Surgery vs. chemoradiotherapy in the treatment of locally advanced squamous cell carcinoma of the hypopharynx – survival analysis and prognostic factors

Original Article

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Abstract

This unicentric retrospective observational study analyzed 132 individuals with squamous cell carcinoma of the hypopharynx in T3 and T4a stages, diagnosed between 2017 and 2021, with the aim of comparing survival outcomes in individuals treated with initial surgery vs. definitive chemoradiotherapy (CRT) and determining prognostic predictors. The median follow-up time was 31.5 months, with a median age of 61 years. No significant differences were found in overall survival (OS) (49.3% vs. 46.5%, p=0.912) or disease-free survival (DFS) (57.8% vs. 56.6%, p=0.646) between the treatment types. T and N classifications were independent predictors of OS. The study suggests that the type of initial treatment does not substantially affect prognosis in this patient group.

Keywords: Surgery; Chemoradiotherapy; Squamous cell carcinoma; Hypopharynx; Overall survival; Disease-free survival; Organ-preserving treatment

Introduction

Hypopharyngeal squamous cell carcinoma (HSCC) is a rare neoplasm, accounting for less than 5% of all head and neck tumors worldwide[1]. It is more prevalent in men, with higher incidence rates reported in Europe and Southeast Asia[2]. The tumor may arise from the piriform sinus, retrocricoid region, posterior pharyngeal wall, and/or aryepiglottic fold. The main risk factors are smoking and alcohol consumption. Patients often present with advanced-stage disease, manifesting as dysphagia and odynophagia[3].

HSCC has the highest mortality rate among all head and neck malignancies, with five-

year overall survival (OS) rates for stages III and IV estimated between 15–40%[4]. The poor prognosis is attributed to several factors, including high propensity for lymphatic and systemic metastasis, predisposition to secondary malignancies, late-stage diagnosis, and comorbidities associated with smoking and alcohol consumption, such as cardiovascular and hepatic diseases. Malnutrition is common due to dysphagia, reduced appetite, and tumor-induced metabolic changes[5]. For locally advanced HSCC, a multimodal approach is recommended, including surgery, radiotherapy (RT), or chemoradiotherapy (CRT). The systemic component of CRT typically involves cytotoxic chemotherapeutic agents, such as cisplatin; however, in patients with contraindications to cisplatin (e.g., renal impairment or hearing loss), monoclonal antibodies such as cetuximab may be used. For several decades, total pharyngolaryngectomy with adjuvant RT was considered the standard treatment for HSCC [6], but this approach significantly impacts the quality of life by affecting essential functions such as phonation and swallowing. The high morbidity associated with this approach prompted the development of organ-preserving strategies in the second half of the 20th century, which initially comprised induction chemotherapy (CT) followed by RT in selected cases, and later concurrent CRT, which became the preferred organ-conserving approach[7,8]. Currently, the optimal balance between survival outcomes and preservation of the quality of life remains a subject of ongoing debate.

This study aimed to compare the survival outcomes in patients with locally advanced HSCC treated with initial surgery followed by RT or CRT versus definitive upfront CRT, and to identify the predictive factors for OS and disease-free survival (DFS) in this population.

Materials and methods

1. Study design

This retrospective, observational, single-center study included patients with locally advanced HSCC diagnosed at the department of otorhinolaryngology of the Portuguese Institute of Oncology (IPO), Lisbon. The study was conducted in accordance with the principles of the revised Declaration of Helsinki (2013)[9].

2. Participants

The inclusion criteria were stage T3 or T4a HSCC; treatment with either initial surgery followed by RT or CRT, or definitive CRT; and diagnosis between January 2017 and December 2021. The exclusion criteria were incomplete clinical records or inconclusive staging, stage T4b disease, distant metastasis (M1), synchronous malignancies at diagnosis, or palliative treatment.

3. Sociodemographic, clinical, and surgical data

The data were collected from the electronic medical records and included sociodemographic information (sex, age, smoking, alcohol consumption, and clinical presentation), tumor characteristics (site, laterality, and T and N stages), and treatment details. For cases treated with surgery, the collected data included the type of procedure, reconstructive flap used (when necessary), tracheoesophageal prosthesis use, need for secondary treatment, and recurrence. Follow-up data were also collected, including time between the first and last appointment, DFS (time from histological diagnosis to recurrence), and OS (time from histological diagnosis to death or the last appointment), all reported in months. Post-treatment laryngeal function was also documented, including requirement for permanent tracheostomy (in patients receiving initial CRT) or enteral feeding via nasogastric tube (NGT) or percutaneous endoscopic gastrostomy (PEG).

4. Statistical analysis

The primary outcomes of this study were OS and DFS. Survival rates were estimated using the Kaplan-Meier method and compared using the log-rank test in univariate analysis. Independent predictors of survival were identified using multivariate analysis with the

Cox proportional hazards model. Continuous variables are presented as mean, median, and standard deviation, while categorical variables are presented as absolute and relative frequencies. Normality was assessed using the Kolmogorov-Smirnov test. Comparisons between patients who underwent surgery versus initial CRT were conducted using the Student's t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed or ordinal variables. A p-value < 0.05 was considered statistically significant. Statistical analyses were conducted using the IBM SPSS software version 26.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 132 patients were included, predominantly men (98.5%), with a median age of 61 years (interquartile range [IQR] 56–68). Most tumors were located in the piriform sinus (88.7%), and odynophagia (41.3%) was the most common symptom. Tumors were staged according to the 7th edition of the American Joint Committee on Cancer (AJCC) Tumor–Node–Metastasis (TNM) classification, with 30 patients (22.7%) presenting with stage III disease, 69 (52.3%) with stage IVa, and 33 (25.0%) with stage IVb. Patients treated with surgery had significantly higher T (p = 0.048) and clinical (p = 0.001) stages compared to those treated with CRT. These and additional clinical and sociodemographic characteristics are summarized in Tables 1 and 2.

The initial treatment was surgery in 94 patients (71.2%) and CRT in 38 (28.8%). The type of surgical procedure, reconstructive flap use, and tracheoesophageal prosthesis placement are described in Table 3. Among the patients who initially underwent surgery, 90 (95.7%) received adjuvant therapy; 47 (50.0%) underwent CRT and 43 (45.7%) underwent RT. Among the patients treated with definitive CRT, six (15.8%) subsequently underwent

Table 1
Patient characteristics

Characteristics	Total (n =132)	Surgery (n = 94)	CRT (n = 38)	p-value
Age, median (IQR)	61 (56-68)	62 (57-69)	59,5 (55-65)	0.054
Male	130 (98,5)	93 (98,9)	37(97.4)	0.504
Smoking	120 (90,9)	86 (91,5)	34 (89,5)	0,184
Alcohol consumption	111 (84,1)	76 (80,9)	35 (92,1)	0,217
T classification				0,048
T3	69 (52,3)	44 (46,8)	25 (65,8)	
T4a	63 (47,7)	50 (53,2)	13 (34,2)	
N classification				0,059
N0	31 (23,5)	18 (19,1)	13 (34,2)	
N1	17 (12,9)	11 (11,7)	6 (15,8)	
N2	51 (38,6)	36 (38,3)	15 (39,5)	
N3	33 (25,0)	29 (30,9)	4 (10,5)	
Staging				0,001
III	30 (22,7)	14 (14,9)	16 (42,1)	
IVa	69 (52,3)	51 (54,3)	18 (47,4)	
IVb	33 (25,0)	29 (30,9)	4 (10,5)	
Recurrence				0,581
Locoregional	18 (13,6)	13 (13,8)	5 (13,2)	0,817
Distant	31 (23,5)	24 (25,6)	7 (18,4)	0,383

Table 2
Clinical characteristics of the patients

Initial symptom	n (%)
Odynophagia	52 (41,3)
Dysphonia	43 (34,1)
Dysphagia	36 (28,6)
Cervical mass	24 (19,0)
Pharyngeal globus	12 (9,1)
Dyspnea	10 (7,9)
Hemoptysis	2 (1,6)
Otalgia	1 (0,8)
Tumor site	
Pyriform sinus	124 (93,9)
Posterior hypopharyngeal wall	7 (5,3)
Postcricoid region	1 (0,8)
Laterality	
Left	67 (50,8)
Right	60 (45,5)
Not applicable	5 (3,8)

Table 3
Surgical characteristics of the patients treated primarily with surgery

Surgical procedure	
TL + PP + HT + ND	64 (68,1)
TL + HT + ND	17 (18,1)
TL + TP + HT + ND	5 (5,2)
TL + PP + HT	4 (4,3)
TL + PP + ND + pharyngotomy	2 (2,1)
TL + PP + HT + orostomy and pharyngostomy	1 (1,1)
TL + TP + HT + ND + orostomy	1 (1,1)
Reconstructive flap	
None	63 (67,0)
Pectoralis major	20 (21,3)
Free	7 (7,4)
Deltopectoral	2 (2,1)
Radial forearm	2 (2,1)
Tracheoesophageal prosthesis	17 (18,1)

Legend: TL , total laryngectomy; PP , partial pharyngectomy; HT, hemithyroidectomy; ND, neck dissection; TP, total pharyngectomy

surgery. Over a median follow-up of 31.5 months (IQR 12.0–49.75), the three-year OS and DFS were 48.5% and 57.3%, respectively. In univariate analysis, age (< 65 vs. ≥ 65 years) and tumor location (piriform sinus vs. other sites) were not significantly associated with OS and DFS (Table 4). The clinical stage was a significant prognostic factor, as illustrated in Figures 1 and 2. A lower clinical stage (III vs. IV) was significantly correlated with improved DFS (72.0% vs. 52.9%, p = 0.045) and showed a trend toward improved OS (56.3% vs. 46.4%, p = 0.080). In the surgery group, 58 patients died (38.3%) and 37 had a recurrence (39.5%), whereas in the CRT group, 22 patients died (42.1%) and 12 experienced a recurrence (31.6%). The treatment modality (surgery vs. CRT) was not significantly associated with OS (49.3% vs. 46.5%, p = 0.912) or DFS (57.8% vs. 56.6%, p = 0.646). Subgroup analysis by stage (III vs. IVA-B) confirmed the absence of a significant correlation between stage III and OS (57.1% vs. 54.7% p = 0.723) or DFS (74.6% vs. 69.1%, p = 0.642), and between stage IVA-B and OS (48.0% vs. 40.4%, p = 0.544) or DFS (54.8% vs. 44.0%, p = 0.214). Multivariate analysis (Table 5) identified T and N classifications as independent predictors of OS. Patients with T3 tumors had a 45.3% lower risk of death compared to those with T4a tumors (p = 0.033). Compared to N0, the risk of death increased by 55.8% for N1 (p = 0.054), 81.5% for N2 (p = 0.001), and 57.2% for N3 (p = 0.004).

After treatment, four (10.5%) patients receiving CRT required a permanent tracheostomy due to respiratory failure. Enteral nutrition was needed in 13 patients (34.2%) receiving CRT, one via NGT and 12 via PEG; and in 11 patients (11.7%) treated with surgery, five via NGT and six via PEG. This difference in enteral feeding requirements was statistically significant (p = 0.001).

Figure 1
OS (A) and DFS (B) based on clinical staging.

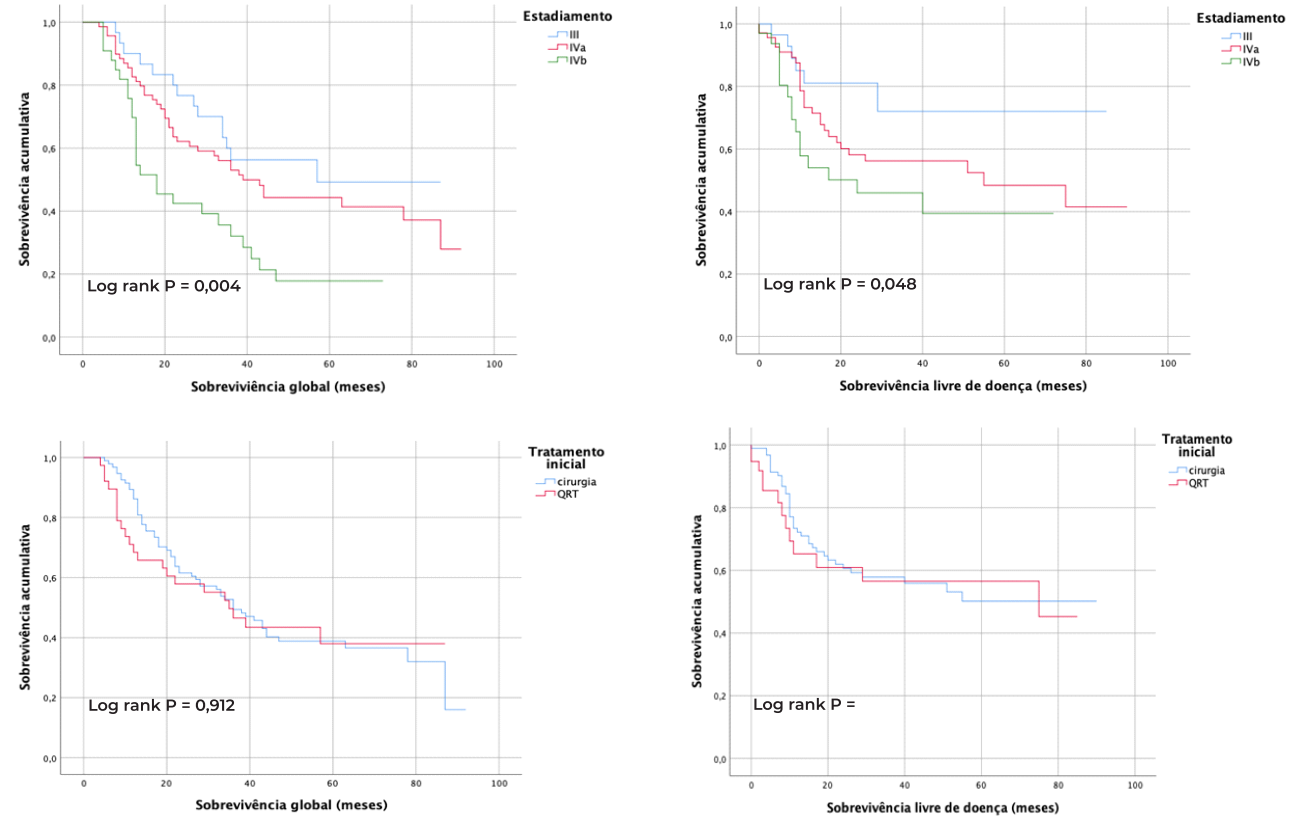

Figure 2
OS (A) and DFS (B) based on initial treatment

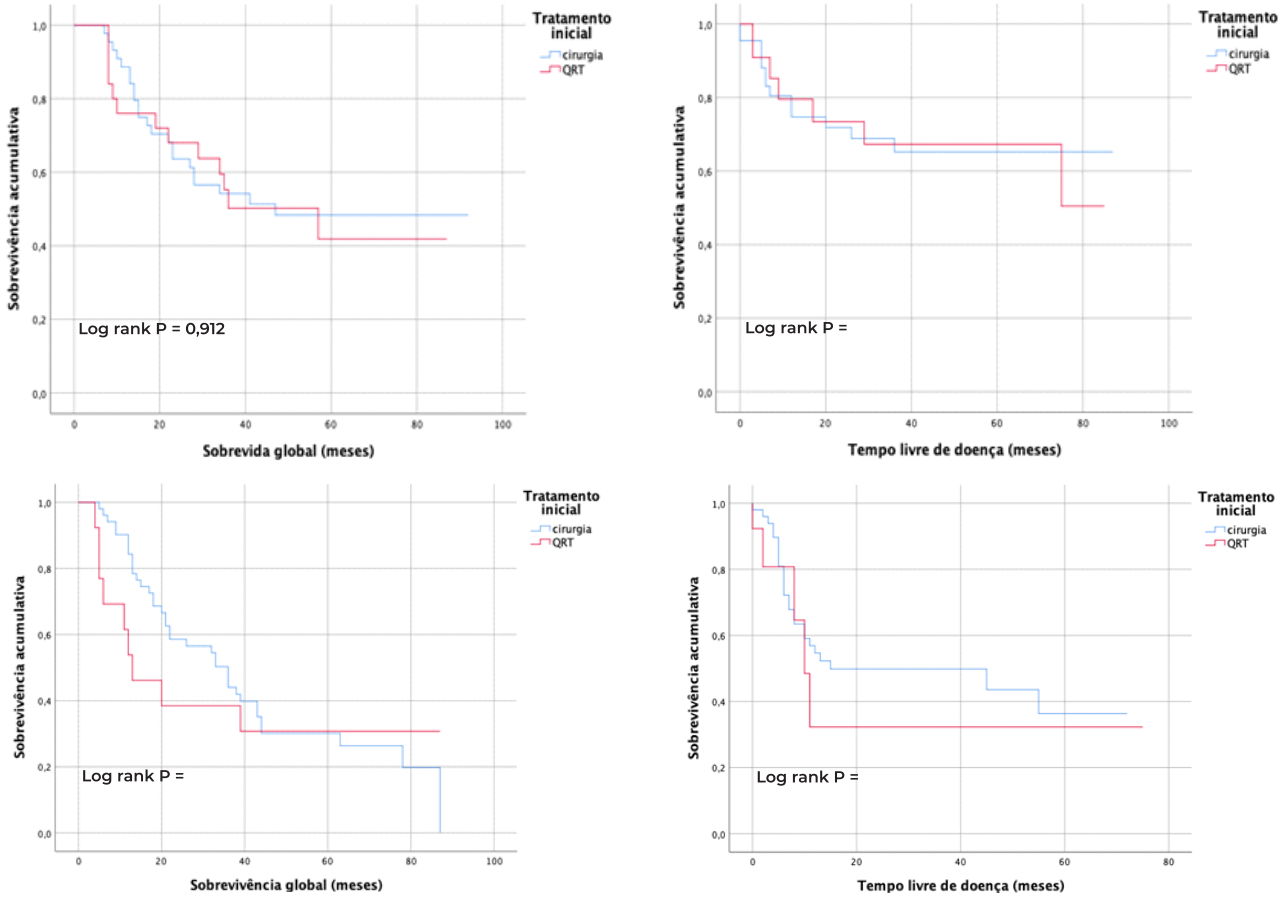

Table 4
Univariate analysis for OS and DFS

Variable	Number of patients	SG		SLD	
		3-years, %	p	3-years, %	p
Age			0,456		0,231
< 65 years	86	47,2		55,8	
≤ 65 years	46	40,9		60,3	
Sublocation			0,739		0,595
Pyriform sinus	116	48,4		57,3	
Other	16	49,2		57,1	
T			0,041		0,023
T3	69	53,0%		66,9%	
T4a	63	48,7%		53,9%	
Clinical staging			0,080		0,045
III	30	56,3		72,0	
IV	102	46,4		52,9	
Treatment			0,912		0,646
Surgery	94	49,3		57,8	
CRT	38	46,5		56,6	

Table 5
Multivariate analysis using the Cox proportional hazards model for OS and DFS

	Overall survival		Disease-free survival	
	HR (95% CI)	p	HR (95% CI)	p
Age (ref. < 65 vs. ≤ 65 years)	0,870 (0,536-1,412)	0,573	0,775 (0,417-1,441)	0,421
Sublocation (ref. pyriform sinus vs. others)	1,344 (0,653-2,765)	0,422	1,387 (0,581-3,315)	0,461
Clinical staging (ref. III vs. IV)	0,848 (0,306-2,348)	0,751	1,780 (0,504-6,284)	0,370
T classification (ref. T3 vs. T4a)	0,547 (0,315-0,952)	0,033	1,708 (0,855-3,410)	0,129
N classification				
N1	0,442 (0,193-1,015)	0,054	0,585 (0,212-1,614)	0,300
N2	0,185 (0,068-0,504)	0,001	0,494 (0,173-1,411)	0,188
N3	0,428 (0,241-0,759)	0,004	0,463 (0,225-0,953)	0,037
Treatment (ref. surgery vs. CRT)	1,305 (0,731-2,330)	0,912	1,926 (0,929-3,990)	0,078

Discussion

In our study, no statistically significant differences in OS or DFS were observed between patients with locally advanced HSCC treated initially with surgery or CRT. The literature on this topic remains inconclusive. A meta-analysis published in 2020, which included 2,539 participants, reported no significant differences in OS between surgical and organ-preserving approaches[10]. Conversely, a 2024 meta-analysis with 1,619 participants reported improved survival among patients who underwent initial surgery compared to those receiving definitive synchronous CRT[6].

In our cohort, this discrepancy may be explained by differences in the baseline prognosis. Patients treated with surgery had unfavorable clinical characteristics, including significantly higher T stage and clinical stage ($p < 0.05$), as well as a trend toward a higher N stage, compared to those receiving CRT. These findings suggests that despite a less favorable initial prognosis, long-term survival outcomes were comparable between the two treatment modalities.

Historically, organ-preserving approaches were advocated to preserve the voice and swallowing function, which are often compromised by surgery. However, in our study, approximately one-third of the patients treated with CRT required enteral feeding due to significant dysphagia, with a statistically significant difference compared to the surgery group ($p = 0.001$). These findings align with those of previous studies [11], including a systematic review published in 2025, which identified pre-treatment dysphagia, body mass index < 18.5, and hypopharyngeal tumors as predictors of need for NGT in patients undergoing CT or RT for head and neck cancer[12]. These observations led to a growing trend toward the use of RT techniques optimized for dysphagia, such as dysphagia-optimized intensity-modulated RT, which aims to reduce radiation exposure of the pharyngeal constrictor muscles and decrease the risk of dysphagia[10].

Multivariate regression analysis identified T and N stages as independent prognostic factors for OS in HSCC, consistent with the results of previous studies. For instance, Zheng et al. reported that age, race, marital status, tumor location, and treatment modality, in addition to T and N stages, were independent diagnostic predictors. These data informed the development of a specific nomogram for patients with T3-T4 or N+ HSCC, which effectively estimates OS and cancer-specific survival[7].

This study has some limitations. First, the retrospective design hindered the control of potential selection bias between the two

treatment groups. Second, detailed data regarding RT and CT protocols, particularly radiation doses, chemotherapy regimens, and timing of synchronous CRT, were not consistently recorded. Third, comorbidities and performance status, which can affect both treatment selection and prognosis, were not included. Fourth, the follow-up period was relatively short, limiting assessment of long-term outcomes. Finally, functional outcomes such as the voice quality, treatment-related complications, and causes of death were not documented.

Conclusion

No statistically significant differences in OS and DFS were observed between patients with HSCC initially treated with surgery and those receiving definitive CRT. T and N stages were identified as independent predictors of survival, emphasizing the critical role of early diagnosis in improving survival rates of HSCC. However, definitive CRT did not demonstrate superior functional outcomes, particularly concerning swallowing function preservation. Further studies with larger cohorts are needed to determine which therapeutic approach provides the best balance between survival and quality of life, given the complex interplay of clinical and functional factors in HSCC.

Conflict of Interests

The authors declare that they have no conflict of interest regarding this article.

Data Confidentiality

The authors declare that they followed the protocols of their work in publishing patient data.

Human and animal protection

The authors declare that the procedures followed are in accordance with the regulations established by the directors of the Commission for Clinical Research and Ethics and in accordance with the Declaration of Helsinki of the World Medical Association.

Privacy policy, informed consent and Ethics committee authorization

The authors declare that they have obtained signed consent from the participants and that they have local ethical approval to carry out this work.

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Scientific data availability

There are no publicly available datasets related to this work.

References

1. Mendenhall WM, Pfister DG. Treatment of head and neck cancers. In: DeVita, Hellman, Rosenberg's. Cancer: Principles and Practice of Oncology. 7th ed. Lippincott Williams & Wilkins, editor. Philadelphia; 2005. 732 p.
2. Mousavi SE, Ilaghi M, Mirzazadeh Y, Mosavi Jarrahi A, Nejadghaderi SA. Global epidemiology and socioeconomic correlates of hypopharyngeal cancer in 2020 and its projection to 2040: findings from GLOBOCAN 2020. Front Oncol. 2024 Sep 2:14:1398063. doi: 10.3389/fonc.2024.1398063.
3. Chen YY, Tsai YT, Tsai MS, Hsu CM, Lai CH, Lu CH. et al. Treatment outcomes of locally advanced hypopharyngeal squamous cell carcinoma. Ther Radiol Oncol. 2018; 2:17. doi: 10.21037/tro.2018.
4. Lo WC, Wu CT, Wang CP, Yang TL, Lou PJ, Ko JY. et al. Lymph node ratio predicts recurrence and survival for patients with resectable stage 4 hypopharyngeal cancer. Ann Surg Oncol. 2017 Jun;24(6):1707-1713. doi: 10.1245/s10434-017-5770-1.
5. Reis I, Aguiar A, Alzamora C, Ferreira C, Castro V, Soares A. et al. Carcinoma espinocelular da hipofaringe: resultados de uma instituição numa coorte de doentes tratados com intenção curativa com ou sem preservação da laringe. Radiol Bras. 2016 Jan-Feb;49(1):21-5. doi: 10.1590/0100-3984.2015.0018.
6. Tsai TY, Yap WK, Wang TH, Lu YA, See A, Hu YF. et al. Upfront surgery versus upfront concurrent chemoradiotherapy as primary modality in hypopharyngeal squamous cell carcinoma: a systematic review and meta-analysis. J Otolaryngol Head Neck Surg. 2024 Jan-Dec:53:19160216241293633. doi: 10.1177/19160216241293633.
7. Zheng L, Fang S, Ye L, Cai W, Xiang W, Qi Y. et al. Optimal treatment strategy and prognostic analysis for hypopharyngeal squamous-cell carcinoma patients with T3-T4 or node-positive: a population-based study. Eur J Surg Oncol. 2023 Jul;49(7):1162-1170. doi: 10.1016/j.ejso.2023.03.215.
8. Cordunianu AGV, Ganea G, Cordunianu MA, Cochior D, Moldovan CA, Adam R. Hypopharyngeal cancer trends in a high-incidence region: a retrospective tertiary single center study. World J Clin Cases. 2023 Aug 26;11(24):5666-

5677. doi: 10.12998/wjcc.v11.i24.5666.
9. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013 Nov 27;310(20):2191-4. doi: 10.1001/jama.2013.281053.
10. Cui J, Wang L, Piao J, Huang H, Chen W, Chen Z. et al. Initial surgical versus non-surgical treatments for advanced hypopharyngeal cancer: a meta-analysis with trial sequential analysis. Int J Surg. 2020 Oct:82:249-259. doi: 10.1016/j.ijsu.2020.04.059.
11. Szuecs M, Kuhnt T, Punke C, Witt G, Klautke G, Kramp B. et al. Subjective voice quality, communicative ability and swallowing after definitive radio(chemo)therapy, laryngectomy plus radio(chemo)therapy, or organ conservation surgery plus radio(chemo)therapy for laryngeal and hypopharyngeal cancer. J Radiat Res. 2015 Jan;56(1):159-68. doi: 10.1093/jrr/rru093J
12. Xiao JB, Cherukupalli A, Tran KL, Prisman E. Predictors of gastrostomy tube placement in head and neck cancer patients undergoing radiation or chemoradiotherapy: a systematic review. Head Neck. 2025 Mar;47(3):1006-1017. doi: 10.1002/hed.28010.