Smoking and alcohol abuse – predictive factors in oropharyngeal squamous cell carcinoma: A retrospective study

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Abstract. Oropharynx is one of the most common localizations for malignant neoplasms in the head and neck region. HPV-positive OPSCCs are the most common subtypes in Western countries with tobacco and alcohol use, remaining the major risk factors for cancer development in this region. The study aims to address the significance of smoking and alcohol abuse in OPSCC cases and perform a survival analysis of the patients with OPSCC treated over a 10-year period in a single hospital in Latvia, correlating these data with patients’ hazardous habits (smoking and alcohol abuse). Out of 247 patients, the majority were smokers (75.95%, n = 180), approximately one third were habitual drinkers (35.19%, n = 82) or were exposed to both aforementioned major risk factors (31.47%, n = 73). Kaplan-Meier survival analysis showed significantly better survival for the patients without the aforementioned hazardous habits. Cox regression analysis proved a higher early death rate when both factors (smoking and alcohol abuse) were present. It seems that smoking has a higher predictive value than alcohol abuse.

Key words: smoking and alcohol use, oropharyngeal squamous cell carcinoma (OPSCC), oropharynx, pharyngeal cancer, hazardous habits.

1 Introduction

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 – 34,000 new cases and age-standardized incidence of 2.9 in Europe [1].

Nowadays, oropharyngeal squamous cell carcinoma (OPSCC) is divided into two major subgroups according to Human Papilloma Virus (HPV) status (HPV-positive and HPV-negative). HPV-negative OPSCCs are believed to be associated with tobacco and alcohol use [2]. However, these hazardous habits can appear as combined risk factors affecting the development of the neoplasm.

For all mentioned, HPV-positive OPSCCs are the most common subtypes in Western countries with tobacco and alcohol use, remaining the major risk factors for cancer development in this region [3].

Furthermore, two etiological pathways for head and neck squamous cell carcinoma have been suggested, one driven by smoking and alcohol abuse and the other by HPV infection [4, 5].

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Therefore, worth the discussion is the fact about the presence of the synergic effect of smoking/alcohol use and HPV infection in the development of HNSCC however some researchers suggest that there is none [6].

A dose-dependent carcinogenic effect on OPSCC development was recognized [7] evidencing that the risk increases 6–7-fold in individuals overusing tobacco or alcohol and as much as 15-fold in subjects who both smoke and drink alcohol [8].

The world incidence of OPSCC 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, we wanted to address the ever-actual question of the significance of smoking and alcohol abuse in OPSCC cases. The aim was to perform a survival analysis (overall and disease-specific) of the patients with OPSCC correlating these data with subjects’ hazardous habits (smoking and alcohol abuse). To achieve the aim, we have conducted a retrospective study using a group of patients with OPSCC treated over a 10-year period in a single hospital in Latvia.

2 Material and methods

We carried out a retrospective study of 247 patients diagnosed with OPSCC, 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 1\textsuperscript{st} 2000 and December 31\textsuperscript{st} 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. Analysis of the patients’ data was performed when the diagnosis of OPSCC was confirmed histologically.

Statistical analysis of correlation of aforementioned covariates with survival, and mean overall survival time after diagnosis was performed. Statistically significant differences between the study groups were assessed using Pearson’s chi-squared and Fisher’s exact test (depending on the size of the group), and the value of $P < 0.05$ was considered as significant. Cramer’s $V$ was used to measure an association between two nominal variables. Kruskal-Wallis test and Mann-Whitney test (depending on the number of groups) were used to assess the correlation between nominal variables and mean survival time after an established diagnosis of OPSCC.

The data collected was 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 statistical data analysis. Statistical testing for differences in survival rates was performed using the log-rank and Breslow tests. Finally, a Cox regression method was used to estimate the hazard ratio. Age, sex, T stage, N status, risk factors (smoking and alcohol abuse), therapy modality (radiotherapy (RT), surgery (OP), chemotherapy (ChT), symptomatic therapy and combinations of aforementioned, primary tumour location, and histo-pathologic variant of tumour were included as covariates in the survival model. Cox regression methods for two-stage randomization designs were applied when conducting univariate, and secondly, multivariate analysis (see Table 1 for the list of covariates).

3 Results

Less than one-tenth of the patients presented with the stage I and II – 3 (1.22%) and 19 (7.72%) patients, accordingly, whereas a major portion – 224 (91.6%) revealed advanced
Table 1. List of covariates analyzed in multivariate analysis.

| Variables                          | Variables          |
|------------------------------------|--------------------|
| N status (N0 >N+)                  | Sex (female >male) |
| Alcohol abuse and/or smoking       | Age group          |
| None                               | <55 years old      |
| 1 of the aforementioned            | 55 – 64 years old  |
| Both                               | >64 years old      |
| T grade                            | Primary tumour location |
| 1                                  | Palatine tonsil    |
| 2                                  | The base of the tongue |
| 3                                  | Pharyngeal wall    |
| 4                                  | Soft palate        |
| Therapy                            | Histological variant |
| RT                                 | Squamous cell carcinoma, keratinizing |
| OP                                 | Squamous cell carcinoma, non-keratinizing |
| RT + OP                            | Carcinoma, undifferentiated (Epit) |
| RT + ChT (Cetuximab) +/−OP         | Squamous cell carcinoma, BCN (unspecified) |
| RT + ChT (Platinum) +/−OP          |                    |
| Sympt (symptomatic)                |                    |

Table 2. Patients’ breakdown by alcohol abuse and disease outcome (14 patients censored).

| Alcohol abuse | Number of patients (count, %) | Result of the disease (therapy) | Number of patients (count, %) | Statistical analysis between groups |
|---------------|-------------------------------|---------------------------------|-------------------------------|-----------------------------------|
|               |                               | Positive (survived)              | 20 (13, 42)                   |                                   |
|               |                               | Negative (deceased)              | 129 (86, 58)                  |                                   |
| No            | 151 (64, 81)                  |                                 |                               |                                   |
| Yes           | 82 (35, 19)                   | Positive (survived)              | 5 (6, 33)                     |                                   |
|               |                               | Negative (deceased)              | 74 (93, 67)                   |                                   |

disease stage. Only 8.10% \((n = 20)\) of all reviewed patients were female and 91.90% \((n = 227)\) – male. The mean patient age was 60 years, median – 60.20 years.

The majority 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%, \(n = 73\)). Most of the smokers were male \((n = 171)\). Median pack-years were 30.0 \((SD = 17.9)\).

We found that cancer death rates are not very much different when the distribution of patients by the total life/disease outcome (without distinguishing between patients whose death is due to cancer) was correlated to alcohol exposure (Table 2).

Different survival rates (in months) were found when estimating the mean overall survival calculated from the time of established diagnosis and correlated to patient alcohol abuse (Table 3), but differences were not statistically significant between the study groups.

Kaplan-Meier survival analysis (Table 4) showed a statistically significant difference between the overall \((P_L = 3.04 \times 10^{-2})\) survival (OS) curves reflecting variations in alcohol exposures – a higher survival rate was estimated in patients without this characteristic.

No statistically significant differences between the results deciphering disease-specific survival (DSS) when including and excluding those patients, whose cause of death is not cancer, were found over time \((P\) value increased with each time period).
Table 3. Correlation between survival and alcohol abuse.

| Alcohol abuse | Time, months | Statistical analysis |
|---------------|--------------|----------------------|
|               | Mean | SD   | CI 95% | P<sub>MV</sub> | η   |
| No            | 30.18 | 39.33 | 23.81...36.55 | 0.08 | 0.14 |
| Yes           | 19.68 | 26.50 | 13.74...25.61 |

Table 4. Kaplan-Meier analysis of hazardous habits for DSS, OS.

| Variable                  | 3-year Kaplan-Meier estimate % | 5-year Kaplan-Meier estimate % |
|---------------------------|--------------------------------|--------------------------------|
|                           | Overall survival (OS) | Disease-specific survival (DSS) | Overall survival (OS) | Disease-specific survival (DSS) |
| Smoking                   | 32.1% | 30.8% | 25% | 26.9% |
| • No                      | 16.5% | 14.6% | 11.4% | 8.7% |
| • Yes                     | P = 0.0035 | P = 0.005 | P = 0.0035 | P = 0.005 |
| Alcohol abuse             | 24.8% | 22.2% | 16.7% | 16.3% |
| • No                      | 13.9% | 13.9% | 11.4% | 8.9% |
| • Yes                     | P = 0.03 | P = 0.08 | P = 0.03 | P = 0.08 |
| Alcohol abuse and smoking |                                |                                |                                |                                |
| • Neither                 | 34% | 31.8% | 23.4% | 25% |
| • 1 factor                | 22.7% | 20.4% | 16.4% | 14.3% |
| • Both                    | 11.4% | 10.9% | 7.1% | 6.3% |

P = 0.002 | P = 0.008 | P = 0.002 | P = 0.008

Table 5. Patients’ breakdown by smoking and disease outcome (10 patients censored).

| Smoking | Number of patients (count, %) | Result of the disease (therapy) | Number of patients (count, %) | Statistical analysis between groups |
|---------|-------------------------------|---------------------------------|-------------------------------|-----------------------------------|
|         |                               | Positive (survived) |                | Negative (deceased) |                | P<sub>X</sub> | V<sub>1</sub> |
| No      | 57 (24,05)                    | 12 (21,43) | 44 (78,57) | 1.77 x 10<sup>-3</sup> | 0.21 |
| Yes     | 180 (75,95)                   | 12 (6,82)  | 164 (93,18) |                                |                                |

Table 6. Correlation between survival and smoking.

| Smoking | Time, months | Statistical analysis |
|---------|--------------|----------------------|
|         | Mean | SD    | CI 95% | P<sub>MV</sub> | η   |
| No      | 36.63 | 42.01 | 25.38...47.88 | 1.44 x 10<sup>-2</sup> | 0.17 |
| Yes     | 22.63 | 32.45 | 17.81...27.46 |

Regarding tobacco abuse, we found that the number of cancer-related deaths was higher for smokers when comparing the distribution of patients by the total life/disease outcome depending on smoking (Table 5). Moreover, this difference between the analyzed groups was statistically significant (P<sub>X</sub> = 1.77 x 10<sup>-3</sup>) revealing a moderately strong correlation between survival and smoking – V<sub>1</sub> = 0.21.

We demonstrated that patients who don’t smoke have a higher mean overall survival time. The difference between the analyzed groups was statistically significant (P<sub>MV</sub> = 1.44 x 10<sup>-2</sup>), whereas the correlation between survival and smoking was weak – η = 0.17 (Table 6).
### Table 7. Patients’ breakdown by alcohol abuse and/or smoking and disease outcome (15 patients censored).

| Alcohol abuse and/or smoking | Number of patients (count, %) | Result of the disease (therapy) | Number of patients (count, %) | Statistical analysis between groups |
|-----------------------------|--------------------------------|-------------------------------|-----------------------------|-----------------------------------|
|                             |                                | Positive (survived)           | Negative (deceased)         |                                   |
| Neither                     | 48 (20,69)                     | 11 (23,40)                    | 36 (76,60)                  |                                   |
| Alcohol abuse or smoking    | 111 (47,84)                    | 10 (9,09)                     | 100 (90,91)                 |                                   |
| Alcohol abuse and smoking   | 73 (31,47)                     | 3 (4,29)                      | 67 (95,71)                  |                                   |

### Table 8. Correlation between survival and alcohol abuse and/or smoking.

| Alcohol abuse dose-dependent smoking | Time, months | Statistical analysis |
|-------------------------------------|--------------|----------------------|
|                                     | Mean         | SD                   | CI 95%               | \( P_{MV} \) | \( \eta \) |
| neither                             | 35.66        | 41.45                | 23.49 ... 47.84     |            |          |
| alcohol abuse or smoking             | 28.96        | 39.12                | 21.57 ... 36.36     | 2.12 \( \times 10^{-2} \) | 0.21   |
| alcohol abuse and smoking            | 16.12        | 20.91                | 11.13 ... 21.10     |            |          |

When comparing smokers and non-smokers, a statistically significant difference in overall survival was found \( (P_L = 3.50 \times 10^{-3}; P_B = 1.45 \times 10^{-2}) \) suggesting that the proportion of survived patients in non-smokers group is higher at all times. Similar observations were made when estimating disease-specific survival.

Comparing the distribution of patients by the total life/disease outcome depending on alcohol consumption and/or smoking (Table 7), we found that the number of cancer-related deaths was lower in the group of patients who do not smoke and do not use alcohol. The difference between the analyzed groups was statistically significant \( (P_L = 6.00 \times 10^{-3}) \), whereas the correlation between survival and alcohol abuse and/or smoking was weak \( - \eta = 0.22 \).

A higher mean total survival time was calculated for patients without hazardous habits (patients who do not use alcohol and do not smoke) when analyzing the mean overall survival time in cancer patients exposed and not exposed to alcohol consumption and/or smoking (Table 8). The difference between these groups was statistically significant \( (P_{MV} = 2.12 \times 10^{-2}) \), whereas the correlation between survival and presence of hazardous habits was not considered significant as it was weak \( - \eta = 0.21 \).

A significantly lower OS and DSS were demonstrated in OPSCC patients when both risk factors (alcohol abuse and smoking) were detected (Fig. 1).

Finally, when applying Cox regression model, we found that the presence of one of the hazardous habits (smoking or alcohol abuse) has an apparent effect and significantly elevates the risk of death.

### 4 Discussion

The main goal of this study was to collect and analyze data on cigarette smoking and alcohol consumption for patients with OPSCC to understand the relevance of these factors, used when assessing survival rates in case of cancer.
The results of this study revealed that a vast majority of patients were smokers (76%) whereas one third (35%) had drinking problems. We found that these habits independently predict OPSCC prognosis contributing to both OS and DSS, with smoking, playing a more important role in survival, especially DSS.

Furthermore, the combination of these two factors significantly decreases indicators of survival (DSS and OS). Supportive pieces of evidence were obtained by using Cox hazard model (multivariate analysis), which showed a higher risk of early death when at least one of the factors – smoking and alcohol abuse was present. These results seem to be similar to the contention made by other scientists [9–12].

Unfortunately, it was not possible to perform exact dose-dependent analysis of the aforementioned risk factors when studying these retrospectively, and it sets certain limitations of the given study.

Undoubtedly, hazardous habits (smoking, alcohol abuse) proved to be strong predictive factors when assessing survival in OPSCC. These should be considered when selecting the appropriate treatment for the patient.

Even with declining smoking rates reported by American physicians in 2018, assessment of the main risk factors for OPSCC – tobacco and alcohol consumption appear of great relevance when making survival-related suggestions [13].

A growing body of evidence accumulated during the last two decades demonstrates that the incidence of OPSCC increases and the role of HPV in the pathogenesis of OPSCC was highlighted. Many studies show that HPV positive OPSCC has a better prognosis than HPV negative [4, 13–15] therefore the value of the prognostic role of the HPV status appears to be in a focus of interest in some future survival-related studies.

5 Conclusion

Hazardous habits as smoking and alcohol abuse are main, independently acting, risk factors recognized and assessed in patients with OPSCC. Collectively, the given study suggested that
patients without hazardous habits had better 3 and 5-year OS and DSS and lower hazard ratio. Furthermore, it appears that smoking has a higher predictive value than alcohol abuse when assessing survival rates in patients with OPSCC.

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