Titu Maiorescu University

DOCTORAL SCHOOL

FIELD OF MEDICINE

Summary of the doctoral thesis

Tracheostomy analysis in hypopharyngeal cancer

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1. INTRODUCTION TO THE THESIS ISSUE

1.1 HYPOPHARYNGEAL CANCER: INTRODUCTORY CONCEPTS

Hypopharyngeal cancer, alongside cervical esophageal cancer, represent some of the most complex and challenging pathologies in the field of ENT (Ear, Nose, and Throat). Hypopharyngeal cancer is a less common pathology, characterized by late diagnosis at advanced stages. In the vast majority of cases, the histopathological aspect is that of squamous cell carcinoma. However, squamous cell carcinoma of the hypopharynx accounts for between 3% and 5% of all squamous cell carcinomas of the head and neck. (1)

Hypopharyngeal carcinoma is the neoplasm with the bleakest prognosis among all head and neck cancers, as it presents significant submucosal extension, hard to evaluate accurately. This makes it one of the most complex and difficult pathologies. At the time of diagnosis, 40% of cases show lymph node metastasis, and 50% of patients are classified in advanced stages (T3 N1-2) (2), which also leads to a high mortality rate (up to 30% in the first year after diagnosis, with a 5-year survival rate of only 25% in Europe) (1).

Since early symptoms, such as swallowing disorders or the presence of lateral cervical masses, are often overlooked, early-stage diagnosis is usually incidental. Most patients present for consultation only when symptoms like dysphonia, dyspnea, and dysphagia with reflex otalgia indicate an advanced disease, which has spread to adjacent structures (larynx, recurrent laryngeal nerve paralysis, or extension to the posterior pharyngeal wall and prevertebral fascia) (1,2).

Treatment methods vary and include surgical techniques such as partial or total pharyngolaryngectomy, with or without adjuvant radiotherapy, as well as non-surgical techniques aimed at preserving the larynx (radiotherapy and chemotherapy). However, all these methods have a major disadvantage: they do not improve survival rates. Oncological techniques are constantly evolving, with various regimens such as concurrent chemoradiotherapy or induction chemotherapy followed by definitive radiotherapy in cases of positive response to treatment. (3)

Additionally, radiotherapy has benefited from improvements through the development of intensity-modulated radiotherapy (IMRT) techniques, which primarily reduce the radiation dose delivered to the parotid gland, thus lowering the degree of xerostomia associated with the

procedure. However, these techniques also have the disadvantage of longer treatment sessions and uneven distribution at the tumor targets compared to earlier techniques (4).

In the context of limited survival due to advanced and aggressive disease, the lack of superiority of one treatment option over the other, the aspect that becomes important in opting for a treatment method is related to the quality of life of patients—that is modified by both treatment methods, though in different ways. Surgical techniques, which may include laryngectomy, alter the physical appearance, self-image, and often lead to communication difficulties and social isolation. On the other hand, conservative techniques (5) frequently cause significant swallowing disorders. Given that most patients who undergo surgery also receive adjuvant radiotherapy, it can be stated that, at least in the treatment of hypopharyngeal neoplasm, surgical treatment typically leads to a more significant reduction in quality of life (6).

Tracheostomy is the surgical technique by which the nasopharyngeal-laryngeal passage is bypassed through opening of the cervical trachea at its anterior wall in the cervical region. Laryngectomy patients remain dependent on this mode of respiration for life, as the organ responsible for primary voice production, the larynx, is excised during the surgical procedure. Oncological techniques may preserve the larynx but can require tracheostomy before radiation therapy, either due to tumor location and volume or because of marked laryngeal edema associated with radiotherapy treatment (7).

Since the majority of patients are diagnosed at advanced stages (T3-T4), partial surgical methods or those aimed at preserving the larynx are not feasible, and the remaining surgical options are radical and mutilating, carrying significant surgical stress. These treatments are often compounded by major comorbidities, advanced age, and, particularly, a significant decrease in quality of life due to the necessity of permanent tracheostomy—something that many patients find difficult to accept.

Non-surgical oncological techniques, while potentially leading temporarily or permanently to the need for tracheostomy due to significant post-radiotherapy edema, are more often accepted as the primary treatment method. This is due to the possibility of decannulation if the patient responds well to treatment, the absence of surgical stress, and, most importantly, the better quality of life they offer. Surgical methods for advanced cases require completion with adjuvant radiotherapy, which adds all the adverse effects of radiotherapy to those of the surgery. From these perspectives, most patients in recent years have chosen the treatment

method that offers them the best possible quality of life and have refused primary surgical treatment.

The most common adverse effects of radiotherapy include: decreased quantity and quality of saliva, dysphonia due to localized edema in the glottis, which can lead to acute respiratory failure in cases of large tumors due to narrowing of the laryngeal lumen, hypogeusia (loss of taste), radiation-induced mucositis throughout the digestive tract, and dysphagia due to reduced sensory sensitivity. All these effects are encountered in patients with ENT neoplasms and significantly impact their quality of life.

This study has the following primary objectives:

- Identify predictive factors for the need for tracheostomy in patients treated conservatively,
- Estimate the therapeutic response and the potential for post-procedural decannulation, as well as
- Perform a comparative analysis of the quality of life of tracheostomized patients based on the treatment received.

Secondary objectives include:

- Epidemiological characteristics of the patient group and comparison of the data obtained with those from the scientific literature (incidence, prevalence, symptoms, clinical semiology, staging, treatment methods and therapeutic response, quality of life, etc.),
- Identification of predictive factors for favorable or unfavorable therapeutic responses and the opportunity for decannulation upon completion of conservative treatments in tracheostomized patients,
- Comparison of aspects related to the quality of life in operated versus conservatively treated patients,
- Comparison of incidents associated with the procedure based on how tracheotomy was performed (emergency vs. elective),
- Identification of predictive factors for the risk of post-radiotherapy pharyngo-laryngeal edema in electively tracheostomized patients.

ORIGINAL RESULTS

1.2 RESEARCH METHODS

The study upon which this thesis is based is a retrospective (January 2018 – July 2022) and prospective (August 2022 – March 2023), objective, analytical, descriptive study. Its main goals are to identify the following aspects in the patient population diagnosed and treated at the ENT Clinic of the "Dr. Carol Davila" University Emergency Military Hospital in Bucharest:

- Epidemiological characteristics of the patient group and comparison of the obtained data with those from the scientific literature (incidence, prevalence, symptoms and clinical semiology, staging, treatment methods, therapeutic response, quality of life, etc.)
- Identification of predictive factors for favorable or unfavorable therapeutic responses and the opportunity for decannulation after the completion of conservative treatments in tracheostomized patients
- Comparison of quality-of-life aspects in surgically treated patients versus patients treated conservatively
- Comparison of incidents and complications associated with tracheotomy (emergency vs. elective) based on the method of its performance
- Identification of predictive factors for the risk of post-radiotherapy pharyngo-laryngeal edema in electively tracheostomized patients

The study used the clinical observation sheets of patients admitted during the mentioned period, paraclinical investigations carried out within the hospital, as well as those performed at other centers with patient consent, laboratory tests, images obtained during complementary ORL clinical examinations and cranial nerve assessments (nasopharyngolaryngoscopy, rigid endoscopy, upper digestive endoscopy), and interclinic assessments. The definitive diagnosis for all patients was confirmed by histopathological report, obtained through biopsy of the tumor mass under general anesthesia (suspended microlaryngoscopy with lesion biopsy).

All patients underwent imaging studies (CT, MRI, and fibroscopic examination), with additional whole-body screenings (to exclude distant metastases). They also underwent upper digestive endoscopy (to assess the extension and presence of any cervical esophageal neoplasm), and in selected cases, a PET-CT scan was performed when there was suspicion of tumor persistence or extension. Staging and reevaluations were conducted by the oncologist, ENT specialist, radiologist, and radiotherapist, and treatment options were discussed in a

multidisciplinary committee, considering all the tumor's objective features, comorbidities, disease stage, and the patient's preferences and expectations.

This study was approved by the University Ethics Committee of Titu Maiorescu University, Bucharest, through Decision No. 15/28.06.2022, and by the Ethics Committee of the "Dr. Carol Davila" University Emergency Military Hospital through Protocol No. 538/04.08.2022.

3. THEORETICAL DEVELOPMENT

3.1 MATERIALS AND METHODS

This study includes a cohort of 53 patients diagnosed with hypopharyngeal neoplasm, diagnosed, treated, and reevaluated at the ENT department of the "Dr. Carol Davila" University Emergency Military Hospital in Bucharest during the period from January 1, 2018, to March 31, 2023. The study is retrospective-prospective, objective, analytic, descriptive, non-randomized.

The selection of patients for the study cohort was done using specific inclusion and exclusion criteria.

Inclusion criteria included:

- A confirmed positive histopathological diagnosis of the disease studied,
- Localization of the neoplasm in the hypopharynx,
- Absence of major psychiatric conditions,
- Presence of informed consent,
- Agreement to use data from the clinical observation sheets for research purposes.

Exclusion criteria included:

- Presence of major psychiatric conditions,
- Patients diagnosed with laryngeal or oropharyngeal neoplasms without extension to the hypopharynx,
- Patients without histopathological confirmation,
- Patients who did not agree to the use of data from the clinical observation sheets for research purposes.

The data used in this study was obtained by consulting the clinical observation sheets of patients admitted to the ENT clinic during the period from January 2018 to March 2023, as well as the hospital's database (electronic clinical sheets).

The clinical evaluation of patients was performed through an ENT clinical examination and cranial nerve assessment, complemented by nasopharyngolaryngoscopy and/or rigid endoscopy with various angulation degrees (0°, 30°, 70°, 90°) (Fig. 1, 2, 3:A,B,C; 4:A,B).

This study has received approval from the Ethics Committee of "Titu Maiorescu University" in Bucharest (Decision No. 15/2022) and the Ethics Committee of the "Dr. Carol Davila" University Emergency Military Hospital in Bucharest (Protocol No. 538/2022). All patients included in the study cohort signed informed consent for the use of their data for research purposes and publication of the results.

Figure 1 Clinical appearance of a patient at diagnosis. Lateral view

Figure 2 Clinical appearance of a patient at diagnosis. Anterior view

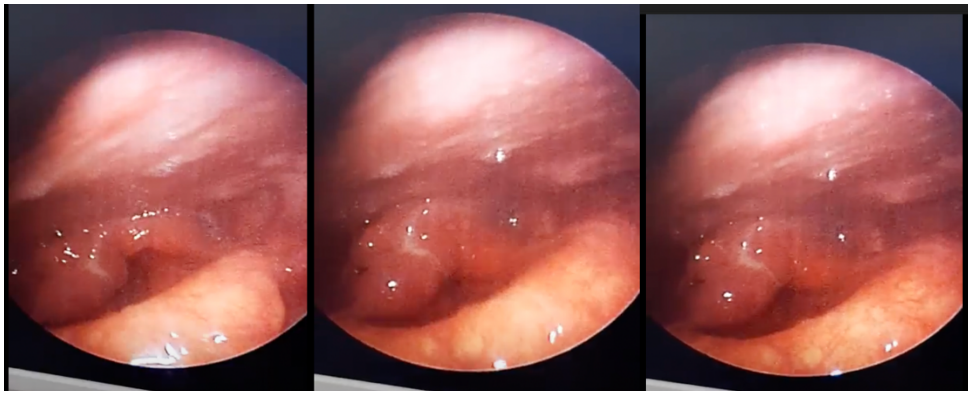

Figure 3. A.B.C. Fibroscopic appearance at diagnosis. Extension at the level of the hemilarynx on the same side as the tumor and fixation of the vocal cords in the paramedian position.

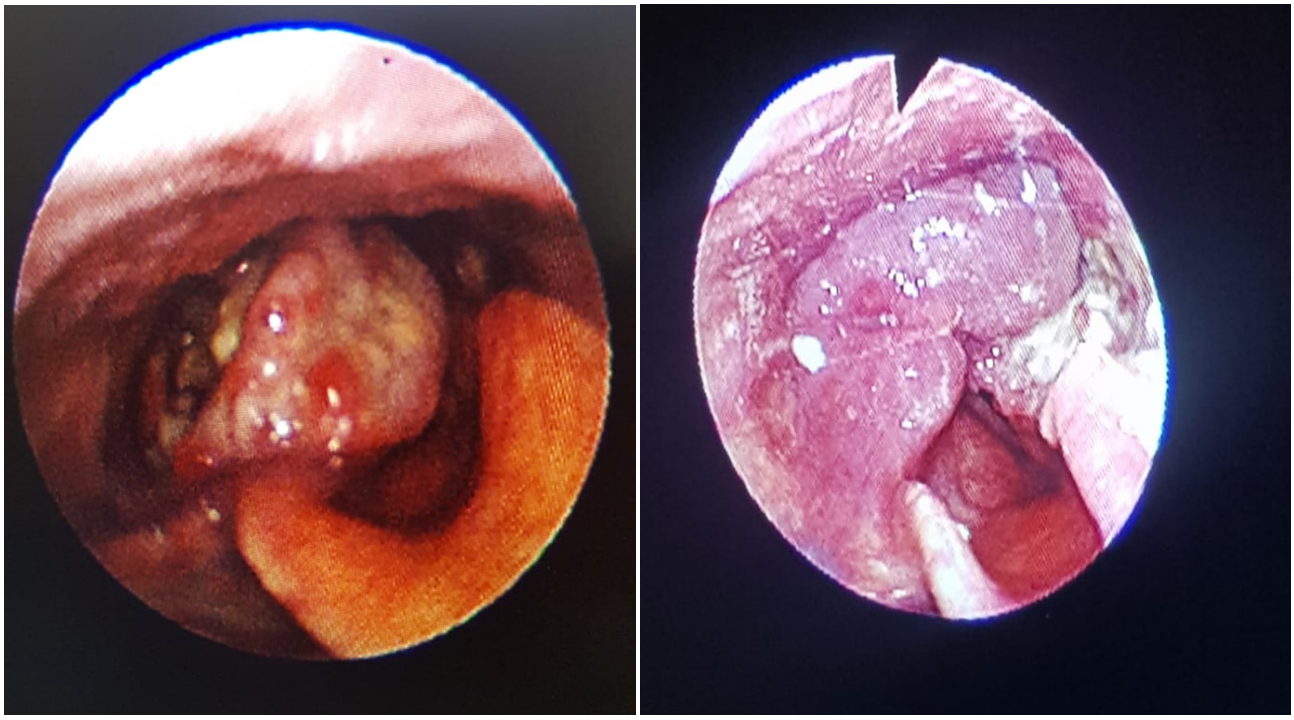

Figure 4.A,B. Fibroscopic features of tumors at diagnosis. Local extension to neighboring regions is observed

Additionally, the patients underwent Upper Digestive Endoscopy (EDS) to assess the potential local extension of the neoplasm to neighboring regions.

Paraclinical testing**:** The laboratory tests for the patients included in the study were performed within the clinic, and the following biological parameters were monitored: from the hemogram (Leukocyte count, Erythrocyte count, Platelet count, Hemoglobin value); from the coagulation profile (INR, Quick Time - TQ, Prothrombin Activity - PA); from biochemistry

(Blood Glucose, Urea, Creatinine, Total Bilirubin, GPT/ALT, GOT/AST); Erythrocyte Sedimentation Rate - ESR.

Staging of cases was carried out based on paraclinical imaging investigations: Contrast-enhanced Computed Tomography (CT), Contrast-enhanced Magnetic Resonance Imaging (MRI), and for a few patients, Positron Emission Tomography (PET-CT) was used to establish the presence of residual disease. Additionally, TNM staging was used, correlated with the AJCC (American Joint Committee on Cancer) staging system.

În order to establish a positive diagnosis, all patients underwent Suspended Microlaryngoscopy (LSS) with biopsy of the lesion, the samples were sent for histopathological examination. General Anesthesia was used for LSS with oro-tracheal intubation (IOT) or endotracheal intubation (ETI) for patients that presented acute respiratory distress and the procedure was performed place after tracheostomy.

Treatment methods performed in the clinic were chosen based on the disease stage, the general condition of the patient, the decision of the oncological committee and last but not least, the patient's informed consent. For the patient group studied, the therapeutic options included: total laryngectomy with partial pharyngectomy and bilateral radical neck dissection, followed by adjuvant radiotherapy; and IMRT VMAT paliative radiotherapy + Chemotherapy.

After being informed about the treatment options based on the disease stage, patients opting for oncological treatment (radio-chemotherapy) were offered preoperative placement of a tracheal cannula. Patients who refused were monitored locally during treatment, and the procedure was only performed in case of an emergency, such as the onset of asphyxic syndrome. In the case of surgically treated patients undergoing laryngectomy with pharyngectomy and jugulocarotid lymph node dissection, the tracheotomy was performed intraoperatively and not separately, as in the case of conservatively treated patients.

The tracheotomy technique used was the transisthmic approach through a vertical incision (from the superior margin of the cricoid cartilage to the sternal notch), using local anesthesia and infiltration of the pre-laryngeal tissues, layer by layer, with 0.5% Xylocaine. Silver tracheal tubes with a mandrel were placed, which were changed daily, and between days 5-7 postoperatively, the silver tube was replaced with a special polymer or silicone tube. During hospitalization, the patients and their relatives were taught how to care for the tracheostoma

and tracheal tube to reduce incidents (accidental decannulation, mucus plug formation in the tracheal tube, wound bleeding).

The complications monitored for each tracheostomized patient included: tracheotomy tube obstruction due to secretions and mucus plugs, accidental decannulation, wound infection due to improper care, the development of granulation tissue at the stoma and peristomal area, which increases the risk of lesions and bleeding at the wound site, as well as the frequency of such events (Fig. 5).

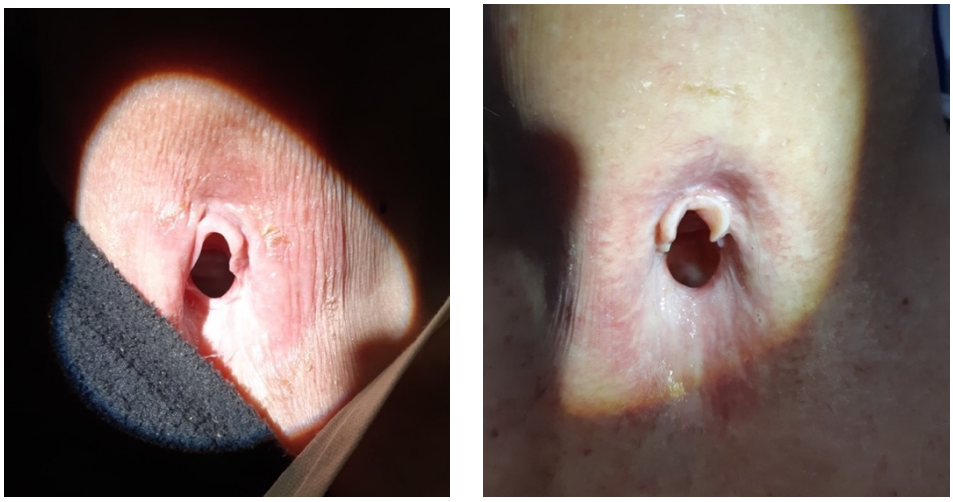

Figure 5. Presence of granulation tissue at the tracheostomy site.

In order to assess as objectively as possible the general status, comorbidities, as well as the risks of mortality and complications, we used standardized questionnaires whose usefulness has been demonstrated in previous studies (141, 142): Adult Comorbidity Evaluation-27 (ACE-27) and Karnofsky Performance Status Scale (KPSS). Quality of life was quantified using the questionnaire developed by the European Organization for Research and Treatment of Cancer (EORTC), using the module for head and neck cancers (EORTC QLQ-H&N35), the Romanian version.

Since the study comprises many patients from a retrospective cohort who could not complete the quality of life questionnaire, we used the key items from the questionnaire (pain, swallowing difficulties, speech, use of analgesics, presence of gastrostomy, social contact, ability to open the mouth, changes in olfactory and gustatory senses), as well as the presence or absence of acute respiratory failure syndrome at the time of presentation.

Patient Data and Statistical Methodology

Tables were created in Microsoft Excel where data obtained from patient observation sheets included in the study were entered, corresponding to the evaluation stages (initial evaluation; evaluation 1 month after tracheostomy, during oncological treatment or postoperatively, and final evaluation – after treatment completion, at least 3 months later). For each of these stages, the following measurement tools were used: values of biological constants, presence and number of incidents related to the tracheostomy, presence of gastrostomy and the method of placement (classic or PEG), presence of subjective complaints related to quality of life.

The statistical analysis was based on the protocol of an observational, unicentric, ambispective clinical study, with the unit of observation being the patient admitted at least once during the period January 2018 - March 2023 to an academic ORL clinic in Bucharest, with a histopathological diagnosis of hypopharyngeal cancer, with or without tracheostomy.

The data sources were represented by:

- The admission register,
- The patient's observation sheet (physical file and electronic database of SUUMC),
- Quality of life questionnaire – QoL adapted from the EORTC questionnaire using the module for head and neck cancers (EORTC QLQ-H&N35), Romanian version, completed by the doctoral researcher-investigator through an interview with the patient/relative, or based on the data from the observation sheet.

The variables of interest considered necessary for the study were structured into quantitative or qualitative variables, including:

- Patient characterization (continuous variables: ID (file number), year of birth, age at diagnosis, age at tracheostomy, age at QoL evaluation; nominal variables: sex (M, F), area of origin (urban/rural), occupation (employee/retired/unemployed/no occupation))
- Disease characterization (ordinal variables: stage (T1-TIV - American AJCC classification, 7th and 8th editions); differentiation grading (G1-4); nominal variables: LT – tumor localization with the segment mentioned; TH – histopathological type; dichotomous variables: presence of lateral cervical adenopathy; presence of recurrence)
- Risk factors related to profession and lifestyle: dichotomous variables: toxic exposure, smoking, alcohol consumption

- Comorbidities – dichotomous variables: cardiovascular, respiratory, diabetes, other cancers, gastrointestinal, coagulation disorders, allergies; continuous variables: ACE-27 score; Karnofsky Performance Status Scale (KPSS) score
- Intervention data – diagnosis date, surgery performed (Y/N), year of surgery, year of tracheostomy, duration from diagnosis to tracheostomy (months), evaluation year (months) (interval between tracheostomy and evaluation), number of admissions, initial treatment
- Evolution at the end of radio-chemotherapy treatment – (F/ST/NF) favorable (tumor volume reduction/laryngeal permeability); stationary; no change due to treatment
- Intervention data: type of tracheostomy – emergency / elective (E/U), incidents during tracheostomy maintenance (Y/N), number of incidents; presence of gastrostomy, and type of gastrostomy (classic/PEG)
- Syndromes present at the time of admission:
- Digestive (odinophagia/dysphagia), Y/N;
- Respiratory (dyspnea), Y/N;
- Phonatory, Y/N;
- Sensory, Y/N (including hyperesthesia, hypoesthesia, paresthesia);
- Sensory (dysgeusia = subjective disturbances)
- Presence of radiation mucositis phenomena Y/N
- Laboratory values at 3 time points: (at the first admission pre-tracheostomy T1, re-evaluation 1 month after tracheostomy T2, T3 at the end of oncological or combined treatment): Leukocytes, erythrocytes, platelets, hemoglobin, INR, TQ, AP, VSH, urea, creatinine, total bilirubin, ALT, AST, PCR, glucose
- Quality of life (QoL) EORTC H&N35 questionnaire, Romanian version adapted for patients treated with radio-chemotherapy as first intention (4 patients)

In the first phase of the statistical analysis, variables were described according to their type: for qualitative variables, summarized in contingency tables "r x c," mostly 2x2, frequency indicators were calculated (absolute and relative frequencies); comparison of these indicators was done using the X^2 test, or when conditions for using the test were not met, Fisher's Exact Test was applied.

Quantitative variables were described by central tendency and dispersion indicators (mean and standard deviation). To compare two means, the Student's t-test for independent samples was applied; for more variables, ANOVA was used, respecting independence, normality, and homoscedasticity conditions. When these conditions were not met (e.g., biological

constants/patient compared to themselves at different monitoring times), the Mann-Whitney test or Kruskal-Wallis test was used.

In order to identify parameters that may predict patient outcomes (prognosis), logistic regression was tested, although its application was conditioned by the study's limits. Correlation analysis also allowed the identification of relationships between some of the studied parameters.

To highlight and/or characterize the quality of the studied factor (risk, protection, or neutrality), where the calculation conditions allowed, the estimated risk odds ratio (OR) was calculated, which is the odds ratio between the probability of the tested risk factor in one subgroup versus the probability in another subgroup (example - the risk of radioedema in the emergency tracheostomy group (U) vs. elective group (E)).

In relation to the objectives of the study and the applied statistical analysis, I considered it useful to detail the methodology in this section to facilitate the interpretation of the results.

Conventionally, regardless of the test applied, the rejection or acceptance of the null hypothesis (H0) and the interpretation of the difference were made at a significance threshold (p-value) of ≤ 0.05; the p-value represents the probability that the statistical difference is due to chance; its value was interpreted according to the table below (Table 1).

p-value	**Interpretation**
$p > 0.05$	The difference is not significant, any difference is attributable to chance
$0.01 < p < 0.05$	The difference is statistically significant; H0 is rejected
$0.001 < p < 0.01$	Very significant difference, H0 is rejected
$p < 0.001$	Highly significant difference, H0 is rejected

Table I Interpretation of statistical differences based on the significance threshold

In the event of no statistical differences ($p > 0.05$), which may be due to the relatively small number of cases, I considered it necessary to calculate the "power of the test"; this shows the probability that a statistical test will detect a "real effect" or the chance of confirming the research results; for the variables studied, the test power varied between 6.8% and 9%, and the maximum accepted error was under 10%.

If the representativeness of the sample is sensitive to the random selection of enrolled cases, the significance threshold "p" as well as the power of the test are sensitive to the size of the study sample - the larger the sample volume, the greater the accuracy of the results.

Regardless of the number of admissions/consultations during the studied period, each patient was included in the study only once, as a unique unit of observation. The initial study cohort consisted of 53 patients diagnosed and histopathological confirmation of hypopharyngeal carcinoma. The final cohort, with the necessary information to achieve the proposed objectives, includes 33 patients; only 2 of the patients excluded from the analysis had an emergency tracheostomy, and the exclusion rate was within the accepted 20% loss-to-follow-up percentage.

It is considered (C. Vlădescu, 2000) that "patients admitted to a university clinic – even if all patients hospitalized in a calendar year are studied – cannot provide a real picture of the entire population in the area, because the characteristics of these patients may differ from those hospitalized in less specialized hospitals" (143).

However, given the random selection of the study base, its high accessibility, and the random selection of the subjects studied, the study cohort can be considered representative, with a 95% confidence level, for any ORL medical unit with the technical and human resources (to evaluate and treat patients under similar conditions) comparable to those in the study, which treats cases of hypopharyngeal carcinoma candidates for tracheostomy, similar in severity and complexity to those enrolled in the thesis.

The existence of specialized programs allows us to easily calculate either the minimum necessary sample size or the approximation error. The data collected, considered to have validity, safety, and accuracy, were entered into an Excel database specifically designed for the study. Since the study has both a global cohort and subgroups with fewer than 100 patients, percentage representations are not usually calculated, but in this study, we will present percentage ratios as it involves a rare pathology and to facilitate the interpretation/visualization of the obtained results.

For data processing, the SPSS software package, version 27, was used. The results were presented using structure charts (PIE chart), frequency bars, or box plots.

When interpreting the results, the limitations of the study must be considered, due to:

- The nature of the studied disease – a rare disease, which involves not only a small number of cases but also conditions/limitations in applying statistical analysis techniques.
- Limited access to the hospital archive – only the observation sheets from 2018 to the present are accessible; the other files are stored in another location, which is difficult to access.
- Lack of a national registry/records for patients with hypopharyngeal carcinoma.
- Lack of information on patient survival.
- Inability to apply the full QoL questionnaire in the retrospective study segment.
- COVID restrictions (limiting patients' access to medical services during the state of emergency, and later, during the state of alert, patients' reluctance to approach medical units).

3.2 CLINICAL RESULTS

3.2.1 Socio-demographic characteristics of the patients enrolled in the study

Based on the inclusion and exclusion criteria, a total of 53 patients diagnosed with histopathologically confirmed hypopharyngeal carcinoma were enrolled in the study. These patients were hospitalized between January 2018 and March 2023 in the ENT clinic. The patient cohort was predominantly male (50 men / 3 women). Among the studied cohort, 20 patients did not undergo any treatment or did not complete the prescribed treatment, and their information was incomplete, leading to their exclusion from the analysis focused on tracheostomy.

In relation to the objectives of the analysis, the global cohort was stratified into subgroups of interest, with a focus on those related to the application of tracheostomy (Table 2). The subgroups used in the study were:

- **E (elective)** – tracheostomy performed in the absence of acute respiratory failure,
- **U (emergency)** – tracheostomy performed in the presence of asphyxia syndrome,
- **F (none)** – patients who did not undergo tracheostomy during the study.

Tracheostomy was performed on a total of 36 patients: 11 patients (1 female, 10 male) (31%) had an elective tracheostomy (E), and 25 patients (25 male) (69%) had an emergency

tracheostomy. A total of 6 patients (1 female, 5 male) (11%) underwent total laryngectomy with partial pharyngectomy, and for one patient, emergency preoperative tracheostomy was necessary due to acute respiratory failure.

MONITORING		Treatment Response	Number of patients	%	Trah -	Trah +	Elective	Emergency
Under medical surveillance	37	**F**	12	22.6	1	11	6	5
		NF	15	28.3		15	4	11
		S	10	18.9	2	8	1	7
Lost to follow-up	16	**X**	16	30.2	14	2		2
TOTAL	53	Total	53	100.0	17	36	11	25

Table II Characterization of the global patient cohort and corresponding subgroups (No Tracheostomy = Trah-, With Tracheostomy = Trah+, F = favourable, NF = non-favourable, S = stationary, X = unknown)

	Tracheostomy type		
	Emergency (N=22)	Elective (N=11)	p
Smoking	16	5	>0.05
Alcohol consumption	10	0	**0.013**

Table III Distribution of patients' habits based on tracheostomy type and their statistical relevance.

Conclusion of the Subchapter

No significant differences were observed in the socio-demographic profiles of the patients. No characteristics were identified that could recommend or predispose to tracheostomy. The association between tracheostomy type and the studied variables, applied to the restricted patient cohort for which there is a complete evolution profile (33 patients), reveals similarities at the level of subgroups defined by tracheostomy type. This allows for their comparison in terms of disease characteristics, comorbidities, and the studied pathology. From the perspective of age, patients with emergency tracheostomies were older than those with elective tracheostomies, with an average age over 65 years. Patients with emergency tracheostomies were more frequently from rural areas (OR=1.44). Favourable results were recorded for patients under the age of 60 at the time of diagnosis. The distribution of lifestyle-associated risk factors confirms excessive ethanol consumption in the etiology of hypopharyngeal carcinoma, as well as a statistically significant predisposition for the need for emergency tracheostomy (p=0.013).

3.2.2. Description of the studied sample in terms of tumor characteristics

The following tumor locations (TL) were considered (Table 4): **F** (pharynx), **FE** (pharyngoesophageal), **FE + FL** (pharynx + larynx + esophagus),**FL** (pharynx + larynx). Additionally, the location within the pharynx was subdivided into the following variants:**OH** (oropharynx + hypopharynx), **HF** (hypopharynx), **HFL** (hypopharynx + larynx), **HFE** (hypopharynx + cervical esophagus).The most common tumor location was the hypopharynx, with extension to the larynx, which was observed in 33 of the patients included in the study (62%).

Tumoral location			Tracheostomy type			
			Elective	Without	Emergency	Total
LT	F	Frequency	**4**	**11**	**2**	**17**
		% of TL	23.5%	64.7%	11.8%	100.0%
		% of Tracheostomy	36.4%	64.7%	8.0%	32.1%
	FE	Frequency		**2**		**2**
		% of TL		100.0%		100.0%
		% of Tracheostomy		11.8%		3.8%
	FE FL	Frequency			**1**	**1**
		% of TL			100.0%	100.0%
		% of Tracheostomy			4.0%	1.9%
	FL	Frequency	**7**	**4**	**22**	**33**
		% din TL	21.2%	12.1%	66.7%	100.0%
		% din Trah	63.6%	23.5%	88.0%	62.3%
Total		Frequency	11	17	25	53
		% din TL	20.8%	32.1%	47.2%	100.0%
		% din Trah	100.0%	100.0%	100.0%	100.0%
P=0.001						

Table IV Patient distribution according to tumor location and tracheostomy]

The placement of the tracheostomy varied significantly ($p<0.05$) with respect to tumor location in the studied patient group (Table V). All patients treated surgically with surgery followed by radiotherapy had tumors located in the pharynx and larynx. Additionally, significant statistical differences ($p<0.05$) were observed in the detailed statistical analysis regarding the affected segment of the pharynx.

		STAGE				
		III	IV A	IV B	IV C	Total
Tracheostomy type	Elective	1	5	5	0	11
	Without	4	6	7	0	17
	Emergency	0	18	3	4	25
Total		5	29	15	4	53

Table V Distribution of the large cohort (53 patients) in relation to the stage and type of tracheostomy performed

The presence of lymph node disease at the time of diagnosis was confirmed in 52 out of 53 patients. All the patients who underwent surgery (6/6 patients – 100%) presented with extension to the cervical lymph nodes. This overwhelming proportion of adenopathy presence at the time of diagnosis confirms the late presentation and advanced stage at the time of clinical presentation.

Analysis of the reduced group

		Tracheostomy Type		
		Emergency (N=22)	Elective (N=11)	Total
STAGE	III	0	1	1
	IV A	16	5	21
	IV B	2	5	7
	IV C	4	0	4
Total		22	11	33

P=0.024, Pearson X^2

Table VI Statistical correlations regarding the type of tracheostomy and tumor stage - restricted sample

The tumor stage showed statistical significance (P=0.024) in the Pearson X^2 test. The most frequent tumor stages were: for emergency tracheostomy – stage IV A (16 patients), and for elective tracheostomies, with a similar frequency (5 patients) – stages IV A and IV B

		Tracheostomy		
		Emergency (N=22)	Elective (N=11)	Total
Affected region	Pharynx	1	4	5
	Pharynx + Larynx+ Esophagus	1	0	1
	Pharynx + Larynx	20	7	27
Total		22	11	33

P=0.048, Pearson X^2

Table VII Distribution of the restricted sample according to the affected segment and type of tracheostomy

The statistical analysis of the subgroups formed after classifying the affected segment (organ) (P=0.048 Pearson X^2) confirmed the significance of pharyngeal tumor location with extension to the larynx as a location with a predisposition for emergency tracheostomy.

Conclusion of the subsection:

The decision to perform or not perform a tracheostomy was based on the characteristics of the studied disease. The significance threshold p ($p<0.05$ for tumor location) showed that those with tracheostomy had a predominant tumor location at the pharynx + larynx, while those without tracheostomy most frequently had a tumor confined to the pharynx.

For patients who were not tracheostomized, the tumor location was at the level of both the oropharynx and hypopharynx, while for patients who underwent tracheostomy, the location was both in the hypopharynx and extended to the larynx. Although not reaching statistical significance, the degree of tumor differentiation showed a different profile when correlated with tracheostomy placement. The frequency of tracheostomy was higher in stage IV C (4/4 patients, all emergency tracheostomies), while for stage IV A, tracheostomy was performed in 23/29 patients, 18 of which were emergency tracheostomies.

In conclusion, simultaneous tumor location at the (hypo)pharynx and larynx can lead to the need for emergency tracheostomy, starting from stage IV A and progressing to further advanced stages.

3.2.3. Analysis of the patient cohort in terms of comorbidities

The presence of comorbidities was evaluated in the study cohort both in terms of the number of associated pathologies (Table VIII, Figure 6-A, B, Figure 7) and the affected systems.

The presence of comorbidities was recorded in 8 out of 10 patients included in the study (44 out of 53 patients), and the number of associated conditions varied between 1 and 15. The frequency of comorbidities was higher in the subgroup of patients who underwent tracheostomy ($p>0.05$) compared to patients who did not undergo tracheostomy. Moreover, most of the patients who underwent emergency tracheostomy presented diseases associated with the primary diagnosis (30/36 patients), while elective tracheostomy patients had associations with more than 4 comorbidities. All patients who were surgically treated presented associated pathologies from other organs and systems.

			Type of Tracheostomy			Total
			Elective	Without	Emergency	
Comorbidities	**YES**	Frequency	**9**	**14**	**21**	**44**
		% from Comorbidities	20.5%	31.8%	47.7%	100.0%
		% from Tracheostomies	81.8%	82.4%	84.0%	83.0%
	NO	Frequency	2	3	4	9
		% from Comorbidities	22.2%	33.3%	44.4%	100.0%
		% from Tracheostomies	18.2%	17.6%	16.0%	17.0%
Total		Frequency	11	17	25	53
		% from Comorbidities	20.8%	32.1%	47.2%	100.0%
		% from Tracheostomies	100.0%	100.0%	100.0%	100.0%

Table VIII The distribution of patients in relation to the presence of comorbidities and tracheostomy

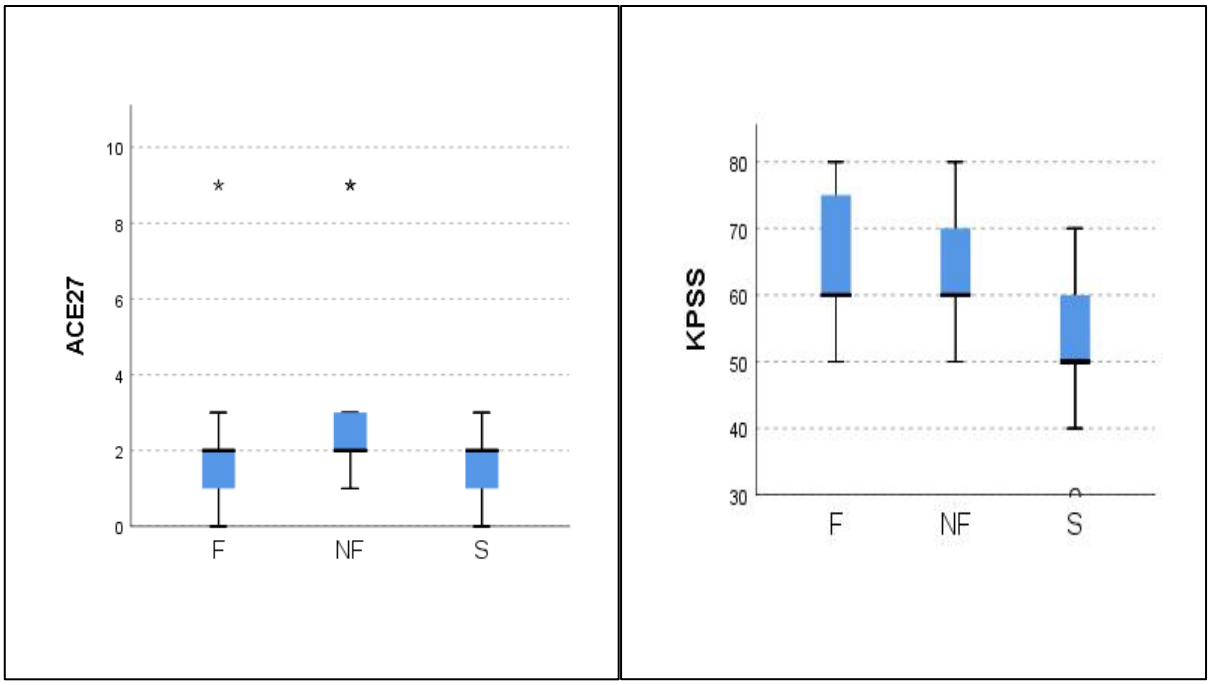

Figure 6 A.B. The graphic representation of the ACE-27 and KPSS indications reported to the end-of-treatment result

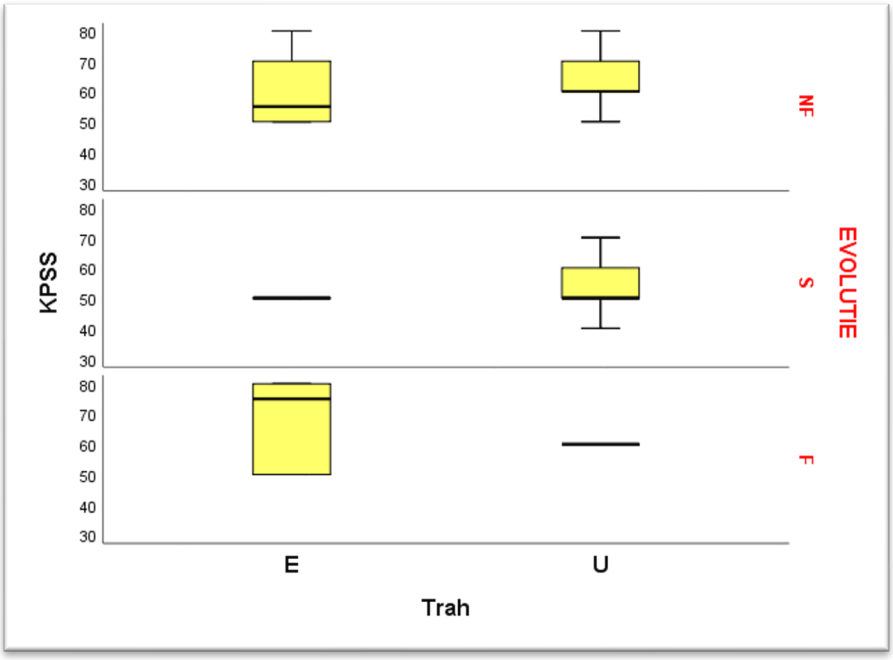

Figure 7 KPSS scores related with the type of tracheostomy and end-of-treatment result

Subchapter Conclusion

In the studied group, the presence of comorbidities was noted in 8 out of 10 patients (44/53 patients), and tracheotomy was performed in 7 out of 10 patients with comorbidities. The main system affected — the cardiovascular system — does not show a significant profile in relation to tracheostomy placement. No significant differences were observed in ACE-27 and KPSS scores in relation to the presence or absence of tracheotomy, and no comorbidities were identified that would favor the necessity of a specific type of tracheotomy. The only comorbidity identified as being significant in unfavorable prognosis was a personal history of neoplasm (p=0.031). Patients with the lowest KPSS values were those in the stationary subgroup (p=0.036).

3.2.4. Initial Main Treatment

Data regarding the main treatment could not be collected for all 53 patients included in the study group, as there were cases where patients did not undergo any treatment at the time of evaluation or were lost to follow-up.

The categories of treatment within the ENT clinic at SUUMC were as follows:For 6 patients, the treatment was surgical (total laryngectomy with partial or total pharyngectomy, followed by radiotherapy), among whom 2 required additional chemotherapy due to the occurrence of recurrences. For 25 patients, the main treatment was conservative, involving two types of radiochemotherapy: concurrent radiochemotherapy or induction chemotherapy followed by

radiotherapy after tumor volume reduction. For a single patient, the treatment consisted of chemotherapy only, as they had a history of full-dose irradiation for another neoplasm, and the tumor exhibited inoperability characteristics. Tracheotomy was performed for 4 patients who were about to begin oncological treatment but had not undergone any other procedure at the time of evaluation. Patients for whom no information regarding treatment could be obtained, or who did not attend scheduled visits, or who did not undergo any treatment between visits to the ENT clinic, were marked with "-". Table IX illustrates the information presented above.

TREATMENT	Tracheostomy		Total
	YES	NO	
-	3	14	17
Chemotherapy	1		1
Surgical+ RT + Chemotherapy	2		2
Surgical + Radiotherapy	4		4
Radiation+ Chemotherapy	22	3	25
Tracheostomy	4		4
Total	**36**	**17**	**53**

Table IX The distribution of the group in relation to the treatment received and the performance of tracheotomy

		END-OF-TREATMENT RESULT			Total
		Favorable	Not favorable	Stationary	
Treatment	Chemotherapy		1		1
	Surgical + RCHT		2		2
	Surgical + RT	4			4
	RCHT	7	10	5	22
	Traheostomy			4	4
Total		11	13	9	33
P=0.005					

Table X Distribution of the small group in relation with the treatment received and end-of-treatment response

3.2.5. Tracheostomy in the Management of Hypopharyngeal Squamous Cell Carcinoma

Out of the total group of 53 patients, 36 patients underwent a tracheostomy. Among these, 25 patients experienced acute respiratory failure and required emergency tracheostomy placement. Eleven patients underwent elective tracheostomy in the absence of acute respiratory failure; however, they presented with massive edema in the hypopharynx, aspiration of secretions from the hypopharynx, large tumors extending to the larynx and reducing the glottic space, or persistent post-radiotherapy edema with a tendency to increase in volume.

Of the 36 tracheostomized patients, 33 had complete data available for analyzing the differences between the two established subgroups. Patients excluded from the analysis had undergone emergency tracheostomy but did not attend subsequent follow-ups, and insufficient information could be obtained about them.

END-OF-TREATMENT RESPONSE		TRACHEOSTOMY TYPE		Without tracheostomy	Total
		EMERGENCY	ELECTIVE		
	Favorable	5	6	1	12
	Not Favorable	10	4	0	14
	Stationary	8	1	2	11
	X (Lost from evidence)	2	0	14	16
Total		25	11	17	53

Table XI End-of-treatment distribution of the study group related with tracheostomy type and end-of-treatment result

		Tracheostomy type		Total
		Elective	Emergency	
Complications	YES	4	16	20
	NO	7	6	13
Total		11	22	33
p=0.044, the frequency of the complications varies statistically				

Table XII Complications associated with tracheostomy

Complications of Tracheostomy	*Traheostomă Electivă*	*Traheostomă de Urgență*
Perioperative		
Hemorrhage	0	0
Pneumothorax	0	0
Early Postoperative		
Infection	0	0
Bleeding	2	11
Infection of the tracheostomy wound	1	4
Accidental decannulation	1	2
Subcutaneous emphysema	0	0
Late Postoperative		
Tracheocutaneous fistula	0	0
Peristomal granulation tissue	2	12
Mucous plugs	1	1
Tracheomalacia	0	0

Table XIII Complications associated with tracheostomy (Note- The total number of complications exceeds the number of incidents, as some patients experienced two or more complications simultaneously during a single visit)

The analysis of incidents focused on the following types of events associated with maintaining the tracheostomy**:** bleeding, local infection, accidental decannulation, formation of granulation tissue obstructing the lumen of the tracheostomy opening, etc.; complications

classified according to the temporal criterion of their occurrence in relation to the tracheostomy procedure (Table XIII).

Type of complication	Tracheostomy type		Total	p
	Elective	Emergency		
Peristomal granulation tissue	2	12	14	0.000
Bleeding	2	11	13	0.000
Mucous plugs	1	1	2	>0.05
Accidental decanulation	1	2	3	0.000
Infection of the tracheostomy wound	1	4	5	0.000

Table XIV Type of complications found in the study lot and their statistical relevance

Table XV presents the complications associated with tracheostomy in patients treated with radical surgery as the primary approach, for whom the only statistically significant complication was the accidental closure of the tracheal stoma (p=0.006). No significant statistical differences were observed in the frequency of incidents between patients treated surgically as the primary approach (67%, 4 out of 6 patients) versus those with conservative treatment (59%, 16 out of 27 patients). However, the frequency of incidents was statistically significantly higher (p<0.05) for patients who underwent emergency tracheostomy in the presence of acute respiratory failure syndrome (73% compared to 36% in those with elective tracheostomy).

Type of tracheostomy complication		Radical surgery		Total	p
		YES	NO		
Peristomal granulation tissue	Frequency	**2**	12	14	ns
Bleeding	Frequency	2	11	13	ns
Mucous plugs	Frequency	1	1	2	ns
Accidental deccanulation	***Frequency***	***1***	***2***	***3***	***0.006***
Infection of the tracheostomy wound	Frequency	1	4	5	ns

Table XV Complications associated in the radical surgery treatment group

Number of complications associated with tracheostomy						
Initial Treatment Method	N	Mean	Std Deviation	Minimum	Maximum	Median
Conservative + Tracheostomy	27	**1.37**	1.471	0	5	1.00
Radical Surgery	6	**2.17**	1.472	0	4	2.50
Total	**33**	**1.47**	**1.482**	**0**	**5**	**1.00**

Table XVI Statistical report of the number of complications associated with treatment methods

Table XVI presents the statistics on the number of incidents related to surgical treatment as the primary approach and tracheostomy placement. It is noteworthy that patients treated surgically as the primary approach experienced up to 4 incidents, compared to patients treated conservatively, who experienced up to 5 incidents, but with a lower average incident rate compared to the surgically treated patients. Statistically, however, $p > 0.05$, meaning the threshold for statistical significance was not reached.

The formation of peristomal granulation tissue was recorded in 42% of patients in the restricted group (14/33 patients), with a frequency of 18% (2/11 patients) in the case of elective tracheostomy and 55% (12/22 patients) in the case of emergency tracheostomy [p=0.051; Fischer's exact Test]. When the analysis is also stratified according to the initial treatment, the frequencies are 17% (1/6 patients) in surgically treated patients compared to 52% (11/21 patients) in conservatively treated patients with radiochemotherapy and emergency tracheostomy.

Bleeding was encountered in 30% of patients in the restricted group (10/33 patients). The frequency was 18% (2/11 patients) with elective tracheostomy compared to 36% (8/22 patients) with emergency tracheostomy. Stratifying the analysis by initial treatment results in a frequency of 38% (8/21 patients) with emergency tracheostomy and conservative treatment, while 0 patients with elective tracheostomy and conservative treatment, and 40% (2/5 patients) with surgical treatment as the primary approach (elective tracheostomy).

Accidental closure of the tracheal stoma was encountered in one patient (1/33 patients), representing 3% of the restricted group. The patient was treated surgically as the primary approach, and during radiation therapy sessions, this incident occurred. The event was resolved quickly, and the tracheostomy tube was placed in the ENT department.

3.2.6. Radiation Mucositis – An Adverse Effect of Radiotherapy

This section examines the development of radiation mucositis phenomena in the pharynx as an adverse effect of radiation therapy, as well as the identification of prognostic factors and therapeutic response. Radiation mucositis phenomena were considered to be the persistence of pharyngeal/laryngeal mucosal edema for more than 12 weeks after the completion of radiotherapy, as well as the appearance of obstruction due to massive edema phenomena.

In the total cohort of 53 patients, radiation mucositis was present in nearly a quarter of the investigated patients (12 patients, representing 23%).

In terms of localization, significant radiation edema that obstructed the lumen was observed in tumors located in the hypopharynx and those extending to the larynx, which was confirmed by statistical correlations ($p<0.05$). The highest frequencies of radiation mucositis were observed in patients with hypopharyngeal tumors extending to the larynx (10/33 patients).

Regarding the method of tracheostomy placement, radioedema was present in 45.5% of patients who required emergency tracheostomy due to acute respiratory failure syndrome (10/22 patients), compared to 9% (1/11 patients) in those with elective tracheostomy, in the absence of acute respiratory failure phenomena.

The distribution of patients in the overall cohort, regarding the presence of radiation edema phenomena, presents 3 subgroups: patients without tracheostomy, patients with emergency tracheostomy, and patients with elective tracheostomy in the absence of acute respiratory failure, but with the presence of tumor edema, persistent post-radiotherapy edema, and aspiration phenomena from the hypopharynx to the larynx.

Conclusion of the Subchapter

Radiation edema phenomena were present in 3-4 patients with tracheostomy out of 10 (11/33 patients), with a frequency of 1 patient/11 in the case of elective tracheostomies, lower than the 10/22 patients found in the case of emergency tracheostomies. In the case of elective tracheostomy, the tumor was located in the hypopharynx, while in the case of emergency tracheostomies, all patients who presented radiation edema phenomena had tumors located in the hypopharynx extending to the larynx.

3.2.8. Quality of Life (QoL) in Patients with Hypopharyngeal Cancer

The analysis of the quality of life in patients with hypopharyngeal cancer addressed the following domains: Eating and swallowing disorders, Communication disorders, Breathing disorders, and Emotional well-being. Table XVII presents the elements recorded for each of the domains analyzed, and the table was developed based on elements from the EORTC H&N35 questionnaire, which could not be applied to the cohort in this analysis due to the study having a significant retrospective component, and because the questionnaire is subjective, requiring completion at each clinic visit by the patient.

For each item with an affirmative response, one point was assigned, and the total score was calculated by summing these points. The quality of life was considered to be lower the higher the score. The score (SQL) ranged from 1 to 12, with statistically significant differences ($p<0.05$) between the subgroups corresponding to the type of tracheostomy (Table XVIII).

TAD	TC	TR	SB
Feeding and swallowing disorders	**Communication disorders**	**Breathing disorders**	**Emotional well being**
Mouth pain	Communication difficulties	Choking (Acute respiratory failure)	Referred otalgia
Difficulty swallowing	Speech difficulties	Hemoptysis	Loss of taste
Weight loss		Respiratory syndrome	Loss of smell
Feeding difficulties			Communication difficulties
Pharyngeal syndrome			Sensory syndrome (Hypo-, Hiperesthesia, Paresthesia)
			Analgesic medication

Table XVII The elements recorded for each of the domains analyzed

No significant statistical differences were observed in relation to the placement of tracheostomy. However, the results show a lower quality of life in patients with tracheostomy (the frequency of patients with tracheostomy having SQL scores over 6 was higher than those without tracheostomy). It is important to note that this difference is explained by the impact of this procedure on the patients, significantly influencing their self-image (144).

Analysis of the domain – Eating and swallowing disorders (TAD) in the subgroup of patients with elective tracheostomy identifies, in 4 out of 6 patients with favorable progression, high TAD scores (>3), with a lower frequency compared to the subgroup of patients with unfavorable progression (3/4 patients).

In the subgroup of patients with emergency tracheostomy, both those with favorable progression (5/5 patients) and those with stationary progression (5/8 patients) show a higher frequency of patients with scores below 3, compared to those with unfavorable progression. The maximum score in this analysis was identified in one patient with emergency tracheostomy, with unfavorable progression (5 criteria).

Analysis of the domain – Communication disorders (TC) in the subgroup of patients with elective tracheostomy identifies, in 1 out of 3 patients with favorable progression, the absence of complaints in this domain. However, in patients with emergency tracheostomy, the maximum scores are recorded in all 3 progression variants. One out of 10 patients reports no communication disorders, with the highest frequency occurring in patients with favorable progression. Four out of five patients report maximum scores, regardless of treatment response.

Analysis of the domain – Breathing disorders (TR) paradoxically identifies the highest frequency of null scores in the subgroup of patients with unfavorable progression (3 patients with score 0 – elective tracheostomy, and 2 patients with score 0 or 1 – emergency tracheostomy). The maximum score (3/3) was identified in a patient with emergency tracheostomy, with stationary progression.

Analysis of the domain – Emotional well-being (SB) identifies a decline in the quality of this item for patients with elective tracheostomy and unfavorable progression (half of the patients have scores of 3 or higher), compared to those with favorable progression, where one-third of the patients have the same values. In patients with emergency tracheostomy, both those with unfavorable and stationary progression present higher frequencies of SB scores compared to patients with favorable progression.

Tracheostomy		TAD	TC	TR	SB	SQL
Elective	N	11	11	11	11	11
	Minimum	1	0	0	0	2
	Maximum	4	2	2	4	12
	Median	**3.00**	**2.00**	**1.00**	**2.00**	**8.00**
	Mean	3.00	1.36	0.91	2.00	7.27
	Std. Deviation	1.00	0.92	0.831	1.342	2.867
Emergency	N	22	22	22	22	22
	Minimum	0	0	0	0	2
	Maximum	5	2	3	4	12
	Median	**3.00**	**2.00**	**2.00**	**3.00**	**10.00**
	Mean	2.91	1.86	1.91	2.41	9.09
	Std. Deviation	1.192	.468	.526	1.008	2.524
				P=0.002		P=0.036

Table XVIII Analysis of the Quality of life domains in relation with the tracheostomy type

Statistically significant differences were found between tracheostomized patients and those who were not in the domains of Communication Disorders (TC) (p=0.006), Breathing Disorders (TR) (p=0.000), and Global Quality of Life Score (SQL) (p=0.009), with higher scores predominantly in the subgroup of tracheostomized patients. These changes can be fully

explained by the fact that the majority of patients in the cohort were tracheostomized in emergency situations, often being diagnosed at advanced stages of the disease.

A more detailed analysis of the types of tracheostomy further reveals statistically significant differences between the two subgroups formed – Breathing Disorders (TR) (p=0.002) and Global Quality of Life Score (SQL) (p=0.036), with higher scores being found more often in the subgroup of patients who had an emergency tracheostomy.Items with statistically significant differences (p<0.05) include **choking**, **difficulty speaking**, and **communication disorders** (Table XIX).

	Tracheostomy		P
	YES	NO	(Fischer's exact Test)
Mouth pain	5	2	p>0.05
Choking	26	1	P=0.000
Smell disorders	1	0	p>0.05
Taste disorders	5	2	p>0.05
Speech difficulties	31	9	P=0.013
Communication difficulties	31	9	P=0.013
Feeding difficulties	31	16	p>0.05
Analgesic medication	17	11	p>0.05
Weight loss	7	3	p>0.05
Referred otalgia	5	3	p>0.05
Hemoptysis	1	1	p>0.05

Table XIX The distribution of patients in the global cohort in relation to quality of life domains and tracheostomy performance (yes/no)

For a better analysis of the symptomatology, to identify and search for associations and predictive factors, laboratory constant values were also used. The symptoms reported by patients upon admission were grouped into syndromes, and the final treatment response was also associated, specifically identifying persistent edema of the pharyngeal and laryngeal tissues due to radiotherapy treatment.

Analysis of the global cohort from the perspective of the presented syndromes (53 patients)

The syndromes into which the patients' symptoms were grouped were: pharyngeal syndrome, respiratory syndrome, and sensory syndrome (which included all sensory disturbances—hypersensitivity, hyposensitivity, or the presence of paresthesia). The only

syndrome that showed statistically significant significance was the respiratory syndrome, which includes variations of inspiratory dyspnea syndrome, from disturbances that occur with moderate to intense efforts, to acute respiratory failure, with the presence of asphyxiation syndrome. This syndrome was found to be statistically significant in the subgroup of patients who were tracheostomized.

	Tracheostomy		Total	P*	OR (95% CI)
	Yes	No			
Pharyngeal syndrome	33	16	49	>0.05	0.68 (0.67-7.14)
Respiratory syndrome	31	5	36	0.000	14.9 (3.64-60.79)
Sensory syndrome	22	9	31	>0.05	1.4 (0.44-4.48)
Significant radiation edema	12	2	14	>0.05	3.750 (0.74-19.14) (for Trach YES, 1.393(1.004-1.9333)
P* - Fischer's Exact Test					

Table XX The distribution of the cohort in relation to the type of syndromes presented and the presence of a tracheostomy

Testing the risk factors/incidents associated with the type of tracheostomy identified the presence of respiratory syndrome (P=0.033), which was present in almost all (21/22 patients) who required urgent tracheostomy placement. With marginal significance (P=0.054), the presence of radiomucitis was identified.

TESTED FACTOR	**TESTED GROUP (N=33)**	**TRACHEOSTOMY**		**P**
		EMERGENCY (N=22)	**ELECTIVE (N=11)**	
COMPLICATION INCIDENCE	20 (61%)	16 (73%)	4 (36%)	>0.05
Granulation tissue	14 (42 %)	12 (55 %)	2 (18 %)	>0.05
Bleeding	11 (33 %)	9 (41 %)	2 (18 %)	>0.05
Mucous plugs	2 (6 %)	1(5 %)	1 (9 %)	>0.05
Accidental closure of the tracheal stoma	2 (6 %)	1(5 %)	1 (9 %)	>0.05
Other incidents	5 (15 %)	4(18 %)	1(9%)	>0.05
Gastostomy	13(39 %)	8 (36%)	5 (46 %)	>0.05
PEG vs CLS	8 (62 %) / 5 (38%)	5 (63 %) vs 3	3 (60%) vs 2	>0.05
Pharyngeal Syndrome	30 (91 %)	20 (91 %)	10 (91 %)	>0.05
Respiratory Syndrome	28 (85%)	21 (96%)	7 (64%)	0.033
Sensory Syndrome	20 (61%)	15 (68 %)	5 (46 %)	>0.05
HYPERESTHESIA	11(33 %)	7(32 %)	4(36 %)	>0.05
HYPOESTHESIA	2 (6 %)	2 (9 %)		>0.05
PARESTHESIA	6 (%)	5 (23 %)	1 (9 %)	>0.05
Radiation edema	11(33 %)	10 (46 %)	1 (9 %)	0.054

Table XXI Testing risk factors/incidents associated with the type of tracheostomy

Analysis of the global quality of life score for patients with favorable outcomes after treatment completion shows statistically significant differences (p=0.030), with patients who had an elective tracheostomy reporting fewer complaints than those who underwent urgent tracheostomy, thus having a superior quality of life.

End-of-treatment result	TAD Feeding and swallowing disorders					TR Breathing disorders			TC Communication difficulties		SB Well being				
	Pharyngeal Syndrome	Mouth Pain	Feeding difficulties	Weight loss	Swallowing difficulties	Acute respiratory failure	Respiratory syndrome	Hemoptysis	Speech difficulties	Communication difficulties	Referred otalgia	Sensory synd	Loss of taste	Loss of smell	Analgesic medication.
F (n=11)	11		9	1	10	7	10		9	9	3	5			6
NF (n=13)	11	3	11	2	11	8	9		11	11	1	9	1	1	7
S (n=9)	8	2	8	2	8	8	9	1	8	8	1	6	4		3
p													0.014		
TOTAL	30	5	28	5	29	23	28	1	28	28	5	20	5	1	16

Table XXII The associative distribution of patients in relation to treatment response and self-reported suffering affectiv quality-of-life (n=33, limited sample)

3.3 Statistical corelations in testing prediction factors

A. Correlations and Influences on the Endpoint

This section aims to identify associations between studied variables and predictive factors for the patient's outcome. The evolution of biological parameters was monitored at three time points (T1 = diagnosis, T2 = during treatment, T3 = at least 3 months after treatment completion). It also included values such as minimum and maximum values, mean, standard deviation, skewness, and kurtosis.

Linear Correlation Analysis

This analysis examines the direction and strength of the relationship between two variables. The correlation coefficient "r" ranges from -1 to +1, with stronger correlations closer to 1. A value of **r** between 0 and 0.2 indicates a *negligible correlation*, 0.2-0.5 indicates a weak correlation, 0.5-0.8 indicates a *moderate correlation*, and above 0.8 indicates a *strong correlation*. A negative **r** value indicates an indirect relationship (when one variable decreases, the other increases), while a positive **r** indicates a direct relationship (both variables change in the same direction). A **p-value < 0.05 is considered statistically significant.**

This analysis may provide clues regarding the association between the patient's progression and the risk factors associated with their characteristics or the characteristics of the disease, with the aim of influencing it; it may also provide clues regarding the association between the studied variables and the undesirable effects of applying the tracheostomy.

The results of the correlation analysis applied to our data are presented in the following tables, with positive significant correlations marked in red and negative ones in green.

Testing the association between the presence of a tracheostomy and variables (alcohol consumption, smoking, comorbidities, and favorable progression) identifies the following positive correlation: the association between ethanol consumption and smoking (p=0.039, .361). The table also presents the indirect correlations between the association of ethanol consumption and the need for a tracheostomy (p=0.006, -.466), the association between smoking and the presence of comorbidities (p=0.042, -.356), as well as the correlation between age at the time of the tracheostomy and subsequent favorable progression (p=0.012, -.434).

The correlation of patient characteristics with the global quality of life score (SQL) identified the following positive correlations:

- Significant links between:
    - The age at which the tracheostomy was performed and the age at which the surgical treatment was performed (p=0.000, 1.000)
    - The patient's age and the age at which the tracheostomy was performed (p=0.000, .845)
    - The patient's age and the age at which the surgical intervention was performed (p=0.041, .830)
- A weak link between:
    - Ethanol consumption and smoking (p=0.039, .361)

The correlation of patient characteristics with SQL (quality of life score) and emergency tracheostomy identifies a significant link (p=0.000, .913) between the patient's age when the emergency tracheostomy is performed**.**

The correlation of patient characteristics with elective tracheostomy and the global quality of life score identifies the following links:

- Positive significant correlations:
    - Between the age at the time of surgery and the age at the time of tracheostomy (p=0.000, 1.000)

    - Between the patient's age and the age at the time of the surgical intervention (p=0.045, .887)
    - Between the age at the time of the tracheostomy (p=.001, .833)
- Moderate indirect/negative correlations:
    - Between the global quality of life score and smoking (p=0.018, -.692) – Quality of life decreases as smoking is a more frequent habit

The correlation of comorbidities with the global quality of life score in patients with emergency tracheostomy identified the following types of connections**:**

- Indirect links:
    - A weak link between the Karnofsky performance status score and favorable and stationary progression (p=.032, -.457)
    - A weak link between the number of comorbidities and favorable progression (p=0.053, marginal value, -.419) – The fewer comorbidities, the higher the chances of favorable progression. A high number of comorbidities reduces the chances of favorable progression.

The correlation of comorbidities with the global quality of life score (SQL) and the KPSS score in patients with elective tracheostomy identified the following types of connections:

- Direct links:
    - A significant link in patients with elective tracheostomy between favorable and stationary progression (p=.002, .828)
    - A significant link between respiratory conditions and other comorbidities (renal, digestive, etc.) (p=.003, .810)
    - A moderate link between the global quality of life score and the presence of comorbidities (p=.010, .737)
    - A moderate link between the presence of cardiovascular comorbidities and their influence on SQL (p=.010, .737)
    - A moderate link between a history of other neoplasms and other comorbidities (renal, digestive, etc.) (p=.040, .624)

- Indirect links:
    - A significant link between the Karnofsky performance score and the global quality of life score (p=.003, -.805) – The lower the performance score, the higher the global quality of life score (quality of life decreases)
    - A moderate link between the history of neoplasm and its influence on the probability of favorable or stationary progression (p=.040, -.624) – Therefore, the presence of a neoplasm history reduces the chances of favorable or stationary progression.

The analysis of the correlation between incidents, progression, SQL, and the likelihood of root mucositis occurrence in patients with emergency tracheostomy identified the following types of connections:

Direct links:

- A significant link between the presence of pharyngeal syndrome and favorable or stationary progression (p=.000, .845)
- A moderate link between the occurrence of incidents and their number in patients with emergency tracheostomy (p=.000, .752)
- A moderate link between the formation of peristomal granulation tissue and the number of incidents (p=.001, .678)
- A moderate link between the occurrence of incidents and the phenomenon of peristomal granulation (p=.001, .671)
- A moderate link between the presence of sensory disturbances and the total quality of life score (p=.001, .658)
- A moderate link between the number of hospitalizations and the number of incidents (p=.001, .654)
- A moderate link between the number of incidents and the presence of bleeding phenomena (p=.001, .643)
- A moderate link between the occurrence of incidents and bleeding phenomena (p=.015, .510)
- A weak link between the presence of sensory disturbances and the occurrence of tracheostomy-related incidents (p=.037, .448)
- A weak link between the final favorable progression in patients with emergency tracheostomy and favorable or stationary progression (p=.035, .451)
- A weak link between the presence of radiomucitis phenomena and the global quality of life score (p=0.037, .448)

Indirect links:

- Moderate links between the number of incidents and favorable or stationary progression (p=.000, -.707) – A higher number of incidents in patients with emergency tracheostomy reduces the chances of favorable or stationary progression.
- A moderate link between the presence of bleeding phenomena and the reduced chances of favorable or stationary progression (p=.002, -.624)
- A moderate link between the number of hospitalizations and favorable or stationary progression (p=.005, -.576) – The higher the number of hospitalizations, the lower the chances of favorable or stationary progression.
- A moderate link between the presence of tracheostomy-related incidents and favorable or stationary progression (p=.015, -.510) – The presence of tracheostomy-related incidents negatively influences the chances of favorable or stationary treatment progression.
- A weak link between the occurrence of incidents associated with wearing a tracheostomy and the phenomenon of root mucositis (p=.029, -.466)

- A weak link between the occurrence of peristomal granulation tissue and the phenomenon of root mucositis (p=.036, -.450)

Model of Quality of Life (QL) Based on Tracheostomy Type and Final Treatment Outcome

A model to assess the impact of the type of tracheostomy on quality of life (QL) and the final treatment outcome was developed by applying linear correlation analysis for each domain affecting quality of life. The results are presented in the following tables.

Subgroups related to end-of-treatment result (F/NF/S) and tracheostomy type (Elective/Emergency)	Quality of life impairment	(r,p)	RANK
FAVORABLE/ ELECTIVE (N=6)	TC	.923	1
		.009	
	SB	.897	2
		.015	
FAVORABLE/ EMERGENCY (N=5)	SB	1.000	UNIC
		.000	
NOT FAVORABLE/ELECTIVE (N=4)	SB	.965	UNIC
		.035	
NOT FAVORABLEL/EMERGENCY (N=9)	TAD	.808	1
		.008	
	TC	.781	3
		.013	
	TR	.722	4
		.028	
	SB	.795	2
		.010	
STATIONARY/EMERGENCY (N=8)	TAD	.935	1
		.001	
	TC	.930	2
		.001	
	SB	.914	3
		.002	
STATIONARY/ELECTIVE (N=1)			

Table XXIII The patterns of quality-of-life impairment in the studied subgroups from the perspective of the type of tracheostomy and end-of-treatment result

Statistical analysis of quality of life scores by subgroups based on progression at the end of treatment and type of tracheostomy performed, which calculated the significance threshold for the studied domains, identified Respiratory Disorders (TR) (p=0.009).

In this analysis, the patients with the lowest quality of life, reflected by the highest median SQL values (median = 10), were those with stationary progression (8 patients with

emergency tracheostomy and 1 with elective tracheostomy), as well as those with unfavorable progression and emergency tracheostomy.

The patients with the best quality of life, as indicated by the lower SQL median values (median = 7 or 7.5), were the elective tracheostomy patients. Specifically:

- Unfavorable progression with elective tracheostomy had a median SQL of 7.
- Favorable progression with elective tracheostomy had a median SQL of 7.5.

This analysis highlights the relationship between the type of tracheostomy (elective vs. emergency) and patient outcomes, showing that elective procedures are generally associated with better quality of life, particularly in patients with favorable progression.

Logistic Regression Analysis:

Risk Factors for Unfavorable Evolution Based on Tracheostomy Type

For identifying independent variables (Xi) that predict the progression of the patient (dependent variable Y) or adverse events (such as incidents, mucositis) (dependent variable Y) in relation to the type of tracheostomy (E vs. U), logistic regression was applied. This method allows for determining the simultaneous effect of various risk factors (independent variables Xi) and even their ranking based on their contribution to modifying the dependent variable (Y).

Logistic regression is a form of regression where the dependent variable Y (e.g., mucositis) is dichotomous (taking values 1/0, equivalent to YES/NO), and the independent variables (predictors) (Xi) can be continuous or categorical.

The logistic regression equation model is: $\mathbf{ln(Y) = b_0 + b_i X_i}$. This can also be written as:

$\mathbf{Y = exp\ (b_0 + b_i X_i)}$ where Y represents the ratio of the probability (p) that the dependent variable has the characteristic (response 1/YES) to the probability (1-p) that the dependent variable does not have the targeted characteristic (response 0/NO).

The logarithmic transformation can be calculated as: $\mathbf{ln(Y)= ln\ [p/1-p];}$ where $\mathbf{b_0}$ **si** $\mathbf{b_1}$ are the logit coefficients provided by data processing. b_i is the regression coefficient, associated with the slope of the regression determined by the predictor X. If b_i equals zero, the corresponding factor has no effect. If b_i is less than 0, the factor reduces the probability of event Y=1; when b_i is greater than 0, the variable-factor X_i increases the probability of event Y=1.

Statistical significance is obtained by applying the Wald test. If it provides a p-value < 0.05, then the independent variable (Xi) can be kept in the model; otherwise, it is eliminated.To remove bias from different measurement scales of independent variables, the variables X_i can be ranked using the standardized regression coefficients b_i.The degree to which the model explains the action of the risk factor is given by Nagelkerke's coefficient (similar to the R^2 coefficient of determination).

Variables and Coding Used:

VARIABLES	CODE EXPRESSION	VARIABILES	EXPRIMARE/COD
SEX	1=M,O-F	Favorable Evolution	F=1, NF=0, S=0
AGE at tracheostomy	under 60=0; over 60=1	Favorable+Stationary Evolution	F=1,S=1,NF=0
ALCOHOL	Frequenctly=1, No or Rarely=0	Complications, syndromes, comorbidities and radiation edema	Yes=1, No=0
SMOKING	1=Smoker; 0=History of smoking, 0=No		
RADICAL SURGERY	Yes=1, No=0	Gastrostomy type	PEG=1, CLS=0
TRACHEOSTOMY	Elective=1, Emergency=0	Stage	III= 0;IV A=1, IV B =2; IV C= 3

Table XXIV Codes used in the tests

In order to identify the predictive factors for adverse events (incidents, root mucositis, non-favorable evolution), the parameters selected in the previous statistical analysis as potential significant risk factors were introduced into a stepwise multiple regression model (see the linear analysis chapter). For the analysis related to the patient's evolution, two situations were considered: the F situation, where only cases declared favorable were considered as a favorable endpoint (coding F=1, NF=0, S=0), and the FS situation, where both F and S cases were coded as 1, and NF cases as 0. This convention was used given the limited number of cases under analysis, and the binary analysis was preferred over multinomial analysis.

The application of this technique is conditioned by the sample size, with each factor-variable introduced in the model requiring at least 15-20 cases.

The results of applying the regression analysis for the data collected in the study are presented in Table 25, with the variables included in the model and those excluded from the equation, along with their respective coefficients. As mentioned, since we could not include all variables in the model, they were initially tested in the univariate analysis.

Prediction model for favorabile evolution F (1=F), total lot 33					
	Coeficient			95% C.I.pentru EXP(B)	
Parameters	B	p	Exp(B)	Lim.Inf.	Lim.Sup
TRAH AGE	1.962	.018	7.111	1.400	36.117
Constant (b_0)	-1.674	.008	.188		
Tested variables *:	Smoking, Alcohol consumption, Comorbidity ,Tracheostomy, Surgical treatment, Complications				

Prediction model for favorable + stationary evolution FS (1=F, 1=S), lot 11, Traheost Electivă, 1=E					
	Coeficient			95% C.I.pentru EXP(B)	
Parameters	B	p	Exp(B)	Lim.Inf.	Lim.Sup
TRAH AGE	-39.311	.998	.000	.000	.
Respiratory Synd	20.790	.999	1069068582.359	.000	.
Constant	19.214	.999	221107417.860		
Variabile testate*:	TRAH AGE, Respiratory Syndrome.				

Table XXV Prediction Model for Favorable Evolution in Hypopharyngeal Cancer, Global lot and type of tracheostomy (Method: Forward Stepwise LR)

Testing of Presumed Predictive Variables (Age at the Time of Tracheostomy, Tumor Localization, Presence of Gastrostomy): the model only yielded a constant = 0.182, $p > 0.05$ for testing presumed predictive variables. It is suggested that ***the variable with the most significant chance of favorable progression for patients with elective tracheostomy is age under 60 years.***

B. Identification of Predictive Factors for Radic Edema

Two patient groups were formed: those who presented persistent radic edema, resistant to treatment or those who required a tracheostomy (radiomucitis), and patients who did not experience this phenomenon. Laboratory values were compared between the subgroups using the Independent Sample Mann-Whitney U Test (vertically). For the same subgroup with or without the studied phenomenon (Yes/No), temporal values (T1 vs T2, T3, etc.) were compared using the Related Samples Wilcoxon Signed Rank Test.

• The Profile of the Patient Without Persistent Radiation Edema from the Laboratory Test Values

The temporal relationship between T2 and T3 was statistically significant (**p = 0.008**) when evaluating leukocyte values, indicating a return to normal values by the end of treatment despite a temporary increase in leukocyte values at the first two testing points (T1, T2).

The analysis of **erythrocyte** values identified erythropenia in both patient groups, but with different profiles: for patients without persistent radiological edema, the mean was consistently below the lower normal limit at all three monitoring points. Statistically significant differences **(p = 0.030)** were observed between the initial presentation (T1) and during treatment (T2), with a decrease in values.The two groups had a statistically significant difference (**p = 0.038**) due to a more pronounced decrease in erythrocyte values in the group with persistent radic edema.

Platelet values recorded were within normal limits, but with statistically significant differences **(p = 0.004**) between the first visit and visits during treatment, showing a slight upward trend in values between the two points of analysis.

Anemia was present in both patient groups, appearing at different evaluation times. For patients without persistent radiation edema, **hemoglobin** values were low at the first visit (T1), with a significant decrease during treatment (**p = 0.017**) (T2), but returning to normal levels at the end of treatment (T3).

INR (International Normalized Ratio), a medical test based on prothrombin time, was used to calculate the time required for thrombus formation in plasma. Elevated INR values were observed at T1 and T2 for patients without radic edema phenomena, with a tendency to normalize by the end of treatment. Between T1 and T2, significant differences **(p = 0.016**) were noted, with maximum values recorded at the first visit.

The **Quick test**, or prothrombin time, showed modifications in both patient groups, with an increase in clotting time. For patients without radic edema, T1 and T2 values were elevated, with statistically significant differences (**p = 0.009**).

The prothrombin activity value is measured as a percentage and is useful in coagulation evaluation, complementing INR and Quick time analysis. In the study, no changes beyond normal limits were found, but significant differences were identified in both groups. In

the group without radic edema, statistically significant differences **(p = 0.008**) were observed between the first visit and during treatment, with a decrease in mean values, followed by an increase at the end of treatment (T3).

Erythrocyte sedimentation rate (ESR) is used to identify inflammatory status and is often used in screening tests along with CRP/PCR (C-reactive protein). ESR analysis identified changes in both groups, with the presence of inflammatory syndrome. In patients without radic edema, increased values associated with inflammatory status were observed, with statistically significant differences. Between diagnosis and treatment periods, a tendency for increased ESR values was identified (**p = 0.036**), followed by a significant decrease at the end of treatment (**p = 0.036**), but with values remaining above the normal threshold (mean = 31.38).

Serum urea is synthesized in the liver and excreted in the kidneys. It is the final product of protein metabolism and a useful test for kidney function. No statistically significant differences were found in urea values in the studied groups, and values were within normal limits at all evaluation points.

Serum creatinine represents the elimination form of creatine and is used to estimate glomerular filtration rate. Creatinine values were normal for both patient groups, with maximum values found in patients with radic edema at all three monitoring points (T1- 1.6 vs 1.24, T2- 1.48 vs 1.29, T3-1.43 vs 1.4).

Bilirubin is a bile pigment resulting from the breakdown of erythrocytes. After breakdown, it appears in two forms—conjugated (water-soluble) and unconjugated (lipid-soluble). It is useful in assessing liver and biliary tract disorders. The average values for the studied groups were within normal limits (N = 0.30-1.20). Maximum values exceeding the limit were recorded in the group of patients without radic edema at T1 (1.46) and T3 (1.43).

Alanine aminotransferase (ALT/TGP/GPT) is a marker of liver activity. Unlike aspartate aminotransferase (AST/TGO/GOT), ALT persists in the body for a longer period. ALT analysis did not show significant changes, with the maximum value (96 U/L) recorded in a patient without radic edema during reevaluation visits after completing treatment.

Serum glucose levels are useful for identifying and monitoring diabetic patients. No significant statistical differences were found between the two subgroups. For the group without radic edema, higher average values were observed compared to the group with persistent radic edema, with the highest value recorded at diagnosis (T1), followed by a temporary decrease

during treatment and an increase after treatment. The highest serum glucose values (T3- 357 mg/dl, T2- 302 mg/dl) were recorded in this group.

B. The profile of the Patient with Persistent Radiation Edema from the Perspective of Laboratory Test Values

The analysis of **leukocyte** count values identified elevated levels in the group of patients with radicular edema across all three assessment points, especially at the evaluation after completing the therapeutic regimen (T3), but without showing statistically significant differences.

Erythrocyte values were lower in both patient groups, but for the patients with radicular edema, the mean values at T1 were within the normal range, with a progressive decrease in values at T2 and T3. Statistically, significant differences (**p=0.028**) were found between the initial consultation (T1) and at the completion of treatment (T3), with the persistence of erythropenia at the end of treatment. A statistically significant difference (**p=0.038**) was observed between the two groups, showing a greater decrease in erythrocyte values in patients with persistent radicular edema.

Platelet values were within normal limits in both patient groups, with no statistically significant differences between assessments for the group with persistent radicular edema. Between patients with radicular edema and those without, significant differences (**p=0.029**) appeared at the evaluations at the completion of treatment (T3), with the group with radicular edema showing slightly elevated values compared to those without edema.

Hemoglobin values highlighted the presence of anemia in both groups, but at different times. The group of patients with radicular edema presented average values within the normal range at the first visit (T1), with a progressive decrease in values and the onset of anemia at T2 and T3. The differences between T1 and T3 were statistically significant (**p=0.028**). Between the two groups, significant differences appeared at the completion of treatment (T3, **p=0.010**), with the persistence of anemia in the group with radicular edema and a return to normal in the group without edema.

The analysis of **INR** values in patients with radicular edema showed mean values within normal limits across the three evaluation points, but with statistically significant differences (**p=0.018**) between the diagnosis moment and post-treatment evaluations, with higher values at T3 compared to T1.

The Quick time showed changes in both patient groups, with an increase in coagulation time. In the group with radicular edema, the mean values at the first visit were within normal limits, with a progressive increase in values beyond the normal threshold both during and after treatment, identifying a trend of increasing values in relation to the evaluation time, without statistical confirmation.

In the group with radicular edema, changes in **AP values** were significant (**p=0.028**) between the diagnosis (T1) and post-treatment evaluations (T3), with patients showing a trend of progressive decrease in values.

The **ESR** analysis identified changes in both patient groups, with the presence of an inflammatory syndrome. In the group with radicular edema, the mean values at all three evaluation moments were elevated, with the highest value recorded at the end of treatment, but without statistical significance.

Regarding urea values, no statistically significant differences were identified between the studied groups, and the values were within normal limits for all evaluation points.

Serum creatinine values were normal for both patient groups, with the highest values found in patients with radicular edema at all three monitoring points (T1- 1.6 vs 1.24, T2- 1.48 vs 1.29, T3-1.43 vs 1.4). These differences were not statistically significant.

The analysis of total serum bilirubin values showed mean values within normal limits for both groups (N=0.30-1.20) and without statistically significant differences.

The analysis of alanine aminotransferase (ALT/TGP/GPT) and aspartate aminotransferase (AST/GOT/TGO) did not reveal any statistically significant changes between the two studied groups.

Serum glucose in patients with radicular edema showed mean values within the normal range at the time of diagnosis (T1), with a rise in values during treatment and a slight decrease at the completion of treatment, but with values still above the normal mean at the end of treatment. Statistically, these differences were not confirmed as significant.

CORRELATIONS BETWEEN TYPES OF TRACHEOSTOMY AND PATIENT OUTCOME

- **Analysis of Patient-Related Factors**

Elective tracheostomy is associated with a favorable prognosis when performed in patients under 60 years of age (**p=0.022**), however, this finding is not confirmed for patients with emergency tracheostomy (**p=0.441**). Testing of other factors did not correlate with statistical significance.

		END-OF-TREATMENT RESPONSE			
TRACH AGE		F	NF	S	Total
	0= under 60 ani	5			5
	1= over 60 ani	1	4	1	6
Total		6	4	1	11

Trah = 1, p=0.022

Table XXVI Association between age at the tracheostomy and end-of-treatment response in elective tracheostomy lot

	EVOLUTION F			EVOLUTION F+S	
Age TRACH	NF+S	F	Total	NF	F+S
Over 60	0	5	5	0	5
Under 60	5	1	6	4	2
Total	5	6	11	4	7
	p=0.015 Fischers'Exact Test			p=0.006 Fischers'Exact Test	

Table XXVII Associations between Favorable and Favorable + Stationary evolution in the elective tracheostomy group

- **Factors Related to the Disease**

Among the factors influencing the disease progression in the elective tracheostomy patient subgroup, tumor localization shows statistical significance (**p=0.021**). This prognostic factor is not confirmed for patients with emergency tracheostomy (p>0.05).

		EVOLUTION			
		F	NF	S	Total
Tumoral location	Pharynx	0	3	1	4
	Pharynx + Larynx	6	1	0	7
Total		6	4	1	11

p=0.021

Table XXVIII Classification of the patients from the end-of-treatment response and primary tumoral location

		FAVORABLE EVOLUTION	
		NF+S	F
Tumoral site	P	4	0
	P+L	1	6
Total		5	6
p=0.006 (p=0.015 Fischer's)			

		FAVORABLE + STATIONARY EVOLUTION		
		NF	F+S	Total
Tumoral site	P	3	1	4
	P+L	1	6	7
Total		4	7	11

a. Trah = 1, p=0.044 (p=0.088 Fischer's)

Table XXIX Classification of elective tracheostomy patients from the evolution point of view and tumoral location

The statistical significance is relevant in the favorable evolution (**p=0.006**) in the chi-square test, and **p=0.015** in the Fisher's Exact Test. Furthermore, statistical significance remains when both favorable and stationary evolutions are considered together, **p=0.044**, in the x^2 test, but the statistical significance is lost in the Fisher's Exact Test, p=0.088.

		EVOLUTION			
		F	NF	S	Total
Affected segment	Hypopharynx + Larynx	6	1	0	7
	Hypopharynx	0	2	1	3
	Oro- + Hypopharynx	0	1	0	1
Total		6	4	1	11

a. Trah = 1, p>0.05

		EVOLUTION		
		NF+S	F	Total
Affected segment	Hypopharynx+Larynx	1	6	7
	Hypopharynx	3	0	3
	Oro- + Hypopharynx	1	0	1
Total		5	6	11

a. Trah = 1, p=0.023

Table XXX End of treatment results regarding the emergency setting tracheostomy.

Regrouping of evolutions (classifying unfavorable evolution with stationary evolution, and favorable evolution separately) shows the significance of the affected segment (**p=0.023**), specifically the simultaneous involvement of the hypopharynx and larynx, with the note that this correlation is not significant in patients with emergency tracheostomy.

- **Factors associated with comorbidities**

The results did not identify any of the comorbidities associated with the studied disease as factors influencing elective tracheostomy.

- **Factors associated with incidents during tracheostomy maintenance**

Except the secretion plug, all incidents identified in the study showed statistical significance ($p<0.05$) in relation to the type of tracheostomy. However, the results suggest that the presence of incidents may influence evolution only in the case of emergency tracheostomy (marginal significance $p=0.053$) for the three groups of evolution, or high significance when regrouping the types of evolution (Unfavorable or Stationary+Favorable).

	EVOLUTION			
Complications	F	NF	S	Total
NO	2	0	4	6
YES	3	9	4	16
Total	5	9	8	22

a. Trah = U, p=0.053

Not applicable for elective tracheostomy

	EVOLUTION		
Complications	NF	F,S	Total
NO	0	6	6
YES	9	7	16
Total	9	13	22

a. Trah = U, p=0.017 (0.046 Fischers's Exact Test)

Table XXXI Correlations between the evolution of the emergency tracheostomy lot and complications associated with tracheostomy

Detailed incidents reveal a significant influence within the subgroup of patients with emergency tracheostomy regarding the number of incidents and the risk of bleeding (Table 31). The statistical significance in the calculation of 3 evolution variants (favorable/unfavorable/stationary) is **p=0.013**, and in the regrouping of evolutions (unfavorable and favorable+stationary) it is **p=0.007**, values obtained using Fisher's Exact Test.

	EVOLUTION			
BLEEDING	F	NF	S	Total
NO	4	2	7	13
YES	1	7	1	9
Total	5	9	8	22

p=0.013

	EVOLUTION		
BLEEDING	NF	F + S	Total
NO	2	11	13
YES	7	2	9
Total	9	13	22

p=0.003 (p=0.007 Fischers's Exact Test)

Table XXXII Associating statistical significance between end-of-treatment evolution and the presence of complications in the emergency tracheostomy group

		END OF TREATMENT RESULT		
		NOT FAVORABLE	FAVORABLE + STATIONARY	Total
Complications number	0	**0**	6	6
	1	1	3	4
	2	1	3	4
	3	5	1	6
	4	1	0	1
	5	1	0	1
Total		9	13	22

p=0.030

Table XXXIII Associations between the number of complications and end of treatment results (not favorable and favorable + stationary)

- **Necessity of gastrostomy and its correlation as a prognostic factor in tracheostomies**

		EVOLUȚIE		
		NF+S	F	Total
Gastrostomă	Traheostomă de urgență	1	5	6
	Traheostomă electivă	4	1	5
Total		5	6	11

a. p=0.036 (p=0.08 Fis)

Table XXXIV Correlations between evolution and tracheostomy type in patients with gastrostomy

A statistical difference was identified (**p=0.036**) in the Pearson Chi-Square test, which identified the need for gastrostomy as a prognostic factor for unfavorable or stationary outcomes in patients with elective tracheostomy. However, in patients with emergency tracheostomy, the need for this procedure was associated with a favorable outcome. It should be noted that in the Fisher's Exact Test (*p=0.08*), the significance was not confirmed.

- **Presence of respiratory impariment at diagnosis**

		EVOLUTION		
		NF	F,S	Total
Respiratory impairment	NO	3	1	4
	YES	1	6	7
Total		4	7	11

a. Elective tracheostomy p=0.044 (p=0.088 Fis)

Table XXXV Correlation between respiratory disorders at diagnosis and evolution in the elective tracheostomy group

The correlation of the presence of respiratory disorders in electively tracheostomized patients, from the perspective of restructured evolution (unfavorable or favorable + stationary) (Table 35), identifies a statistically significant correlation (**p=0.044**, Pearson X2) that

associates the presence of respiratory disorders with favorable or stationary evolution, while the absence of these disorders is more frequently associated with unfavorable evolution. However, Fischer's Exact Test (p=0.088) does not confirm this association.

- **Evolution of the tracheostomized patients in correlation with persistent radiotherapy edema**

Radiation edema	EVOLUTION			Total
	F	NF	S	
NO	6	4		10
YES			1	1
Total	**6**	**4**	**1**	**11**
a. Elective tracheostomy, p=0.004				

Table XXXVI Correlation between evolution and persistent radiotherapy edema in the elective tracheostomy group

The analysis of the end of treatment results and the persistance of radiotherapy edema in the elective tracheostomy group identifies a significant statistic association (p=0.004) with the stationary evolution.

C. Analysis of the tumoral recurrence in the study

		TRACHEOSTOMY		
		Elective	Emergency	Total
Tumor recurrence	YES	2	4	6
	NOT KNOWN (NP)	0	6	6
	NO	9	12	21
Total		11	22	33

Table XXXVII Association between tumor recurrence and tracheostomy type

Table 37 presents the associations between the type of tracheostomy performed and the tumor recurrences identified in the study group. The analysis of the cases for which the information is complete (recurrence yes/no) is also presented in Table 38. To ensure a more accurate statistical analysis, the group is restructured again to n=27.

		Tracheostomy		
		Elective	Emergency	Total
Tumor recurrence	YES	**2**	**4**	**6**
	NO	9	12	21
Total		11	16	27

Table XXXVIII Associations between tumoral recurrence and tracheostomy type - regrouped

Tracheostomy type			EVOLUTION			Total
			F	NF	S	
Elective	Recurrence	YES	**0**	**2**	**0**	2
		NO	6	2	1	9
	Total		6	4	1	11
Emergency	Recurrence	YES	**0**	**4**	**0**	**4**
		NO	4	3	5	12
	Total		4	7	5	16
Total	Recidivă	YES	0	6	0	6
		NO	10	5	6	21
	Total		10	11	6	27

Table XXXIX Association between tumoral recurrence, tracheostomy type and evolution

The frequency of tumor recurrence was higher in the group of emergency tracheostomized patients (33% Emergecy vs 18% Elective). For the subgroup of patients with emergency tracheostomy, the results identified a significant association (**p=0.032**) between recurrence and treatment outcomes.

The analysis of the correlation between the presence of persistent radiotherapy edema and tumor recurrences identified the absence of tumor recurrences in patients with radiation edema, regardless of the type of tracheostomy.

The survival period without recurrence did not vary significantly in relation to the type of tracheostomy (p-Log-Rank Test > 0.05).

4. CONCLUSIONS AND SUGGESTIONS

4.1. Conclusions of the study

The present study followed the evolution of a group of patients diagnosed with advanced hypopharyngeal cancer, one of the most aggressive forms of head and neck cancer. This pathology is considered rare, but according to the 2020 Globocan (17) data, the study was conducted in one of the regions with a high incidence of cases (Eastern Europe), specifically Romania.

The first step in the statistical protocol was to compare the two groups of tracheostomized patients in terms of socio-demographic characteristics, lifestyle, and biological status. This analysis is necessary because these factors can influence treatment responses or complication patterns identified in the patient group (patients with complex comorbidities may have an unfavorable response to treatment or a higher chance of complications).

The analysis of patient comorbidities was performed both in terms of the number of associated pathologies and the degree of decompensation. This analysis was conducted using the ACE-27 score and KPSS score for each patient. The analysis of these scores did not show statistically significant differences between the elective and emergency tracheostomy patient groups, confirming that the two groups are similar and can be compared without bias.

Elements identified in the study, confirmed by previous studies:

I. The patients' age at the time of diagnosis ranged from 46 to 84 years, with a mean age of 66 years and a standard deviation of 8 years. The mean age of patients at the time of emergency tracheostomy was 62 years ± 6 years, with variations between 51 and 71 years. 97% of the patients studied (35/36) were men, and only one woman was included in the study group. No statistically significant differences were identified between the emergency and elective tracheostomy subgroups (Student's t-test, $p > 0.05$), confirming the homogeneity of the groups. Testing the association between the type of tracheostomy and the studied variables for the restricted patient group with a complete profile of evolution (33 patients) shows that the subgroups defined by the type of tracheostomy are similar in terms of socio-demographic characteristics, comorbidities, and the characteristics of the studied disease.

II. Nearly 70% of the patients included in the study group (37 patients, 69.8%) were retirees, 11 patients were salaried employees (20.8%), and 9.4% (5 patients) were unemployed. The low socio-economic status (retirees, unemployed) represents a large part of the studied group (79%) and significantly influences the profile of a patient diagnosed with hypopharyngeal cancer through various factors: poor living conditions expose individuals to environmental carcinogens, with limited opportunities for physical activity or proper nutrition. These factors contribute to a long-term decrease in the body's immunity. Additionally, habits (smoking, chronic alcohol consumption) directly increase the risk of cancer development. Furthermore, professions with high exposure to pollutants and toxic substances are often associated with low socio-economic status. These cumulative factors increase the risk of hypopharyngeal cancer in individuals with precarious socio-economic status.

III. Chronic alcohol consumption was identified as a statistically significant factor ($P = 0.013$, Fischer's Exact Test), where 10/22 patients with emergency tracheostomy confirmed alcohol consumption, while none of the patients in the elective tracheostomy group confirmed this habit. A surprising finding was that smoking was not statistically significant ($P > 0.05$;

Fischer's Exact Test), although 16/22 patients with emergency tracheostomy and 5/11 patients with elective tracheostomy stated they were smokers.

IV. All patients enrolled in the study had carcinoma variants, with the most frequent being keratinized squamous carcinoma (36 patients/53, representing 68% of the group). The need for tracheostomy varied significantly ($p = 0.001$) depending on the tumor's location in the study group, which was also confirmed by detailed statistical analysis of the affected pharyngeal segment, especially for patients with both pharyngeal and laryngeal extension.

V. Regional lymph node involvement at diagnosis was confirmed in 52 of 53 patients, and all 6 patients who underwent primary surgery had confirmed lymphatic tumor extension.

VI. Analysis of biological constants:

- **Leukocyte values analysis**
  Statistically significant differences ($p = 0.028$) were identified between the values at the time of diagnosis (T1) and those at the end of treatment (T3) for patients with favorable evolution. Furthermore, statistically significant differences were identified between treatment values (T2) and evaluations after treatment (T3) ($p = 0.036$). Correlation identified: increased leukocyte values at diagnosis, peaking during treatment, and returning to normal after treatment are associated with favorable outcomes at treatment completion.
- **Hemoglobin values analysis**
  At diagnosis (T1), normal hemoglobin values were associated with favorable and stationary profiles, while anemia was linked to unfavorable evolution. During treatment (T2), anemia was present in both groups, and at the end of treatment (T3), anemia persisted in all groups, with the highest values associated with favorable evolution, followed by unfavorable and stationary evolutions. This analysis was confirmed to be statistically significant ($p = 0.046$).
- **INR values analysis**
  INR analysis was found to be statistically significant at T3 ($p = 0.018$) between the three subgroups of evolution. The pattern identified: higher INR values are associated with poorer prognosis (1.21 = unfavorable, 1.16 = stationary, 1.04 = favorable).
  The analysis between T1 and T2 showed a significant increase in INR within normal limits in the favorable evolution group ($p = 0.046$).

- **Quick Time (TQ) analysis**

  Quick Time values were significant (p = 0.002) at T3, associating elevated values above the normal limit with unfavorable and stationary evolution, while favorable evolution was associated with normal values. Additionally, within the subgroup of unfavorable evolution (p = 0.028), a significant difference was identified between T1 and post-treatment evaluations, showing a growing pattern of values.
- **Prothrombin activity analysis**

  In T3, this was statistically significant (p = 0.005), with values falling within normal limits for both subgroups. The pattern revealed higher values for favorable prognosis, and a tendency for lower values in the unfavorable prognosis group.

  In the unfavorable evolution group, significant differences were identified (p = 0.028) between T1 and T3, showing a decline in prothrombin activity, even though the values remained within the normal range.
- **ESR (Erythrocyte sedimentation rate)/VSH values analysis**

  The presence of the inflammatory syndrome was identified at all monitoring points and for all patients, regardless of subgroup. Statistically significant differences at T3 (p = 0.005) associated the lowest average value with favorable evolution, followed by unfavorable and stationary evolution.

  In the negative evolution subgroup, additional correlations were found between T1 and T2, showing a significant increasing trend (p = 0.028).
- **AST values analysis**

  AST values were significantly different during treatment (T2, p = 0.043), with the highest average values associated with favorable evolution, followed by unfavorable and stationary evolutions.

New elements identified in the study:

I. The necessity of tracheostomy increased with the stage, which was confirmed statistically (p = 0.024, Pearson's X2), beginning with stage IV A (where 23/29 patients required tracheostomy, 18 of them in emergency) to stage IV C (4/4 patients were tracheostomized in emergency). The conclusion of these data is that simultaneous tumor localization at the hypopharynx and larynx can lead to the need for emergency tracheostomy starting at stage IV A and advancing to more advanced stages.

II. The only comorbidity with significant statistical relevance was the history of another neoplasm at the time of diagnosis with hypopharyngeal cancer ($p = 0.031$), correlated with an unfavorable prognosis at the end of treatment.

III. Incident frequency was statistically significant ($p = 0.044$), with 21 patients reporting incidents. Emergency tracheostomized patients reported complications more frequently (17/36, 68%) compared to elective tracheostomized patients (4/36, 37%).

The study group was resized ($n = 33$) by further excluding patients with insufficient data regarding complications and treatment response to better compare and identify associations between tracheostomy type and associated complications.With the exception of tracheal cannula obstruction, all complications analyzed were statistically significant ($p > 0.05$; Fischer's Exact Test).

In the emergency tracheostomy patient group, the most frequent complications were granulation tissue formation requiring surgical tracheostomy correction, followed by bleeding. These same complications were identified in the elective tracheostomy group but with much lower frequency.

In the group of patients who underwent primary surgical treatment, the significant incident identified was the accidental closure of the tracheal stoma ($p=0.006$). However, there were no statistical differences in the occurrence of tracheostomy-related incidents compared to patients who underwent primary conservative treatment with radio-chemotherapy. No complications such as hemorrhage, pneumothorax, mediastinal infections, subcutaneous emphysema, tracheocutaneous fistula, or tracheomalacia were observed in the study group.

IV. Persistent radiotherapy edema was present in 45.5% of patients with emergency tracheostomy (in the presence of acute respiratory failure syndrome), compared to 9% (1/11 patients) with elective tracheostomy.

Persistent radiation edema was identified in nearly a quarter of the patients included in the study group (12 patients, 23%). The tumor locationa significantly associated with lumen obstruction were hypopharyngeal and hypopharyngeal with laryngeal extension, with the latter showing the highest frequency of this phenomenon (10 out of 33 patients).

The analysis of quality of life (SQL) showed a lower quality of life in patients with tracheostomy compared to those without tracheostomy. Additionally, for a more in-depth

analysis to identify associations and predictive factors, laboratory constant values tested at three time points were used, symptoms reported by patients upon admission were grouped into syndromes, and the association of final treatment response or the presence of persistent edema of the pharyngeal and laryngeal tissues during radiotherapy treatment.

V. In the general cohort (53 patients), only one statistically significant syndrome was identified (respiratory syndrome—encompassing variations of inspiratory dyspnea syndrome, ranging from disturbances occurring during moderate and intense effort to acute respiratory failure with asphyxial syndrome), which was associated with tracheotomized patients ($p=0.000$, OR 14.9). This analysis confirms the necessity of the procedure in the study cohort.

VI. The analysis of the overall quality of life score for patients with favorable outcomes at the end of treatment showed statistical differences ($p=0.030$) in the subgroup of patients with elective tracheostomy, who reported fewer complaints compared to those with emergency tracheostomy, thus confirming a better quality of life.

Statistically Significant Correlations Identified Regarding the Endpoint

Linear regression and univariate analysis identified age under 60 years as a variable of interest for favorable outcomes in patients with elective tracheostomy ($p=0.022$). However, this was not confirmed for patients undergoing emergency tracheostomy ($p=0.441$).

Elective tracheotomy also showed statistical significance concerning tumor localization at the time of diagnosis ($p=0.021$), proving beneficial for patients with simultaneous laryngeal and hypopharyngeal involvement.

Case Study I

The first case study presents an example from the cohort of patients with favorable outcomes, despite requiring emergency tracheostomy. It highlights both subjective (via EORTC QLQ-H&N35) and objective (observer-based, ACE-27, and Karnofsky) evaluations, where the results aligned. Notably, the need for emergency tracheostomy did not negatively impact the treatment response.

Case Study II

The second case study discusses a patient whose unfavorable progression—confirmed through imaging, biological, and clinical evaluations—contradicted the patient's self-

assessment using EORTC QLQ-H&N35. Despite the unfavorable prognosis, the patient consistently reported signs of improvement and progressively better scores, validated by oral feeding despite having a gastrostomy. This case underscores the importance of quality of life for patients with unfavorable outcomes, a factor that can sometimes be overlooked in the pursuit of therapeutic success at all costs.

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