

Reviewer #1:

1. The title can be modified to better indicate the type of study and the objective of the study.

VULCU CORDUNIANU et al.: HYPOPHARYNGEAL CANCER TRENDS IN A HIGH-INCIDENCE REGION – A RETROSPECTIVE TERTIARY SINGLE CENTRE STUDY

2. The introduction can highlight the current existing literature on hypopharyngeal cancer, what is the lacunae existing in the literature and emphasize the aim and objectives of the study.

Hypopharyngeal cancer treatment was based up to the 1980 on standard radical surgical excision associated postoperative with radiation therapy or radiotherapy alone. Conservative procedures begun to be used when the laryngeal conservation procedures were developed in 1960. Nowadays even if there is a lack of standard treatment for this type of pathology, the most frequent used methods remain primary radiochemotherapy and others continue to use the primary surgical technique followed by adjuvant radiotherapy (1). Because it is a rare pathology usually found in late stages, the treatment options are limited and consist in surgical excision of larynx and partial or complete resection of the pharynx, followed by radiation therapy and organ conservation procedures which aim to keep the larynx and pharynx – radiation therapy and chemotherapy, either simultaneously (CCRT- concurrent chemoradiation therapy) or induction therapy followed by radiation therapy in case of treatment response and in case of failure, surgical excision. The main issue in the treatment methods available today is that none of them associates significant improved survival.

TNM Stage	Standard	Option
cT1-2 cN0 cM0	RT	
	Conservation larynx surgery (T and N), followed by RT and CRT if indicated	
cT1-2 cN1-3 M0	Concomitant CRT	

cT3 cN0-3 M0	If laryngectomy necessary, concomitant CRT (T and N), or induction ChT followed by RT (T and N) in case of complete or partial response after induction or surgery in case of stable or progressive disease after induction	Surgery followed by RT or CRT if indicated
cT4a cN0-3 cM0	Surgery (T and N), followed by RT or CRT if indicated	CRT Induction ChT followed by RT (T and N) in case of complete or partial response after induction or surgery (T and N) in case of stable or progressive disease after induction
cT4b cN0-3 cM0		Induction ChT followed by RT for responders (T and N) Concomitant CRT Palliative treatment: systemic ChT/ immunotherapy and/or palliative RT and/or BSC

Figure 1 Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up-Management of hypopharyngeal cancer (Stage I-IV B) - BSC, best supportive care; ChT, chemotherapy; CRT, chemoradiotherapy; M, metastasis; N, node; RT, radiotherapy; T, tumour.

- 3. The discussion and conclusion should better indicate whether the objectives of the study are accurately answered and describe the clinical considerations of the study findings. A note on future implications of the study findings could be added.
- 4. The reasons for delayed diagnosis of hypopharyngeal cancer in the specific geographical area can be included with recommendations on improving the public health system for early diagnosis can be added

Considering the fact that in this study the average age of patients upon diagnosis was 62,5 years old, that 50 patients out of 53 were smokers or with a long history of smoking (more than 10 years), with affirmative habitual drinking and 44 out of 53 patients presented with moderate

and severe decompensation of concurrent pathologies, we highlight the necessity of a screening plan for the public health system in order to improve early diagnosis such as- for patients that present in a hospital setting, if they are aged over 60 years old, with positive alcohol and tobacco history it would be helpful to include an ENT exam when, which is a noninvasive procedure but can be useful in detection of early staged disease alterations. All the data we found was similar to the one found in literature, but with a higher degree of severity and a younger age at diagnosis compared to the most studies (1,4).

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cT3 cN0-3 M0	If laryngectomy necessary, concomitant CRT (T and N), or induction ChT followed by RT (T and N) in case of complete or partial response after induction or surgery in case of stable or progressive disease after induction	Surgery followed by RT or CRT if indicated
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Figure 2 Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up-Management of hypopharyngeal cancer (Stage I-IV B) - BSC, best supportive care; ChT, chemotherapy; CRT, chemoradiotherapy; M, metastasis; N, node; RT, radiotherapy; T, tumour.

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Reviewer #2: I consider the manuscript worthy of attention because it contains data that could be interesting if further implemented with additional information that would make the manuscript richer in data that can also be used by the international community in meta-analysis of the sector (therefore more visibility and citations) major comment

- specify in the title the type of study (retrospective, prospective, etc.)

A descriptive, observational, nonrandomized retrospective epidemiological clinical study was conducted on data retrieved from patients diagnosed and treated for hypopharyngeal cancer between January 2018 and August 2022 in the ENT department of “Carol Davila Central University Emergency Military Hospital” Bucharest. In this period, 53 patients were treated for hypopharyngeal cancer. The goals of this study were to observe, analyze and compare the epidemiological data (incidence, prevalence, risk factors) with the available literature, considering the fact that Romania is a high-incidence region for this rare pathology. Also, the implications of tracheotomy, the associated risks when is made as a life-saving procedure versus as an elective procedure and how it might affect the quality-of-life.

- Provide the number or a code referring to the ethics committee approval

This study was authorized by the Ethics Committee of Titu Maiorescu Doctoral School (Bucharest, Romania) number 15/2022 and by the Ethics Committee of Carol Davila Central University Emergency Military Hospital (Bucharest, Romania) number 538/2022. All patients provided written informed consent for data usage and publication in research purposes.

- I would provide if there is more information on the patients (alcohol abuse, smoking) and pharmacological therapies in progress, I would also like to know if the patient survival data are available (Hazard RATIO) between the gradings (G1-2 and G3-4) of patients and possibly report them.

Due to the fact that is a small group-based study on a rare pathology, we cannot correctly estimate the survival rate of patients (Hazard RATIO) between gradings.

An aspect that we find important to emphasize is the lack of early detected cases (T1-2), with 48 cases out of 53 diagnosed in stage IV. In our study group, the grading with the highest incidence (16 patients out of 53) was G2, followed by G3 (12 patients), G1 (3 patients) and G4 (1 patient). For 21 patients, the grading was not specified (Table).

Grading	G1	Frequency	Tracheotomy			Total
			Elective	Without	Emergency	
		% of same grading			100.0%	100.0%
		% of Tracheotomies			12.0%	5.7%

	G2	Frequency	4	4	8	16
		% of same grading	25.0%	25.0%	50.0%	100.0%
		% of Tracheotomies	36.4%	23.5%	32.0%	30.2%
G3	Frequency		7	5	12	
	% of same grading		58.3%	41.7%	100.0%	
	% of Tracheotomies		41.2%	20.0%	22.6%	
G4	Frequency			1	1	
	% of same grading			100.0%	100.0%	
	% of Tracheotomies			4.0%	1.9%	
N	Frequency	7	6	8	21	
	% of same grading	33.3%	28.6%	38.1%	100.0%	
	% of Tracheotomies	63.6%	35.3%	32.0%	39.6%	
Total		Frequency	11	17	25	53
		% of same grading	20.8%	32.1%	47.2%	100.0%
		% of Tracheotomies	100.0%	100.0%	100.0%	100.0%

- I would add a few elements in the introduction also referring to the etiopathogenesis of pharyngeal tumors and risk factors (for example: doi: 10.1155/2021/7312611)

In the literature described another general aspect of this disease, found all around the globe—that is usually found in patients with low socio-economic status, with a positive history of alcohol and tobacco abuse, factors that also lead to diagnosis delays, usually when the disease is advanced, their quality of life is severely impaired and their survival might be affected. The hypothesis available today on alcohol mechanisms that lead to carcinogenesis are: alcohol is a direct carcinogen to the cells, alcohol acts as a carcinogenic promotor of smoking, or both variants (1). Others factors that were proven to be involved in the hypopharyngeal cancer development are: presence of infection with Human Papilloma Virus (HPV) (1, 3), a controversy factor, that other studies missed to show a connection to cancer survival or hypopharyngeal cancer development, limited only to the oropharyngeal region (2, 4, 5, 6). Other proven risk factors that predispose to hypopharyngeal cancer are: from a genetic predisposition (Plummer-Vinson, also known as Paterson-Brown-Kelly syndrome (1), in the Japanese population, Yamashita found genetic predisposition on patients with Alcohol dehydrogenase 1B (ADH1B), aldehyde dehydrogenase 2 as additional factors to smoking cigarettes and alcohol consumption (7)), environmental related factors (long term exposure to asbestos (5), formaldehyde and coal dust (8))

- add study limit

The main limit of the present study is the low number of patients and the fact that due to the Coronavirus pandemic the public health system was limited, so the patients had a restrictive access to health care.

Reviewer 2

Ethics approval and consent to participate

1. Patel, E. J., Oliver, J. R., Jacobson, A. S., Li, Z., Hu, K. S., Tam, M., Vaezi, A., Morris, L. G. T., & Givi, B. (2022). Human Papillomavirus in Patients With Hypopharyngeal Squamous Cell Carcinoma. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*, 166(1), 109–117.
2. Dahm V, Haitel A, Kaider A, Stanisz I, Beer A, Lill C. Cancer stage and pack-years, but not p16 or HPV, are relevant for survival in hypopharyngeal and laryngeal squamous cell carcinomas. *Eur Arch Otorhinolaryngol*. 2018;275(7):1837-1843.
3. Patel, E. J., Oliver, J. R., Jacobson, A. S., Li, Z., Hu, K. S., Tam, M., Vaezi, A., Morris, L. G. T., & Givi, B. (2022). Human Papillomavirus in Patients With Hypopharyngeal Squamous Cell Carcinoma. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*, 166(1), 109–117.
4. Kühn JP, Schmid W, Körner S, et al. HPV Status as Prognostic Biomarker in Head and Neck Cancer-Which Method Fits the Best for Outcome Prediction?. *Cancers (Basel)*. 2021;13(18):4730, 2021.
5. Patel, E. J., Oliver, J. R., Jacobson, A. S., Li, Z., Hu, K. S., Tam, M., Vaezi, A., Morris, L. G. T., & Givi, B. (2022). Human Papillomavirus in Patients With Hypopharyngeal Squamous Cell Carcinoma. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*, 166(1), 109–117.
6. Marchlang JL, Luce D, Leclerc A, Goldberg P, Orlowski E, Bugel I, Brugère J. Laryngeal and hypopharyngeal cancer and occupational exposure to asbestos and man-made vitreous fibers: Results of a case-control study. *Am J Ind Med*. 2000;37:581–589. doi: 10.1002
7. Yamashita Y, Ikegami T, Suzuki M, et al. Hypopharyngeal cancer risk in Japanese: Genetic polymorphisms related to the metabolism of alcohol- and tobacco-associated carcinogens. *J Cancer Res Ther*. 2019;15(3):556-563. doi:10.4103/jcrt.JCRT_980_17
8. Laforest L, Luce D, Goldberg P, Begin D, Gerin M, Demers PA, Brugere K, Leclerc A. Laryngeal and hypopharyngeal cancers and occupational exposure to formaldehyde and various dusts: A case-control study in France. *Occup Environ Med*. 2000;57:767–773. doi: 10.1136/oem.57.11.767.

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