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Oral Cancer Report from Northeastern Hungary

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Abstract In Hungary oral and pharyngeal cancers have been reported the fourth most common malignancy in males and the sixth for both sexes. The aim of the present study was to characterize oral squamous cell carcinoma (OSCC) patients in Northeastern Hungary. 119 randomly selected patients with OSCC were included in the study. Epidemiological data, clinicopathological parameters and the risk factors were registered. The most common sites of OSCC were the floor of the mouth (27.7%), the lip (26.9%) and the tongue (22.7%). The majority of the patients was diagnosed with early stage (I–II) lesions and moderately differentiated tumors. The 5-year overall survival rate was 38.7%. There was a significant correlation between survival and tumor size, lymph node involvement and clinical stage. At the time of diagnosis 65.5% of the patients were smokers. Smoking significantly correlated with younger age, male gender, advanced clinical stages and alcohol consumption. 75.5% of the patients consumed alcohol, 41.1% of them exceeding the conventional amount regularly. Drinking habit significantly correlated with younger age, male gender and tumor site i.e. gingiva, retromolar region, tongue. The dental status was acceptable only in 12.6% of the cases. There was a significant correlation between dental status and age, smoking and drinking habits. Clinical stage has the most significant impact on survival and the most important high-risk habits in Northeastern Hungary are smoking and alcohol consumption. Therefore, early detection and treatment, cessation of tobacco and alcohol abuse, and a regular dental care may improve patients' survival in the region.

Keywords Oral cancer · Squamous cell carcinoma · Survival · Northeastern Hungary

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Introduction

Oral cavity cancer (OCC) represents a major health problem worldwide. Globally, cancers of the lip, oral cavity and pharynx (ICD-10 Codes: C00-C14) were the eighth most common malignancy in the year of 2000 causing 4.7% of all cancer related deaths [1]. In Hungary, oral and pharyngeal cancers have been reported the fourth most common malignancy in males and the sixth for both sexes [2]. In Europe, Hungary tops both the morbidity as well as the mortality lists for both sexes regarding oral cancer statistics. In 1999, the mortality rate for all oral and pharyngeal sites was 20.2 per 100,000 in males of all ages and 2.6 per 100,000 in females [3]. In Hungary, the prevalence of oral and pharyngeal tumors displays the most dynamic growth among malignancies. Between 1984 and 1994, the Hungarian mortality rates for oral cancers rose by 83.5% and 72.3% in males and females, respectively [3].

The incidence of oral cancer in males is higher than in women worldwide. Tumor onset is mainly in the sixth and seventh decade of life, but the proportion of patients under 45 years is increasing [4, 5]. The prognosis of epithelial forms of cancer of this region is still very unfavorable. The overall 5-year survival of oral cancer patients is around

40% [6]. Tumor site, clinical stage at the diagnosis and the applied therapy are the most important factors influencing the survival of the patients.

Squamous cell carcinoma (SCC) accounts for over 90% of all lip and oral cavity malignancies [7]. Oral SCC (OSCC) develops from precancerous epithelial dysplasia. It has been generally accepted that tobacco, betel quid, and alcohol abuses represent the major environmental risk factors of OSCC. However, some patients develop OSCC without exposure to these three risk factors. This fact suggests that additional causes, such as genetic predisposition, altered immunity, dietary factors or oncogenic viruses may also be involved in cancerogenesis.

In this study we analyzed first a retrospective case series of patients from Northeast Hungary with SCC of the lip and oral cavity. Our aim was to determine the distribution of SCC according to age, gender, clinicipathological parameters and risk factors such as tobacco and alcohol abuse, dental status, urban vs. rural differences, and to investigate the influence of these factors on survival.

Material and Methods

One hundred and nineteen randomly selected patients of 493 admitted patients with primary OSCC (ICD-10 C00-C06) diagnosed between 1 May 1996 and 30 April 1999 in the Department of Oral Surgery, Faculty of Dentistry, University of Debrecen, Hungary, were studied.

Formalin-fixed, paraffin-embedded blocks were retrieved from the surgical pathology archives of the Department of Pathology. Serial 4 μm thick sections were cut from the tissue blocks and mounted on silanized slides. One section was stained with hematoxylin–eosin and examined to confirm the original diagnosis and tumor grade. Histological grading was done according to WHO classification [8]. According to this classification, three parameters reflecting tumor cell features, including keratinization, polymorphism, and mitoses were evaluated in the whole thickness of the tumor and each scored from 1–4. Inflammatory infiltration and mode of invasion representing tumor-host relationship were graded in the most invasive margins and scored from 1–4. Then the sum of scores was grouped as follows: 5–10 grade I, 11–15 grade II, 16–20 grade III. All tumors were classified according to the International Union Against Cancer (UICC) TNM classification [9].

Clinicopathological information on each case, including age, gender, tumor size, nodal status, location and survival was obtained from patient record files. Among the risk factors we investigated smoking and alcohol consumption history, oral health data and urban vs. rural residence (Table 1).

Data were stored and analyzed by means of SPSS.11 software (SPSS Inc., Chicago IL, USA). Chi square test was used for univariate analysis of categorical data whereas a t-test was used for continuous data. Correlation among variables was estimated by Spearman-rank correlation coefficient. Survival curves were generated using Kaplan–Meier method and compared using the log-rank test. Tests were considered significant when their P values were less than 0.05.

Results

A total of 119 patients were included for assessment with a median age of 57.4 years (range 38–93 years). The male: female ratio was 5.2:1 (Table 2). The tissue samples were derived from the following sites: 33 mouth floor (27.7%), 32 lip (26.9%), 27 tongue (22.7%), 9 palate (7.6%), 8 gingiva (6.7%), 6 retromolar region (5.0%) and 4 other oral sites (3.4%). The median age of patients with lip cancer

Table 1 Variables used for survival analysis

Variables	Description
Age	≤39; 40–49; 50–59; 60–69; 70–79; ≥80
Sex	Male; female
Tumor size (T)	T1 (≤2 cm); T2 (2-4 cm); T3 (≥4 cm); T4 (tumor invades adjacent structures)
Lymph node (N)	N0 (no palpable node); N1 (≤3 cm, ipsilateral node); N2 (3-6 cm, contralateral/bilateral node); N3 (≥6 cm node)
Metastasis (M)	M0 (no distant metastasis); M1 (clinical/radiological evidence of metastasis)
Stage	I (T1N0M0); II (T2N0M0); III (T3N0M0/T1N1M0/T2N1M0/T3N1M0) ; IV (T4 with any N or M/ any T or N with M1)
Differentiation	Grade I (well); grade II (moderate); grade III (poor)
Site	Lip; tongue; mouth floor; gingiva; retromolar region; palate; other unspecified
Cigarette smoking	Never; ex-smoker; <20 cigarettes/day; ≥20 cigarettes/day
Alcohol drinking	Never; ex-drinker; <50 g ethanol/day; ≥50 g ethanol/day
Dental status	Toothless; 1–5 teeth; missing teeth without replacement; regularly treated (affordable oral hygiene); untreated (carious, un-affordable oral hygiene)
Residence	Urban; rural

Table 2 Age and gender distribution in the OSCC patient group

Age (year)	No. (%)	Male	Female	Ratio
−39	3 (2.5)	2	1	2:1
40–49	36 (30.3)	30	6	5:1
50–59	37 (31.1)	35	2	17.5:1
60–69	18 (15.1)	17	1	17:1
70–79	20 (16.8)	12	8	1.5:1
80+	5 (4.2)	4	1	4:1
Total	119 (100)	100	19	5.2:1

with 66.4 years was significantly higher than the age of other groups of patients ($p<0.001$, Table 3).

Analyzing the size of the tumors, 70.6% of the cases belonged to the favorable group (T1, T2). Regional lymph nodes were involved in 28.4% of cases, in 3.4% of cases distant metastases were present. Sixty-five percent of patients with primary lip SCCs were diagnosed with stage I disease while only 25.9% and 24.2% of patients with tongue and mouth floor primary sites, respectively belonged to this group ($p<0.001$). Stage IV patients were 10.6 years younger than patients with stage I disease ($p=0.002$, Table 3).

Histologically, 43.0% of SCC were well differentiated, 48.6% were moderately, and 8.4% were poorly differentiated. The degree of differentiation was not associated significantly with the investigated clinical parameters and survival, although in case of well differentiated tumors we found a tendency for a better 5-year overall survival rate (43% vs. 30%, $p=0.741$; Table 5).

Overall survival rate was 55.5% after 2 years and 38.7% after 5 years. The size of the tumor, the regional lymph node involvement and the clinical stage significantly influenced the overall survival. The strongest association was found with clinical stage (Spearman correlation coefficient −0.423, Table 4).

At time of diagnosis 65.5% of the patients were smokers, 41.1% of patients smoked ≥20 cigarettes per day (Table 5). Among smokers we found a male predominance (71.0% vs. 36.8%, $p=0.004$). Above 65 years of age, the ratio of smokers was 38.3%, under the age of 45 it was 86.4%. In advanced clinical stages (III and IV), the ratio of smokers was significantly higher than in early stages (83.3% vs. 52.4%, $p=0.044$). We found a significant association between smoking and drinking habits ($p<0.001$, Table 5).

Seventy-five percent of patients reported on alcohol consumption. The daily intake was ≥50 g ethanol (heavy drinkers) in 41.2%. Among males, the ratio of abstainers was 19.0%, among women it was 52.6% ($p=0.002$). We found a significant association between alcohol consumption and the site of the tumor ($p=0.033$, Table 6).

Dental status was significantly associated with the age of the patients ($p<0.001$), smoking habits ($p<0.001$) and alcohol consumption ($p=0.005$). Toothless patients were usually older than 65, they were non-smokers and abstainers (Table 6).

Sixty percent of the patients were urban, 40% were rural residents. We found no significant urban-rural differences.

Discussion

OSCC and SCC of the lips are mostly affecting males with a male:female ratio between 1.35:1 and 9.65:1 in Europe. In our series we found a 5.2:1 ratio, consistent with other reports from Eastern Europe [10]. The median age of patients was 57.4 years, which is somewhat lower than in other regions [11-14]. This fact can be explained with the high (18.5%) frequency of patients younger than 45 years in our study population. This age group accounts for approximately 4-6% of all oral cancers in the Western world [4, 5].

The most frequent tumor localizations were the floor of the mouth, the lips and the tongue. In developed Western countries the tongue, while in Asian countries the bucca are the most common anatomical sites of OSCC [14-16]. This difference can be explained with a difference in etiological factors. In Europe alcohol and tobacco consumption, in Asia betel quid chewing represent the leading environmental risk factors.

There are several factors affecting survival. In our patient group the 5-year overall survival (OS) rate was 38.7%, which is consistent with the literature [17, 18]. Age and gender had no significant effect on survival. The 5-year OS rate of lip cancer was more than 20% higher than OS figures of cancer arising from the tongue and the floor of the mouth, although the difference was not significant. We found a significant correlation between 5-year OS and tumor size, regional lymph node involvement and clinical stage. Tumor size and lymph node involvement were significant independent prognostic factors in this study and together they had an even more severe impact on disease outcome. In parallel with advancing clinical stages 5-year OS rates decreased from 68.3% (stage I disease) to 11.1% (stage IV disease).

Histological grading of OSCC has been used as a routine tool for predicting prognosis. In a number of studies however, pattern of invasion has been shown to be a stronger indicator than the grade of histological differentiation [19, 20]. Although in our series we found a better 5-year OS rate in cases of well differentiated tumors, the degree of histodifferentiation, similar to other studies, did not influence the prognosis significantly [21, 22].

In the Western world smoked tobacco and alcohol consumption have been strongly associated with the development of OSCC. These habits appear to account for

Table 3 Patient and tumor characteristics

Variable	Number (%)	Mean age (year)	*p* Value
Age			
≥65 years	34 (28.6)	–	–
<65 years	85 (71.4)	–	–
Gender			
Male	100 (84.0)	56.66	
Female	19 (16.0)	61.05	0.163
Tumor size			
T1	43 (36.1)	58.50	
T2	41 (34.5)	58.05	0.867
T3	25 (21.0)	57.76	0.820
T4	10 (8.4)	48.60	0.021
Lymph node involvement			
No	85 (71.4)	58.40	
Yes	34 (28.6)	57.08	0.652
Clinical stage			
I	42 (35.3)	58.98	
II	28 (23.5)	60.21	0.684
III	31 (26.1)	57.68	0.664
IV	18 (15.1)	48.61	0.002
Histological differentiation			
Grade I (well)	51 (42.9)	59.22	
Grade II (moderate)	58 (48.7)	56.75	0.313
Grade III (poor)	10 (8.4)	51.70	0.098
Tumor site			
Lip	32 (26.9)	66.41	
Tongue	27 (22.7)	53.96	<0.001
Mouth floor	33 (27.7)	53.85	<0.001
Gingiva	8 (6.7)	51.75	0.003
Retromolar region	6 (5.0)	52.67	0.006
Palate	9 (7.6)	56.89	0.034
Other	4 (3.4)	56.25	0.101
Tobacco smoking			
Never	34 (28.6)	64.53	
Ex-smoker	7 (5.9)	60.86	0.527
<20 cigarettes / day	29 (24.4)	58.28	0.050
≥20 cigarettes / day	49 (41.1)	51.35	<0.001
Alcohol drinking			
Never	25 (21.0)	63.36	
Ex-drinker	4 (3.4)	57.00	0.448
<50 g ethanol / day	41 (34.5)	58.17	0.123
≥50 g ethanol / day	49 (41.1)	53.65	0.003
Dental status			
toothless	30 (25.2)	64.80	
1–5 teeth	13 (10.9)	63.69	0.784
Missing teeth w/o replacement	40 (33.7)	53.78	<0.001
Regularly treated	15 (12.6)	52.73	0.002
Untreated	21 (17.6)	52.95	0.002
Residence			
Urban	72 (60.5)	57.72	
Rural	47 (39.5)	56.81	0.700

more than 75% of oral cancer cases [23]. In case of tobacco smoking the risk of tumor development appears to increase with the number of cigarettes smoked daily and with the duration of the habit [24].

Only 13.6% of our OSCC patients were free of known environmental risk factors. Seventy-one percent of the patients were tobacco users and 79% consumed alcohol. At the same time 35% and 60% of the average Hungarian

Table 4 Five-year overall survival data according to clinicopathological parameters and risk factors

Variable	Number	5-year overall survival (%)	*p* Value (Spearman correlation)
Gender			0.736
Male	100	38 (38.0)	
Female	19	8 (42.1)	
Age			0.084
≥65 years	34	9 (26.5)	
<65 years	85	37 (43.5)	
Tumor size			<0.001
T1	43	27 (62.8)	(−0.391)
T2	41	13 (31.7)	
T3	25	4 (16.0)	
T4	10	2 (20.0)	
Lymph node involvement			0.003
No	85	40 (47.1)	(−0.289)
Yes	34	6 (17.6)	
Clinical stage			<0.001
I	42	28 (66.7)	(−0.432)
II	28	9 (32.1)	
III	31	7 (22.6)	
IV	18	2 (11.1)	
Histological differentiation			0.741
Grade I (well)	51	22 (43.1)	
Grade II (moderate)	58	21 (36.2)	
Grade III (poor)	10	3 (30.0)	
Tumor site			0.104
Lip	32	18 (56.3)	
Tongue	27	9 (33.3)	
Mouth floor	33	11 (33.3)	
Gingiva	8	1 (12.5)	
Retromolar region	6	4 (66.7)	
Palate	9	2 (22.2)	
Other	4	1 (25.0)	
Tobacco smoking			0.455
Never	34	14 (41.2)	
Ex-smoker	7	3 (42.9)	
<20 cigarettes / day	29	14 (48.3)	
≥20 cigarettes / day	49	15 (30.6)	
Alcohol drinking			0.706
Never	25	11 (44.0)	
Ex-drinker	4	2 (50.0)	
<50 g ethanol / day	41	17 (41.5)	
≥50 g ethanol / day	49	16 (32.7)	
Dental status			0.585
toothless	30	9 (30.0)	
1–5 teeth	13	4 (30.8)	
Missing teeth w/o replacement	40	16 (40.0)	
Regularly treated	15	8 (53.3)	
Untreated	21	9 (42.9)	
Residence			0.749
Urban	72	27 (37.5)	
Rural	47	19 (40.4)	

population were identified as regular smokers and drinkers, respectively [25, 26]. Twenty-seven percent of patients were not only serious alcohol abusers but were heavy smokers (≥20 cigarettes daily). This behavioral pattern is not exceptional in Hungary [27]. Abstainers were significantly older than abusers. The prevalence of identified environmental risk factors was higher in the younger age groups. Bundgaard et al. found that smoking and alcohol

Table 5 Smoking and drinking habits at diagnosis of patients with oral squamous cell carcinoma (%)

Tobacco Alcohol	Never	Ex-smoker	<20 cigarettes/day	≥20 cigarettes/day	Total
Never	16 (13.6)	1 (0.8)	4 (3.4)	4 (3.4)	25 (21.8)
Ex-drinker	–	1 (0.8)	2 (1.7)	1 (0.8)	4 (3.4)
<50 g ethanol/day	14 (11.8)	3 (2.5)	12 (10.2)	12 (10.2)	41 (34.5)
≥50 g ethanol/day	4 (3.4)	2 (1.7)	11 (9.2)	32 (27.2)	49 (41.1)
Total	34 (28.6)	7 (5.9)	29 (24.4)	49 (41.1)	119 (100.0)

$p<0.001$

drinking habits were associated with poor prognosis [28]. In our patient group we found a decreasing overall survival time along with increasing intensity of risk habits, but this association was not significant. This finding was consistent with the results of Gorsky et al. [29].

Some reports identified poor oral hygiene and poor dentition as risk factors for oral cancer, independently of smoking and alcohol drinking [30–32]. In our case series only 12.6% of patients had a proper oral hygiene and treated dentition. We found no significant correlation

Table 6 Clinicopathological parameters according to smoking and drinking habits at diagnosis of OSCC (%)

Clinicopathologic	Smoking		*p* Value	Drinking		*p* Value
	Yes	No		Yes	No	
Gender			0.004			0.002
Male	71 (91.0)	29 (70.7)		81 (90.0)	19 (65.5)	
Female	7 (9.0)	12 (29.3)		9 (10.0)	10 (34.5)	
Age			<0.001			0.026
≥65 years	13 (16.7)	21 (51.2)		21 (23.3)	13 (44.8)	
<65 years	65 (83.3)	20 (48.8)		69 (76.7)	16 (55.2)	
Tumor site			0.204			0.033
Lip	17 (21.8)	15 (36.6)		25 (27.8)	7 (24.2)	
Tongue	16 (20.5)	11 (26.8)		22 (24.4)	5 (17.2)	
Mouth floor	23 (29.5)	10 (24.4)		21 (23.3)	12 (41.4)	
Gingiva	6 (7.7)	2 (4.9)		8 (8.9)	–	
Retromolar	6 (7.7)	–		6 (6.7)	–	
Palate	6 (7.7)	3 (7.3)		4 (4.4)	5 (17.2)	
Other unspecified	4 (5.1)	–		4 (4.4)	–	
Histo-differentiation			0.336			0.255
Grade I (well)	29 (37.2)	21 (51.2)		34 (37.8)	16 (55.2)	
Grade II (moderate)	42 (53.8)	17 (41.5)		48 (53.3)	11 (37.9)	
Grade III (poor)	7 (9.0)	3 (7.3)		8 (8.9)	2 (6.9)	
Clinical stage			0.044			0.609
I	22 (28.2)	20 (48.8)		33 (36.7)	9 (31.0)	
II	22 (28.2)	6 (14.6)		21 (23.3)	7 (24.2)	
III	19 (24.4)	12 (29.3)		21 (23.3)	10 (34.5)	
IV	15 (19.2)	3 (7.3)		15 (16.7)	3 (10.3)	
Dental status			<0.001			0.005
Toothless	11 (14.1)	19 (46.3)		16 (17.8)	14 (48.3)	
1-5 teeth	5 (6.4)	8 (19.5)		11 (12.2)	2 (6.9)	
Missing teeth	33 (42.3)	7 (17.1)		37 (41.1)	3 (10.3)	
Regularly treated	12 (15.4)	3 (7.3)		11 (12.2)	4 (13.8)	
Untreated	17 (21.8)	4 (9.8)		15 (16.7)	6 (20.7)	
Residence			0.133			0.499
Urban	51 (65.4)	21 (51.2)		56 (62.2)	16 (55.2)	
Rural	27 (34.6)	20 (48.8)		34 (37.8)	13 (44.8)	
5-year outcome			0.648			0.433
Alive	29 (37.2)	17 (41.5)		33 (36.7)	13 (44.8)	
Dead	49 (62.8)	24 (58.5)		57 (63.3)	16 (55.2)	

between tumor site and dental status, but similarly to Lockhart et al., the rate of edentulous patients was highest in cases of tumors of the floor of the mouth [31]. Though dentition alone is a weak risk factor, together with alcohol abuse, it may multiply their disadvantageous effect [33, 34]. Thirty-seven percent of our OSCC patients were heavy drinkers with a poor dentition.

In the etiology of oral, especially of lip cancers, people with a rural life-style (open-air agricultural work) were found at risk [35]. However, we did not find any significant differences between patients living in a rural vs. in an urban environment, either in the prevalence of OSCC, or in any of the investigated clinicopathological factors. This means that in our region residence is not an independent risk factor in the etiology of lip or oral cavity cancer.

Conclusion

Oral cancer is a constant adverse public health issue in Hungary. The occurrence is relatively high in the younger age groups compared with Western reports. Traditional risk habits, including tobacco smoking and consumption of alcoholic beverages, are the most important environmental factors in the development of oral squamous cell carcinoma. The cessation of these adverse habits together with participation in regular dental care may improve patients' survival. More than 40% of the OSCC patients have been diagnosed at advanced stages, suggesting that more intensive preventive programs with regular screening is strongly recommended in Northeastern Hungary.

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