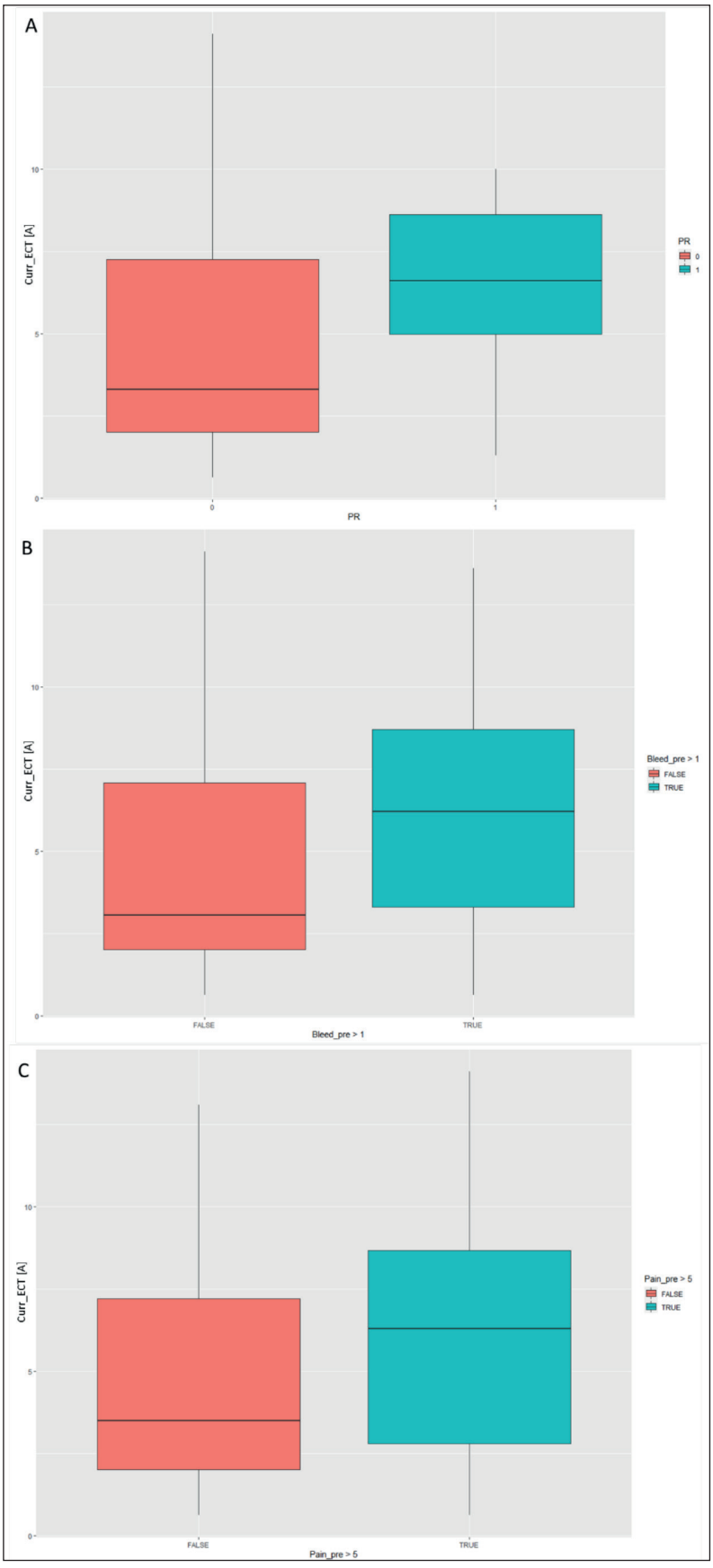

Figure 1. Boxplots of median current delivered during ECT respect to PR **(A)**, to pain pre-treatment **(B)** and to bleeding pre-treatment **(C)**.

Table II. Pain information before and after the treatment.

VAS	VAS pre-treatment N. (%)	VAS post-treatment N. (%)	*p*-value*
VAS < 3	38 (29.0%)	69 (52.7%)	<0.001
3 ≤ VAS < 7	59 (45.0%)	58 (44.32%)	<0.001
VAS ≥ 7	34 (26.0%)	4 (3.1%)	<0.001

*Chi square test.

Table III. Bleeding information before and after the treatment.

Bleeding	Bleeding pre-treatment N. (%)	Bleeding post-treatment N. (%)	*p*-value*
Moderate	39 (29.8%)	24 (18.3%)	<0.001
Severe	26 (19.8%)	6 (4.6%)	<0.001
No	66 (50.4%)	101 (79.4%)	<0.001

*Chi square test.

= 3.5 A) with a *p*-value at Kruskal-Wallis test less than 0.01. Finally, the distribution of current delivered during the treatment had a higher median value in patients with bleeding pre-treatment ≥ 2 compared to patients with bleeding pre-treatment = 1 (Curr_ECT median value of 6.2 A and 3.1 A, respectively; *p*-value at Kriskal-Wallis test less than 0.01).

Pain reduction after ECT was also observed (Table II) with a median VAS score of 5 before treatment *vs.* 2 at 1 week after ECT (Kruskal-Wallis test, *p*-value < 0.01).

Bleeding was well controlled in 34 out of 39 patients with initially moderate symptom and, in 25 out of 26 patients with severe bleeding at diagnosis (Table III).

No toxicities related to ECT were seen except for slight edema in the site of electrode implant, which disappeared one week after the procedure.

Table II and Table III report, respectively, information on pain and bleeding before and after the ECT.

Multivariate Analysis

As Table IV shows, good performances are achieved in predicting the PR variable; thus, the variables considered as predictors show their usefulness in evaluating the partial response in patients that underwent ECT treatment. The tree-based algorithms have shown to be an adequate choice for the purpose of the study, since the accuracy achieved are well above the baseline (0.733). Moreover, the best performance (0.840) is obtained with the BART method, which allows us to use its results to validate those obtained with the CART and RF algorithms.

Variables' importance was assessed running the GLM, CART, RF, Boruta and BART algorithms. While the GLM algorithm tries to use all the predictors in the model, CART and RF perform variables selection, which is attractive considering the purpose of the analysis. Importance of predictors used in these three algorithms is reported in Table V.

Notably, it is useless to consider only the importance of the variables in each model without taking into account the performance, in terms of accuracy, that it achieves. For this reason, although CART and RF algorithms were able to perform the variables selection, a more specific evaluation was deemed necessary, in light of the performances achieved.

Table IV. Values of the tuning parameters (TP) used in the algorithms and related performances achieved.

		GLM	CART	RF	BART
PR	Accuracy	0.733	0.755	0.804	0.840
	TP	-	cp: 0.110	mtry: 6	-

*Chi square test.

Table V. Overall importance of predictors that each algorithm has considered.

	GLM	CART	RF
Pain_pre	100.000	18.292	14.062
Curr_ECT	69.884	9.393	13.751
N_ECT	64.437	3.540	5.332
Bleed_pre	58.310	10.994	10.209
Localization	-	-	2.069
Localization: oral cavity	50.798	-	-
Diagnosis	-	3.284	2.023
Diagnosis: bcc	49.884	-	-
Sex	-	-	0.423
Sex: F	41.816	-	-
Loc: pharyngeal/laryngeal	24.823	-	-
Prev_treat	-	-	0.595
Prev_treat: CT+RT	22.673	-	-
Electrode		-	1.656
Electrode: hexagonal	22.628	-	-
Localization: lip	16.836	-	-
Electrode: finger	15.842	-	-
Age	13.816	-	6.043
Diagnosis: adenocarcinoma	6.661	-	-
Localization: head	1.445	-	-
Size	-	6.825	4.215
Size: < 2	0.261	-	-
Size: ≥ 2, < 3	0.235	-	-
Size: ≥ 3, < 4	0.234	-	-
Size: ≥ 4, < 5	0.196	-	-
Diagnosis: epidermoid	0.098	-	-
Prev_treat: CT	0.088	-	-
Localization: neck	0.000	-	-

As shown Figure 2, Pain_pre and Curr_ECT are, in order, the most important variables when predicting the partial response with both the Boruta and RF algorithms.

This was confirmed by BART results (Figure 3), where the most often included variables were confirmed to be the current delivered during the treatment and the pain felt by the patient before treatment.

Furthermore, Boruta algorithm found also Bleed_pre and Size to have a role in the prediction of patient partial response.

The decision tree representation is shown in Figure 4 (CART method).

As shown in the figure, the CART algorithm has included, in the decision tree, the variables found to be important. The graphical representations also add specific decision-making conditions, which lead to following a specific branch of the tree until the final classification is obtained. For instance, following the chart in Figure 3 with a pain pre-treatment more than 5 and with a median delivered current not less than 2.8 A, the branches on the right would been followed, leading to predicting a partial responsive patient. The probability of a correct classification is reported in each node and is equals to 75% for the previous example.

Discussion

Patients with locoregional R/M HNSCC hardly benefit from surgery or reirradiation; moreover, palliative care is often the only option in patients with recurrent or metastatic disease. The interest for ECT of H&N tumors is due to its ability to control local disease with a minimal functional impairment. The healing of treated tumor lesions is reached without damage of healthy tissue. Furthermore, ECT as suggested by several clinical trials, is a valid alternative to palliative chemo/radiotherapy demonstrating low toxicity profile, good functional and aesthetic results and partial and complete remission rates[27-29]. ECT is more effective than other therapeutic options in treating locally advanced SCC treatment; particularly, they showed an objective response rate (ORR) after ECT treatment of stage III SCC in 81% of patients, with a CR of 22.7%[41]. ECT treatment is

generally well accepted by patients and can be repeated without worsening the quality of life. A sensible improvement of pain, bleeding reduction, and need for medical/paramedical care is observed even in case of partial response[42]. In our previous series[31] of 93 patients with R/M HNSCC, we observed an ORR of 45% with a 5% of CR, a significantly poorer response rate in patients bearing lesions larger than 3 cm, while we reported that the primitive tumor site did not affect the outcome and the 94% and 93% of pain and bleeding control.

However, some clinical factors could influence the ECT response rate, such as tumor diagnosis/

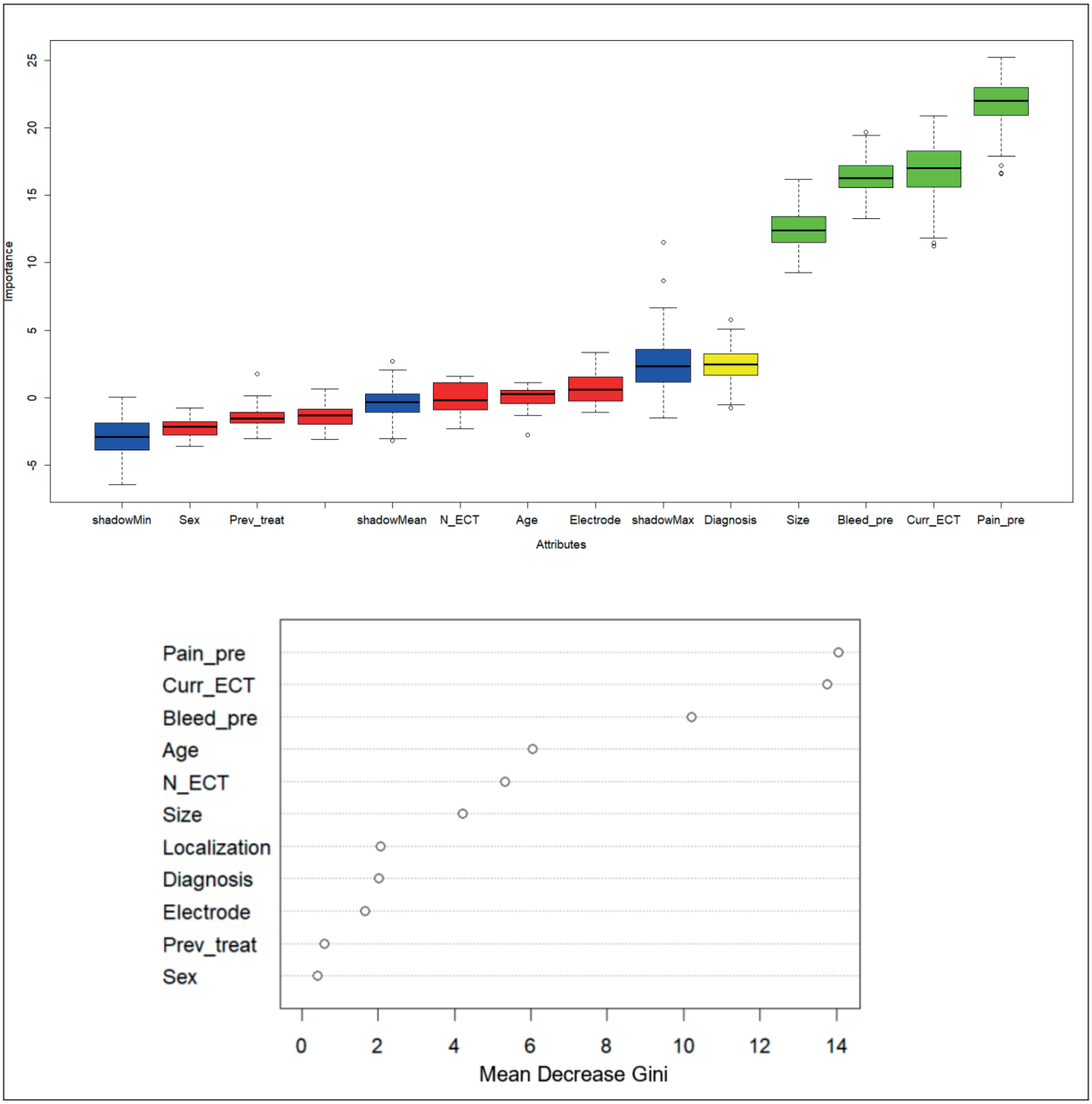

Figure 2. Top: Variable's importance assessed with the Boruta algorithm. Blue boxplots correspond to minimal, average and maximum Z score of a shadow attribute. Red, yellow and green boxplots represent Z scores of rejected, tentative and confirmed predictors respectively. As the plot shows, the pain felt (Pain_pre) and the bleeding observed (Bleed_pre) pre-treatment, as well as the delivered current (Curr_ECT) and the tumor size assessed pre-treatment (Size) are confirmed to be predictive of the partial response. Bottom: Variables importance assessed with the Random Forest algorithm. As the plot shows, Pain_pre, Curr_ECT and Bleed_pre are, respectively, the most predictive variables.

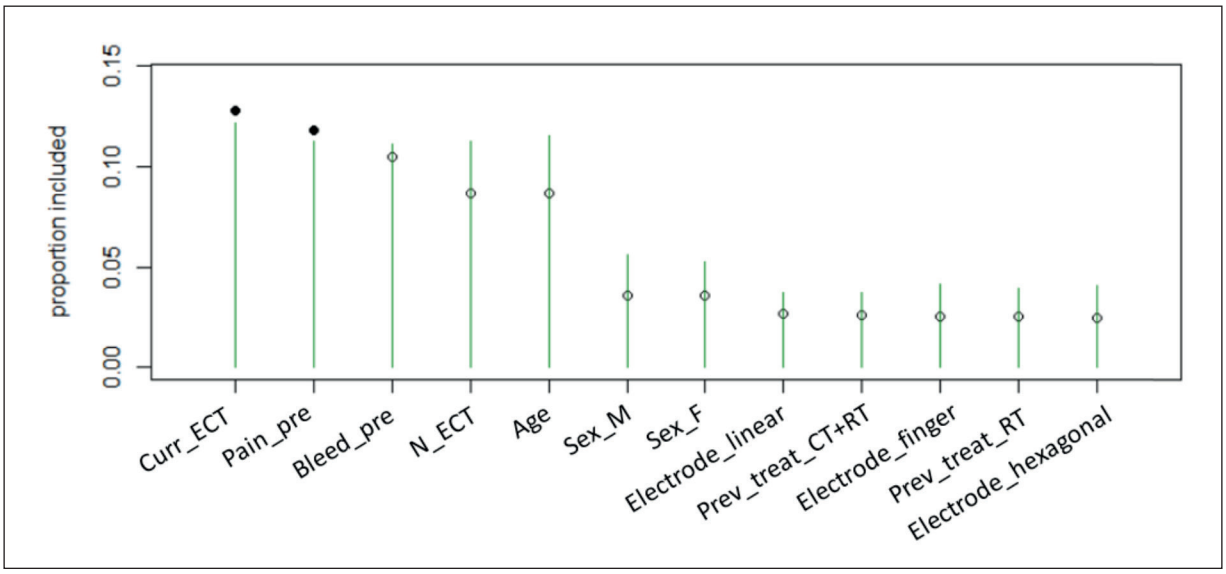

Figure 3. Variables' importance assessed with the BART algorithm. The plot shows only the first 12 variables with the related proportion of times each predictor is chosen as a splitting rule. The green lines are the threshold levels that must be exceeded for a variable to be selected. In the prediction of PR, Curr_ECT and Pain_pre variables are selected (solid dots) having shown a proportion include of about 13.

histotype, tumor size, anatomical location, and exposure to previous oncologic treatments. Difference in the ECT effectiveness respect to tumor histotype were described by Mali et al[43] and Sersa et al[18]. Superficial sarcomas (OR 99.3%, CR 73.9%) exhibited a better response of carcinomas (OR 81.1%, CR 62.7%) or melanoma (OR 80.6%, CR 56.8%). This observation was not confirmed by a Multi-institutional IMI-GIDO study by the Italian Melanoma Inter-group[45]. According to the

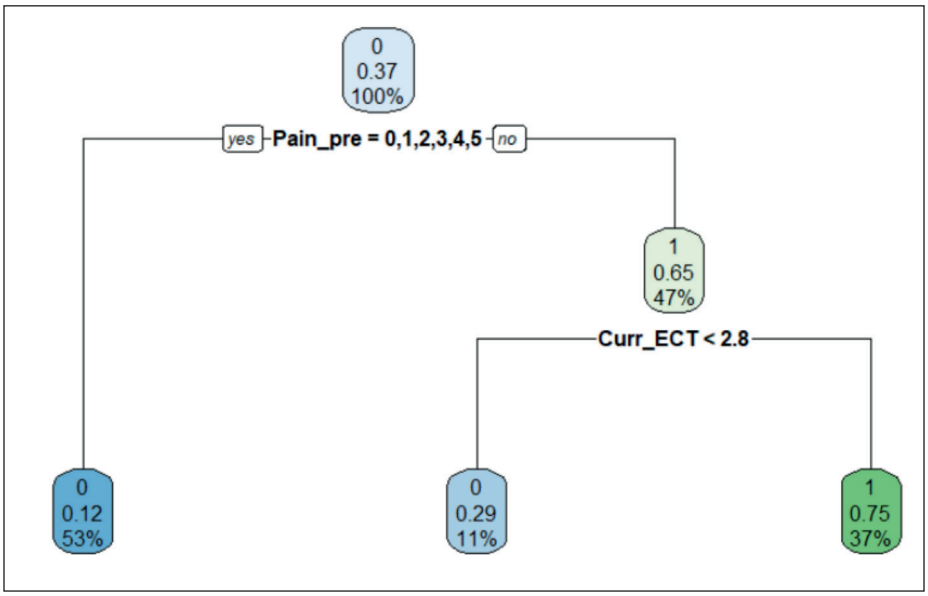

Figure 4. Decision tree obtained with CART algorithm and using the PR variable as a response. As the graph shows, pain felt before the treatment and median delivered current are useful to assess the patient's partial response. Each node shows: the predicted class ("0", progressive/stable disease or complete response, or "1", partial responsive patient), the predicted probability and the percentage of observations in the node.

recent comprehensive analysis of the InspECT registry (2482 lesions in 987 patients)[46] different tumors have different degrees of sensitivity to ECT. Among skin cancers, basal cell carcinoma seems to have the highest sensitivity, whereas melanoma is associated with relatively lower response rates. A more recent series indicated a CR rate of 66-100% for basal cell carcinoma, 55-80% for squamous cell carcinoma, and 25-55% for melanoma[47]. In this study, we confirmed a CR rate of 4% and a PR rate of 36% of the patients with the tumor size that significantly influenced the response to ECT [higher PR rate in 28/489 (58.3%) of patients whose lesion was smaller than 3 cm]. Moreover, other clinical variables with statistically significant relationship with the outcome were found to be: the diagnosis, the pain felt and bleeding observed pre-treatment. Higher pain (>5) and bleeding (≥ 2) values determined a major PR rate [83.3% (40/48) and 85.4% (41/48) respectively]. Moreover, SCC lesions had a higher PR rate (24/48) compared to BCC (13/48) or adenocarcinoma (11/48) diagnosis. The higher PR rate in bleeding lesions, which are also the most painful, could be related to the higher median current value that flowed, which is due to the greater vascularization of the lesions.

In the 86% of subjects, ECT was able to obtain a control of the disease, thus patients were completely or partially responsive or were diagnosed with a stable disease. In order to evaluate benefits from ECT, pain reduction and bleeding control were also considered, as well as possible side effects, except for slight edema in the site of electrode implant, which disappeared rapidly, no toxicities related to ECT were registered.

Significant differences in tumor response and lesions size have been underlined by several ECT clinical studies[18]: lesions smaller than 3 cm in size, either superficial or deep-seated, exhibit a higher response rate than larger lesions. Instead, a 2-cm cut-off associated with the most significant complete response was proposed by Mali et al[43]. The InspECT registry[46] documented a steady progressive decrease in the complete response with the increase in tumor size, with rates consistently higher than 70% for tumors up to 1.5 cm in size. Pre-irradiated tumors respond less to ECT[46] due to radio-, chemo- and targeted drug resistance. The previous observations are confirmed in Bertino's study[17] on skin cancer of the H&N group. Improved responses were obtained with small lesions (≤ 3 cm), primary, and naïve. Radiotherapy (chemo) or multiple treatments of recurrent tumor nodules affected the outcome more than previous surgery[17]. Instead, in our study, previous treatments did not influence the PR rate after ECT.

Considering the main objective of this study regarding the identification of the clinical factors that have been shown to be mainly involved in determining the PR in patients with R/M HNSCC, we found that the best performances are achieved with the BART method (accuracy of 84%). The main clinical factors to predict the partial response, among investigated features, that have shown to be considered were the pain value felt before performing the treatment and the median current delivered during the ECT treatment. This was confirmed by BART results, where the most often included variables were found to be Curr_ECT and Pain_pre. These results led to the choice of realizing a decision tree for the evaluation of the patient partial response, with the clinical purpose of promptly assessing the need for further treatment (for example, the patients could be benefit of a second ECT session), without having to wait for the follow-up period. A decision-making support tool to predict the patient prognosis in terms of response rate could be represented by the decision tree obtained with CART algorithm, where a pain pre-treatment more than 5 and a median delivered current not less than 2.8 A led to the prediction a partial responsive patient with an accuracy of 75%.

While the lesions size previous treatments and the diagnosis were clinical factors often investigated in the ORR or overall survival prediction, to the best of our knowledge, there was not study in literature that assessed in the patient prognosis, in terms of partial response rate, the pain and the bleeding pre ECT and the median current delivered during the ECT procedure.

Some limitations of the study are: a single center population; the small size of population; the retrospective nature of the study and the small number of investigated clinical features. A future study with a larger dataset should be performed to confirm the results.

Conclusions

The study confirmed that ECT is an interesting antitumoral therapy in advanced chemo- and radio-refractory H&N neoplasms, able to reduce frequent symptoms and to improve the quality of life. Moreover, the study confirmed that ECT can be used also on mucosal head and

neck tumors in palliative setting without serious side effect.

Pain pre-treatment and delivered current are the most important variables when predicting the partial response of patients. A decision-making support tool to predict the PR could be represented by the decision tree, where a pain pre-treatment more than 5 and a median delivered current not less than 2.8 A led to predict a partial responsive patient.

Authors' Contributions

Conceptualization, Fabio Maglitto, Franco Ionna and Francesco Perri; Data curation, Gianluca Renato De Fa-zio; Formal analysis, Piera Maiolino and Luigi Califano; Investigation, Fabio Maglitto, Giovanni Salzano, Cor-rado Aversa, Ettore Pavone, Monica Pontone, Giulia Togo, Maria Grazia Maglione, Luigi Angelo Vaira, Mi-chela Bergonzani and Francesco Antonio Salzano; Methodology, Francesco Longo, Maria Luisa Marciano and Maria Grazia Maglione; Resources, Daniele Ordano; Supervision, Franco Ionna and Francesco Perri; Visuali-zation, Luigi Angelo Vaira, Michela Bergonzani and Luigi Califano; Writing – original draft, Elio Di Bernardo, Valeria D'Alessio and Roberta Fusco; Writing – review & editing, Roberta Fusco and Francesco Perri.

Institutional Review Board Statement

Local Ethical Committee approved the clinical trial. Pre-, intra-, and post-ECT out-comes were stored in an electronic database and retrospectively collected.

Informed Consent Statement

Each patient signed a written informed consent to participate to the study.

Data Availability Statement

All data are reported in the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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