

Characteristics of and Survival in Oral Squamous Cell Carcinomas in Norway (NOROC) 2005-2009

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Abstract

Background: Incidence of oral squamous cell carcinomas (OSCC) is rising worldwide, and population characterization is important to follow future trends. **Methods:** Patients treated for primary OSCC at all four University Hospitals in Norway between 2005 and 2010 were retrospectively included in this study. The median follow up time was 48 months (range 0-125 months). **Results:** 535 patients with primary OSCC were identified. The overall survival (OS) was found to be 47%, disease specific survival (DSS) was 52%. When extracting the patients given treatment in curative intent the OS was found to be 56.2% and DSS 62.3%. Median age at diagnosis was 67 years (range 24-101 years), and men were in general eight years younger than women. The male/female ratio was 1.2. No gender difference was found in T status or N status, but both factors influenced significantly on survival. **Conclusions:** We present a large and validated cohort of primary OSCC. Patients with small tumors and stage I-II at time of diagnosis had better outcome, and habitual examination of the oral cavity by patients, dentists and physicians may shift more tumors to a more beneficial starting point.

Background

Oral cancer is the most common subtype of head and neck (HN) cancer [1], and includes cancers in the mobile tongue, floor of mouth, buccal and labial mucosa, upper and lower gingiva and alveolar mucosa, retromolar trigone and hard palate [2-4]. Cancers of the oral cavity and the oropharynx (soft palate, uvula and base of tongue) [5, 6] are in many epidemiological studies merged, or there is diffuse description of cancer locations [6-9]. The mobile tongue is the most common site for oral cancer accounting for up to 50% of the cases [9-11].

In 2012 the global incidence of oral cancer was estimated to 275 000 [1], and is steadily rising worldwide according to global cancer statistics in 2018 [12], with a wide geographical variation as it may account for 25% of all cancers in high-risk countries in South-East Asia [7, 12]. In Europe, the incidence is higher in Southern and Central/Eastern parts compared to Northern and Western parts [7, 8, 13]. For cancer of the tongue, there is a trend of increasing incidence in the Nordic countries as well as in the United States [10, 14-16].

Squamous cell carcinoma (SCC) account for more than 90% of malignant neoplasms of the oral cavity and oropharynx [5, 6, 8], and they are classified according to the TNM system that includes primary tumor size (T), regional lymph node spread (N), and distant metastasis (M)[4].

For oral squamous cell carcinoma (OSCC) tobacco smoking, betel chewing and excessive alcohol drinking are the major risk factors [6, 7, 17, 18]. Poor dental health is also considered to be a risk factor [18-21]. Field cancerization increases the risk of second primary tumors in some of patients previously treated for malignant tumors [22-25].

There are different treatment protocols for OSCC. Primary surgery is the preferred treatment in most institutions when tumor is regarded resectable, with or without reconstruction and neck dissection. Postoperative adjuvant radiotherapy (RT) is often necessary, but chemotherapy is rarely used [26-28]. The treatment should be decided by a multidisciplinary team (MDT) [29]. In Norway there has not yet been established a national treatment protocol for head and neck cancer management, but is soon to be implemented. Empirically, treatment has mostly been based on the protocol published by the Danish Head and Neck Cancer Group (DAHANCA)[30].

Five-year survival rates for cancers of the oral cavity and oropharynx are around 50% for most countries [7, 8, 31]. Despite earlier detection and more treatment options, the survival rates have not improved more than three to five percent over the last decades [5, 8]. The SEER database has published a five-year relative survival rate of 66% for tongue, and 53% for the floor of mouth in the period 2009-2015. For the oropharynx the number was 69% [32].

The epidemiological and survival data for oral cancer are hampered with uncertainty as many studies report results from small patient cohorts, often selected from a single or referral hospital, or a small region. Also, some studies include only patients with curative intention, and many merge patients with cancers of various subsites of the HN region that may be caused by different etiological factors, have distinct treatment regimens and have different mortality [9-11, 14, 33].

The aim of this study and collaboration was to present a cohort with validated clinicopathological characteristics both from clinical and histopathological data. We present a large, retrospective, population based study where all patients diagnosed with primary OSCC in the four University Hospitals in Norway in a five year period from 2005 to 2010 were included, whereas patients with cancers of the external upper or lower lip and the oropharynx were excluded. This was possible through a close collaboration in the Norwegian Oral Cancer (NOROC) group study, giving a comprehensive description of the Norwegian population. For all patients included, the localization and histopathological diagnosis were confirmed, giving well validated epidemiological and survival data for primary OSCC in Norway.

Methods

Inclusion and exclusion criteria

The NOROC study was a retrospective study that included all patients diagnosed with primary OSCC in the four University Hospitals in Norway between January 1st 2005 through December 31st 2009. The patients diagnosed during this period were classified according to the TNM 5th Edition 2005 UICC [3]. The relevant International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes were C02-C06 [34], which refers to cancers in the buccal and labial mucosa, upper and lower gingiva and alveolar mucosa, hard palate, mobile tongue and floor of mouth. We did not include cancer of the external upper or lower lip (vermilion) because these almost exclusively arise in the lower lip and are more likely to act as skin cancer [5]. We excluded ICD-10 codes C05.1 and C05.2 which are regarded as oropharyngeal sites. Patients with cancers other than SCC in the oral cavity were excluded, as well as patients with second primaries or previous cancer treatment, see flowchart Figure 1.

Identification of patients

In Norway, management of oral cancer is centralized to the University Hospitals of Rikshospitalet (Oslo), Haukeland (Bergen), St.Olavs (Trondheim) and North Norway (Tromsø), where Rikshospitalet in Oslo (The National Hospital) also is regarded as a tertiary referral hospital. Four hundred unique patients were identified by searching for the relevant ICD-10 codes in the electronic health record (EHR) in Oslo. Patients treated in Bergen, Trondheim and Tromsø were first identified by searching the hospital's pathology archives for cancers with topographic SNOMED coding T51 and T53, which were subsequently matched with the relevant ICD-10 codes recorded in the EHR. Three hundred and eighty unique patients were found in the three latter hospitals, but a review of the files revealed that 115 patients (30.3%) had been incorrectly coded, and did not have oral cancer. The majority (91 patients) of these had oropharyngeal cancer, accounting for 24% of the 380 identified patients.

After having excluded patients with oropharyngeal and lip location, duplicates and technical fault from the initial data, 646 patients with strict oral location were included. After rejecting patient of causes listed over, a total of 535 patients with histopathologically confirmed primary SCC of the oral cavity were included in the study as shown in Figure 1. The 535 primary OSCC found in this cohort included 322 patients (60.2%) from Oslo, 90 patients (16.8%) from Bergen, 67 patients (12.5%) from Trondheim and 56 patients (10.5%) from Tromsø respectively.

Extracting clinical data

Anonymized clinical data were recorded in a web based Case Report Form (CRF), and the last day of follow-up of included patients was set to June 1st 2015. At this time all patients had been followed throughout a minimum of five years. The patient medical records were screened from date of diagnosis until date of death, or from date of diagnosis until last day of follow-up. Recording was done by experienced clinicians (IHB, OJ, GK, EJ and ÁK). Relevant patient data, ICD-10 diagnosis, TNM classification, treatment and follow up were registered. Since these patients were diagnosed between 2005-2010 the stage grouping was done according to AJCC 6th edition 2002 [5].

Tumors with missing stage information lacked T, N or M status. However, a T4 tumor could be staged without knowledge of N and M as it automatically classifies as a stage IV tumor. This was also true with N status \geq N2 and M1. In this study we pooled stage IVA, IVB and IVC into Stage IV.

The study was approved by the Northern Norwegian Regional Committee for Medical Research Ethics (REK Nord; 2013/1786 and 2015/1381). Cause of death was acquired from Norwegian Cause of Death Registry. A patient information and consent letter was sent to those still alive giving them the option to opt-out of the study. The address used was the latest address given in the EHR. No letters were returned from patients or postal services.

Categorical grouping

Patients in this study were divided into groups based on age at time of diagnosis, with ten years interval (51-60 years, 61-70 years and 71-80 years), but those younger than 50 and older than 80 were few and thus pooled in a younger (\leq 50 years) and an older (\geq 81 years) age group. We also organized the patients according to an indicator called Integrated Risk Factor (IRF) based on extent of tobacco and alcohol consumption as previously described by Rikardsen et al. [33]. Patients with alcohol consumption marked as seldom in the medical records were classified as "light drinkers" (\leq 1 times weekly), whereas those with consumption denoted as current, moderate,

heavy and former alcoholic abuse were classified as “drinkers” (> 1 times weekly or daily) [35, 36]. Based on information from the EHR, dental status was categorized as good (no need for treatment), needs treatment (before start of cancer treatment there was a need of dental treatment) or edentulous [37]. Cancer treatment described in the EHR was defined into 10 different groups/combinations of treatment modalities of either curative or palliative intention. Cancer treatment combinations found in this cohort are listed in Table 1. Palliative treatment in Table 6 was pooled together with patients where no precise statement about treatment was found. Level of education was poorly described in the EHR and could not be used to describe socioeconomic status.

Statistical analyses

The association between gender and different variables was evaluated using Person bivariate correlation and bootstrapping at 95% confidence interval (CI) [38]. This was applied in table 2, 4 and 6. For evaluation of survival Cox regression allowed us to report significance, hazard ratio (HR) and 95% confidence interval after bootstrapping as shown in table 2 and 4. Results were considered to be significant at $p < 0.05$. For survival the variables significant on univariate analysis were analyzed for multicollinearity applying linear regression, testing independent variables against a dependent variable. VIF values < 2 were regarded to indicate no multicollinearity. The variables with limited data were excluded from calculations because of risk of sparse data bias [39, 40]. Kaplan-Meier was used to construct survival analyses plot in Figure 2. All statistical analyses were performed with IBM Statistical Package for the Social Sciences (SPSS) version 25.

Results

Our study population consisted of 535 patients diagnosed with primary OSCC between 2005 and 2010 in Norway. The male/female ratio was 1.2, and the median follow-up time from end of primary treatment till death or last day of follow up was 48 months (range 0-125 months).

Clinicopathological characteristics

The clinicopathological characteristics are given in Table 2. Median age at time of diagnosis for the whole cohort was 67 (range 24-101 years) with very few patients under the age of 40 and over the age of 90 (13 and 11 cases respectively, data not shown). However, men were in general eight years younger than women at the time of diagnosis, and the median age for men was 64 (range 25-101 years) and for women 72 (range 24-96 years).

In almost 97% of the cases TNM staging was completed, and 93% of the cases was discussed in MDT meetings. There was no significant gender difference in T status, N status or stage of disease at time of diagnosis. T1 and T2 tumors constituted 53% of the cases, almost 11% were T3 tumors, and 33% were T4. When T, N and M categories were combined in the AJCC staging, almost 43% of the patients had stage I and II disease, 12% had stage III, and 42% had stage IV disease.

There was no significant gender difference in location of the primary tumor (Table 2). In both genders mobile tongue was the most common site for cancer, accounting for almost 50% of the cases for men and 40% for women. The second most common tumor location in men was the floor of mouth while gingiva and alveolar mucosa was more frequent in women. Cancers in the mobile tongue were most often T1-T2 tumors, whereas the gingiva and alveolar mucosa had more T4 tumors. Tumors of the floor of mouth were most often T2 and T4, as shown in Table 3. There was no correlation between age group and location ($p = 0.068$, CI: 0.001-0.164). Only three patients all together were noted to have distant metastasis. Because of few cases no calculations was performed on this variable.

Risk factors

Risk factors are listed in Table 4. Smoking habits were recorded for 93% of the patients. There was a significantly lower proportion of never-smokers among male compared to female patients (14% vs. 34%) and 60% of the male patients were current smokers compared to 40% of the female patients. Only two patients were recorded consuming Scandinavian snuff, but both were former smokers and recorded as such. Current smoking did not correlate with site of primary cancer ($p = 0.175$, CI: -0.025-0.141), nor to T status ($p = 0.909$, CI: -0.093-0.085) or N status ($p = 0.628$, CI: -0.064-0.109).

Of note, 35% of the EHR lacked information of alcohol consumption, but in information available men consumed significantly more alcohol than women, with 11% of the men being heavy drinkers compared to 2.5% of the women. Alcohol consumption was not associated with site of primary cancer ($p = 0.858$, CI: -0.068-0.094), and not related to T status ($p = 0.522$, CI: -0.111-0.054) or N status ($p = 0.770$, CI: -0.084-0.069).

The combination of smoking and alcohol consumption (IRF) revealed that many more men than women were classified as smoker and drinkers, but the difference as a whole was not found to be significant. Correlation was found for IRF and T status ($p=0.001$, CI: 0.067-0.237), but not for site of primary cancer ($p=0.265$, CI: -0.035-0.125) nor N status ($p=0.856$, CI: -0.060-0.081).

Half of the patients needed some form of dental therapy before oral cancer treatment, 20% needed no treatment, and 20% of the patients were edentulous. Ten percent of the patients lacked information in the EHR about dental status. There were more edentulous patients in the older than the younger age groups ($p<0.001$, CI: 0.178-0.348). When adjusted for age, there was no gender difference in dental status ($p=0.708$, CI: -0.071-0.104).

Patients with tongue cancer needed less dental treatment than patients with tumors in other sites. 32% of the patients with cancer of the mobile tongue were recorded with good dental status compared to 9-14% of patients with cancer at the other sites. The difference between location and the need of dental treatment was significant ($p=0.002$, CI: 0.039-0.213).

Treatment

Patients with both curative and palliative treatment were included in this study. Table 6 gives a summary of treatment. In 70% (377) of the patients the treatment was surgery with curative intention, and around 64% (240) of these received postoperative RT. About six percent of the patients had radiation planned prior to surgery, and there was no gender difference in this stratification of treatment ($p=0.215$, CI: -0.171-0.026). Primary RT without surgery of primary site was documented for 19%, and palliative treatment was stated for 11% (six percent with RT, the rest with some debulking surgery or chemotherapy).

There was a significant difference in use of RT between age groups ($p<0.001$, CI: -0.334- -0.173, data not shown). Among the oldest patients (≥ 81 years) almost 30% were given primary RT and no surgery. For patients younger than 80 years, 43% to 56% of the patients received postoperative RT. Women seemed to receive significantly less radiation than men. When adjusting for age there was no difference in use of RT among the genders ($p=0.381$, CI: -0.049-0.124). There was no correlation between RT and site ($p=0.683$, CI: -0.070-0.100), but T status ($p=0.008$, CI: 0.027-0.207) and N status ($p=0.031$, CI: 0.007-0.171) were significantly associated.

Survival

Five-year overall survival (OS) was 46.9% for the whole cohort, and disease specific survival (DSS) was 51.7% (225 of 435 patients). Kaplan-Meier DSS-plot for the whole cohort and different stages of disease is shown in Figure 2. Five-year DSS for the whole population was 80.2% for stage I, 67.7% for stage II, 45.3% for stage III and 32.6% for stage IV.

When excluding patients given palliative treatment, the five-year OS and DSS increased to 56.2% and 62.3%, respectively for the remaining patients. Separated into stages, the five-year DSS for patients treated with curative intent were 80.2% for stage I, 68.4% for stage II, 51.1% for stage III and 43.1% for stage IV ($p<0.001$, HR= 1.435, CI: 0.261-0.481).

The clinicopathological factors age-groups, tumor size, lymph node status and stage of disease were all significant in univariate tests at p value <0.005 level (Table 2). There was a possible multicollinearity between stage of disease and tumor size (VIF 4.68) and most likely between stage of disease and lymph node status (VIF 7.88), and therefore stage of disease was omitted for the multivariate test. All three variables (age-groups, tumor size and lymph node status) were significant ($p=0.001$, HR; 1.487, CI: 0.288-0.517, $p=0.003$, HR; 1.201, CI: 0.063-0.303 and $p=0.001$, HR; 1.682, CI: 0.363-0.679) in multivariate analyses for overall survival. This was also true for the multivariate analyzes for disease specific survival (data not shown).

Discussion

Our study is larger than most other comparable cohorts, and includes only well validated primary OSCC patients. The five-year DSS for the whole cohort was about 52%, and this is in accordance with Warnakulasuriya et al. [7]. The five-year OS in our Norwegian cohort was about 47%, which is somewhat higher than reported in a Danish cohort for the same period (44%)[15], but lower than in a Finnish study (61%). However, the Finnish study included only patients with oral squamous cell carcinoma of the tongue treated in curative intent [10]. When we excluded the patients given palliative treatment the five-year OS increased to 56.2% , and the DSS increased to 62.3%, which is better than in the global and the Danish cohorts, but still lower than in the Finnish. Although the OSCC treatment in Norway is centralized to the four University Hospitals, some patients with small T1 tumors may have been treated at their local hospital without referral to the HN cancer centers, and would be missed from our cohort. Patients with T1 tumors have significantly better survival rates than patients with more advanced disease. If some of the patients with T1 tumors have not been included in this material the consequence may have

caused a negative shift in the survival data. Despite earlier detection of cancer and more treatment options our findings show survival rates have improved little, corroborating results from other studies [5, 8].

This is a large and homogeneous cohort of primary OSCC described in a Norwegian patient population. HN squamous cell carcinomas consist of tumors of the oral cavity, oropharynx, hypopharynx and larynx where the OSCC make up the largest group [1, 41]. However, many epidemiological studies present data for HN cancer or oral cancer without further description of site, and often with a mix of locations [1, 6, 7]. Separating oral and oropharyngeal cancers is important as they are associated with distinct risk factors. For cancers arising in the neighboring oropharyngeal region, high-risk human papilloma virus (HPV) is considered to be an additional risk factor [42-44]. There is little scientific evidence to consider HPV as a risk factor for oral cancer, and the frequency of HPV positive SCC in the oral cavity is generally very low with less than four percent in a Brazilian cohort [45] and less than 10% in a previous study from our group [33]. OSCC also differ in primary treatment protocols, respond differently to treatment and have different survival rates. The estimated number of annual new cases for oropharyngeal cancers in 2012 was 96 000 [46], compared to 275 000 for oral cancer [7].

In our study nearly a quarter of the cases recorded as oral cancers in the pathology archives were oropharyngeal cancers and thus excluded from the study population. This suggests that there is a need to raise the awareness among both clinicians and pathologists of the importance of a correct anatomical description of the cancer site in the patient medical records. Correct coding is crucial for proper cancer statistics. In Sweden health authorities have since 2009 focused on avoiding use of the ICD-10 diagnose C02.4 (tongue tonsils) as this can easily be misinterpreted as an oral location. Tumors arising in the root of the tongue is best coded as C01 (base of the tongue) recognized as an oropharyngeal location [47]. We assume that the awareness of separating oral and oropharyngeal cancers is rising, and that new editions of TNM classification will emphasize on this important issue [4].

In the current study, 45% of the patients had cancer of the mobile tongue, which corresponds well to reports from previous studies [9-11]. The site and TNM classification are generally the most important prognostic factors for oral cancer [31]. In the present study, we found significantly longer survival for patients having tumors with low T status and stage, whereas the anatomical site of the tumor had no significant impact. In our cohort there was no gender difference in T status.

Early detection and treatment is important for overall survival [1, 8], and there were more T1-T2 tumors in the tongue and more T4 tumors in the gingiva and alveolar mucosa. The latter might reflect the short distance from the mucosa to the bone at these sites, and a tumor involving the bone is classified as a T4 tumor irrespective of tumor size. The mobile tongue is relatively easy to self-inspect compared to other intraoral locations and the use and function of the mobile tongue may give a sooner awareness of a tumor. Early stages of oral cancer are often curable, thus early detection and treatment is of vital importance. In Norway, a large proportion of adults have regular dental examinations, and both dentists and dental hygienists are trained to examine the oral mucosa for malignant lesions. Still, we found that 44% of the tumors were stage T3 and T4 at diagnosis, which could indicate that dentists and dental hygienists fail in detecting early signs of cancer. However, patients diagnosed with large tumors were more often edentulous or needed dental treatment before cancer treatment could start, and may suggest that these patients did not seek dental treatment or consult their general practitioner as frequently as those with good dental status and smaller tumors. Older patients had larger T status, perhaps reflecting more silent growth of tumor and later awareness of illness and neglect in seeking their physician or dentist. It may also reflect that symptoms such as changing diet and losing weight may be regarded differently in elderly patients. More elderly were edentulous, and might therefore rarely be examined by a dentist.

Globally, men have higher risk of oral cancer than women and we found a male/female ratio of 1.2. This ratio is slightly lower than reported from a Danish and a US study (1.5 and 1.8 respectively) [15, 16], and slightly higher than reported in a Finnish study with 0.9 [10]. This relatively small gender difference in oral cancer incidence may reflect that the tobacco and alcohol consumption has become more similar for men and women over the last three decades. However, men were on average eight years younger than women at time of diagnosis, which may reflect the fact that more men were heavy drinkers and smokers than women and therefore developed the disease earlier.

We found the median age for time of diagnosis to be 67 years. This is somewhat older than reported in our neighboring countries Finland and Denmark (65.6 and 63 years, respectively) [10, 15] and in the US (62 years) [7]. If smoking and drinking habits are important risk factors one could speculate that the Norwegian population is less addicted to such stimuli. Proportion of daily smokers of cigarettes in 2014 was for Finland 11.6%, for Denmark 12.3%, Norway 12.5% [48]. In the US the percentage of smokers in 2016 was recorded to 15.5 [49]. The total alcohol consumption per capita in liters pure alcohol in 2015 was 12.3% for Finland, 11.4% for Denmark, 7.7% for Norway [50], and 8.7% for US [51]. These figures do not seem to explain the older age at time of diagnosis in Norway.

The men in our population were eight years younger at time of diagnosis compared to the women. Similar gender differences in age at diagnosis have also been reported in other cohorts described from Denmark, the United States and in Northern Norway [15, 16, 33]. The younger age at diagnosis for men may be due to more cigarette smoking and a higher consumption of alcohol than for women [35]. The prevalence of smoking is nowadays low compared to when the patients in our study were young. In the US the numbers of smokers have declined over the last decades, with a slower rate of decrease for women than for men. Today the gender difference is low (0.4 to 2.2%) for Finland, Denmark and Norway [52], and in the US the percentage of current cigarette smokers in 2016 was 17.5% for men and 13.5% for women [49]. The percentage of drinkers has also decreased both in Europe and in the US by approximately 10% since 2000 [51, 53]. There is a gender difference as WHO report that fewer women drink than men in all WHO regions, they drink less than men when they do, and have fewer episodes of heavy drinking [51]. One must assume that this gender difference in alcohol consumption has been fairly constant over decades, but the difference in gender is not very high.

The incidence of oral cancers is rising despite the change in smoking habits and a reduction in alcohol consumption over the last decades, and one must consider if there are other important mechanisms responsible for this increase. Interestingly younger people in Norway now use Scandinavian snuff instead of cigarette smoking [54]. It will therefore be interesting to follow the characteristics of the patients with oral cancer in the coming years.

The choice of treatment was decided at MDT meetings for the vast majority of patients. This is according to current recommendations [29], and was a positive finding as these patients were treated six to 13 years ago when MDT meetings were less established than today. Cancer in the oral cavity is normally managed by surgical removal of the primary tumor, sometimes combined with neck dissection and/or RT, while chemotherapy is rarely used [26-28]. The same standard of treatment was also found in our cohort.

Cancer immunotherapy has in recent years shown success in anti-tumor therapy. Cancer cells have the ability to activate different immune checkpoint pathways that harbor immunosuppressive functions, and antibodies that target these checkpoints is now coming into cancer treatment. In 2016, two anti-PD-1 checkpoint inhibitors provided a new option for patients with metastatic head and neck cancer resistant to treatment to cisplatin [55, 56]. This has led to many new trials involving established checkpoint inhibitors, and in the future there seems to be an urgent need to find good biomarkers that can identify and stratify responsive patient cohorts to one or more of these antibodies [57, 58].

There are limitations to our study. The Eighth Edition of the TNM classification has been introduced since this study was initiated, and in the new TNM classification tumor thickness is included in the T stage [4]. To find epidemiological data about a population, a prospective study would have given more accurate data about the patient socioeconomic status, smoking and alcohol consumption and exact treatment. It was not possible to specify the amount of tobacco use in pack-years or drinking units as this was a retrospective study. In as many as 35% of the EHR the information of either smoking or drinking habits or both were missing. The patient files stated present or past occupation, but not level of education. Level of education is interesting as a measure of cancer incidence in different socioeconomic classes.

Conclusions

We present a study of a large cohort of 535 validated primary OSCC. Five-year DSS for the whole cohort was near 52%, and included patients receiving curative as well as palliative treatment. When extracting patients given treatment of curative intent the five-year DSS increased to 62%. There was no gender difference regarding survival even if men on average were eight years younger than the women at the time of diagnosis.

Alcohol and smoking habits are often discussed as the most important risk factors, but with the trend of decreasing consumption with a coincidental escalation in the incidence of oral cancer, other etiological factors cannot be excluded and should be searched for in further studies.

Abbreviations

OSCC: Oral Squamous Cell Carcinomas; OS: Overall Survival; DSS: Disease Specific Survival; HN: Head and neck; SCC: Squamous Cell Carcinoma; TNM: classification of Tumor, Node and Metastasis;

RT: Radiotherapy; MDT: Multidisciplinary team; NOROC: Norwegian Oral Cancer group; UICC: Union for International Cancer Control; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; EHR: Electronic health record;

SNOMED: Systematically organized computer processable collection of medical terms providing codes; CRF: Case report form; AJCC: American Joint Committee on Cancer; REK: Regional committee for medical research ethics; IRF: Integrated risk factor; SPSS: Statistical package for the social science.

Declarations

Ethics approval and consent to participate

The study was approved by the Northern Norwegian Regional Committee for Medical Research Ethics (REK Nord; 2013/1786 and 2015/1381). Cause of death was acquired from Norwegian Cause of Death Registry. A patient information and consent letter was sent to those still alive giving them the option to opt-out of the study. The address used was the latest address given in the EHR. No letters were returned from patients or postal services.

Consent for publications

Not applicable.

Availability of data and materials

The dataset used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare they have no competing interests.

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Authors' contributions

IHB participated in the design of the study, retrieved the clinical information from patient health records, performed statistical analyses and drafted the manuscript. OJ, GK, ÁK and EJ participated in the design of the study, retrieved clinical information from the patient health records and critically reviewed the manuscript. LUH was central in the conception and design of study and critically reviewed the manuscript. OGR and EHO participated in the design of the study and critically reviewed the manuscript. SES was central in the conception and design of study, performed statistical analyses and critically reviewed the manuscript. The final manuscript have been read and approved by all authors.

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Tables

Table 1. Ten different treatment options found in this cohort.

Primary site surgery-no neck surgery-no RT
Primary site surgery-elective neck surgery-postoperative RT
Primary site surgery-selective neck surgery-postoperative RT
Primary site surgery-modified/radical neck surgery-postoperative RT
Primary site surgery-elective neck surgery-no RT
Primary site surgery-selective neck surgery-no RT
Primary site surgery-preoperative RT-selective/modified/radical neck
Curative RT
Palliative RT
Only stated palliative treatment (often chemotherapy)

Table 2. Clinicopathological characteristics of 535 oral squamous cell carcinomas 2005-2009 an five year Overall Survival (OS) and Disease Specific Survival (DSS).

				OS (%)	p HR(CI)	DSS (%)	p HR(CI)
Gender	Male (%)	Female (%)	p (CI)	Male/female		Male/female	
Number	294 (55)	241 (45)		137 /114		122/103	
Age, median (range)	64 (25-101)	72 (24-96)					
Age groups							
≤50	31 (10.5)	19 (7.9)	<0.001 (0.158-0.317)	35 (70.0)	<0.001 1.435; (1.299-1.586)	35 (72.9)	0.001 1.580 (0.338-0.594)
51-60	72 (24.5)	36 (14.9)		65 (57.4)		59 (60.2)	
61-70	108 (36.7)	55 (22.8)		88 (54.0)		81 (61.4)	
71-80	54 (18.4)	66 (27.4)		48 (40.0)		38 (41.3)	
>80	29 (9.9)	66 (27.0)		18 (19.1)		12 (18.5)	
Primary site							
Anterior tongue	142 (48.3)	98 (40.7)	0,107 (-0.013-0.157)	117 (48.8)	0.338 1.041; (-0.046-0.121)	106 (54.4)	0.228 1.058 (-0.041-0.152)
Gingival/alveolar	46 (15.6)	61 (25.3)		49 (45.8)		44 (48.9)	
Floor of mouth	69 (23.5)	33 (13.7)		50 (40.9)		43 (54.4)	
Cheek/bucca/retromolar	35 (11.9)	44 (18.3)		33 (41.8)		30 (45.5)	
Hard palate	2 (0.7)	5 (2.1)		2 (28.6)		2 (40.0)	
Tumor status							
T1	65 (22.1)	46 (19.1)	0.404 (0.052-0.108)	70 (63.1)	<0.001 1.401; (0.232-0.437)	66 (72.5)	<0.001 1.531 (0.311-0.553)
T2	100 (34.0)	73 (30.3)		95 (54.9)		83 (61.9)	
T3	29 (9.9)	29 (12.0)		19 (32.8)		16 (34.0)	
T4	92 (31.3)	85 (35.3)		60 (33.9)		53 (34.6)	
Missing	8 (2.7)	8 (3.3)		7 (38.9)		7 (70.0)	
Lymph node status							
N0	186 (63.3)	143 (59.3)	0.426 (-0.050-0.112)	193 (58.7)	<0.001 1.825; (0.469-0.741)	174 (65.2)	<0.001 1.929 (0.509-0.816)
N1	34 (11.6)	23 (9.5)		21 (36.8)		18 (37.5)	
N2	53 (18.1)	56 (23.2)		22 (20.2)		22 (22.9)	
N3*	4 (1.4)	1 (0.4)		0 (0)		0 (0)	
Nx/Missing	17 (5.8)	18 (7.5)		7 (50.0)		3 (51.3)	
Stage of disease							
Stage I	61 (20.7)	40 (16.6)	0.107 (-0.013-0.162)	69 (68.3)	0.001 1.435; (0.261-0.481)	65 (80.2)	0.001 1.665 (1.356-1.729)
Stage II	75 (25.5)	51 (21.2)		77 (61.1)		67 (67.7)	
Stage III	35 (11.9)	28 (11.6)		29 (46.0)		24 (45.3)	
Stage IV	112 (38.1)	111 (46.1)		68 (30.5)		62 (32.6)	
Missing	11 (3.7)	11 (4.6)		8 (36.4)		7 (58.3)	

* Were not included in calculations because of risk of sparse data bias

Table 3. Tumor site (ICD-10) and T status of 519 patients with OSCC in the Norwegian cohort 2005-2009.

ICD-10 site	T1 n (%)	T2 n (%)	T3 n (%)	T4 n (%)	Total n (%)
Mobile tongue	73 (31.3)	95 (40.8)	29 (12.4)	36 (15.5)	233 (44.3)
Gingiva and alveolar mucosa	10 (9.5)	17 (16.2)	7 (6.7)	71 (67.6)	105 (20.2)
Floor of mouth	18 (18.6)	34 (35.1)	10 (10.3)	35 (36.1)	97 (18.7)
Cheek/Bucca/Retromolar area	10 (13.0)	24 (31.2)	11 (14.3)	32 (41.6)	77 (14.8)
Hard palate	0 (0)	3 (42.9)	1 (14.3)	3 (42.9)	7 (1.3)
T status n (%)	111(20.7)	173 (32.3)	58 (10.8)	177 (33.1)	519 (100)*

*16 patients had missing T status and are not included in this table.

Percentage shown within the tumor site group, but summed up in T status and percentage of total number (n).

Table 4. Risk factors for 535 patient with oral squamous cell carcinoma in Norway 2005-2009 and five-year Overall Survival (OS) and Disease Specific Survival (DSS).

				OS (%)	p HR; (CI)	DSS (%)	p HR (CI)
Gender	Male (%)	Female (%)	p (CI)	Male/female		Male/female	
Number	294 (55)	241 (45)		137/114		122/103	
Smoking							
Never	41 (13.9)	82 (34.0)	<0.001 (-0.328- -0.159)	61 (49.6)	0.222 0.915; (-0.232-0.057)	56 (52.8)	0.388 0.926 (-0.260-0.099)
Current	169 (57.5)	97 (40.2)		125 (47.0)		111 (52.4)	
Former	70 (23.8)	37 (15.4)		51 (47.7)		45 (51.1)	
Missing	14 (4.7)	25 (10.4)		12 (32.4)		11 (40.7)	
Alcohol consumption							
Never (Non-drinkers)	12 (4.1)	36 (14.9)	<0.001 (-0.228- -0.082)	18 (37.5)	0.237 0.929; (-0.100-0.053)	14 (38.9)	0.733 0.996 (-0.031-0.019)
≤1 times weekly (Light drinkers)	42 (14.3)	55 (22.8)		49 (50.5)		48 (55.8)	
>1 times weekly or daily (Drinkers)	155 (52.7)	49 (20.3)		90 (44.1)		80 (48.5)	
Missing/unknown	85 (28.9)	101 (41.9)		94 (50.5)		83 (56.1)	
Integrated Risk Factor							
Non-smoker/Non-drinker	12 (4.1)	32 (13.3)	0.021 (0.012-0.181)	17 (38.6)	0.095 0.969; (-0.069-0.005)	12 (37.5)	0.177 0.936 (-0.067-0.013)
Non-smoker/Light drinker	39 (13.3)	41 (17.0)		46 (57.5)		44 (62.0)	
Smoker/Non-drinker*	1 (0.3)	5 (2.1)		3 (50.0)		3 (60.0)	
Smoker/Light drinker	15 (5.1)	20 (8.3)		18 (51.4)		18 (56.3)	
Smoker/drinker	138 (46.9)	42 (17.4)		70 (38.9)		63 (43.8)	
Unknown	89 (30.3)	101 (41.9)		97 (51.1)		85 (56.3)	
Dental status							
Good	68 (21.4)	44 (18.3)	0.055 (-0.004-0.169)	66 (61.7)	0.020 1.218; (0.030-0.372)	63 (68.5)	0.001 1.472 (0.157-0.644)
Needs treatment	158 (53.7)	112 (46.5)		138 (51.1)		124 (54.6)	
Edentulous	45 (15.3)	64 (26.6)		31 (28.4)		24 (28.6)	
Missing	28 (9.5)	21 (8.7)		14 (30.4)		12 (41.4)	

* Were not included in calculations because of risk of sparse data bias

Table 5. Tumor site (ICD-10) and alcohol and smoking habits (Integrated risk factor, IRF) for 535 patients with oral squamous cell carcinoma 2005-2009.

ICD-10 diagnose	NS/ND n(%)	NS/LD n(%)	S/ND n(%)	S/LD n(%)	S/D n(%)	Unknown n(%)	Total n
Mobile tongue	17 (7.1)	42 (17.5)	3 (1.3)	13 (5.4)	74 (30.8)	91 (37.9)	240
Gingival/alveolar mucosa	14 (13.1)	17 (15.9)	3 (2.8)	5 (4.7)	24 (22.4)	44 (41.4)	107
Floor of mouth	4 (3.9)	4 (3.9)	0 (0)	8 (7.8)	58 (56.9)	28 (27.5)	102
Cheek/Bucca/ Retromolar area	8 (10.1)	16 (20.3)	0 (0)	8 (10.1)	22 (27.8)	25 (31.6)	79
Hard palate	1 (14.3)	1 (14.3)	0 (0)	1 (14.3)	2 (28.6)	2 (28.6)	7
	44 (8.2)	80 (15.0)	6 (1.1)	35 (6.5)	180 (33.6)	190 (35.5)	535 (100)

NS=Non-smoker, ND=Non-drinker, LD=Light Drinker, S=Smoker, D=Drinker. Percentage shown within the tumor site group, but summed up within IRF-group.

Table 6. Treatment of 535 oral squamous cell carcinoma patients 2005-2009.

	Male n (%)	Female n (%)	p (CI)	All n (%)
Primary Surgery	216 (73.5)	161 (66.8)	0.125 (-0.171-0.026)	377 (70.5)
Preoperative RT	18 (6.1)	16 (6.6)		34 (6.4)
Palliative/Non/Missing	60 (20.4)	64 (26.6)		124 (23.2)
No neck surgery				
No neck surgery	133 (45.2)	122 (50.6)	0.149 (-0.161-0.024)	255 (47.7)
Elective neck	49 (16.7)	27 (11.2)		76 (14.2)
Selective neck	30 (10.2)	22 (9.1)		52 (9.7)
Modified Radical neck	38 (12.9)	24 (10.0)		62 (11.6)
Radical neck	3 (1.0)	3 (1.2)		6 (1.1)
Missing	41 (14.0)	43 (17.8)		84 (15.7)
No RT				
No RT	73 (24.8)	85 (35.3)	0.008 (-0.200- -0.033)	158 (29.5)
Primary RT (no surgery)	53 (18.0)	51 (21.2)		103 (19.3)
Postoperative RT	150 (51.0)	90 (37.3)		240 (44.9)
Preoperative RT	16 (5.4)	15 (6.2)		32 (6.0)
Both Pre- and Postopr.RT	2 (0.7)	0 (0)		2 (0.4)

Figures

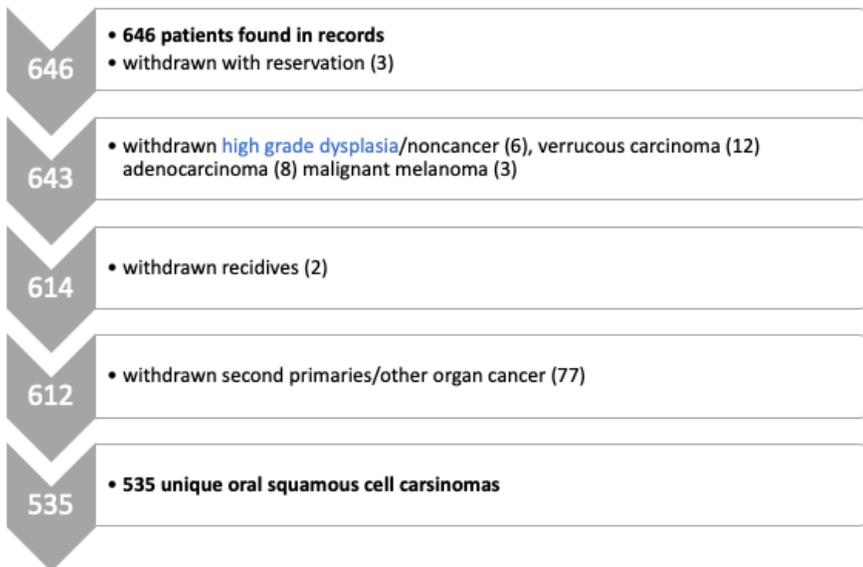


Figure 1

We identified 535 unique primary oral squamous cell carcinomas at the four University Hospitals of Norway in the time period 2005-2009.

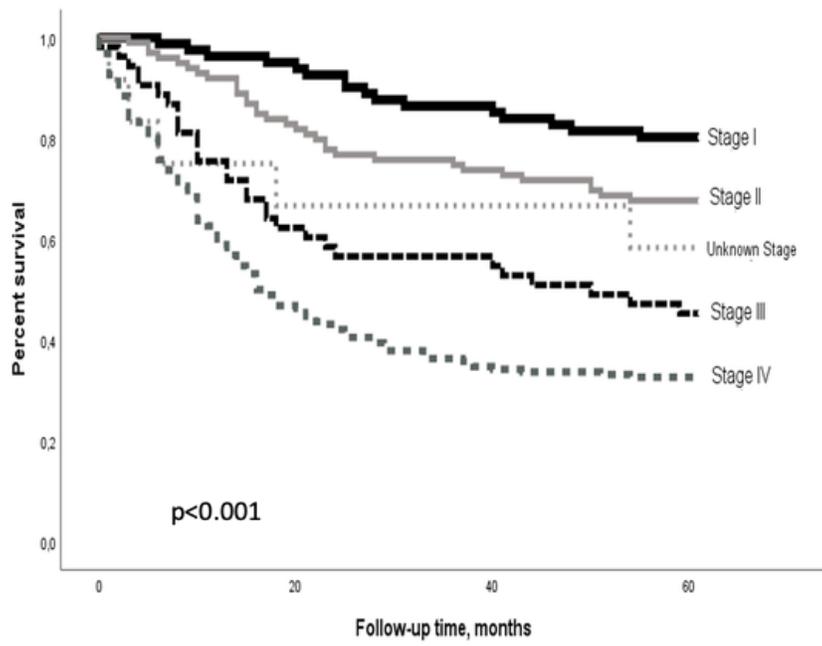


Figure 2

Disease-specific survival by stage in 435 patients with primary oral squamous cell carcinoma in Norway in the years of 2005-2009.