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VARIA

Tonsillar neoplasm: experience of the 2nd Otorhinolaryngology Clinic from Cluj-Napoca

Ionuț I. Jeican[1,2], Dan Gheban[3], Veronica Trombitas[1], Iacob Domşa[4], Bogdan Fetica[5], Carmen Crivii[2], Andra Piciu[6], Mihai Dumitru[7,8], Maria Aluaș[9], Silviu Albu[1]

Abstract: *Introduction. The primary tonsillar neoplasm is a common malignancy of the head and neck, alcohol and/or cigarette smoke and Human Papilloma Virus is the main etiological agent. This study offers a retrospective analysis of the tonsillar neoplasm cases in a tertiary medical center from Romania.*

Patients and methods. We present a 4-year (2015-2018) retrospective study on 72 patients diagnosed with tonsillar neoplasm in our clinic, previously untreated patients. The study was included only the patients diagnosed through histopathological evaluation with tonsillar neoplasm. We searched the cases in our clinic database, and we collected data about age, gender, symptoms on admission, findings of the objective physical examination, oro-pharyngoscopy, medical imaging examination results, histopathological results, stage of the disease, therapeutic management.

Results. The group composition is: 75% men and 25% women, 62.5% of them are smokers. Dysphagia/swallowing discomfort was the most common symptom identified, and the non-keratinized squamous cell carcinoma was the most common histopathological form. Stage I tonsil carcinoma was diagnosed in 25% of the cases, stage II in 15.3%, while 47.2% of the cases had stage III or IV. None of the patients presented distant metastases. Lymphoma was diagnosed in 12.5% of the cases.

We performed for all patients in stages I and II underwent total unilateral tonsillectomy. For the patients in stages III and IV, we performed surgery after radiotherapy-chemotherapy treatment or only radiotherapy-chemotherapy.

Conclusions. In Romania, smoking is still the most important risk factor for tonsil cancer. The majority of patients have visited a doctor only when dysphagia and, above all, palpable cervical adenopathy, were present, and the tumor was in the advanced stage. In Romania, the ENT-oncology integrated medical services are few, in most cases patients are lost from otorhinolaryngological follow-up.

Keywords: *tonsillar neoplasm, palatine tonsil, squamous cell carcinoma*

[1] Department of Head-Neck Surgery and Otorhinolaryngology, University Clinical Hospital of Railway Company, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[2] Department of Anatomy and Embryology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[3] Department of Pathology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[4] Department of Pathology, University Clinical Hospital of Railway Company, Cluj-Napoca, Romania
[5] Department of Pathology, Ion Chiricuta Institute of Oncology, Cluj-Napoca, Romania
[6] Department of Medical Oncology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[7] Department of Head and Neck Surgery and Otorhinolaryngology, University Emergency Hospital, Bucharest, Romania
[8] Department of Anatomy and Embryology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[9] Department of Oral Health, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

INTRODUCTION

Head and neck cancer is the fifth most frequent form of cancer worldwide [1]. The primary tonsillar neoplasm is the third most common malignancy of the head and neck, after thyroid and larynx cancer [2]. Every year, around 264,000 cases of oral cavity cancer are diagnosed in the world. At the time of diagnosis, approximately 50% of patients have lymphatic dissemination [3].

Corresponding author: Maria Aluaș
maria.aluas@umfcluj.ro

Within five years, 15% of patients with a tonsillar neoplasm present a secondary carcinoma in the head-neck area, especially those patients who are chronically exposed to the carcinogenic factors of the upper aero-digestive tract [3].

The risk factors for the development of tonsillar cancer are alcohol and/or cigarette smoke, and, especially for young patients without these risk factors, Human Papilloma Virus (HPV) may be an etiological agent [4]. Irrespective of the etiology, T1 or T2 stage tonsillar primary lesions can be treated successfully with acceptable loco-regional control and good survival rates by using either surgery or primary radiotherapy. The therapeutic success rates for T3 or T4 stage disease are less encouraging regardless of the treatment modality or medical center [5].

This study aims to make a retrospective analysis of this pathology, based on 72 cases diagnosed during 2015-2018, in a tertiary medical center from Romania.

PATIENTS AND METHODS

The study design is a retrospective observational study. It included patients admitted into the clinic for tonsillar neoplasm between 1 January 2015 – 31 December 2018. The inclusion criteria: histopathological diagnosis of tonsillar neoplasm during this period. The search for cases in the database was conducted based on the main diagnosis at discharge from the hospital, i.e. malignant tonsil tumor and disease code. The exclusion criteria: patients whose data were inaccessible, incomplete, or did not fulfill the inclusion criteria.

The statistical basis and clinical records were examined by the same investigator; the following data were collected: age, sex, symptoms on admission, findings of the objective physical examination, oro-pharyngoscopy, medical imaging examination results, histopathological results, stage of the disease, therapeutic management. The patient's privacy and confidentiality were protected under the laws in force.

All cases in the study were biopsied and all the specimens were fixed in 10% (v/v) buffered formalin and sent for the histopathological evaluation. For the classical histopathological examination, hematoxylin-eosin (HE) staining was used, while for the immunohistochemical (IHC) tests we used the antibodies: CD20 (cloneL26), CD10 (cloneSP67), bcl2 (clone124), CD5 (cloneSP19), bcl6 (cloneL26), CD3 (clone 2GV6), Ki67 (clone30-9) - Ventana Medical Systems, Tucson, AZ, on Benchmark XT Ventana-Roche platform.

None of the patients had been tested for HPV.

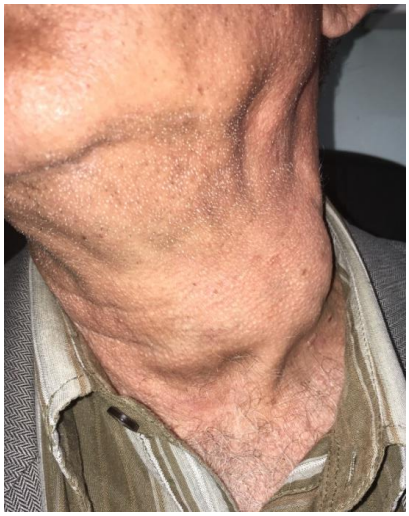
The patients were staged following the TNM classification of the American Joint Committee on Cancer (stage groups for non–HPV-mediated (p16 -) oropharyngeal cancer) [6].

The study protocol was approved by the University Clinical Hospital of Railway Company Ethics Council under the No. 11/09.12.2020.

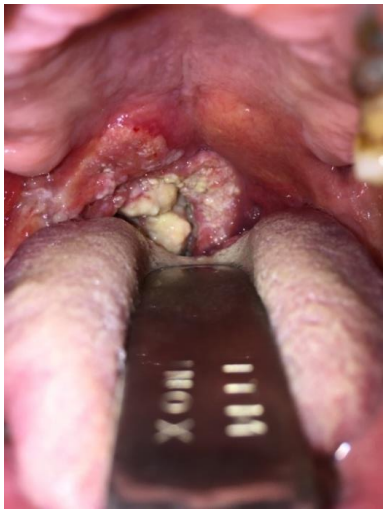
RESULTS

Of the 72 patients, 75% (n=54) were men and 25% (n=18) women. The average age was 62.8 (range 42-79 years) in the men subgroup and 56.3 (range 37-69 years) in women. The number of patients from rural and urban areas was about equal. The newly diagnosed cases each year were relatively constant.

Figure 1: Advanced stage tonsillar neoplasm – macroscopic aspect



A: Lateral-cervical adenopathic block in a patient with tonsillar neoplasm



B: Vegetative tumor with a starting point in the right tonsil (keratinized squamous-cell carcinoma).

C, D: Infiltrative tumor with a starting point in the right tonsil (non-keratinized squamous-cell carcinoma).

E: Ulcerated-infiltrative tumor with a starting point in the left tonsil. Bucco-nasal fistula (non-keratinized squamous-cell carcinoma).

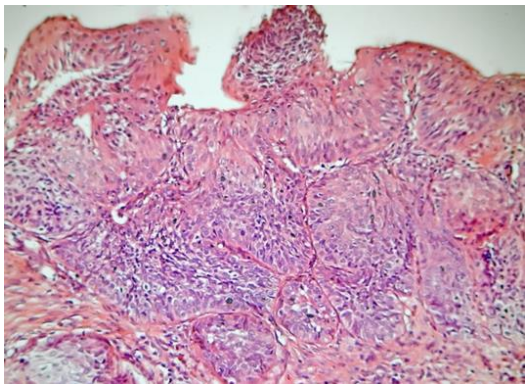
Risk factors. Smokers accounted for 62.5% (n=45, 35 men and 10 women), while 29.2% admitted to concomitant alcohol and tobacco consumption (n=21, 18 men and 3 women).

Clinical evaluation. The symptoms on admission to the hospital were: dysphagia/swallowing discomfort in 63.8% (n=46), palpable homolateral adenopathy (Figure 1A) in 20.8% (n=15), negative body weight curve in 36.1% (n=26), reflex otalgia 9.7% (n=7), trismus 8.3% (n=6), and pain in the oropharynx, tolerable without analgesic medication in 4.1% (n=3).

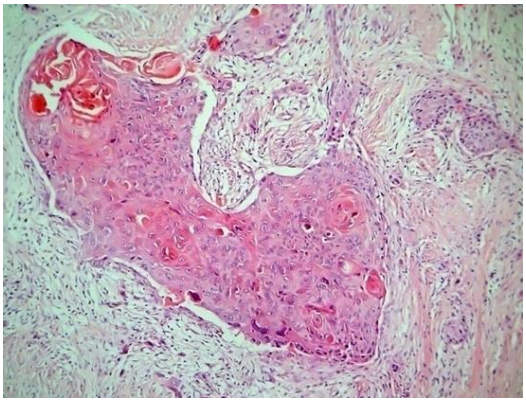
The macroscopic aspect of the tonsil tumor indicated a vegetative form in 34.7% (n=25) - Figure 1B, infiltrative in 30.5% (n=22) - Figure 1C-D, ulcero-infiltrative in 26.4% (n=19) - Figure 1E, while occult forms with metastatic lateral cervical adenopathies were present in 8.4% (n=6) of the patients, in which a triple biopsy (palatine tonsil, rhino pharynx, tongue base) was performed, with positive results at the tonsillar level.

Histopathology. The non-keratinized squamous cell carcinoma (Figure 2A) was evidenced in 58.3% (n=42) of the cases, keratinized squamous cell carcinoma (Figure 2B) in 29.2% (n=21) of cases, and B cell lymphoma (Figure 3) in 12.5% (n=9) of cases. The G2 histologic grade (moderately differentiated) was identified in the majority of cases (71%, n=51).

Figure 2: Squamous tonsillar carcinoma

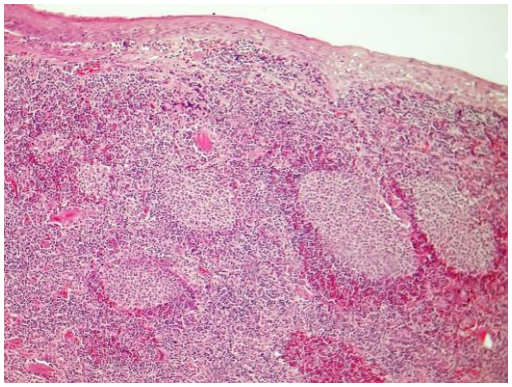


A – non-keratinized, moderately differentiated (G2) HE staining: ×100;

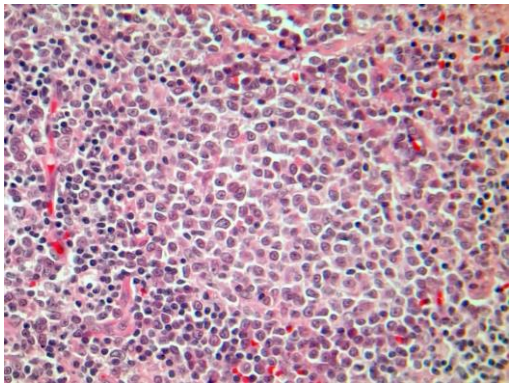


B – keratinized, moderately differentiated (G2) HE staining: ×200

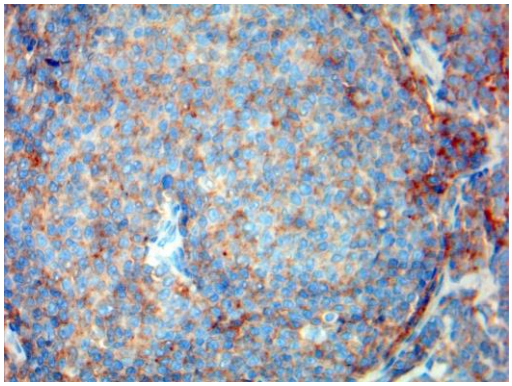
Figure 3: B cell tonsillar lymphoma



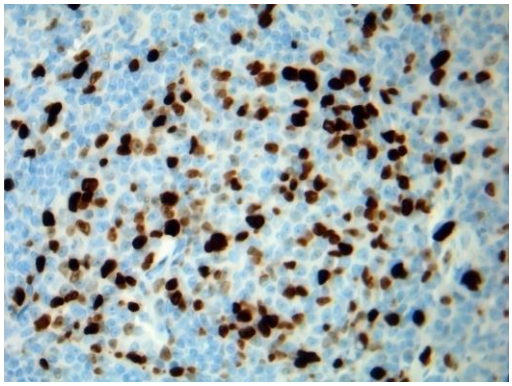
A - Different dimension follicles with no tingible bodies. HE staining: ×200



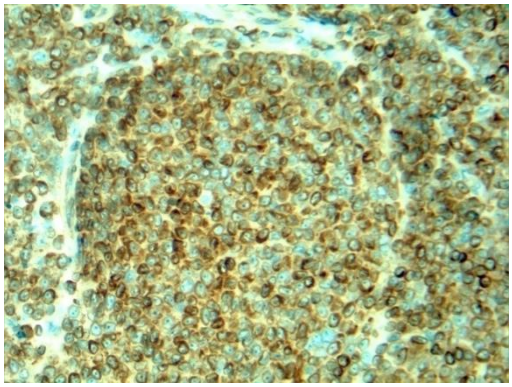
B - Small follicle made of centrocytes and centroblasts without mantle zone. HE staining: ×400



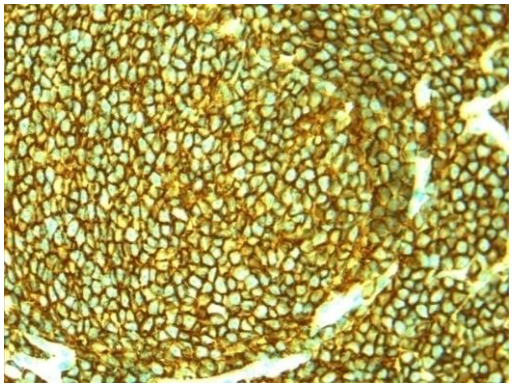
C - CD10 positive in and outside the germinal center. ×400



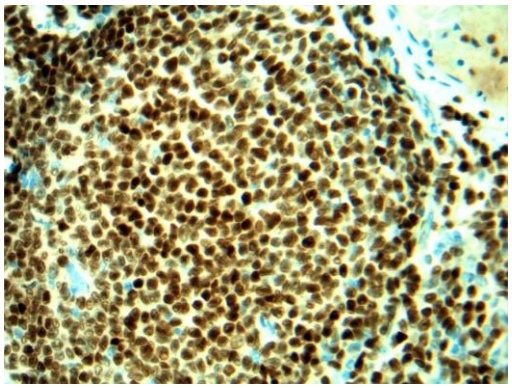
D - Low ki67 positivity in the germinal center. ×400



E - BCL2 positive in the germinal center. ×400



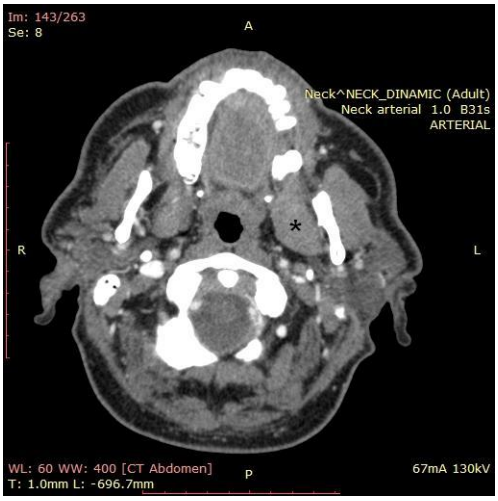
F - CD20 positive in and outside the germinal center. ×400



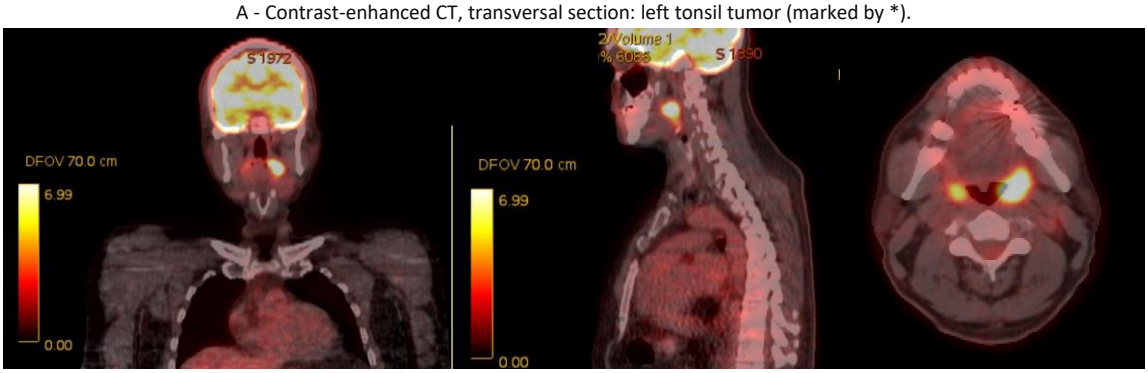
G - BCL6 positive in and outside the germinal center. ×400

Imaging investigations. After the confirmation of the histopathological diagnosis, a contrast-enhanced computer tomography (CT) was performed (Figure 4A) in 70 patients, while positron emission tomography (PET-CT) was performed in one patient (Figure 4B).

Figure 4: CT images of the tonsillar neoplasm



A - Contrast-enhanced CT, transversal section: left tonsil tumor (marked by *).



B - PET-CT, frontal, sagittal, and transversal sections: high perfusion tumor of the left tonsil.

Treatment. All patients in stages I and II, and the lymphoma cases underwent total unilateral tonsillectomy through a direct transoral approach (Figure 5A).

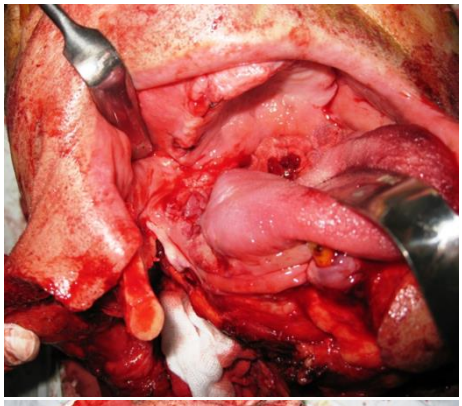
For the patients in stages III and IV (surgical cases), we performed, after radiotherapy-chemotherapy treatment, pharyngectomy with partial glossectomy in 2 cases (Figure 5B), tonsillectomy, and partial palatectomy in 9 cases.

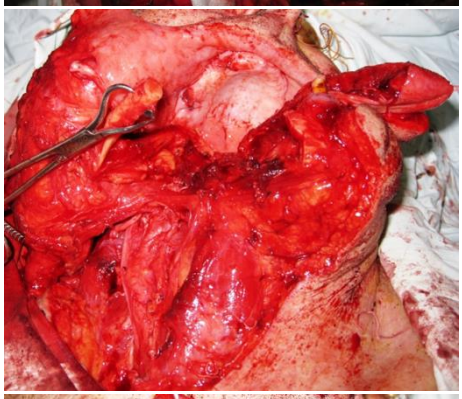
In all cases operated, lateral-cervical lymph node ablation was performed: for N0 cases – selective supra omohyoid neck dissection, and for N+ cases – radical neck dissection

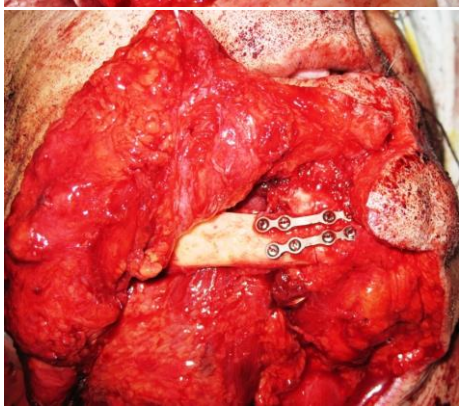
modified (Figure 5C-E).

Figure 5: Intraoperative aspects

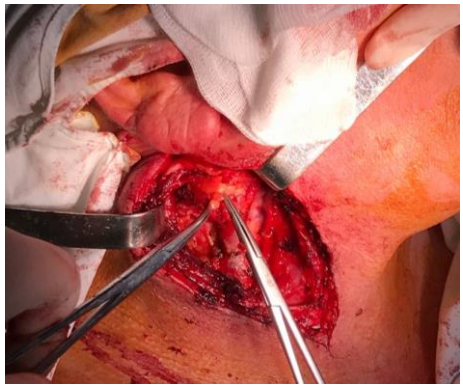
A - Transoral extended left tonsillectomy (T2N0M0).



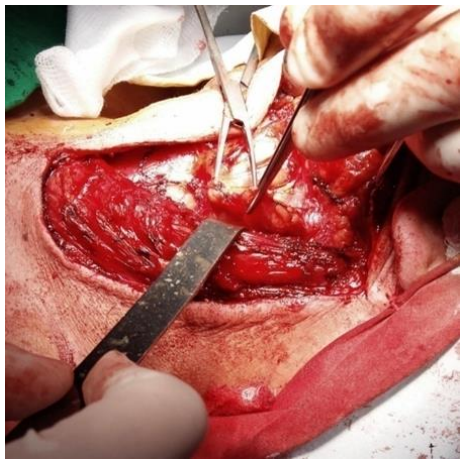




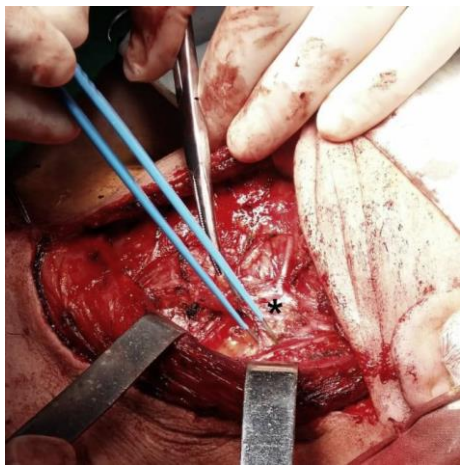
B1-3 - Transmandibular pharyngectomy with pectoralis major reconstruction.



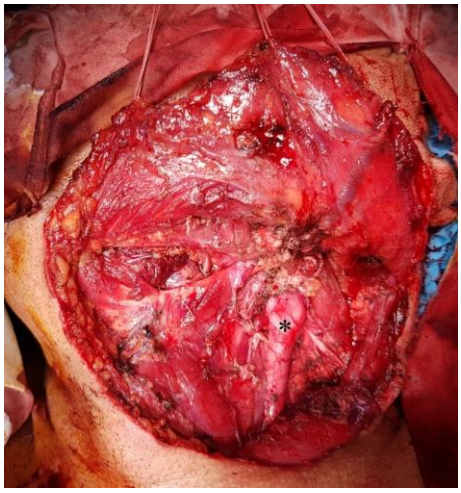
C - Right lateral-cervical lymphadenectomy.



D1: Dissection below the sternocleidomastoid muscle.



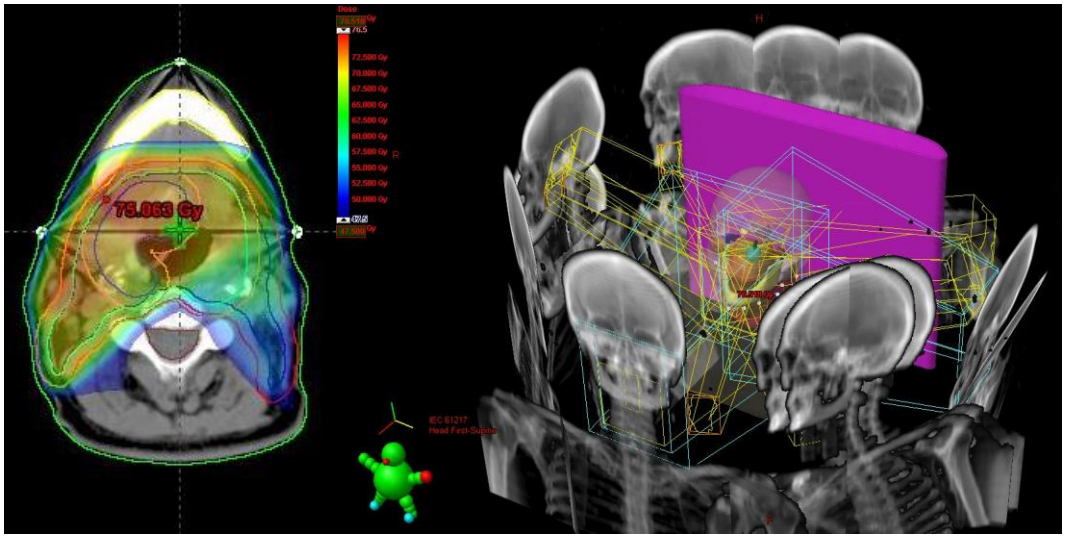
D2: Exposure of the right internal jugular vein (marked by *).



E - Radical dissection of the neck in a case with T4bN2M0. The tumor includes the left secondary carotid arteries (carotid glomus marked by *).

The cases considered beyond surgical therapy were referred only to radiotherapy (Figure 6), chemotherapy.

Figure 6: A, B CT - based treatment plans for a patient with right tonsil squamous carcinoma cT4N2cM0, stage IVB (Collection of Chiricuta Institute of Oncology Cluj-Napoca)



In Table 1 we present the distribution of cases according to Stage Groups for Non–HPV-Mediated (p16 -). At the time of imaging tests, we did not evidence metastases of the tonsillar neoplasm to other organs, so no patient was identified in stage IV C.

Table 1: TNM distribution of cases

Stage	Number of cases	Percent
Lymphoma	9	12.5%
I (T1N0M0)	18	25%
II (T2N0M0)	11	15.3%
III (T2N1M0)	9	12.5%
III (T3N1M0)	8	11.1%
IV A (T4aN2M0)	5	6.9%
IV A (T3N2M0)	5	6.9%
IV B (T4bN2M0)	4	5.6%
IV B (T4aN3M0)	3	4.2%

DISCUSSION

Tonsillar cancer was already recognized in the 19thcentury and attempts were made to characterize it [7].

Risk factors. Tobacco and alcohol remain the major risk factors for tonsillar neoplasm, especially for squamous cell carcinoma [8-9]. In our study 62.5% of the patients were smokers, and 29.2% took alcohol and tobacco concomitantly. There is a high probability that some patients did not admit to having these habits (especially in the case of alcohol). The percentage of about 60% for smokers was also reported in the United States of America, but it presents variations in region and sex [10].

Tobacco is a risk factor independent of alcohol drinking, as demonstrated by studies on individuals who have never consumed alcohol [11]. There is an interaction between

tobacco and alcohol well established for oral cavity cancers. The studies show that most cases are attributed to tobacco alone or a combination of tobacco and alcohol, while very few cases would be attributed to alcohol alone [12].

In high-income countries, tobacco prevalence has been decreasing in the last decades, due to the antismoking campaigns, which proves their importance [10].

Brandsma and Abramson found HPV in tonsillar squamous cell carcinomas in 1989, and subsequent studies have confirmed that HPV, especially the oncogenic subtype 16, increases the risk for developing tonsillar neoplasm [13-16]. The most frequent neoplasm sites associated with HPV infection in the head-neck area are the base of the tongue and palatine tonsils [13]. These patients have distinctive risk factors, such as a large number of sexual partners. Today, the link between oral sex behavior and oropharyngeal HPV infection is well known, HPV infection being the most common sexually transmitted disease in the United States [8]. The patients are usually younger, do not use cigarette smoke or alcohol, and have a better prognosis [17-18].

The HPV status of the tumor can be revealed by PCR or immunohistochemical staining [8, 19]. In our study, HPV viral analyses of the tumors had not been performed.

Clinical evaluation. The early injury, frequently asymptomatic, is mostly detected accidentally – 15% of our patients were found in stage 1. The patient may have no symptoms even in stage 2, due to submucosal tumoral development or deep formations in the tonsillar crypts [3]. However, in most cases the patients go to the doctor later, when dysphagia, cervical lymphadenopathy, and tumoral local extension are present – 54% of our patients were diagnosed in stages 3-4. The tonsillar asymmetry, palpable firmness, the visible lesion in the tonsil, cervical lymphadenopathy, unexplained weight loss, history of head-neck cancer can be local signs for a tonsillar neoplasm [20].

As well, the trismus (caused by pterygoid involvement), and otalgia (referred pain from the ninth and 10th cranial nerves) may be encountered [21].

The most frequently found symptom in our case series was dysphagia (63.8%).

Histopathology. A tissue biopsy can generally be performed with local anesthesia and is an essential step for confirming the suspect diagnosis.

The most frequent tonsillar cancer type is squamous cell carcinoma (75% of tonsillar neoplasm cases and 10% of head and neck malignancies [22]), followed by lymphoma [4], though other, rare histological forms have also been reported (small cell neuroendocrine carcinoma [23], mucoepidermoid carcinoma [24], small cell cancer of the tonsil [25]). The majority of tonsillar lymphomas are of B-cell origin. The association of B-cell tonsillar lymphoma with Epstein-Barr Virus infection is uncommon [26]. In our study, we evidenced squamous cell carcinoma in 80.6% of cases (51.4% non-keratinized, 29.2% keratinized), and B cell lymphoma in 18% of the cases.

Pediatric tonsil cancer is rare, with non-Hodgkin lymphoma accounting for the majority of pediatric tonsillar neoplasms. It raises suspicion in children who present with relatively rapid tonsil enlargement, tonsillar asymmetry characterized by a difference in the tonsillar size of ≥2 degrees on the Brodsky scale, or simultaneous cervical lymphadenopathy [27].

A meta-analysis on 54901 patients has shown that in current practice, the incurred cost of routine histological examination of tonsillectomy and adenoidectomy specimens is not warranted. The histopathological exam is warranted only when patients demonstrate findings associated with malignancy: tonsillar asymmetry, history of cancer, cervical adenopathy, tonsil injuries, weight loss [28]. Through biopsies, false-negative results may arise if the tumor is localized in the submucosa or deep crypts [29]. A tonsillar cancer is more likely to be missed by biopsies than by tonsillectomy [3].

Metastases of tonsillar neoplasm. The head-neck neoplasms usually extend firstly to the regional lymph nodes, but sometimes may metastasize to distant sites. The metastasis to distant lymph node groups is a rarely [30]. Furthermore, delayed multiple metastases without local recurrence are uncommon [31]. Approximately 15-20% of oropharyngeal carcinomas develop distant metastases, most commonly in the lung, liver, and bone [32-33].

The cutaneous metastasis from tonsillar cancer is rare but should be considered; new skin lesions should be searched and biopsied because the morphology of the cutaneous metastases from tonsillar squamous cell carcinoma is variable [22]. Cutaneous metastases result either from the local spread of cancer to overlying skin, (from direct extension through contiguous tissue planes), or more distant spread through either dermal lymphatics or blood vessels [34].

The metastases to tonsils are also rare, accounting for 0.8% of all tonsillar tumors [35]. The extension is due to the hematogenous dissemination and is associated with advanced-stage disease [36-37]. We did not identify metastases of tonsillar neoplasm or metastases to tonsils in this study.

Imaging investigations. The computed tomography or magnetic resonance imaging (MRI) is the best suited for the evaluation of oropharynx neoplasm. The cervical lymph node metastases are optimally evaluated by contrast CT. MR imaging is preferred for soft tissue assessment because of the greater resolution [38-39].

PET-CT scanning is indicated in search of an unknown primary tumor in patients who have a neck mass secondary to carcinoma, if a recurrent carcinoma may be present when there are metastatic with N0 cervical lymph nodes, or CT is inconclusive [39]. By ultrasound, we can perform an initial indicative TNM staging of the case before other expensive imaging studies such as CT and MRI [40].

In our study all the patients were examined by head-neck contrast-enhanced CT, with one exception – a patient requested a PET-CT in another unit.

Treatment. The treatment decision for tonsil cancer should be made by a multidisciplinary team.

According to the guidelines [41], early-stage tonsil cancer may be treated by transoral primary surgery [42] or open resection of the primary tumor, with or without neck dissection or definitive radiotherapy [43], the difference in the therapeutic benefit being insignificant.

The direct transoral approach provides the quickest and most direct way with the least potential of morbidity. However, advanced cancer or trismus, kyphosis, dental obstruction can limit access [44]. Transoral robotic surgery may be an effective alternative to open surgery or radiotherapy, especially for early-stage oropharyngeal squamous cell carcinoma [45].

Either Intensity–Modulated Radiation Therapy or 3D conformal radiotherapy of the primary tumor (Figure 6) and the involved lymph nodes with a total dose up to 70Gy is recommended, to minimize the irradiation to critical structures [46]. The addition of systemic therapy to radiotherapy should be considered for HPV-negative N1 disease and HPV-positive T2 disease and the involvement of a single node ≤3 cm [47].

Though the local-regional control and survival are similar following surgery or radiotherapy, primary surgery can be accomplished with minimal functional morbidity while reserving radiation for recurrent disease. Surgical salvage after radiotherapy may be difficult technically, being associated with a significant increase of complications [4]. Tonsil resection before radiation therapy is associated with improved survival in low-stage tonsil cancer [48].

For locally advanced resectable tonsil cancer the recommendations do not differ between the HPV status [41]. The treatment can be made either by giving concurrent systemic therapy and radiotherapy [49], or transoral or open resection of the primary and neck with appropriate adjuvant therapy, meaning systemic therapy concomitant with radiotherapy or radiotherapy alone, or as a third option induction chemotherapy followed by radiotherapy or concomitant systemic therapy with radiotherapy. Surgery and postoperative radiotherapy continue to provide a superior outcome in locally advanced tonsil squamous cell carcinoma in patients with the surgically resectable disease [50].

When concurrent systemic therapy/radiotherapy for the locoregionally advanced cancer of the tonsil is administered, the high-dose cisplatin is the preferred systemic agent. As induction chemotherapy, the preferred regimen consists of taxane/cisplatin/5-fluorouracil, known as TPF [51] or paclitaxel/cisplatin/5-fluorouracil [52].

Though data are scarce regarding the prevalence of bilateral synchronous tonsil cancer (the first report in 1971 [53]), certain authors maintain that this form of the disease is under-reported, and they recommend bilateral tonsillectomy in all patients with suspected or proven unilateral tonsil cancer and in patients with cervical carcinoma metastasis from an unknown primary tumor [54]. The recommendation for a bilateral tonsillectomy may be found in the literature but without application in clinical practice or integration into guidelines [3, 55]. On the other hand, unanimity exists for ipsilateral tonsillectomy.

Due to the deficiency of integrated services, many patients are lost from otorhinolaryngological follow-up. The most of our patients in the advanced stage never returned to our clinic after the start of oncological treatment. Because of this, we cannot show survival rates for our patients.

CONCLUSIONS

In Romania, smoking is still the most important risk factor for tonsil cancer, and HPV detection analysis is not available in public hospitals.

Most patients have visited a doctor when dysphagia and, above all, palpable cervical adenopathy, were present, but the tumor was in an advanced stage, which means that the therapeutic management requires close collaboration between otorhinolaryngologist and the radiotherapist-oncologist.

In Romania, the ENT-oncology integrated medical services are few, in most cases patients are lost from otorhinolaryngological follow-up.

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