MEDICINE AND MATERIALS

Volume 1, Issue 1, 2021: 3-10 | ISSN: 2784 – 1499 & e-ISSN: 2784 – 1537
DOI: 10.36868/MEDMATER.2021.01.01.003 | www.medicineandmaterials.com |

STUDY ON THE RHINOPHARYNX NEOPLASMS

Alina Mihaela CĂLIN[1], Anamaria ZAHARESCU[1]*, Corina Cecilia Manole PALIVAN[1],

Faculty of Medicine and Pharmacy, Dunarea de Jos University of Galati, Str. Al. I. Cuza Nr. 35, Galați, Romania

Abstract

In order to receive the food bolus, the muscular-fibrous walls of the pharynx contract by reflex, first widening the pharynx, and the palatine veil rises, closing the passage to the rhinopharynx. Then the base of the tongue rises, the piers approach, closing the bucco-pharyngeal passage in the isthmus. The airway is simultaneously interrupted by the posterior displacement of the base of the tongue, the folding of the mucosa of the posterior pharynx, and the lifting and closing of the larynx. The food bolus is thus forced to follow the hypopharyngeal-esophageal pathway, the only one that remains open. In case of paralysis of the nerves that coordinate the swallowing process, the laryngeal sphincter remains open, favoring the false pathway and aspiration bronchopneumonias. The paralysis of the palatine veil prevents its horizontalization during swallowing, which favors the discharge of fluids into the nose, which is significant when the paralysis is bilateral and more discrete when it is unilateral. The clinical prospective and retrospective study material was represented by a number of 190 individuals aged 0 to 80 years, who were hospitalized between 01.01.2011 and 31.12.2019 in the ENT Department of the Teaching Hospital in Galați for follow-up of malignant rhinopharyngeal tumors. Most of these patients subsequently underwent sequential examination to determine their treatment response. Due to its deep location and limited clinical accessibility, onset symptoms are often absent or inconclusive for both the physician and the patient. CT scan is superior to clinical examination in primary tumor evaluation, especially in advanced T3 and T4 cases, which are largely clinically under-rated. Performing the coronal rhinopharynx sections and double-window recording greatly increase the accuracy of examination and they should be considered at least for the initial assessment procedure.

Keywords*: rhinopharynx; rhinopharyngeal tumors; CT scan; surgery*

Introduction

From the respiratory point of view, the pharynx has the role of a two-way airway between the nasal cavity and the larynx. Due to the abundance of the pharyngeal vascular network and the presence of mucous glands, the air is heated, humidified and purified. Thus, the pharynx completes and partly supplements the nasal respiratory function. Obstruction of the rhinopharynx by a benign or malignant tumor process prevents the passage of breathed in air from the nostrils to the larynx, leading to nasal obstruction which, if it is bilateral, determines the individual to breathe through his/her mouth.

Rhinopharynx obstruction also prevents volatilized olfactory substances from ingested foods and beverages from reaching the nasal olfactory mucosa with the inhaled or exhaled air, thus causing true gustatory anosmia [1-3].

During normal breathing, i.e. breathing through the nose, the pharynx is immobile and the palatine veil is relaxed and lowered, allowing the air column from the nostrils to pass into the larynx. The palatine veil rises suddenly when the individual starts breathing through his/her mouth. The process of heating, humidifying and purifying the inhaled air is completed in the rhinopharynx, a process that has started in the nostrils [4-6].

The pharynx has the role of a resonance cavity in the speech process, which influences the tone of voice. The rhinopharynx is one of the resonant cavities of the fundamental laryngeal sound.

Corresponding author: anamaria_zaharescu@yahoo.com

The palatine valley plays a major role in this resonance, because by its contraction it can exclude or not the rhinopharynx and nostrils from the pronunciation of nasal or buccal letters or phonemes. Thus, the oropharynx may separate or not the rhinopharynx from the adjacent parts through the palatine veil. When the rhinopharynx is obstructed by a tumor mass or by pharyngeal tonsil hypertrophy, posterior closed rhinolalia sets in and changes the tone of voice.

Depending on defense, the rhinopharynx participates by the anti-infectious and neutralizing action of the secretion of the mucous glands that cleans the mucous membrane of foreign particles and by lysozyme, which has bactericidal action [7-9].

Auditory function - The rhinopharynx is involved in the proper functioning of the auditory apparatus through the Eustachian tubes, the internal openings of which reach as far as the lateral walls of the rhinopharynx. The pharyngeal time of swallowing triggers the contraction of the tensor veli palatini muscles inserted in the fibro-cartilaginous section of the tubes. Thus, the lumen of the tube is opened and the pressure in the middle ear is equalized with that in the rhinopharynx, and with atmospheric pressure, respectively. As a result, the eardrum and the ossicular chain can vibrate normally and transmit the sound wave to the oval window [10-12].

Immune function - The pharyngeal lymphoid system (Waldeyer ring) influences pharynx physiology through Luschka's pharyngeal tonsil and tube tonsils, with the own action of the general lymphatic system. Due to its reticulo-histocytic origin, pharyngeal lymphoid tissue mainly plays a microbial defense and immunological process development role. It is involved in fibrinogen and proteolytic diastases formation, in the leukopoiesis process and in local water metabolism. This tissue is interwoven in the tonsils (belonging to Waldayer's lymphatic ring) and produces thymo-dependent lymphocytes (ly T) with a role in cell immunity and thymo-independent lymphocytes (ly B) with a role in humoral immunity (in the production of G,A,M,D,E immunoglobulins) [13-15].

The agglomeration of lymphoid tissue that constitutes the palatal tonsils and the pharyngeal tonsil is also likely to have a pituitary and thyroid-dependent endocrine function, responsible for growth during childhood.

From a pathological physiology point of view, by disturbing the balance between aggression and bodily defense abilities, acute infection of the lymphoid tonsil tissue can overcome the first defense barrier and affect the parapharyngicervical lymphoganglionic system [16-18].

Rhinopharynx neoplasm is the subject of very thorough epidemiological studies, due to the etiological theory that consists of the association of *infectious factors (Epstein –Barr virus), particular genetic and immunological factors, as well as the patient's environment factors (microclimate or macroclimate).*

These studies have highlighted the etiopathogenic factors mentioned, which creates a broader basis for understanding the etiology of cancer in general. New aspects have been specified regarding the possibility of improving early diagnosis and a more accurate knowledge of the histogenesis and natural evolution of these cancers, as well as improving the cure rate by the use of new therapeutic methods such as high energy radiotherapy and associated chemotherapy [19-21].

The epidemiology of cavum cancer suggests multiple determining factors including diet, viral agents, and genetic susceptibility. An obvious epidemiological possibility incriminated in the onset of cavum cancer is the *Epstein-Bar virus (EBV)*. Potential genetic determinations of cavum cancer have been suggested by the high incidence of the illness in subjects with profiles belonging to the *specific major histocompatibility complex (MHC)*. Loci associated with a relatively high risk also include the site of the *H2 antigen*. *Simons* et al. reported how the so-called *Singapore antigen, BW46,* is associated with a high risk of cavum carcinoma. The risk of illness is significantly higher in subjects with *H2* and *BW46* antigens. A high incidence of the illness has been found in the *B17* antigen carrier population. Recent studies on the correlation between the presence of a certain genetic determination of *HLA* antigens and cavum cancer support this assumption. The epidemiological picture is complicated by the presence of *Epstein-Barr Virus* antibodies in the serum of patients with cavum cancer but not in the serum of those

with other head and neck cancers. In fact, cavum neoplasm cells have been shown to contain the *Epstein-Barr virus* genome. It remains to be seen whether the *Epstein-Barr virus* is independently associated with cavum cancer, or whether it acts as a carcinogen or is a carcinogen [22-25].

Burkitt's lymphoma is also associated with a viral etiology, just like rhinopharyngeal cancer. *'It seems that these two types of cancer (Burkitt's lymphoma and rhinopharyngeal cancer) are the first human model to reveal a possible causal relationship between viruses and human cancers'* (G. de The).

We are currently aware of three groups of risk factors involved in rhinopharyngeal neoplasm: genetic predisposition; environmental factors; the Epstein – Barr virus.

Research has shown that genes that determine histocompatibility factors, i.e. the surface antigens responsible for the recognition and removal of non-sense tissues, are closely linked and located on chromosome 6. These genes make up the major histocompatibility system or HLA (Human Leukocyte Antigen) system.

The development of the malignant phenotype is the result of multiple interactions between various exogenous and endogenous factors (genetic, hormonal, immunological and metabolic).

The pathological anatomy study of rhinopharyngeal neoplasm refers to the following aspects: the starting point of the tumor, the relations with the walls of the pharynx, the macro and microscopic aspect of the tumor and its progression.

Rhinopharyngeal tumors originate in the tissues of this cavity, most commonly in the lymphatic tissue on the pharyngeal palate, and less in the lateral, posterior and anterior walls (N.Costinescu).

Malignant rhinopharyngeal tumors appear in three main forms: ***infiltrative form*** - it develops mainly under the mucous membrane, being difficult to detect clinically in its early stages and requiring repeated biopsies for its histological diagnosis; ***ulcerative form*** - it appears as a result of the necrosis that occurs in the tumor mass. It comes in the form of crateriform ulcerations, with irregular, bleeding edges, covered by muco-purulent secretions (severe infections). They occur as a result of the necrosis that occurs in the tumor mass. Its main clinical manifestation is epistaxis; the ***vegetative form*** appears in the form of a fleshy, bulging mass and can have two varieties: sessile and pedunculated, which in the advanced stages obstruct the choanae and produce specific nasal obstruction symptoms. These forms may combine and result in different types of tumors such as: ulcerative-infiltrative, ulcerative-vegetative [25].

Most of these tumors, i.e. about ¾, are epithelial tumors (basal cell, spinocellular and intermediate carcinoma), while the remaining ¼ are system tumors (reticulosarcoma, lymphosarcoma, gigantofollicular, plasmocytoma, Hodgkin's disease) and connective tissue tumors (fibrosarcoma, angiosarcoma). An increase in the number of system tumors has been noted lately [26].

The clinical progression of rhinopharyngeal neoplasm is divided into successive periods. There is sometimes no clear correlation between its clinical progression and its pathological anatomy structure, or between tumor extension and its clinical appearance.

Rhinopharyngeal cancer increases by infiltration or expansion. The first growth pattern described is also the most common. Mucosal abnormalities may reflect only a small section of the tumor extension. Occasionally, there are no abnormal mucosal appearances that may be identified by macroscopic examination. In these cases, the tumor may exist in the submucosa and from here extend beyond the anatomical limits of the cavum [27].

The close contact between the rhinopharyngeal mucosa and its neighboring structures contributes to the rapid expansion of the tumor process. This extension is done by progressively invading the submucosa in 4 main directions: ***inside*** - along the posterior and lateral walls, including the tonsillar fossa; ***anterior*** - the tumor process extends through the choanae into the nasal cavity. In these cases, it is important to carefully examine by CT scan the ethmoidal cells and maxillary sinuses, which may be the starting point of the tumor process, the rhinopharynx being only a secondary site; ***superior*** - towards the base of the skull and sphenoidal sinus [28].

The base of the skull is most frequently invaded by tumors located in the area of the Eustachian tube and of the fossa of Rosenmuller, which may have the following types of

propagation: outwards and backwards towards the base of the large sphenoid wing and the oval hole; forwards and upwards towards the sphenoid sinus; backwards towards the middle and inner ear, along the Eustachian tube; outwards and forwards towards the pterygoid processes and the pterygo-maxillary fossa, backwards and upwards towards the basilar membrane. ***Cavernous sinus*** - may be clinically involved without radiographic signs, the only symptoms being the paralysis of the cranial nerves (III, IV, V, VI), which are involved in this order. ***Orbit*** - is rarely involved in the first medical examination, but can often be the site of recurrences [29].

Regional adenopathies are present in 70-90% of cases, being frequently bilateral on the very first clinical examination. Cervical lymph node metastases occur early, as the rhinopharynx has a rich submucosal lymphatic network. ***TNM staging*** is currently used worldwide for the clinical assessment of the stage of malignancies.

Clinical symptoms guide clinical diagnosis towards a rhinopharyngeal cancer. A positive diagnosis may be set by clinical, paraclinical and laboratory methods and means.

Rhinopharyngeal tumors can be examined by cytological means: puncture, smear from ulcerated tumors and even prints, or by histological means, i.e. biopsy. The biopsy can also be done from the cervical adenopathy by puncture or by the removal of a lymph node. Serological laboratory tests - detection of specific antibodies to Epstein-Barr virus antigens: Ig G/EA, Ig G/CA and Ig A/VCA. The titer of these antibodies varies depending on the tumor stage; Blood hematology and biochemistry, as well as urine examination - are necessary to assess the general condition of the patient in order to choose the appropriate treatment plan. The radiological examination includes CT scan, MRI scan, etc. If it left untreated, rhinopharyngeal cancer extends in all directions, exceeding the limits of the rhinopharynx and invading the neighboring structures. Death is caused by meningeal, infectious or hemorrhagic complications [30].

We recommend that the development of the treatment plan, which must be customized for each patient, be carried out by a team consisting of the ENT surgeon, radiotherapist, oncologist, forensics doctor, dentist and nutritionist. The prognosis of rhinopharyngeal tumors is in most cases guarded and severe, depending on a number of factors.

Material and methods

The clinical prospective and retrospective study material was represented by a number of 190 individuals aged 0 to 80 years, who were hospitalized between 01.01.2011 and 31.12.2019 in the ENT Department of the Teaching Hospital in Galați for follow-up of malignant rhinopharyngeal tumors. Most of these patients subsequently underwent sequential examination to determine their treatment response.

Results and discussions

The study is a dynamic one, as some of the analyses were done retrospectively based on the data in the patients' records and therapeutic protocol reports. For our study, we used the findings of the histopathological examinations, and of the pre- and post-therapeutic imaging examinations. All patients included in the study had the histopathological confirmation of their clinical diagnosis. Although the histopathological examination of the surgical excision pieces was the rule, confirming in the case of functional lymph node removal any histological positivity of the lymph nodes, it did not systematically specify the positivity or negativity of the surgical resection margins. The treatment methods were chosen depending on the location of the primary tumor, its stage and its loco-regional and remote extension, its histopathological form, the patient's age and general condition, the existence of associated diseases, the technical equipment available, the expertise of the doctor or of the medical team that conducted the treatment, the patient's informed consent, his/her ability to understand the purpose and consequences of the treatment, as well as his/her adherence to the treatment and his/her subsequent recovery.

According to the data that we analyzed, 142 of the 190 patients were male, 74.73%, and 48 were female 25.26%.

Depending on its location, laryngeal cancer ranked 1st, with 53.5%, cavum cancer 5th, while oropharyngeal, pharyngeal-laryngeal and hypopharyngeal cancers ranked 2nd, 3rd and 4th, respectively.

From the histopathological point of view, most of the cavum cancers diagnosed in our clinic were undifferentiated carcinomas - 63.89%. Non-Hodgkin lymphomas ranked second with 12.50%, followed by invasive keratinizing spinocellular epidermal carcinomas -11.11%, large cell Hodgkin lymphomas - 4.17%, poorly differentiated carcinomas and non-invasive non-keratinizing spinocellular epidermal carcinomas - 2.08% (Fig. 1).

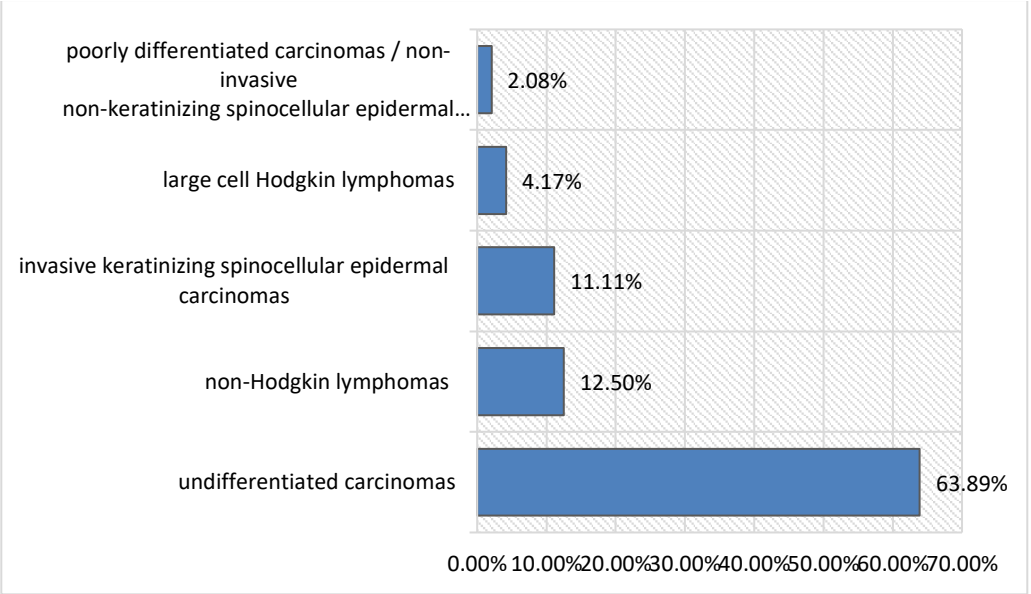

Fig. 1. Distribution of clinical entity from the histopathological point of view

The *World Health Organization* classified cavum neoplasm into three types: *type 1*, keratinizing spinocellular carcinoma; *type 2* non-keratinizing carcinoma; *type 3* undifferentiated carcinoma.

The distribution of the number of cases studied by histological groups is: non-differentiated carcinoma 148 cases (80.43%); moderately differentiated carcinoma 17 cases (9.24%); differentiated carcinoma, 13 cases (7.07%); Hodgkin lymphomas, 3 cases (1.63%), other forms 3 cases (1.63%) (Fig. 2).

The most common histological type is undifferentiated carcinoma - 148 cases – 80.43%, a result consistent with those mentioned in literature.

Most tumors are located around the fossa of Rosenmuller (above and behind the tube) and biopsies performed in this region have a high degree of positivity even if the tumor is not visible but a tumor process is suspected. The extension of the process in the para-pharyngeal space revealed by medical imaging means determines changes not only in tumor staging but also in its therapeutic approach. Very few cancers are strictly limited to the rhinopharynx at the time of their diagnosis.

Leukoplakia, erythroplathy, hyperplasia and dysplasia are all premalignant states. Each of these types of premalignant states has its own susceptibility to malignant transformation. Due to its deep location and limited clinical accessibility, onset symptoms are most often absent or inconclusive for both the physician and the patient.

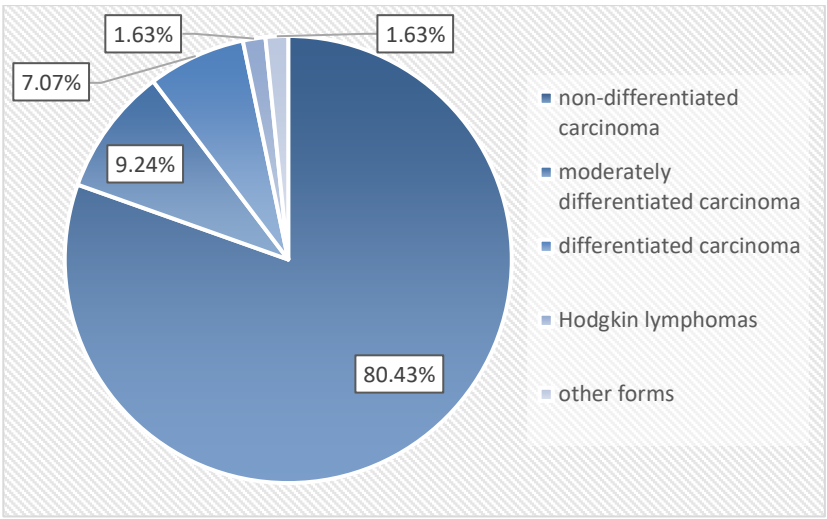

Fig. 2. Distribution of carcinoma type

Rhinopharyngeal neoplasm has four possible starting points: *rhinological, otic, ganglionic, neurological*.

The choice of the type of treatment should be customized for each patient, considering its esthetic consequences or functional results, the speed with which the complete treatment can be administered, the sequelae of each type of treatment, the rehabilitation of the patients, the risk of recurrence, and the capacity of salvage therapy (Fig. 3).

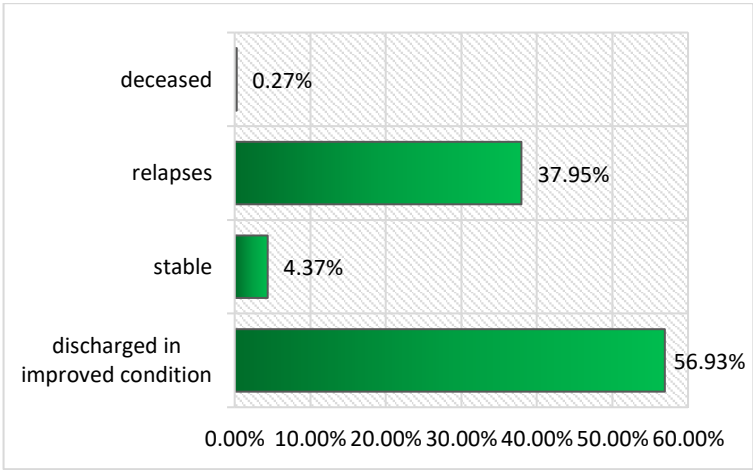

Fig. 3. Distribution with patients according with therapy and evolution

137 of the 190 patients were treated in the ENT Department, of whom 78 patients, 56.93%, were discharged in an improved condition, 6 patients were stable – 4.37%, 52 patients had relapses – 37.95% and just one died – 0.27%. 6 patients, 4.37%, underwent chemotherapy. Relapses occurred after 5 months to 2.5 years.

Conclusions

Rhinopharyngeal cancer localization has many particular aspects: **histological** (predominance of non-differentiated carcinomas with lymphocyte infiltration) **epidemiological** (endemic tumor in certain regions of the world), **etiological** (involvement of the Epstein-Barr virus, a particular diet and specific genetic susceptibility) and **natural history** (loco-regional disease at presentation, having the most expressed tendency to hematogenous metastasis among all ENT tumors).

The main therapeutic approach of rhinopharyngeal cancer was external radiotherapy, which was administered in stages I and II as the only treatment, or a combination between radiotherapy and chemotherapy and/or surgical treatment in advanced stages. When patients refused multimodal treatment, external radiotherapy was also the only treatment in stages III-IV. Surgical treatment has limited indication in rhinopharyngeal neoplasm therapy, being used only for the treatment of adenopathies and local lymph node recurrences after irradiation. Brachytherapy was applied to selected patients with recurrence of cavum tumors.

References

[1] Ataman T., **Otologie (Otology)**, Ed.Tehn., Bucureşti (Tech. Publ. House, Bucharest), 2002.

[2] Ataman T., ***Examinarea oto-rino-laringologică (Otorhinolaringological examination)***, Ed.Tehn. Bucureşti,(Tech. Publ. House, Bucharest), 2003.

[3] Călăraşu R., Ataman T., Zainea V., **Manual de patologie otorinolaringologică şi chirurgie cervico-facială (Manual of otorhinolaryngological pathology and cervico-facial surgery)**, Ed. Univ. "Carol Davila", Bucuresti, ("Carol Davila" Univ. Publ. House, Bucharest), 2002.

[4] Carvalho A.L., Nishimoto I.N., Califano J.A., et al. *Trends in incidence and prognosis for head and neck cancer.* **Int. J. Cancer**,**114**(5), 2005, pp:806-16.

[5] Comşa G.H., Hangan L., Murariu I. C. **Cancerul de rinofaringe (Rhinopharyngeal cancer)**, Ed. Fund. Axis (Publ. House Axis Found.) Iaşi, 2000.

[6] Chen M.H., Chang A.R., Lo S.Y.,*The usefulness of cytodiagnosis and DNA cytometry on nasopharyngeal brush smears for the diagnosis of nasopharyngeal carcinoma.* **Head Neck Journal**, **24**(3), 2002, pp. 223–227.

[7] Snow J.B., Snow W., Ballenger J., **Ballenger's Otorhinolaryngology Head and Neck Surgery.** (Ed. PMPH-USA), 2009, pp.201-209, 481-493, 769-782, 839-846, 1021-1062, 1081-1120.

[8] Sheu L.F., Chen A., Lee H.S., Hsu H.Y., Yu D.S., *Cooperative interactions among p53, bcl-2 and Epstein-Barr virus latent membrane protein 1 in nasopharyngeal carcinoma cells*. **Pathol. Int**., **54**(7),2004, pp. 475-85.

[9] Dora L. W. Kwong, John Nicholls, William I. Wei, Daniel T. T. Chua, Jonathan S. T. Sham, P. W. Yuen, Ashley C. K. Cheng, et al. *Correlation Of Endoscopic And Histologic Findings Before And After Treatment For Nasopharyngeal Carcinoma*. **Head and Neck Journal**, **23**(1), 2000, pp. 34-41.

[10] Cummings. **Otolaryngology - Head And Neck Surgery**, 4th Ed. Rev., 2005, Ed. Mosby, pp. 1457-1508, 1620-1645.

[11] Gershburg E., Pagano J.S. *Epstein Barr virus infections: prospects for treatment*. **Journal of Antimicrobial Chemotherapy**, **56**(2), 2005, pp. 277–281.

[12] J.L. Oh, E.E. Vokes, M.S. Kies, B.B. Mitta, M.E. Witt, R.R.,et al. *Induction chemotherapy followed by concomitant chemoradiotherapy in the treatment of locoregionally advanced nasopharyngeal cancer.* **Annals of Oncology**, **14**(4), 2003, pp. 564–569.

[13] Bearelly S.,Wang S. J.,Cheung S.W. *Oral sensory dysfunction following radiotherapy*, **The Laryngoscope**,**127**(10), 2017, pp.2282-2286

[14] Ottosson S., Lindblom U., Wahlberg P., Nilsson P.,Kjellén E., Zackrisson B. et al. *Weight loss and body mass index in relation to aspiration in patients treated for head and neck cancer*: *a long-term follow-up*. **Supportive Care in Cancer**, **22**(9), 2014, pp.2361-2369.
[15] Ram S., Clark G.T. *Management of Orofacial Pain and Other Co-Morbidities in Oropharyngeal and Nasopharyngeal Cancer Patients*. In: **Orofacial Pain**,(Ed. Wiley), 2012, pp. 212-231.
[16] M. Halle, I. Bodin, P. Tornvall, M. Wickman, F. Farnebo, C. Arnander. *Timing of radiotherapy in head and neck free flap reconstruction – a study of postoperative complications*. **Journal of Plastic, Reconstructive & Aesthetic Surgery**, **62**(7), 2009, pp.889-895.
[17] D. L. Schwartz, A. S. Garden. *Radiotherapy for Head and Neck Cancer*. **Hematology/Oncology Clinics of North America**, **20**(2), 2006, pp.259-285.
[18] American Cancer Society. **Cancer Facts & Figures 2020**. Atlanta, Ga: American Cancer Society; 2020.
[19] American Joint Committee on Cancer. *Pharynx.* In: **AJCC Cancer Staging Manual**, 7th ed. New York, Springer; 2010, pp.41–49.
[20] Chang ET, Adami HO. *The enigmatic epidemiology of nasopharyngeal carcinoma*. **Cancer Epidemiol Biomarkers Prev, 15**(10), 2006, pp.1765–1777.
[21] Howlader N, Noone AM, Krapcho M, et al. *SEER Cancer Statistics Review*, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014.
[22] Hui EP, Ma BB, Leung SF, et al. *Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma.* **J Clin Oncol**., **27**(2), 2009, pp. 242–249.
[23] Kong L, Hu C, Niu X, Zhang Y, Guo Y, Tham IW, Lu JJ. *Neoadjuvant chemotherapy followed by concurrent chemoradiation for locoregionally advanced nasopharyngeal carcinoma: interim results from 2 prospective phase 2 clinical trials.* **Cancer, 119**(23),2013, pp. 4111-8.
[24] Kushi LH, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, Gapstur S, et al. *Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity.* **Cancer J Clin, 62**(1), 2012 ,pp. 30-67.
[25] Langendijk JA, Leemans ChR, Buter J, et al. *The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: A meta-analysis of the published literature.* **J Clin Oncol, 22**(22), 2004, pp.4604–4612.
[26] Ma BB, Hui EP, Wong SC, et al. *Multicenter phase II study of gemcitabine and oxaliplatin in advanced nasopharyngeal carcinoma--correlation with excision repair cross-complementing-1 polymorphisms*. **Ann Oncol, 20**(11), 2009, pp.1854–1859
[27] Mendenhall WM, Werning JW, Pfister DG. *Treatment of head and neck cancer*. In: **Cancer: Principles and Practice of Oncology**. 9th ed. Philadelphia, (Pa. Lippincott Williams & Wilkins), 2011, pp.729–780.
[28] Mertens R, Granzen B, Lassay L, et al. *Treatment of nasopharyngeal carcinoma in children and adolescents.* **Cancer**, **104**(5), 2005, pp. 1083–1089.
[29] Pan JJ, Zhang SW, Chen CB, Xiao SW, Sun Y, Liu CQ, Su X, Li DM, Xu G, Xu B, Lu YY. *Effect of recombinant adenovirus-p53 combined with radiotherapy on long-term prognosis of advanced nasopharyngeal carcinoma*. **J Clin Oncol., 27**(5), 2009, pp. 799–804.
[30] Rock CL, Thomson C, Gansler T, et al. *American Cancer Society guideline for diet and physical activity for cancer prevention.* **A Cancer Journal for Clinicians**,**70**(4), 2020, pp. 245-271.

Received: October 22, 2020
Accepted: January 28, 2021