

The management of the oropharyngeal anterior wall cancer

NICOLAE CONSTANTIN BALICA¹⁾, MĂRIOARA POENARU¹⁾, CAIUS ION DOROȘ¹⁾, FLAVIA BADERCA²⁾, MARIA-ALEXANDRA PREDA³⁾, VASILE CIPRIAN IOVAN⁴⁾, HORIA TUDOR STANCA⁵⁾, CRISTINA JANA BUSUIOC⁶⁾, IOANA CRISTINA OPRIȘCAN⁷⁾, OVIDIU BORUGA³⁾

¹⁾Department of ENT, "Victor Babeș" University of Medicine and Pharmacy, Timișoara, Romania

²⁾Department of Microscopic Morphology, "Victor Babeș" University of Medicine and Pharmacy, Timișoara, Romania

³⁾Department of Ophthalmology, "Victor Babeș" University of Medicine and Pharmacy, Timișoara, Romania

⁴⁾Department of Preclinical Sciences, Faculty of Medicine and Pharmacy, University of Oradea, Romania

⁵⁾Department of Ophthalmology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

⁶⁾Research Center for Microscopic Morphology and Immunology, University of Medicine and Pharmacy of Craiova, Romania

⁷⁾PhD Student, Department of ENT, University of Medicine and Pharmacy of Craiova, Romania

Abstract

Introduction: Anterior wall of the oropharynx or the base of the tongue is the site of different types of cancers, most of them usually diagnosed in advanced stages. The most common histological type of cancer diagnosed in these patients is squamous cell carcinoma (SCC). The treatment methods are multiple, but the optimal therapeutic option with best results on outcome and on the patients' quality life has not been established. The objectives of our study were to evaluate the tongue base SCCs treated by transhyoid approach and the oncological outcomes of the surgery combined with radiotherapy. **Patients, Materials and Methods:** The retrospective study was performed over a period of 10 years (2001–2010) on 37 previously untreated patients. All the tumors were biopsied and after histopathological (HP) diagnosis, the tumors were excised. All the specimens were fixed in 4% (v/v) buffered formalin and sent for the HP evaluation. **Results:** In the study were included only the patient diagnosed on biopsy with different types of SCC. The mean age was 61 years old, most of the patients (94.59%) being males. We performed a tongue base transhyoid tumor resection in 23 (62.17%) cases followed by epiglottectomy in five (13.51%) cases or horizontal supraglottic laryngectomy in nine (24.32%) cases, respectively. Bilateral neck dissections and postoperative radiotherapy were performed in all cases. The postoperative and post-therapeutic evolution was favorable at three years (81.1%) and five years (75.67%). There were no signs of local or regional recurrences. The tumor specific three-year and five-year survival rates were: pT2 100%, pT3 87.5%, pT4a 71.42% and 57.14%, and pT4b 50% and 25%, respectively. The stage specific three-year and five-year survival rates were: stage II 100%, stage III 85.71%, stage IVA 83.33% and 79.16%, and stage IVB 50% and 25%, respectively. **Conclusions:** The prognosis for the SCC of the tongue base is poor. Cancer resection by transhyoid approach is a feasible procedure, which permits a good tumor control with limited postoperative morbidity, with an important benefit on the life quality of the patients.

Keywords: transhyoid approach, oropharyngeal anterior wall cancer, tongue cancer, squamous cell carcinoma.

Introduction

Oropharyngeal anterior wall squamous cell carcinoma (SCC) is associated with a poor prognosis and relatively low five-year survival rates [1, 2]. Oropharyngeal carcinoma represents 10–15% of the head and neck neoplasms [3]. Of these, cancer of the base of the tongue accounts for between 20–35% [4]. These cancers have traditionally been treated with combined therapy, surgical resection followed by radiation therapy [5, 6]. The best option in the treatment of these lesions has still not been established. The transhyoid approach for the tongue base tumor resection is one of the best mandible-sparing procedures, providing exact anatomical entry with wide exposure, while avoiding injury to key neurovascular structures [7–9].

Surgery and radiotherapy comprise similar oncological and functional results in early stages (I–II) [3, 10] but in advanced cancers, the treatment is controversial, with three therapeutic options: surgery (with radiotherapy), chemo-radiotherapy or radiotherapy alone. Radiation therapy

alone (6000–8000 rads) can be offered to inoperable patients, in patients whose medical conditions do not warrant surgery or to patients who do not desire surgical intervention [11]. The majority of authors agree on performing bilateral neck dissections at the time of resection of the primary, even in stages I and II, due to the high probability of occult cervical metastases [12, 13].

Aim

Oropharyngeal anterior wall SCC localized at the tongue base has, in general, a poor prognosis. Major problems might be related to treatment options. It is very important to recognize which patients will benefit from treatment with curative intent and which treatment method to use. We have selected, over a period of 10 years, 37 previously untreated patients diagnosed with tongue base cancer and employed a transhyoid resection of the base of the tongue, with or without epiglottectomy and a horizontal supraglottic laryngectomy accompanied in all the cases with bilateral neck dissections. After surgery,

all patients underwent postoperative radiotherapy. Our study aim is to evaluate the patient survival, preservation of swallowing and speech, tumor exposure and cosmetic aspect related to the transhyoid resection of the tumor (a less frequent approach) followed by the radiotherapy.

Patients, Materials and Methods

A retrospective study was carried out from January 2001 to December 2010 and included 37 previously untreated patients diagnosed with tongue base cancer. None of the patients presented with distant metastases. All the patients were biopsied, the specimens being fixed in 4% (v/v) buffered formalin and sent to the Service of Pathology for histopathological (HP) diagnosis. In the study were enrolled only the patients with microscopic features on biopsies consistent of SCC.

For the classical HP study, there was used the Hematoxylin–Eosin (HE) staining, and for the immunohistochemical (IHC) study, there were used the following antibodies: anti-HPV (monoclonal mouse anti-human papillomavirus, clone K1H8, 1:100 dilution, Dako); anti-Ki67 (monoclonal mouse anti-human Ki67, clone MIB-1, 1:50 dilution, Dako); anti-p53 (monoclonal mouse anti-human p53 protein, clone DO-7, 1:100 dilution, Dako). The chromogen used for IHC reactions was 3,3'-diaminobenzidine (DAB) (Dako), the positive reactions being highlighted by the onset of a brown color.

The patients were staged following the TNM classification of the *International Union against Cancer* (6th edition) and

the *American Joint Committee on Cancer* (AJCC) [14].

Results

Of the 37 patients, 35 (94.59%) were males and two (5.41%) were females. Ages ranged from 41 to 70 years old, with the mean age of 61 years old. All of the patients were habitual alcohol drinkers and smokers.

The onset symptoms and signs were nonspecific: dysphagia, odynophagia, referred otalgia or the presence of a neck mass.

All patients were carefully evaluated prior to surgery. The decision to opt for surgical treatment was based on biopsy, preoperative imaging studies (magnetic resonance imaging – MRI), clinical evaluation marking the extent of the tumor prior to surgery and the presence of normal pulmonary function. Of the 37 patients, two (5.4%) were staged II, seven (18.91%) were staged III, 24 (64.86%) patients were staged IVA and four (10.81%) patients were staged IVB. A biopsy was performed in each case.

The patient's clinicopathological data are presented in Table 1.

A transhyoid resection of the base of the tongue was performed in 23 (62.17%) of cases. Additionally, in five (13.51%) cases, we performed epiglottectomy (Figures 1 and 2) and in nine (24.32%) cases, horizontal supraglottic laryngectomy. In all the cases, we performed bilateral neck dissections; 27 (72.97%) of these were functional dissections and 10 (27.03%) were radical dissections. All patients underwent frozen section evaluation in order to obtain clear margins.

Table 1 – Patients' clinicopathological data

| pT | No. of cases | N0 | N1 | N2a | N2b | N2c | N3 | Stage II | Stage III | Stage IVA | Stage IVB | G1 | G2 | G3 |
|-------|--------------|----|----|-----|-----|-----|----|----------|-----------|-----------|-----------|----|----|----|
| T2 | 2 | 2 | – | – | – | – | – | 2 | – | – | – | 2 | – | – |
| T3 | 24 | 3 | 4 | 9 | 7 | – | – | – | 7 | 16 | – | 6 | 17 | 1 |
| T4a | 7 | – | 3 | 2 | 2 | 1 | – | – | – | 8 | – | 1 | 4 | 2 |
| T4b | 4 | – | – | – | – | 2 | 2 | – | – | – | 4 | – | – | 4 |
| Total | 37 | 5 | 7 | 11 | 9 | 3 | 2 | 2 | 7 | 24 | 4 | 9 | 21 | 7 |

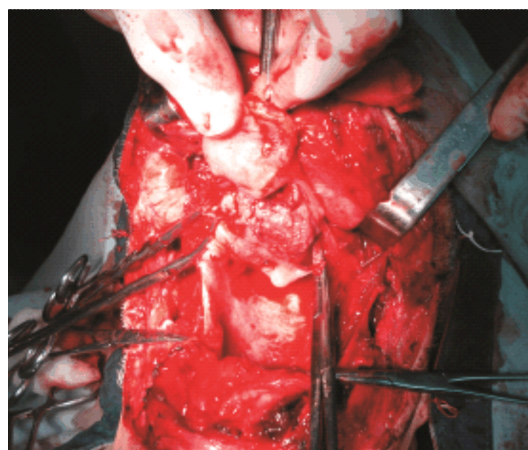


Figure 1 – Transhyoid resection of the base of the tongue with epiglottectomy.

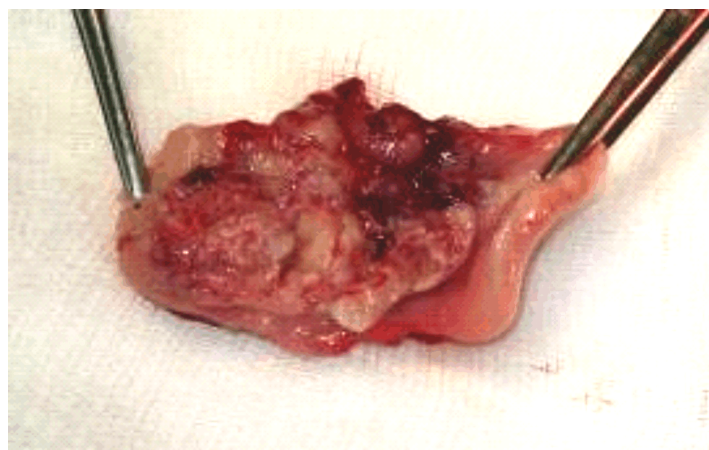


Figure 2 – L.D., 57-year-old patient: T3N0M0 specimen, tongue base and epiglottic tumor.

The median follow-up period was 58 months (range 54–68 months). All patients had clear margins at paraffin HP examination, revealing SCC.

The HP and IHC examination highlighted extremely variable aspects of the tumors. The tumoral cells presented an emphasized pleomorphism, being identified cells

with variable forms and sizes, with the loss of polarity and the increase of the nucleo-cytoplasmic ratio. The nuclei were mostly round, hypochromic, with 2–4 nucleoli, with loose chromatin, being also highlighted ovalary fusiform or monstrous nuclei, with dense chromatin, with uneven margins. There were also highlighted polykaryotic cells,

as well as mitosis cells. The cytoplasm was uneven, from a hypochromic aspect to intensely acidophilic aspects (Figure 3a). From the tumoral grading point of view, most of cases (21, representing 56.76%) were considered as moderately differentiated SCCs (Figure 3b), nine (24.32%) cases were considered as well-differentiated SCCs, and seven (18.92%) cases were poorly differentiated carcinomas (Figure 3c).

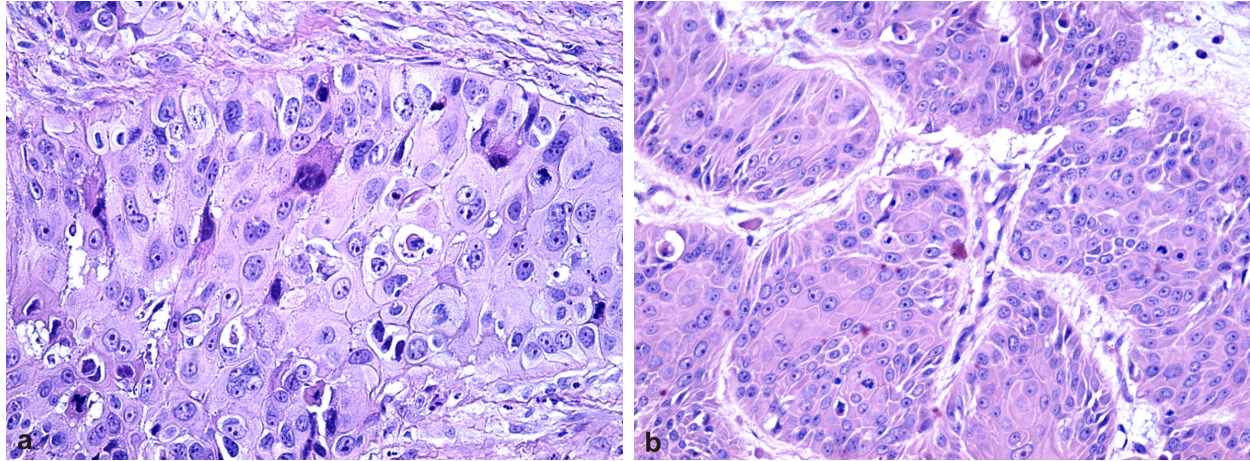


Figure 3 – (a) Microscopic image of a moderately differentiated SCC with emphasized cellular pleomorphism; (b) Moderately differentiated SCC (G2) formed of tumoral cell islands with a tendency for synthesis of keratotic pearls; (c) Poorly differentiated SCC (G3). HE staining: (a) $\times 400$; (b and c) $\times 200$. HE: Hematoxylin–Eosin; SCC: Squamous cell carcinoma.

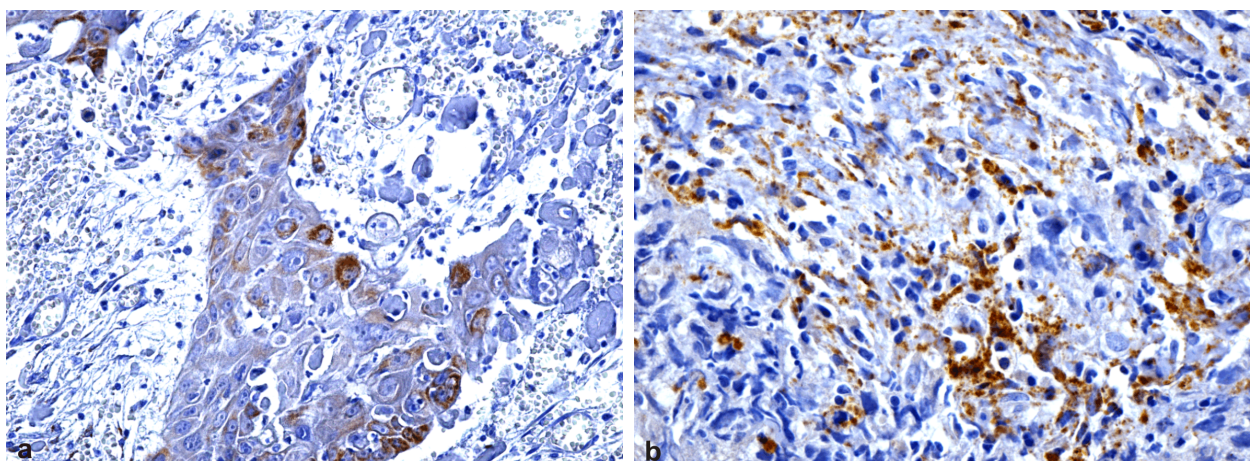


Figure 4 – (a) Moderately differentiated SCC with a poor and uneven reaction to anti-HPV antibody; (b) Poorly differentiated SCC with a moderate reaction to anti-HPV antibody. Anti-HPV antibody immunostaining, $\times 200$. SCC: Squamous cell carcinoma; HPV: Human papillomavirus.

The IHC evaluation of the Ki67 tumoral proliferation index was intense in all the cases included in the study, but it was positive only in the basal and suprabasal layers of well and moderately differentiated carcinomas

The tumoral stroma presented various aspects, being identified areas of loose, hemorrhagic or desmoplastic aspect. The IHC study highlighted a positive reaction for HPV in 16 (43.24%) patients, still it was poor and unevenly positive in well and moderately differentiated carcinomas, and more intense in poorly differentiated carcinomas (Figure 4, a and b).

(Figure 5a) and intense and uneven in poorly differentiated carcinomas (Figure 5b).

The IHC reaction to the anti-p53 antibody was positive in 32 (86.48%) patients. Also, to this antibody there was

observed an intense reaction of the nuclei in the basal and suprabasal layers in well-differentiated carcinomas (Figure 6a) and a very intense reaction in the nuclei of the poorly differentiated tumors (Figure 6b).

A primary closure was achieved in all patients. A tracheostomy was performed in all of the patients and was maintained until after the radiotherapy was completed. All patients underwent postoperative radiotherapy. Decannulation was possible in 33 (89.18%) patients. No patient required a gastro/jejunostomy. No major post-operative complications were encountered. Deglutition

was present in all the patients after the nasogastric tube was removed at two weeks postoperatively. The Kaplan–Meier survival analysis overall three-year and five-year survival rates were 81.1% and 75.67%, respectively. The tumor specific three-year and five-year survival rates were: pT2 100%, pT3 87.5%, pT4a 71.42% and 57.14%, and pT4b 50% and 25%, respectively. The stage specific three-year and five-year survival rates were: stage II 100%, stage III 85.71%, stage IVA 83.33% and 79.16%, and stage IVB 50% and 25%, respectively (Table 2).

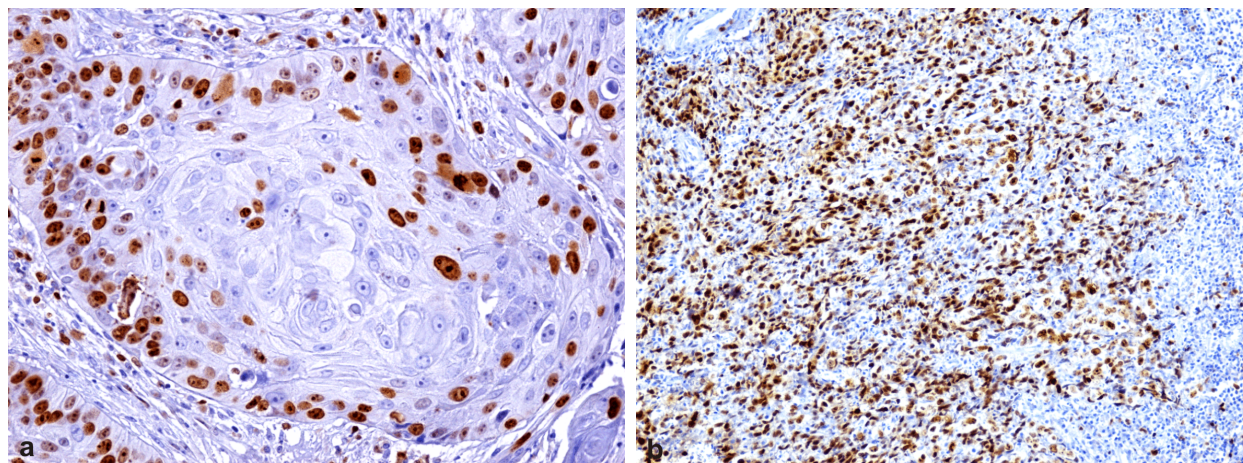


Figure 5 – (a) Well-differentiated SCC with an intense positive reaction to Ki67 in the nuclei of the cells of basal and suprabasal layers of the tumor; (b) Poorly differentiated SCC with intense reaction of the tumor cells to Ki67. Anti-Ki67 antibody immunostaining: (a) $\times 200$; (b) $\times 100$. SCC: Squamous cell carcinoma.

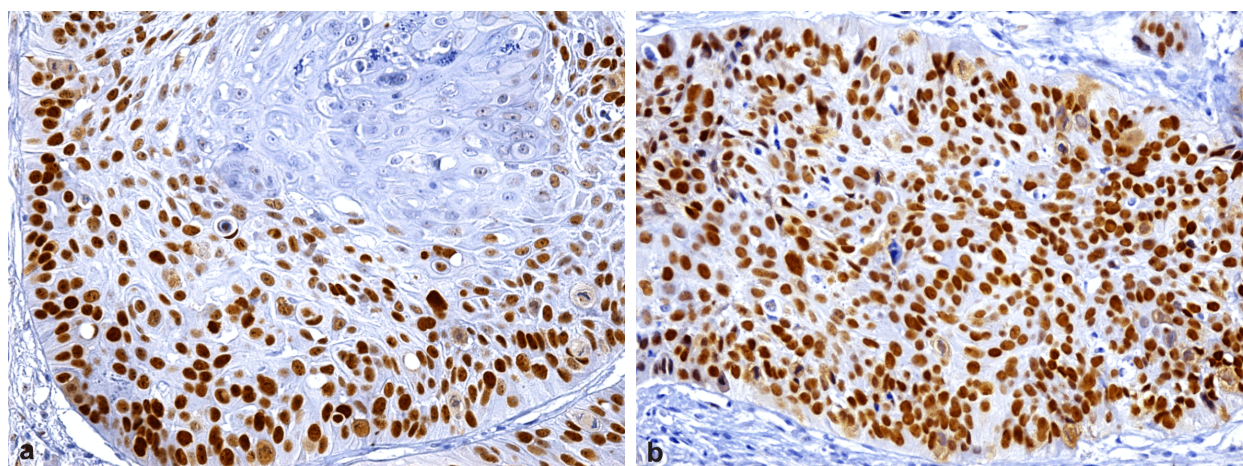


Figure 6 – (a) Intense immunohistochemical reaction of the nuclei in the basal and suprabasal layers to p53, in well-differentiated SCC; (b) Poorly differentiated SCC with intense reaction to p53. Anti-p53 antibody immunostaining, $\times 200$. SCC: Squamous cell carcinoma.

Table 2 – Survival rates according to tumor pT and stage

| pT | Three years follow-up | Five years follow-up |
|-------|-----------------------|----------------------|
| T2 | 100% | 100% |
| T3 | 87.5% | 87.5% |
| T4a | 71.42% | 57.14% |
| T4b | 50% | 25% |
| Stage | Three years follow-up | Five years follow-up |
| II | 100% | 100% |
| III | 85.71% | 85.71% |
| IVA | 83.33% | 79.16% |
| IVB | 50% | 25% |

Discussions

Head and neck cancers comprise a heterogeneous group of tumors that affect oral cavity, the pharynx and larynx, known as the sixth most frequent cancer world widely, with a yearly incidence estimated over 686 000 cases and about 300 000 deaths [14–18]. Approximately 85–90% of the head and neck cancers are represented by squamous carcinomas [19]. There is estimated that in the following years the number of head and neck cancers will increase, in 2020 there will be recorded about 833 000 new cases, of which 151 000 in Europe, thus representing 4–5% of the total of new cancer cases [20, 21].

Oropharyngeal cancer with squamous cells is the fourth

most common cancer all over the world, representing more than 90% of oral cancer [15, 22]. In the US, every year, there are about 49 670 new cases, which represents about 2.9% of all new cancer cases and about 9700 related deaths [23].

In the etiology of oropharyngeal cancer, there are involved two main risk factors, namely smoking and alcohol intake, a reason for which this type of cancer appears more frequently in elderly persons [24, 25]. It is considered that 80% of head and neck cancers are caused by smoking and alcohol intake [25]. In the last 20 years, alongside with the reduction of smoking, there was also expected a decrease of oropharyngeal cancer. Unexpectedly, numerous studies showed that, worldwide, there was recorded a significant increase of oropharyngeal cancers due to the HPV infection [26–29]. Numerous cellular, IHC and molecular studies showed significant increases of human immunodeficiency virus (HIV)-positive oropharyngeal cases, starting with the '80s, especially in Western countries [30, 31]. These tumors mainly affect men less than 60 years old.

In our study, of the 37 patients, 35 (94.59%) were males, alcohol intakers and chronic smokers, therefore exposed to carcinogenic risk factors. The average age in our study group was 61 years old. Of the 37 patients, most of them – 28 (75.67%) – presented to the doctor in late stages of the disease: 24 patients in stage IVA and four patients in stage IVB. These clinical data show that oropharyngeal tumors present a low symptomatology, and that our patients did not have any medical knowledge for identifying tumors in an early stage.

The HP and IHC study showed that all tumors in our study group were SCCs, more or less differentiated. Regarding the IHC study to anti-HPV, we observed that this is correlated with the tumor differentiation degree, being more intense in the poorly differentiated carcinomas.

Due to the fact that in the oropharynx there were also identified other types of tumors (sarcomas, lymphomas, etc.) [32–37] and the clinical symptoms are non-specific, we also state, like other authors [38–42], that the HP, IHC and molecular medicine studies are essential in establishing the positive and differential diagnosis of oropharynx tumors, in establishing the treatment conduct and prognosis estimation.

Treatment of SCC of the base of the tongue has evolved, but the overall survival rate has not improved very much. The majority of the patients are usually without specific symptoms until relatively late stage.

The main risk factors for the development of oropharyngeal cancer are tobacco and alcohol abuse [43]. The presence of HPV has been identified in many patients, heaving a better prognosis, especially if they are not smokers. The HPV-positive patients follow a different oncogenic pathway [44, 45].

The asymptomatic progression, the rich lymphatic drainage and the difficulty in exploring this area are some of the reasons why most of these cancers are diagnosed at stage IV (>70% of cases) [46].

Stages III and IV have been associated with a poor prognosis. Some authors [47] demonstrated that survivorship from tongue base SCC is governed by the size and depth of the primary rather than the nodal stage and the regional metastases do not significantly influence survival.

Surgical management ensures a local control in early stage cancer between 74% and 100%, while in advanced

stage the local control is between 22% and 27% [11, 47–49]. Obtaining clear resection margins is essential to optimize local control and hence patient survival. Frozen sections should always be employed if available. Byers *et al.* reported that the inability of the surgeon to obtain clear margins by frozen section resulted in a very high incidence of local recurrence and death. Frozen section for tongue base SCC is therefore of great benefit, not only to obtain clear margins, but also to avoid overly aggressive surgery achieving organ preservation and minimizing functional deficits [50, 51].

When tumors are limited to the base of tongue regardless of nodal status, a mandible-sparing approach, such as transhyoid, appears to decrease morbidity and enhance survival when combined with adjuvant therapy [11].

The combination of resection of the primary cancer and neck dissection with adjuvant postoperative radiation therapy has been shown to increase the degree of local control compared with the separate application of either of these two methods [49, 51, 52]. Zhen *et al.* [47] working with data obtained from the *U.S. National Cancer Database*, reported that patients with tongue base SCC in advanced stages had a better outcome when the therapeutic approaches combined surgery with postoperative radiation therapy. The disease-specific survival at five years in 851 patients with advanced cancer of the pharynx (stages III–IV) treated with radiotherapy was 24.3% and 25.6% for 651 patients treated with chemoradiotherapy. Disease-specific survival at five years in our patients was similar, *e.g.*, 30% for patients in stages III–IV (44% in stage III and 25% in stage IV). In our study, the five-year survival rates were 75.67% (stage II 100%, stage III 85.71%, stage IVA 79.16% and stage IVB 25%).

Functional outcome after surgery is significantly worse with increasing stage of the primary tumor and more radical resection [53]. The patients who underwent epiglottectomy or supraglottic laryngectomy and tongue base tumor removal presented an additional degree of swallowing difficulty.

Some authors shown that the patient survival is depending more on lymph node metastases than on the stage of the primary [54, 55].

Nasri *et al.* [9] compared the patients who were treated with the transhyoid approach with those who were treated with composite resection or mandibulotomy. There were no significant differences between the two groups regarding disease-free survival, status of surgical margins, recurrences, or operative complications. However, they did observe significantly superior postoperative speech and swallowing function in the transhyoid group.

Many centers have successfully broadened the indication of primary radiotherapy to include early and advanced cancer of the base of the tongue [52, 56, 57]. These groups have reported T1 and T2 five-year survival rates of 73% to 96%, respectively. Proponents of primary radiation therapy argue that survival outcome and tumor control are comparable to those of surgical resection, while the morbidity associated with primary radiation is significantly less.

Shen *et al.* [58] analyzed 24 cases of oropharynx anterior wall carcinoma operated by transhyoid approach, with preoperative radiotherapy (five cases) and postoperative radiotherapy (16 cases). Kaplan–Meier survival analysis showed the three-year overall survival rate was 72.6%.

In the present study, we report high overall five-year survival rates in cases oropharyngeal anterior wall cancer with the use of primary surgical resection *via* a transhyoid approach, neck dissection, and postoperative radiation therapy. By maintaining swallowing function and a good rate of voice preservation, the patient's quality of life has been improved.

Conclusions

The advantages of the transhyoid approach to tongue base SCC in conjunction with neck dissection and postoperative radiation therapy include an improved long-term patient survival, preservation of swallowing and speech, tumor exposure and minimal cosmetic deformity. Surgical treatment allows the swallowing function to be maintained in most patients, in addition to good rates of voice preservation.

Conflict of interests

The authors declare that they have no conflict of interests.

Acknowledgments

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Author contribution

Nicolae Constantin Balica and Mărioara Poenaru are article's first authors, with equal contribution and credit.

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Corresponding authors

Vasile Ciprian Iovan, Associate Professor, MD, PhD, Department of Preclinical Sciences, Faculty of Medicine and Pharmacy, University of Oradea, 1 December Square, 410073 Oradea, Bihor County, Romania; Phone +40744–660 376, e-mail: dr.iovan@biostandard.ro

Horia Tudor Stanca, Associate Professor, MD, PhD, Department of Ophthalmology, “Carol Davila” University of Medicine and Pharmacy, 37 Dionisie Lupu Street, Sector 2, 020021 Bucharest, Romania; Phone +40746–288 006, e-mail: balica@umft.ro