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SURVIVAL ANALYSIS OF OROPHARYNGEAL SQUAMOUS CELL CARCINOMA PATIENTS LINKED TO HISTOPATHOLOGY, DISEASE STAGE, TUMOR STAGE, RISK FACTORS, AND RECEIVED THERAPY

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Background: Survival of oropharyngeal squamous cell carcinoma (OSCC) patients depends on the risk and environmental factors, tumor biology, achievements in diagnostics and treatment approaches. *Aim*: To perform a survival analysis of the patients with OSCC treated over a 10-year period in a single hospital in Latvia linking these data to histopathological findings, risk factors and received therapy. *Materials and Methods*: The main outcome measures were overall and disease-specific survival (OS and DS) along with histopathology analysis. *Results*: Kaplan − Meier survival analysis showed better survival for females, younger patients lacking bad habits, operated and received radiotherapy, with lower T grade and disease stage. Cox regression showed diminished early death risk in patients with lower T grade, no regional metastases (N0) and bad habits, operated and received radiotherapy. A vast majority of tumors were localized in palatine tonsils and the base of the tongue. The localization did not correlate with mean survival time/survival. Lower OS ($p = 0.03$) and DS ($p = 0.026$) were estimated for patients with pharyngeal wall and tonsillar involvement compared to tumors localized in the soft palate. A histological variant of tumor seemed irrelevant estimating OS and DS, whereas therapeutic modalities significantly affected survival. *Conclusions*: OSCC patients with lower T grade, N0 status, lacking bad habits, and surgically treated had better survival.
Key Words: oropharyngeal squamous cell carcinoma, survival rates, risk factors.

The oropharynx is one of the most common localizations for malignant neoplasms in the head and neck region. The GLOBOCAN data (2012) confirm over 140,000 new cases of pharyngeal cancer worldwide and age-standardized incidence of 1.9 per 100,000, whereas in Europe — about 34,000 new cases and age-standardized incidence of 2.9 [1].

Histopathologically, most malignancies found in the oropharynx (~ 90%) are squamous cell carcinoma (SCC) [2]. Although SCC of the oropharynx is diagnosed predominantly in people over the age of 45 years, some studies suggest an increased incidence of the disease in people less than 45 years of age, over the past 20–30 years [3]. Commonly, these tumors arise from certain regions — palatine tonsils, the base of the tongue, soft palate, and posterior pharyngeal wall and in greater than 60% of patients present with cervical lymph node involvement and 10–15% with distant metastases [2]. It has been found that the rates of lymph node metastasis vary considerably by localization with tumors of the tonsil and base of the tongue more likely presented with positive nodes than tumors of the soft palate and pharyngeal wall [4]. Approximately 60% of oropharyngeal SCCs (OSCC) have been found to be moderately differentiated, 20% well-differentiated, and 20% poorly differentiated

[5]. Other tumors, namely minor salivary tumors (adenomas/adenocarcinomas), primary lymphoid tumors, undifferentiated tumors, various sarcomas, and mixed neoplasms also present in the oropharynx [6], and clinicopathological findings vary from country to country [7].

Major etiological and predisposing factors for this neoplasm include smoking and drinking habits, and several other factors such as human papillomavirus (HPV) and *Candida* infections, nutritional deficiencies and genetic predisposition [7–10]. Furthermore, it has been demonstrated that the carcinogenic effects of both alcohol and tobacco smoke on the oropharynx appear to function in dose-dependent manners [6], and increase 6–7-fold in individuals overusing tobacco or alcohol and as much as 15-fold with those who both smoke and drink alcohol [11].

Analysis of survival rates in the case of SCC reveals greatly varying data due to the variability of the observation period, patients' features, surgeons' expertise, percentage of starting tumors compared with advanced ones, quality of radiotherapy (RT), and the use of adjuvant treatments [12]. Pathologically, the significant predictors of 5-year disease-free survival proposed very recently by analyzing invasive tumor patterns of SCC were defined as the mode of invasion, worst pattern of invasion, and tumor budding as well as lymphovascular and perineural invasion [13]. The 5-year survival rate has been shown to range from 58% up to 94% [14]. A decrease in survival rate in a long-term follow-up happens mostly due to the development of new primary tumors, which have the same etiologic factors, and intercurrent deaths often caused by the same etiologic factors and by the age of the patients [15]. Other studies suggest an improvement in the 5-year

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overall survival (OS) and disease-specific survival (DS) rates during the past decade compared with the previous decade even despite older age, more advanced disease stage, and a higher rate of distant metastases, presumably due to the recent advances in tumor imaging and therapy [12, 14]. The world incidence of OSCC varies and estimated differences in the incidence and survival are generally related to the distinct risk and socioeconomic factors, environmental agents, public health awareness and accessibility of health services, as well as advances in diagnostics and therapy. Therefore, the aim of this study was to perform a survival analysis of the patients with OSCC treated over a 10-year period in a single hospital in Latvia correlating these data with histopathological findings, disease stage, tumor grade, nodal grade, patients' age and sex, habits (smoking, alcohol abuse), primary tumor location, and received therapy.

MATERIALS AND METHODS

We carried out a retrospective study of 247 patients diagnosed with OSCC, staged following the TNM classification of the International Union against Cancer (6th edition) for oropharyngeal carcinoma and treated in Riga Eastern Clinical University Hospital Stationary Oncology Centre of Latvia between January 1st, 2000 and December 31st, 2010. Patients are admitted to this hospital from all over the country, which has an estimated population of 1.91 million. The patients' data were collected from the Hospital Archive and The Centre for Disease Prevention and Control and included in the study when the diagnosis of OSCC was confirmed histologically. The study was approved by the Ethical Committee of Riga Stradins University.

The data collected were processed to calculate the overall and disease-specific 3 and 5-year survival rates for all patients. The Kaplan — Meier survival analysis was used for the estimation of statistical data. Statistical testing for differences in unadjusted survival rates was performed using the log-rank test. A Cox regression method was used to estimate hazard ratio (HR). Age, sex, T stage, N status, risk factors (smoking, alcohol abuse), therapy modality (RT, surgery (SUR), chemotherapy (ChT), symptomatic therapy and combinations of aforementioned, primary tumor location, histopathological variant of tumor were included as covariates in the survival model. ChT consisted of a single-agent regimen with cetuximab or platinum medication (cisplatin).

Statistical analysis of correlation of aforementioned covariates with survival, and mean OS time after diagnosis was performed. We used Pearson's chi-squared test or Fisher's exact test (depending on the size of the group) to find out if differences between analyzed groups are statistically significant, the value of $p < 0.05$ was considered significant. Cramer's V was used to measure an association between two nominal variables. For analysis of the correlation between nominal variables and mean survival time after diagnosis Kruskal — Wallis test or Mann — Whitney test (depending on the number of groups) were used.

Formalin-fixed paraffin-embedded OSCC samples obtained from all major subsites and sections cut off were retrieved from the archival files of the Department of Pathology Oncology Centre of Latvia, and pathology reports for all tumors were reviewed. Hematoxylin and eosin (H&E) stained sections were analyzed, and the tumors were classified according to their histologic features. Patterning of the invasion at the advancing tumor edge, the presence of perineural invasion, and immune system response as proposed by Brandwin *et al.* [16] and thereafter commented by the other scientists [17] were underestimated in the early years of this retrospective study. Therefore, the histopathological assessment was done not taking into account the revision of surgical margins and the evaluation of supplemental tissue. Microphotographs were obtained using Leitz DMRB brightfield optics equipped with a digital camera DC 300F.

RESULTS

The retrospective cohort consisted of 247 patients with pathologically confirmed OSCC, stage I–IV presented by the following subsites — palatine tonsils (n =110, 44.52%), base of tongue (n = 76, 30.77%), soft palate (n = 20, 8.10%), and posterior pharyngeal wall (n = 41, 16.60%). Unfortunately, less than one-tenth of the cohort presented with stage I and II — 3 (1.22%) and 19 (7.72%) patients, accordingly, whereas a major portion — 224 (91.6%) revealed advanced disease stage. By gender, 8.10% (n = 20) of all reviewed patients were female and 91.90% (n = 227) — male. The mean patient age was 60 years (range 27–85), median — 60.20 years.

When the patients' data were collected and summed-up we found that most of the patients were regular smokers (75.95%, n = 180), habitual drinkers (35.19%, n = 82) or were exposed to both aforementioned major risk factors (31.47%, n = 73). The general characteristics of the patients are summarized in Table 1.

Table 1. Characteristics of the patients

Sex – n (%):	
Male	227 (91.90)
Female	20 (8.10)
Age – yr:	
Mean (SD)	60 (8.985)
Range	27–85
Disease stage – n (%)*:	
I	3 (1.22)
II	19 (7.72)
III	61 (24.80)
IV	163 (66.26)
Tumor stage – n (%)**:	
T1	23 (9.39)
T2	59 (24.08)
T3	73 (29.80)
T4	90 (36.73)
Node stage – n (%)*:	
N0	77 (31.30)
N1	54 (21.95)
N2	82 (33.33)
N3	30 (12.20)
Nx	3 (1.22)
Alcohol abuse – n (%)***:	
Yes	82 (35.19)
No	151 (64.81)
Smoking – n (%)****:	
Yes	180 (75.95)
No	57 (24.05)
Alcohol and smoking – n (%):	73 (31.47)

Note: *Unknown for 1 patient; **unknown for 2 patients; ***unknown for 14 patients; ****unknown for 10 patients.

Female patients had significantly longer mean survival time than males, but we found no correlation between survival and gender ($V_1 = 0.09$, $p = 0.25$) as well as mean survival time and gender ($\eta = 0.17$). OS analysis showed better survival for females, but it wasn't significantly different when compared to males ($p = 0.06$). By contrast, DS survival in female patients appeared to be significantly better ($p = 0.0486$).

Additionally, survival was estimated subdividing the subjects into three age groups — younger than 55 years; 55 to 64 years old and older than 65 years. There were significantly more deceased patients in the subgroup with advanced age when compared to younger individuals ($p = 0.028$). However, no correlation was found between both age group and survival ($V_1 = 0.17$), and mean survival time ($\eta = 0.16$). Kaplan — Meier estimates showed a decrease in survival with increasing age, but the differences in OS and DS weren't statistically significant when all three age groups were considered ($p = 0.092$ and $p = 0.108$). In spite of that, pairwise comparisons showed statistically significant differences in survival between patients younger than 55 years and older than 64 years ($p = 0.048$). Table 2 deciphers a decrease in OS with more advanced age.

There was a moderate correlation between survival and disease stage ($V_1 = 0.32$, $p_\chi = 0.0014$). Kaplan — Meier survival analysis showed almost statistically significant (overall comparisons, $p = 0.058$) OS and DS differences according to the disease stage (see Table 2). In pairwise comparisons, a statistically significant difference in OS between stage I and stage II disease ($p = 0.139$), stage II and stage III disease ($p = 0.112$), stage III and stage IV disease ($p = 0.104$) was not found. Similar observations were made in pairwise comparisons between stages in DS.

Mean survival time and the positive outcomes (the patient survived) of the disease appeared to decrease with higher T grade, and there was a moderate correlation between outcome and T grade ($V_1 = 0.27$), whereas no correlation between mean survival time and T grade ($\eta = 0.2830$). Kaplan — Meier survival analysis showed a better OS and DS when lower tumor grade (T1–2) was compared to higher tumor (T3–4) grade (see Table 2).

There was no correlation between N status and mean survival time/survival (outcome). We found no statistical difference in OS and DS ($p = 0.11$ in both cases) according to N status (N0 *vs* N+; see Table 2).

Table 2. Kaplan — Meier analysis of potential prognostic factors for DS, OS

Variable	3-year Kaplan — Meier estimate, % (95% CI)		5-year Kaplan — Meier estimate, % (95% CI)	
	OS	DS	OS	DS
Age, years (n; %):				
<55 (62; 25.10)	25.8% (14.8–36.8)	24.1% (13.1–35.1)	22.6% (12.2–33.0)	20.7% (10.3–31.1)
55–64 (105; 42.51)	21.6% (13.6–29.6)	19.6% (11.8–27.4)	15.7% (8.6–22.8)	14,4% (7.3–21.5)
≥65 (80; 32.39)	14.1% (6.5–21.7)	12.3% (4.3–20.3)	7.7% (1.8–13.6)	7.7% (1.2–14.2)
	$p = 0.092$	$p = 0.108$	$p = 0.092$	$p = 0.108$
Sex:				
Male	19.8% (14.5–25.1)	19% (12.7–23.3)	14% (9.5–18.5)	12,8% (8.3–17.7)
Female	30% (10.0–50.0)	30% (10.0–50.0)	25% (6.0–44.0)	25% (6.0–44.0)
	$p = 0.06$	$p = 0.0486$	$p = 0.06$	$p = 0.0486$
Stage:				
I	100% (−)	100% (−)	100% (−)	100% (−)
II	36.8% (15.0–58.6)	37.5% (13.8–61.2)	31.6% (10.6–52.6)	31.3% (8.6–54.0)
III	21.7% (11.3–32.1)	23.6% (12.4–34.8)	13.3% (4.7–21.9)	14.5% (5.1–23.9)
IV	16.3% (10.6–22.0)	13.0% (7.5–18.5)	11.1% (6.2–16.0)	10.3% (5.4–15.2)
	$p = 0.0058$	$p = 0.0058$	$p = 0.0058$	$p = 0.0058$
T grade:				
T1	42.9% (21.7–64.1)	37.5% (13.8–61.2)	42.9% (21.7–64.1)	37.5% (13.8–61.2)
T2	34.5% (22.3–46.7)	35.8% (22.9–48.7)	22.4% (11.6–33.2)	22.6% (11.4–33.8)
T3	16.4% (8.0–24.8)	16.4% (7.6–25.2)	9.6% (2.9–16.3)	10.4% (3.1–17.7)
T4	11.4% (4.7–18.1)	8.5% (2.4–14.6)	6.8% (1.5–12.1)	6.1% (1.0–11.2)
	$p < 0.0001$	$p < 0.001$	$p < 0.0001$	$p < 0.001$
N status:				
N0	27.6% (17.6–37.6)	27.9% (17.3–38.5)	21.1% (11.9–30.3)	22.1% (12.3–31.9)
N+	19% (12.9–25.1)	16.8% (10.7–22.9)	12.3% (7.2–17.4)	10.7% (5.8–15.6)
	$p = 0.11$	$p = 0.11$	$p = 0.11$	$p = 0.11$
Primary tumor location:				
Palatine tonsil	18.5% (11.2–25.8)	16.8% (9.5–24.1)	12% (5.9–18.1)	9.9% (4.0–15.8)
Base of the tongue	24.3% (14.5–34.1)	22.7% (12.5–32.9)	17.6% (9.0–26.2)	18.2% (9.0–27.4)
Pharyngeal wall	15% (4.0–26.0)	13.5% (2.5–24.5)	7.5% (0–15.7)	8.1% (0–16.9)
Soft palate	40% (18.4–61.6)	43.8% (19.5–68.1)	35% (14.0–56.0)	37.5% (13.8–61.2)
Alcohol abuse and smoking:				
Neither	34% (20.5–47.5)	31.8% (18.1–45.5)	23.4%(11.2–35.6)	25% (12.3–37.7)
1 factor	22.7% (14.9–30.5)	20.4% (12.4–28.4)	16.4% (9.5–23.3)	14.3% (7.4–21.2)
Both	11.4% (4.0–18.8)	10.9% (3.3–18.5)	7.1% (1.0–13.2)	6.3% (0.4–12.2)
	$p = 0.002$	$p = 0.008$	$p = 0.002$	$p = 0.008$
Treatment (n):				
RT (175)	14% (8.7–19.3)	12.6% (7.5–17.7)	7.6% (3.7–11.5)	7.5% (3.4–11.6)
SUR (7)	42.9% (6.2–79.6)	40% (0–82.9)	42.9% (6.2–79.6)	40% (0–82.9)
RT+SUR (39)	52.6% (36.7–68.5)	54.8% (37.4–72.2)	42.1% (26.4–57.8)	41.9% (24.5–59.3)
RT+ChT (Cetuximab)+/−SUR (17)	23.5% (3.3–43.7)	25% (3.8–46.2)	17.6%(0–35.6)	18.8% (0–38.0)
RT+ChT (Cisplatin)+/−SUR (3)	33.3% (0–86.6)	33.3% (0–86.6)	33.3% (0–86.6)	33.3% (0–86.6)
Symptomatic (6)	0% $p < 0.001$	0% $p < 0.001$	0% $p < 0.001$	0% $p < 0.001$

A moderate correlation between smoking and survival ($V_1 = 0.21$, $P_x = 1.77 \cdot 10^{-3}$) was found, but there was no correlation between mean survival time and smoking ($\eta = 0.17$). Kaplan — Meier survival analysis showed a statistically higher OS and DS in subjects nonsmokers ($p < 0.05$). There was no correlation between alcohol abuse and survival/ mean survival time.

Significantly higher OS was estimated for patients who didn't abuse alcohol ($p = 0.03$), whereas a decrease of the significance was found regarding DS ($p = 0.08$). However, there was a statistically significant decline in the OS and DS in the patients' group who smoked and abused alcohol simultaneously (yes *vs* no) (see Table 2, Fig. 1).

OSCC analyzed in the study developed from different subsites, but there was no impact of tumor location on mean survival time/survival. Worst OS ($p = 0.03$) and DS ($p = 0.026$) estimates were found for subjects presented with pharyngeal and tonsillar tumors, thus opposing estimates for patients presented with tumors of the soft palate (see Table 2).

Keratinizing SCC (KSCC) tissue samples showed large polygonal squamous cells with distinct cell borders and keratin formation revealing a spectrum of grades from well-differentiated to poorly differentiated tumors with various degrees of keratinization (Fig. 2, 3, 4). Keratin pearls were present. Squamous
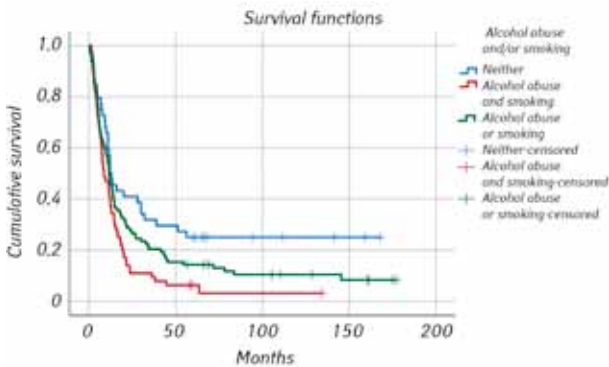
maturation was diffuse even in poorly differentiated tumors that lack keratinization. Keratinizing tumor samples with abundant eosinophilic cytoplasm were often composed in discrete nests and displayed nuclear pleomorphism (see Fig. 2 and Fig. 5). The infiltrative nests of tumor cells usually were found within stroma revealing prominent desmoplasia.

Fig. 3. Base of the tongue. NKSCC. Densely packed mitotically active epithelial cells forming the pushing and infiltrating masses of carcinoma. H&E, original magnification, ×200

Fig. 1. Kaplan — Meier DS plot according to hazardous habits

Fig. 4. Palatine tonsil. NKSCC. Nests of tumor cells with ill-defined borders and necrosis. H&E, original magnification, ×200
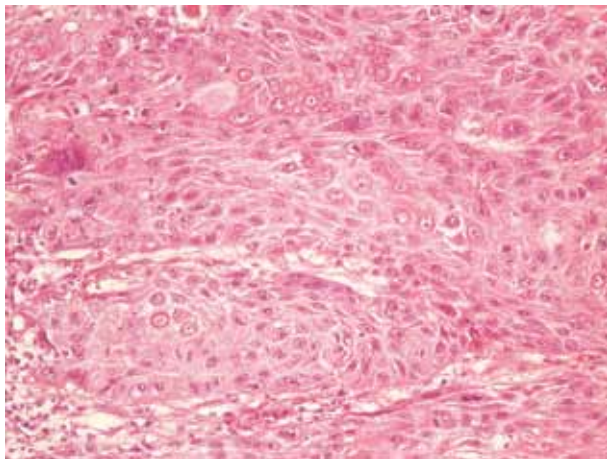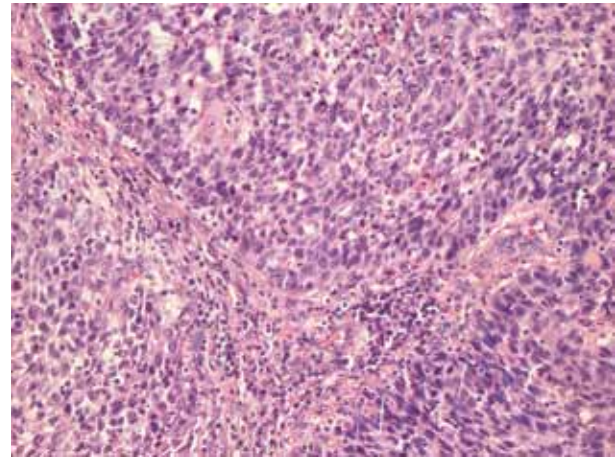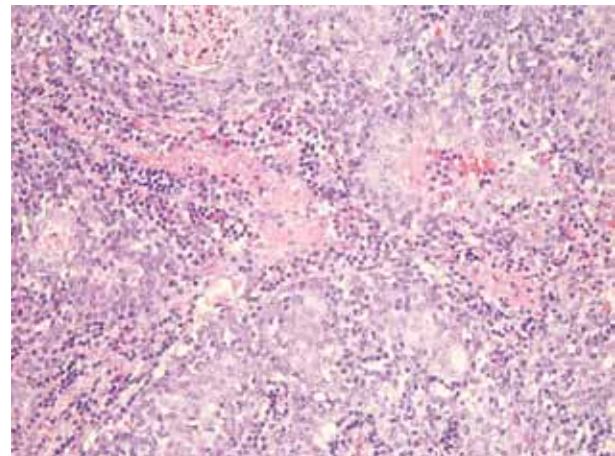

Fig. 2. Soft palate region. KSCC (verrucous type) showing folded and thickened neoplastic epithelium comprised of large polygonal cells with distinct cell borders and varying degree of eosinophilia. Nuclei are pleomorphic. H&E, original magnification, ×200
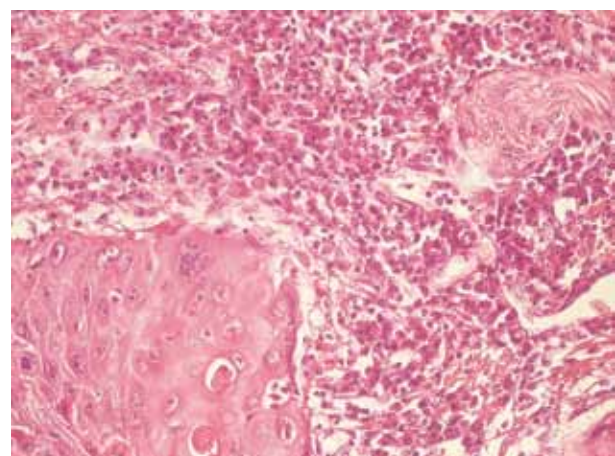

Fig. 5. Soft palate region. KSCC. Tumor cells demonstrate nuclear pleomorphism, mitotic and apoptotic features. Some tumor cells contact the nerve bundle. H&E, original magnification, ×250

Nonkeratinizing SCC (NKSCC) tumors often formed nests, sheets, and cords with well-defined borders. These tumors were characterized by relatively monomorphic, densely packed, ovoid, and spindle-shaped basaloid cells with indistinct cell borders. Mitotically active tumor cells revealed highly hyperchromatic nuclei and high nuclear-to-cytoplasmic ratio.

Although this study did not attempt to distinguish HPV driven tumors from those, which are HPV negative, we might speculate that KSCC are highly likely HPV negative whereas NKSCC highly suggestive of HPV association. Usually, these NKSCC formed sheets, nests, and cords with sharply defined borders; tumor cells displayed basaloid features and peripheral palisading (Fig. 6).

Most of the tumors were KSCC (n = 175, 70.85%), 19.43% were NKSCC (n = 48), 1.21% — undifferentiated carcinomas (n = 3), 1 (0.4%) — adenosquamous carcinoma, for the remainder of tumors keratinization pattern wasn't specified (n = 20, 8.10%). A histological variant of tumor seemed irrelevant estimating OS and DS ($p > 0.05$). Furthermore, a correlation between histological variant and mean survival time/survival was not found.
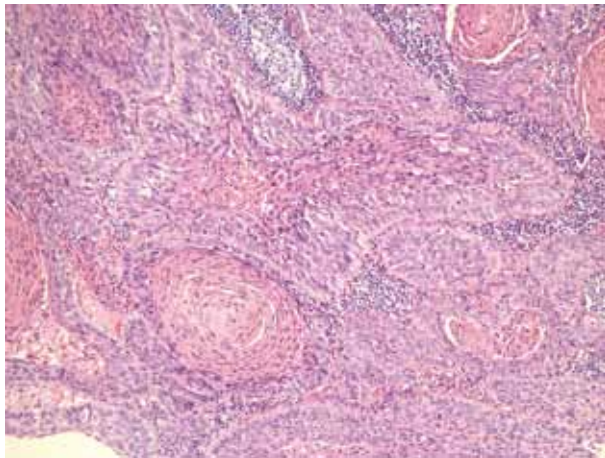

Fig. 6. Base of the tongue. NKSCC. Nests and cords of tumor cells with basaloid features, peripheral palisading, intraluminal necrosis, keratocysts. H&E, original magnification, ×100
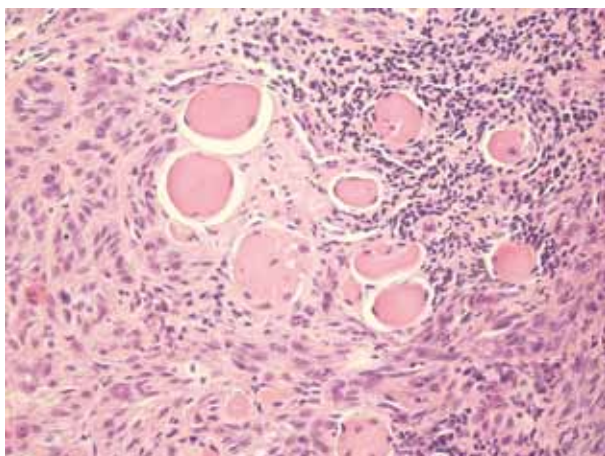

Fig. 7. Posterior pharyngeal wall. Poorly differentiated SCC. Tumor nests and nodules reveal muscular invasion; lymphoplasmacytic infiltration. H&E, original magnification, ×250

When recognizing that histological grade based on the amount of keratinization is not a consistent predictor of clinical behavior we fixed the presence of perineural spread, lymphovascular and muscular invasion to better understand aggressive behavior of the tumor. We found that perineural invasion and lymphovascular invasion are frequently observed in SCCs causing a decrease of survival (see Fig. 6). Additionally, the islands and cords of malignant cells infiltrated the underlying skeletal muscle tissue when the deeper invasion of the tumor masses took a place (Fig. 7).

We found a strong correlation between survival and therapy ($V_1 = 0.32$), but no correlation between therapy and mean survival time ($\eta = 0.33$). There were significant OS and DS differences ($p < 0.001$) between therapeutic modalities (Table 2), with better survival in SUR and RT+SUR groups. Pairwise comparisons revealed significant OS differences only in RT *vs* RT+SUR, RT+SUR *vs* RT+ChT (cetuximab)+/−SUR groups ($p < 0.05$), and borderline significance in RT *vs* SUR group, showing higher survival in those patients who underwent SUR and lowest survival in RT group. Similar observations were made performing pairwise comparisons between therapy modalities and DS.

Most of the patients didn't receive SUR as therapeutic modality (n = 196), 10 patients had primary tumor excision, 28 underwent neck dissection, and 13 had both, primary tumor excision and neck dissection. When suggesting the outcome of the disease and the impact of SUR as well as the type of operation done, we found that the number of deceased patients was much higher when no operation was done (Table 3). Furthermore, mean OS time after establishing the diagnosis of the disease was significantly longer in surgically treated patients; however, the correlation between mean OS time and the aforementioned treatment modality was not found. Kaplan — Meier analysis showed significant differences in survival (OS and DS) depending on whether the patient was operated on or not, with a much higher survival rate in patients who underwent SUR ($p < 0.0001$). However, OS and DS pairwise comparison of SUR type didn't show any significant differences ($p = 0.29$ for OS and $p = 0.11$ for DS).

Cox regression method was applied in two stages: (1) all the factors were analyzed without distinguishing subgroups of each factor (univariate analysis; Table 4); and then (2) subgroups of each factor were assessed (multivariate analysis, see Table 5). T grade ($p < 0.00001$), N status ($p = 0.017$) and sex ($p = 0.049$) appeared to have a statistically significant or probable impact on the mortality after detection of the disease in the common comparison model (see Table 4) (value of B is positive). Individually for grade T, the risk of death increases by 39% (Exp (B) = 1.39) if T grade increases with other values remaining constant. By contrast, the risk of death increases by 51% (Exp (B) = 1.51) in case of N status, if there is a change from N0 to N + when other values remain fixed. Finally, the risk increases

Table 3. Breakdown of patients by type of operation and outcome of the disease

Type of operation	N of patients (incidence, %)*	Outcome of the disease (therapy)	N of patients (incidence, %)	Statistical analysis between groups			
				All groups		Only operations	
				P_x	V_1	P_x	V_1
Primary Tu excision	10	Positive (survived)	3 (30.00)				
	(4.05; 19.61)	Negative (deceased)	7 (70.00)	7.11×10^{-6}	0.33	0.19	0.26
Neck dissection	28	Positive (survived)	5 (18.52)				
	(11.34; 54.90)	Negative (deceased)	22 (81.48)				
Both	13	Positive (survived)	6 (46.15)				
	(5.26; 25.49)	Negative (deceased)	7 (53.85)				
None	196	Positive (survived)	12 (6.25)				
	(79.35; -)	Negative (deceased)	180 (93.75)				

Note: *The incidence among all patients and the incidence only between operations.

Table 4. Cox proportional hazard, univariate analysis

Variable	B	P	Exp(B)	CI 95% Exp(B)
Sex	0.53	$4.88 \cdot 10^{-2}$	1.70	1 ... 2.88
Age groups	0.14	0.14	1.15	0.95 ... 1.4
Alcohol abuse and/ or smoking	0.02	0.83	1.02	0.85 ... 1.22
T grade	0.33	$2.40 \cdot 10^{-5}$	1.39	1.2 ... 1.63
N status (N0 *vs* N+)	0.41	$1.35 \cdot 10^{-2}$	1.51	1.09 ... 2.09
Therapy	−0.10	0.14	0.90	0.79 ... 1.03
Primary tumor location	−0.08	0.29	0.92	0.79 ... 1.07
Histological variant	0.07	0.36	1.07	0.92 ... 1.25

by 70% (Exp (B) = 1.70) within the gender axis (female > male). Other features in a particular regression model didn't have a statistically significant impact on the risk of earlier death. Cox regression plot for cumulative survival shows that 50% of patients die before 12 months after the diagnosis of cancer (Fig. 8).

It was found that T2 grade, N status, presence of one of the hazardous habits (smoking or alcohol abuse) and treatment modality — RT+SUR have a statistically significant impact on the risk of death when accounting nine factors and analyzing the HR between subgroups of factors (see Table 5). Patients with T2 grade tumor have 57% and 77% reduction in the risk of early death when compared to patients with T3 and

T4 grade tumors. Finally, we found that there is a 34% reduction in the risk of early death when N0 status is compared to N+.

Significantly ($p = 0.0467$) lower early death risk was determined for patients exposed to SUR in combination with RT ($p = 0.002$) when compared to other treatment modalities, including RT alone or in combination with cetuximab (Fig. 9). When compared to symptomatic treatment, RT+SUR therapy has 300% or 3 times lower early death risk, but compared to RT+ChT (cetuximab) +/−SUR therapy — 154% or 1.54 times lower early death risk. When a combination of two — RT+SUR treatment modalities are compared to RT or SUR alone, there is 2.02 and 1.27 times greater death hazard estimated for RT and SUR, respectively.

Cox regression multivariate analysis showed that alcohol abuse and/or smoking significantly increase the risk of early death. Results of the Cox proportion hazard model are summarized in Tables 4 and 5.

DISCUSSION

We performed a survival analysis of the patients with OSCC treated over a 10-year period in a single

Table 5. Cox proportional hazard model, multivariate analysis

Variables	P	Exp (B) or HR*	CI 95% Exp (B)	HR comparing to other groups^
Sex (female > male)	0.11	0.63	0.36 ... 1.11	
Age group	0.15			
<55 years old	0.10	0.70	0.46 ... 1.06	
55−64 years old	0.08	0.74	0.52 ... 1.04	
>64 years old		(1.00)		
Alcohol abuse and/or smoking	0.06			
None	0.43	0.84	0.55 ... 1.29	
1 of aforementioned	**0.051**	1.42	1 ... 2.01	
Both		(1.00)		
T grade	$3.51 \cdot 10^{-2}$			
1	0.13	0.60	0.31 ... 1.17	1.06
2	**$6.72 \cdot 10^{-3}$**	**0.57**	**0.37 ... 0.85**	
3	0.51	0.89	0.62 ... 1.26	1.57
4		(1.00)		1.77
N status (N0 > N+)	**$1.58 \cdot 10^{-2}$**	**0.66**	**0.47 ... 0.93**	
Therapy	0.09			
RT	0.42	0.67	0.26 ... 1.75	2.02
OP	0.20	0.42	0.11 ... 1.56	1.27
RT+SUR	**$4.67 \cdot 10^{-2}$**	**0.33**	**0.11 ... 0.98**	
RT+ChT (cetuximab) +/−SUR	0.70	0.80	0.26 ... 2.44	2.41
RT+ChT (platinum) +/−SUR	0.44	0.51	0.09 ... 2.82	1.54
Symptomatic		(1.00)		3.00
Primary tumor location	0.55			
Palatine tonsil	0.19	1.48	0.82 ... 2.64	
Base of the tongue	0.37	1.32	0.72 ... 2.4	
Pharyngeal wall	0.20	1.52	0.79 ... 2.92	
Soft palate		(1.00)		
Histological variant	0.73			
KSCC	0.78	0.93	0.54 ... 1.59	
NKSCC	0.90	0.96	0.52 ... 1.78	
Carcinoma, undifferentiated (Epit)	0.35	1.84	0.51 ... 6.67	1.91
SCC, BCN (unspecified)		(1.00)		1.04

Note: *HR − hazard ratio-calculation using the last group as a reference; ^calculated for significant groups (bold) against others, taking a significant group as a reference.
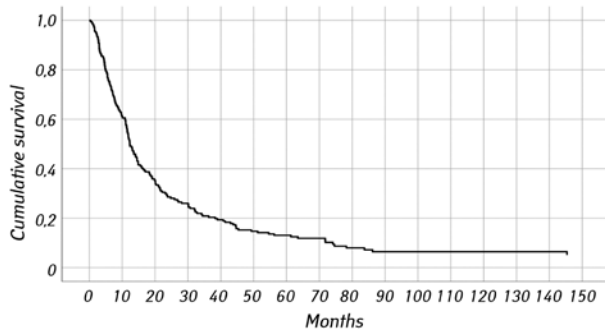
Fig. 8. Cox regression plot for cumulative survival (overall) accounting for all covariates (sex, age group, T grade, N status, alcohol abuse and/or smoking, therapy, primary tumor location, histological variant)
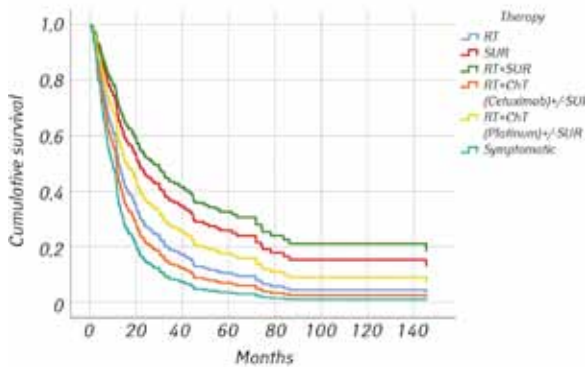

Fig. 9. Cox regression plot for cumulative survival. Covariates — sex, age group, T grade, N status, alcohol abuse and/or smoking, therapy, primary tumor location, histological variant. Plot for therapy

hospital in Latvia making attempts to link the data with disease stage, tumor stage, patients' age and sex, habits (smoking, alcohol abuse), histopathological variant of the tumor, primary tumor localization, and received therapy.

We found that two-thirds of the patients (76%) were smokers, whereas one third — (35%) had drinking problems. Regarding the relevance of habits, our study confirmed the independent role of these risk factors in survival (OS and DS), where smoking seems to play a more important role in survival, especially DS. Moreover, the combination of these two factors significantly decreases survival (DS and OS). Similar evidence has been reported previously [18–21]. Furthermore, according to our Cox hazard model (multivariate analysis) an early death risk is higher when at least one of the risk factors is present.

Our study showed that a vast majority of patients were diagnosed in advanced disease stages (III and IV) resulting in poorer outcome prognosis. Kaplan — Meier estimates of OS and DS for disease stage showed worse survival for late disease stages. Our investigation revealed that of 247 subjects used in the present study, there were only 3 and 19 patients with stage I and stage II disease, accordingly. The importance of early cancer diagnosis and fast referral to the specialist has been previously highlighted [22]. Our estimations of survival appear to support this.

OSCC is an aggressive tumor commonly diagnosed in advance stages and characterized by a high rate of lymphatic metastasis [23]. This was also true for our study where 68.4% of patients presented with clinically positive neck disease (locoregional spread of cancer to neck lymph nodes). Furthermore, N+ patients had higher early death risk (Cox regression multivariate analysis), although there were no significant differences in OS and DS.

We found that lower T grade tends to correlate with better disease outcome. This statement was confirmed by Kaplan — Meier estimates of OS and DS, which showed a significant ($p < 0.001$) decrease in survival by T grade revealing the longest survival for lower T grades. Nevertheless, it is worth noting that our estimates of survival are lower than those demonstrated in the western hemisphere [24].

Our study showed the worst OS and DS for tumors of pharyngeal wall and palatine tonsils, and these data partially agree with the literature [6]. In our study, the majority of the patients had palatine tonsil and base of tongue SCC associated with poorer survival.

In the given study, better OS and DS estimates were demonstrated for the surgically treated patients. Indeed, it may be argued that there is a selection bias in the treatment modalities. The present study brought evidence that SUR might have a clear role in better disease outcome, and the best outcome was demonstrated for the RT+SUR group. We were not able to show any significant differences in survival based on the type of SUR applied (primary tumor excision, neck dissection or both), however, these appeared when SUR *vs* no SUR at all was compared. However, we must admit that the numbers of patients constituting the study groups we used were unequal and not very high. Reviewing the literature, we found that surgical treatment has emerged as the necessary treatment modality for most patients [25].

Furthermore, other studies have shown a survival benefit in operated patients, even when stratified by HPV status [26–28]. However, controversy in results when HPV status was taken into account appears to be elucidated [29]. In his study, Münscher *et al.* showed that the HPV status seemed to have no impact on survival [29]. We hope that our observations have highlighted the necessity of further studies when OSCC outcome is compared in patients with uni- or bilateral neck dissection.

However, there are some studies that state no difference in long-term survival between uni- and bilateral neck dissection in patients with contralateral clinically negative neck [30–33].

Gillison *et al.* in their study have proved the superiority of cisplatin plus RT as opposed to cetuximab plus RT in HPV-positive OSCC [34]. Unfortunately, we should confirm that cetuximab is the only chemotherapeutic agent for the head and neck used in Latvia when treating SCC. There is compelling evidence for reconsidering the chemoradiotherapy regimen. In this study, performing survival analysis of patients with OSCC we found that younger patients had lower early death risk than older ones. Furthermore, by reviewing

the literature one should note that RT produces the long-lasting depression of the immune system and makes some OSCC patients more susceptible to tumor recurrence and worse survival [35].

Prognostic factors have been recognized to be important in selecting the appropriate treatment for the patient. In the current study, we made attempts to predict the course of OSCC investigating the possible prognostic factors. We found that the patient's eventual outcome is strongly predicted by the T stage, therapeutic modality received (RT+SUR), hazardous habits (smoking, alcohol abuse), and the presence of lymph node metastases. Collectively, these results are suggestive of neck dissection necessity, and other studies have reported on the effectiveness of ipsilateral elective neck dissection in clinically negative necks [36–38]. Unfortunately, in our study, data on the HPV status were lacking cutting off the evaluation of the prognostic value of this factor recommended by other scientists [39–44].

In the given study, statistically significant differences in survival rates estimated for patients with OSCC revealing various types of tumor differentiation were not found. Unfortunately, completeness of records deciphering the differentiation of tumor cells, the type of growth (exophytic or endophytic), and the presence of perineural invasion were not absolute. However, some previous studies have demonstrated that endophytic growth, perineural invasion, and extracapsular extension of tumor allow suggesting on contralateral neck metastasis and lower 5-year OS [33, 45].

Problems related to early diagnostics of tumors are well recognized worldwide based on statistical data analysis, we suggest that the majority of patients are diagnosed with stage IV OSCC which means a worse outcome of the disease. Effective measures must be taken to ensure OSCC diagnosis at the early stages. Supportive evidence on the necessity of neck dissection as one of the therapeutic modalities (best results in RT+SUR group) was found by us.

The incidence of OSCC has grown in the last two decades, which, at least partly, may be explained by a contributive role of HPV. HPV positive OSCC has a better prognosis than HPV negative; therefore, HPV status should be determined for prognostic reasons and selection of an appropriate treatment plan. Indeed, bad habits as smoking and alcohol abuse are risk factors that should be included in assessing the disease outcome.

The limitation of the study is that it is a retrospective analysis with a relatively small population. It is also difficult to assess the importance of treatment modalities because some patients treated with RT alone presented with an advanced stage of cancer at the time of diagnosis and poor general health, furthermore, the chemotherapeutical interventions should be presented by more treatment schemes than cetuximab alone. Other studies reporting on similarity in regional recurrence rates observed in patients with SCC of the tongue when selective and radical neck dissections were performed have suggested on supraomohyoid neck dissection as a primary treatment for patients with clinical N0 tumor [46]. This statement agrees with the study results and suggestions, however, our study didn't attempt an assessment of various neck dissection types as well as comparison of SUR and other treatment modalities.

CONCLUSION

Collectively, the study showed that patients with lower T grade, N0 status, lacking bad habits and when SUR was applied as one of the treatment modalities had better 3 and 5-year OS and DS, and lower HR. Future studies leading to more efficient research should be undertaken combining tests for HPV validation with traditional histopathology methods independently performed in several institutions.

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