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ORIGINAL ARTICLE

Prognostic factors in patients with advanced hypopharyngeal squamous cell carcinoma treated with concurrent chemoradiotherapy

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Summary

Purpose: *The aim of this study was to evaluate different prognostic factors affecting response to treatment, locoregional control (LRC) and survival in patients with advanced hypopharyngeal squamous cell carcinoma (HPSCC).*

Methods: *A retrospective analysis of 41 patients with advanced HPSCC who had undergone definitive concurrent chemoradiation treatment between January 2006 and October 2009 was performed.*

Results: *Complete composite response (CCR) was achieved in 27 patients (65.9%). Significant prognostic factors for CCR were T stage, technique of radiation, and gross tumor volume (GTV). Unfavorable prognostic factors for CCR in multivariate analysis were higher T stage and radiation technique with electron-photon fields. The 2-year LRC rate was 51.3%. The 2-year disease-free survival (DFS) and overall survival (OS) rates were 29.3% and 32.8%, respectively. Significant prognostic factors for LRC, DFS, and OS in univariate analysis were T stage, overall stage, and GTV. OS was also significantly influenced by N stage. In multivariate analysis T stage was found to be the only significant independent prognostic factor for LRC (p=0.003), DFS (p=0.01), and OS (p=0.005).*

Conclusion: *Revealing the significant prognostic value of T stage for CCR, LRC, DFS, and OS in the multivariate analysis, we consider that the implementation of intensity-modulated radiotherapy (IMRT) and the adoption of intensified concurrent chemoradiotherapy (CCRT), sequential therapy, and targeted therapy should be strongly advocated in order to improve outcome in patients with locally advanced HPSCC.*

Key words: concurrent chemoradiotherapy, hypopharyngeal carcinoma, prognostic factor, survival

Introduction

HPSCCs arise from the mucosa of one of the three anatomical subsites of the hypopharynx i.e. the pyriform sinus, the posterior pharyngeal wall and the postcricoid area. HPSCCs are characterized by advanced disease at presentation, mainly because the hypopharynx, laying outside the glottis and being a silent area, allows tumors to grow for a substantial period of time before symptoms occur [1,2]. HPSCC is a relatively rare neoplasm and has one of the most unfavorable prognoses among all cancers of the upper aerodigestive tract [3,4]. The reasons for the remarkably poor prognosis of HPSCCs is their aggressive behavior represented by strong tendency for submucosal spread, early occurrence of nodal metastatic involvement, propensity for direct invasion of adjacent structures in the neck and high incidence of distant metastases [1,5,6].

More than 50% of patients with HPSCC have clinically positive neck nodes at the time of presentation [7-9]. Patients with HPSCC are at higher risk of distant metastases compared with the patients with other head and neck cancers [10,11]. The 5-year survival rate for advanced stages of HPSCC is low and varies between 20 and 60% [2,5,12-14].

In the 1970s and 1980s, total laryngectomy and pharyngectomy, combined with neck lymph node dissection and followed by adjuvant radiotherapy was an often recommended form of treatment in patients with advanced HPSCC [15-17]. In the 1980s, the demon-

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strated efficacy of induction chemotherapy in patients with advanced head and neck cancer with regard to larynx preservation suggested that surgery could be omitted in responding patients without compromising survival [18,19].

The results of two large randomized trials showed that induction chemotherapy allowed conservation of the larynx in nearly two-thirds of patients with advanced laryngeal and hypopharyngeal carcinomas [20,21]. However, induction chemotherapy as an organ preservation approach was characterized with higher incidence of locoregional failure and its lack of survival benefit was confirmed in the meta-analysis of Pignon et al. [22]. Another treatment option for advanced HPSCC was CCRT, but notably, in the large number of randomized trials investigating this combined therapy, HPSCCs were represented with small groups only, without specific reports of treatment results [23-27].

Although there is no level one evidence on best treatment [28] or agreement on optimal therapy for advanced HPSCC [29], further efforts should be made in the decision-making process including consideration of stage, site, age, performance status, and personal preferences [30].

The aim of this study was to evaluate prognostic factors for LRC, DFS and OS in a series of patients with locally and/or regionally advanced HPSCC treated with CCRT. Factors potentially influencing response to this combined treatment approach were also analyzed.

Methods

Between January 2006 and October 2009, 41 patients with advanced stage III-IV HPSCC were treated with definitive CCRT at the University Clinic of Radiotherapy and Oncology in Skopje. Patients were staged according to the 2002 criteria of the American Joint Committee on Cancer [31]. The patient population consisted of 33 men and 8 women. The median age was 52 years (range 29-70). Eastern Cooperative Oncology Group (ECOG) performance status 0 at presentation was recorded in 26 patients (63.4%). The primary subsite was the pyriform sinus in 32 patients (78.0%), posterior pharyngeal wall in 5 patients (12.2%), and postcricoid area in 4 patients (9.8%). Patients' distribution by stage is shown in Table 1. High levels of nodal involvement were present in 19 patients (46.3%). Histological differentiation was found in the following decreasing order: moderate (n=17), poor (n=16), and good (n=6). In 2 patients the degree of histological differentiation was unknown. Most patients (46.3%) had GTV between 81 and 160 cm^3. GTV ≤ 80 cm^3 was present in 13 patients (31.7%), and GTV > 160 cm^3 was recorded in 9 patients (22.0%).

The first assessment of tumor response was performed 3 months after completion of chemoradiotherapy by physical examination, fiberoptic endoscopy and computed tomography (CT) and/or magnetic resonance imaging (MRI) of the hypopharyngeal and cervical region. CCR was defined as a complete disappearance of clinical and radiological evidence of disease at the primary site with a complete recovery of larynx mobility and a complete disappearance of the enlarged lymph nodes. Patients were followed at regular intervals (every month during the first year, every other month in the second year, and every 6 months thereafter). Median patients' follow-up was 13 months (range 7-36). LRC was defined as absence of locoregional (primary tumor and regional lymph nodes) progression based on physical exam, endoscopy, or CT scans after complete response at the end of CCRT. Patients who did not achieve CCR after the planned chemoradiotherapy were assigned as failures on the day treatment start. Patients who did achieve CCR were considered as failures on the study day when a recurrence at the primary site and/or a nodal recurrence were first reported. DFS was measured from the start of treatment to the date of the occurrence of local, regional or distant relapse, or the date of the last patient's visit. In case of persistent local and/or regional disease, DFS was calculated from the date of commencement of treatment to the date of the first follow-up. OS was calculated from the start of treatment until death, or to the most recent follow-up date.

Table 1. Patient distribution by stage (n = 41)

Stage	*Number of patients (%)*
T stage	
T3	16 (39.0)
T4	25 (61.0)
N stage	
N0	17 (41.5)
N1	6 (14.6)
N2	12 (29.3)
N3	6 (14.6)
TNM stage	
III	11 (26.8)
IV	30 (73.2)

Treatment

Radiotherapy was performed on a linear accelerator Varian 23EX in accordance with three-dimensional conformal radiotherapy plan. Photons with beam qualities of 6 MV and 15 MV and electrons with energies 9-16 MeV were used. The dosimetric calculation was performed using Eclipse treatment planning system. Patients were immobilized in supine position with a thermoplastic head and neck mask. The CT scanning was made for each patient in the treatment position with slice thickness of 0.5 cm. Target volumes and organs at risk were delineated on the CT data set by the radiation oncologist. The GTV70 was defined as the extension of the primary hypopharyngeal tumor and the gross nodal disease if revealed on imaging studies and/or physical examination. The clinical target volume (CTV50) was delineated following recommendations of Gregoire et al. [32,33] and included bilateral nodal levels for elective irradiation depending on the tumor and nodal stage. This volume also encompassed the gross primary tumor volume plus a margin of 1.0-2.0 cm for the potential microscopic extension of the disease. The planning target volumes were PTV70 and PTV50. The PTV50 provided a margin of 0.5 cm around CTV50. The PTV70 was obtained by adding a margin of 0.5 cm around GTV70. Concurrent chemotherapy consisted of weekly cisplatin (30 mg/m^2) starting on the first day of radiotherapy.

Radiation techniques

Two different radiation techniques were applied. The first

technique used in 14 patients (34.1%) was the classical technique of conventional mixed electron-photon fields. The field set-up for PTV50 consisted of two opposing lateral semi-fields including nodal regions and irradiating the spinal cord up to 46 Gy. The two lateral fields were reduced from the dorsal side in order to exclude the spinal cord, and two lateral electron fields matched to the photon fields were used to deliver the remaining dose to the shielded dorsal part of the PTV50. Separate anterior and posterior semi-fields were used for the lower part of the neck. For the posterior semi-field we used 15 MV photons, and for the other fields, 6 MV photons. Arrangements with 2 to 4 photon fields with beam quality 6MV in lateral or oblique directions with occasional use of electron fields with the spinal cord being completely out of fields were used for the coverage of PTV70.

The second technique, named "oblique photon fields" technique, was introduced in order to eliminate the use of electron fields, because of the inconveniences that occur when matching photon and electron fields (the cold spots at the surface or the hot spots at greater depth). This technique was used in 27 patients (65.9%). The field set-up for PTV50 consisted of 4 oblique isocentric photon fields of beam quality 6MV. Two of the fields, the anterior ones, were positioned at gantry angles 300˚ and 60˚ and covered the whole PTV50. The posterior oblique fields were at gantry angles between 210˚ and 220˚ from the right side of the patient, and between 135˚ and 145˚ from the left side. The spinal cord was shielded in these fields, so they covered only part of the PTV50. Field arrangements for the coverage of PTV70 were identical with those used in the first technique. In both techniques the prescribed doses were 50 Gy and 70 Gy for the PTV50 and PTV70, respectively. The prescribed dose per fraction was 2 Gy. Treatment was delivered once daily, 5 fractions per week. The maximum spinal cord dose was 50 Gy.

Analysed potential prognostic factors

The following potential prognostic factors were investigated in relation to CCR: gender, age, ECOG performance status, subsite of the primary hypopharyngeal tumor, T stage, N stage, levels of nodal involvement, histological differentiation, technique of radiation, and GTV. The potential prognostic factors investigated in relation to LRC, DFS and OS were: gender (male vs. female), age (< 50 vs. 50-60 vs. > 60 years), ECOG performance status (0 vs. 1), subsite of the primary tumor (pyriform sinus vs. posterior pharyngeal wall vs. postcricoid area), T stage (T3 vs. T4), N stage (N0 vs. N1 vs. N2 vs. N3), overall stage (III vs. IV), levels of nodal involvement (none vs high levels [I-III] vs. low levels [IV, V]), histological differentiation (good vs. moderate vs. poor), technique of radiation (electron-photon fields vs. oblique photon fields), and GTV (< 80 vs. 81-160 vs. > 160 cm^3).

Statistical analysis

Statistical analysis of potential prognostic factors for CCR involved logistic regression run on the binary outcome of presence or absence of CCR. Factors with $p<0.05$ were considered to be statistically significant and were subjected to logistic forward stepwise regression for the multivariate model for association with CCR. Statistical analysis of potential prognostic factors for LRC, DFS and OS involved univariate and multivariate analysis. LRC, DFS and OS were calculated for each potential prognostic factor with the Kaplan-Meier method [34] and measured from the first day of CCRT. The significance of the relation of certain factors with LRC, DFS and OS was tested by log-rank test and p value. Statistical significance was defined as p-value < 0.05. Potential prognostic factors found to be significant in the univariate analysis by log-rank test and p-value were evaluated in a multivariate analysis using the Cox's regression model.

Results

CCR was achieved in 27 patients (65.9%). Partial composite response was registered in 14 patients (34.1%). Distant metastases were the most frequent initial failure occurring in 7 patients and accounting for 46.7% of 15 cases who manifested disease relapse. Recurrence at the primary site developed in 3 patients, 1 patient developed regional recurrence, and 4 patients developed both.

The 2-year LRC rate was 51.3%. The 2-year DFS and OS survival rates were 29.3 and 32.8%, respectively. Of the 41 patients 19 (46.3%) remained alive at the time of analysis, 21 (51.2%) died of disease-related causes, and the cause of death was unknown in 1 patient (2.5%).

Significant prognostic factors in univariate analysis that influenced CCR were the stage of the primary tumor (T stage) ($p=0.008$), the technique of radiation ($p=0.030$), and the GTV ($p=0.018$) (Table 2). Thus, patients with primary tumor classified as T4 were more likely to be without CCR following treatment. The absence of CCR was more likely to occur in patients treated with electron-photon fields and in those with tumor volume > 160 cm^3. A logistic forward stepwise regression analysis confirmed the significance of T stage and technique of radiation (Table 3).

The results of the univariate analysis with respect to LRC, DFS and OS are summarized in Table 4. Univariate analysis revealed T stage, overall stage and GTV as factors significantly associated with LRC, DFS and OS. N stage was found to be a factor that significantly influenced OS.

Patients with primary lesions classified as stage T4 had worse prognosis related to LRC, DFS and OS compared with the group of patients with T3 primary tumors ($p<0.0001$, $p=0.0027$ and $p=0.0012$, respectively). Kaplan-Meier curves of LRC in relation with T stage are shown in Figure 1. Overall stage IV had a significant negative influence on LRC, DFS and OS compared with overall stage III ($p=0.0012$, $p=0.0037$ and $p=0.0022$, respectively). Kaplan-Meier curves of DFS related to the overall stage are shown in Figure 2. A significant correlation was found between the tumor volume stratified into volume classes and LRC, DFS and OS ($p=0.0364$, $p=0.0454$ and $p=0.0284$, respectively). The most significant negative influence on LRC, DFS and OS had the presence of GTV > 160 cm^3. Kaplan-Meier curves of OS in relation with GTV are shown in Figure 3. Patients with nodal involvement had signifi-

Table 2. Univariate analysis of factors influencing response to treatment*

Factors	*Total number of patients*	*Number of patients (%)*		*p-value*
		With CCR	*Without CCR*	
Gender				
Male	33	22 (81.5)	11 (78.6)	
Female	8	5 (18.5)	3 (21.4)	0.824
Age (years)				
< 50	11	7 (25.9)	4 (28.6)	
50-60	22	15 (55.6)	7 (50.0)	
> 60	8	5 (18.5)	3 (21.4)	0.943
Performance status (ECOG)				
0	26	18 (66.7)	8 (57.1)	
1	15	9 (33.3)	6 (42.9)	0.549
Subsite				
Pyriform sinus	32	21 (77.8)	11 (78.6)	
Posterior pharyngeal wall	5	3 (11.1)	2 (14.3)	
Postcricoid area	4	3 (11.1)	1 (7.1)	0.895
T stage				
T3	16	16 (59.3)	0 (0)	
T4	25	11 (40.7)	14 (100.0)	0.008
N stage				
N0	17	13 (48.1)	4 (28.6)	
N+	24	14 (51.9)	10 (71.4)	0.233
Levels of nodal involvement				
None	17	13 (48.1)	4 (28.6)	
High	19	12 (44.4)	7 (50.0)	
Low	5	2 (7.4)	3 (21.4)	0.326
Histopathological grade				
Good	6	6 (22.2)	0 (0)	
Moderate	17	13 (48.1)	4 (28.6)	
Poor	16	8 (29.6)	8 (57.1)	
Unknown	2	0 (0)	2 (14.3)	0.300
Technique of radiation				
Electron-photon fields	14	6 (22.2)	8 (57.1)	
Oblique photon fields	27	21 (77.8)	6 (42.9)	0.030
GTV (cm^3)				
< 80	13	11 (40.7)	2 (14.3)	
81-160	19	14 (51.9)	5 (35.7)	
> 160	9	2 (7.4)	7 (50.0)	0.018

CCR: complete composite response, ECOG: Eastern Cooperative Oncology Group, GTV: gross tumor volume. *Because of rounding, not all percentages total 100

Table 3. Multivariate model for association with complete composite response

Factors	*Odds ratio*	*95% CI*	*p-value*
T stage			
T4 vs. T3	61.92	2.88 to 1333.15	0.008
Technique of radiation			
Electron-photon fields vs. oblique photon fields	0.04	0.01 to 0.66	0.024
GTV (cm^3)			
81-160 vs. < 80	0.56	0.06 to 5.45	0.613
> 160 vs. < 80	24.97	0.86 to 726.13	0.061

CI: confidence interval, GTV: gross tumor volume

cantly worse prognosis with respect to OS compared with patients without evidence of nodal disease in the neck (N0) (p=0.0037). The most unfavorable influence on OS had metastasis in lymph node(s) > 6 cm in the greatest dimension (N3).

The results of multivariate Cox regression analysis indicated T stage as the only significant independent prognostic factor determining LRC (T4 vs. T3: p=0.003, HR=9.42, 95% CI 2.17-40.79), DFS (T4 vs. T3: p=0.010, HR=3.49, 95% CI 1.35-9.0), and OS (T4 vs. T3: p=0.005, HR=5.89, 95% CI 1.71-20.36) (Table 5).

Table 4. Univariate analysis correlating prognostic factors with locoregional control, disease free survival and overall survival

Prognostic factors	*Number of patients*	*2-year LRC (%)*	*p-value for LRC*	*2-year DFS (%)*	*p-value for DFS*	*2-year OS (%)*	*p-value for OS*
Gender							
Male	33	68.8		30.2		36.3	
Female	8	30.2	0.0928	22.7	0.8080	0	0.9759
Age (years)							
< 50	11	49.3		39.3		23.8	
50-60	22	55.7		31.8		36.3	
> 60	8	62.7	0.6713	0	0.9279	34.2	0.8952
Performance status (ECOG)							
0	26	42.2		26.3		39.2	
1	15	31.3	0.3048	45.7	0.9870	17.8	0.2051
Subsite							
Pyriform sinus	32	47.8		28.8		36.8	
Posterior pharyngeal wall	5	39.8		60.2		49.7	
Postcricoid area	4	0	0.3138	0	0.7729	0	0.8871
T stage							
T3	16	80.3		48.3		64.2	
T4	25	14.8	< 0.0001	18.7	0.0027	15.7	0.0012
N stage							
N0	17	49.8		37.3		45.8	
N1	6	44.2		55.7		37.8	
N2	12	50.3		27.2		27.2	
N3	6	0	0.0797	0	0.0558	0	0.0037
TNM stage							
III	11	83.3		55.8		79.7	
IV	30	24.2	0.0012	21.7	0.0037	19.3	0.0022
Levels of nodal involvement							
None	17	49.8		37.3		45.8	
High	19	34.7		23.2		19.3	
Low	5	20.2	0.3460	40.3	0.6279	19.8	0.1678
Histopathological grade							
Good	6	61.7		62.2		49.7	
Moderate	17	42.3		18.8		37.2	
Poor	16	28.8		28.7		30.8	
Unknown	2	0	0.1298	0	0.1304	0	0.2698
Technique of radiation							
Electron-photon fields	14	28.3		21.3		28.3	
Oblique photon fields	27	45.2	0.1409	38.3	0.2318	36.3	0.5379
GTV (cm^3)							
≤ 80	13	68.3		47.8		49.7	
81-160	19	28.3		26.7		29.2	
>160	9	11.7	0.0364	11.2	0.0454	22.3	0.0284

LRC: locoregional control, DFS: disease-free survival, OS: overall survival, ECOG: Eastern Cooperative Oncology Group, GTV: gross tumor volume

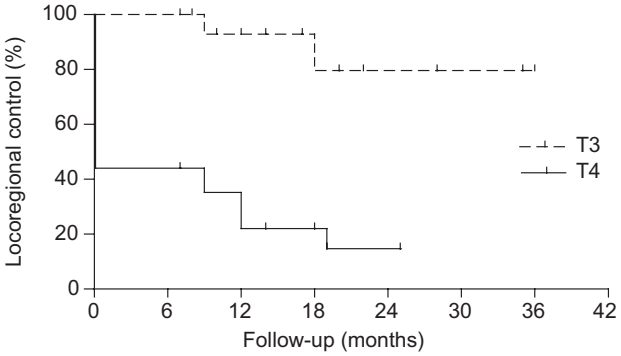

Figure 1. Kaplan-Meier locoregional control according to T stage. Log-rank test; chi square=16.95; p<0.0001.

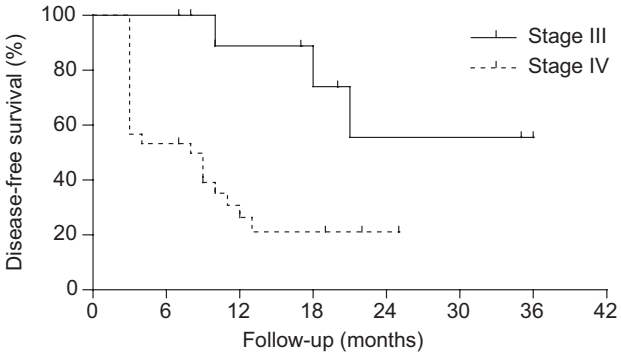

Figure 2. Kaplan-Meier disease-free survival according to overall stage. Log-rank test; chi square=8.43; p=0.0037.

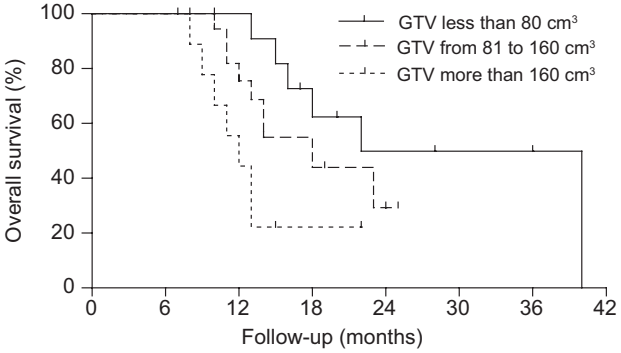

Figure 3. Kaplan-Meier overall survival according to the gross tumor volume (GTV) classes. Log-rank test; chi square=7.13; p=0.0284.

Discussion

The optimal treatment method for patients with stage III-IV HPSCC remains controversial [1,35-38]. Total laryngectomy, combined with neck lymph node dissection, is an often recommended treatment option in patients with stage III or IV lesions. CCRT as definite treatment for advanced head and neck cancers including those arising from the hypopharynx has been studied in the past 15 years. However, despite the specific characteristics and prognosis of HPSCC as one of the main tumor sites in head and neck cancer [39], it has been usually represented with only smaller subgroups in studies on CCRT with details of treatment being rarely specifically reported [28,40]. In the prospective randomized trial on 859 patients with advanced head and neck cancer including those having hypopharynx as a primary site, significant improvement in survival was obtained in groups treated either with CCRT or altered fractionation [41]. In a single institution randomized trial enrolling patients with stages III and IV squamous cell head and neck carcinoma including patients with HPSCC, CCRT led to significant improvement in the rates of local control, distant metastasis-free survival, and recurrence-free survival [42]. However, in the retrospective review with long-term follow-up studying radiotherapy and concurrent multiagent chemotherapy in 222 patients with locoregionally advanced head and neck cancer, Adelstein et al. [24] reported a significantly worse distant control in patients with hypopharyngeal primary sites. The results of the largest meta-analysis performed by the meta-analysis of chemotherapy on head and neck cancer (MACH-NC) Collaborative group [22] and the results of the update of this meta-analysis [43] confirmed the superiority of CCRT with 8% improvement in 5-year overall survival with an evident benefit when cisplatin was used in the combined approach. Highly significant improvement in overall survival with platinum-based CCRT has been also confirmed in the meta-analysis of Browman et al. [44]. Recently, the results of a comprehensive analysis of the MACH-NC database by tumor site including 2767 patients with HPSCC revealed that the chemotherapy benefit was higher for CCRT for all tumor sites, but the interaction test between chemotherapy timing and treatment effect was not significant for hypopharyngeal tumors with 5-year absolute overall survival benefit associated with the concomitant chemotherapy of 3.9% [39].

Table 5. Multivariate analysis of locoregional control, disease-free survival and overall survival

Prognostic factors	*HR*	*95% CI*	*p-value*
Locoregional control			
T stage			
T4 vs. T3	9.42	2.17-40.79	0.003
TNM stage			
IV vs. III	1.86	0.11-32.30	0.672
GTV (cm^3)			
81-160 vs. ≤ 80	1.04	0.31-3.50	0.946
>160 vs. ≤ 80	2.13	0.59-7.65	0.249
Disease-free survival			
T stage			
T4 vs. T3	3.49	1.35-9.0	0.010
TNM stage			
IV vs. III	1.84	0.32-10.72	0.499
GTV (cm^3)			
81-160 vs. ≤ 80	1.43	0.46-4.46	0.534
>160 vs. ≤ 80	2.41	0.67-8.59	0.176
Overall survival			
T stage			
T4 vs. T3	5.89	1.71-20.36	0.005
N stage			
N1 vs. N0	0.93	0.19-4.61	0.926
N2 vs. N0	1.48	0.45-4.92	0.522
N3 vs. N0	4.40	0.26-15.38	0.610
TNM stage			
IV vs. III	4.33	0.30-61.83	0.280
GTV (cm^3)			
81-160 vs. ≤ 80	1.43	0.49-4.89	0.539
>160 vs. ≤ 80	2.31	0.69-9.13	0.191

HR: hazard ratio, 95% CI: 95% confidence interval, GTV: gross tumor volume

CCRT as an adopted standard treatment approach for patients with locally advanced head and neck cancer has been also shown to allow organ preservation in almost two thirds of the patients without affecting survival [45]. Thus, CCRT, being a laryngeal preservation scheme, also represents an accepted therapeutic modality and is always suggested for patients with advanced HPSCC, who are anatomically unsuitable or medically unfit for surgery [35]. The potential of CCRT for organ preservation was confirmed in several studies, but the function of the larynx in these studies was not evaluated [4,24,39,40,46]. According to Brizel and Esclamado [47], successful tumor eradication by CCRT in patients with locally advanced hypopharyngeal carci-

noma could result in pharyngeal dysfunction, a nonfunctional larynx, and esophageal stricture. Carrara et al. [48] reported impaired laryngeal function after combined treatment with chemotherapy and radiotherapy in patients with advanced-stage laryngeal or hypopharyngeal cancer. In the study of Lee et al. [49], esophageal stricture formation was found in 21.0% of patients with hypopharyngeal cancer treated with CCRT. According to Hall et al. [29], although CCRT has become a standard of care for many head and neck cancers, the true effectiveness of the addition of chemotherapy to radiotherapy is impossible to be understood without knowing the baseline outcomes of radiotherapy vs. surgery in patients with advanced HPSCC.

Intensified radiotherapy regimens in combination with chemotherapy in advanced head and neck cancer including patients with hypopharyngeal cancer have been also explored in several randomized trials [50-54]. In the study of Akman et al. [55], accelerated concomitant boost radiotherapy with concurrent administration of cisplatin was shown as an intensive treatment regimen that can be given to a highly selected group of patients in the routine outpatient-based setting. Budach et al. [54] have shown that no efficacy benefit was revealed when altered fractionation in combination with chemotherapy was used in patients with advanced hypopharyngeal cancer.

Advances in tumor biology have offered new opportunities to develop specific molecular strategies that selectively increase the tumor response to radiation [45]. Based on the evidence of increased levels of epidermal growth factor receptor (EGFR) expression in the majority of head and neck cancers-being a feature associated with poor clinical outcome-the addition of cetuximab as a molecular targeted therapy in advanced head and neck cancer including HPSCC was shown as a method offering further outcome improvement [56].

In our retrospective study carried out on 41 patients with HPSCC characterized by advanced disease, the administered definitive treatment approach was CCRT realized with three-dimensional conformal radiotherapy and concomitant cisplatin given weekly during the radiotherapy course.

The multivariate model for association of prognostic factors with CCR in our study revealed the significance of T stage and technique of radiation. From the radiobiological point of view, the confirmation of T4 as unfavorable prognostic factor for achievement of CCR is a quite obviously expected finding. The probability for tumor eradication, i.e. the probability for achieving complete primary response, is inversely related to the number of clonogenic tumor cells which increases proportionally with the size of the tumor [57,58]. A possible explanation for the negative impact of radiation technique with electron-photon fields in achieving CCR could be the occurrence of cold spots at the surface when matching photon and electron fields, especially in cases when extensive primary and/or nodal lesions invade muscles and soft tissue in the neck.

In our study the results of the multivariate analysis with respect to LRC, DFS and OS indicated T stage as the only significant independent prognostic factor.

In the study of Mochiki et al. [59] with surgery being the main initial treatment in 82% of 142 patients with hypopharyngeal cancer, T stage was found to be an independent prognostic factor for distant recurrence-free survival in the multivariate analysis.

In the study of Johansen et al. [5], T stage was identified as a factor with a greater prognostic value than the size of the tumor in the multivariate analysis, suggesting that information about tumor volume could not influence the prognostic strength of the T classification in predicting LRC or survival.

On the contrary, in the analysis of the prognostic impact of tumor volume in patients with advanced-stage hypopharyngeal cancer treated with definitive CCRT, Chen et al. [35] did not confirm the significance of T classification as an independent prognostic factor for local control and survival. These authors, emphasizing the GTV as the only independent prognostic factor for primary tumor relapse-free survival and cause-specific survival in the multivariate analysis, concluded that pretreatment CT-based GTV measurements could be considered as strong predictor of local control and survival for stage III-IVA hypopharyngeal cancer when the patients are treated using definitive CCRT.

In our study, the univariate analysis revealed the GTV as a prognostic factor for LRC, DFS, and OS, but its significance was not retained in the multivariate analysis.

The multivariate analysis in the retrospective study of Gupta et al. [30] carried out on patient populations with hypopharyngeal cancer treated with radical radiotherapy with or without systemic therapy, showed borderline significance of T stage for DFS, while the significance of T stage for LRC was not confirmed.

In the retrospective study of Kim et al. [14], the multivariate analysis showed that T stage and N stage were significant prognostic factors for OS.

The univariate analysis in our study revealed that N stage was a factor that significantly influenced only OS, but its significance for OS was not confirmed in the multivariate analysis.

Reporting the results of their retrospective study in 101 patients with pyriform sinus carcinoma, Elias et al. [1] revealed significant correlation of overall stage

and tumor control, proclaiming the overall stage as a more important prognostic factor than T stage or N stage alone.

In summary, regarding the data from the literature concerning prognostic factors for HPSCC, it is apparent that the results of the analysis of different authors are not consistent. Thus, some authors showed nodal stage as the most important independent prognostic factor [30,60-62], whereas other authors confirmed the statistical significance of T stage, overall stage, and tumor volume in their multivariate analysis [1,5,14,35].

Our study has certain limitations i.e. it is a retrospective single-institution study on the role of CCRT in the treatment of advanced HPSCCs with a rather short median follow-up time, slightly more than 1 year. We also assume that in the absence of PET evaluation of the neck region in our study, the percentage of lymph node-negative patients (40%) in T3 and T4 disease seemed to be underestimated and this could be reflected in the results of the analysis of prognostic factors that had not revealed an independent prognostic value of N stage for LRC, DFS, and OS.

In conclusion, according to the confirmed independent prognostic significance of T stage for CCR, LRC, DFS, and OS in the multivariate analysis of our study, we consider that implementation of IMRT as a sophisticated radiotherapy technique combined with concomitant chemotherapy has a potential to increase the probability for complete response following treatment as well as to increase the rate of LRC in locally advanced HPSCC. We can also conclude that more aggressive treatment approaches including the use of intensified CCRT, the adoption of sequential therapy, and the administration of targeted therapies concurrently with conventional or altered fractionation should be strongly advocated in order to increase the rates of LRC, DFS and OS in patients with locally advanced HPSCC.

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