MASTEROPPGAVE
Oral cancer in Northern Norway (1986-2009)

A study of different factors' possible effect on survival of patients diagnosed with oropharyngeal cancer

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Content

1.0 Abstract

This was a retrospective clinical study looking at those diagnosed with primary oropharyngeal cancer at the University hospital of Northern Norway (UNN) from 1986-2002 (follow up to 2009) and various factors' influence on patient survival. In this period 162 persons were diagnosed with primary cancer in the oral cavity, patients with metastasis to the oral cavity were not included. Information about age, gender, time of diagnosis, smoking habits, alcohol consumption, TNM grading and differentiation of the primary tumor, treatment regiments and whether or not the disease had recurred were collected from the hospital journals. Information on cause of death was retrieved from the Norwegian institute of Public Health after application.

Descriptive and survival statistical analyses were performed, and the results were compared with national data from the Norwegian Cancer Registry as well as with results from international studies. Calculation of incidence showed that there was an increasing incidence of head and neck squamous cell carcinomas (HNSCC) in the Northern Norwegian population from 1994-2002, most notably of tongue SCCs. Distribution of male and female were 56 % and 44 % respectively, and 62 % of the patients were ≥60years at the time of diagnosis. The majority of the tumors were either well (32 %) or moderately (64 %) differentiated. Sixty-three percent of the tumors were diagnosed at T-stage 1 or 2, meaning that they were rather small, whereas 28 % were diagnosed at T-stage 3 or 4. Fifty-four percent of the patients had no metastatic disease at time of diagnosis (N0, M0). Gender stratification showed that a higher proportion of females than males were diagnosed before the onset of metastases (~60 % and ~50 % respectively). In the study population 45 % were smokers and 19 % reported that they consumed alcohol more than once a week.

We found that high alcohol consumption had a significant negative influence on survival. Smokers also showed a lower 5-years survival rate than non-smokers, but the differences were not statistically significant. Women showed significantly better 5-year survival rate than men with the same TNM-staging.

2.0 Introduction

The subject of our thesis is oral cancer and factors possibly influencing survival and prognosis in patients with this disease. In this study we define oral cancer as squamous cell carcinomas (SCCs) arising in the oral cavity and/or oro-pharynx (OSCCs).

Carcinomas are malignant tumors of epithelial origin. The oral cavity is covered by stratified squamous epithelium, and SCCs represents 90-95% of malignant tumors in this localization. They often evolve from premalignant, dysplastic changes, which may appear as a red, white or red/white spot. These lesions are often termed erythroplakias or leukoplakias [1]. OSCCs occur mainly in people over 40 years, and affect men more often than females [2]. The rates of incidence and mortality of OSCCs are broadly varying around the world, with notably high rates in Southeast Asia and Eastern Europe [3]. Over the past 50 years, the incidence of oral cancer in Norway has showed a marked increase in females but for men it has been unchanged. According to data from the Norwegian Cancer Registry, the incidence (per 100 000) of mouth and throat cancer in 1956-1960

for men was 8.0 and for women 2.3. In 2006-2010, the incidence was 7.9 for males and 4.3 for females [2].

Based on data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database, in the period 2005-2009 only 8.9 % of the patients diagnosed with oral cancer where under the age of 45 years [4]. So the majority of OSCCs are to be found in older age groups, most frequently in the sixth to seventh decades of life [4]. Results from the NORDCAN database showed that the incidence of oral cancer in the Nordic countries was increasing over the last ten years [5]. Incidence in young adults seems to be increasing in both the United States and worldwide. The analysis of SEER showed an annual increase in the incidence of oral tongue, palatine tonsil, and base-of-tongue cancers, by 2.1%, 3.9% and 1.7% respectively, in 20-to 44-year-old white patients in Norway. Incidents of squamous cell carcinomas at other sites in the head and neck region declined [6].

Recent matched-control studies and national cancer database reviews do not support the belief that younger age is associated with a poorer prognosis. Reviews using SEER demonstrated that disease-specific survival decreased with increasing age even after adjusting for specific treatment or tumor factor [7]. A report from the NORDCAN database regarding incidence rate in Norway of lip, oral cavity and pharynx cancer in the period 2005-2009, showed that the incidence of this type of cancer is increasing with age both for males and females. Mortality is also increasing with age. The same trend was seen in NORDCAN reports of Nordic countries regarding incidence and mortality [8].

In the Western world, the most common localization of OSCCs is the lower lip. The lateral border of the tongue is the most frequent intraoral localization, but the floor of the mouth and the lingual sides of the mandible are also frequently affected [1]. OSCCs metastasize quickly, and about 50% of the patients already have regional lymph node metastases at the time of diagnosis. According to the Norwegian Cancer Registry, overall survival and survival for those with localized disease has remained unchanged at about 60 % and 80 %, respectively over the past 40 years in Norway. During the same period, the prognosis for those with lymph node metastasis and distant metastasis has improved, from 20% to 50% and 4% to 18% respectively. In general, the TNM classification, histological differentiation and localization are regarded as the most reliable prognostic factors [9].

It is well known that alcohol and tobacco are two of the most important risk factors for development of OSCCs [10]. Pooled data from seventeen European and American case-control studies, published by the American Association for Cancer Research, confirmed a greater than multiplicative joint effect between tobacco and alcohol and head and neck cancer risk, particularly for oral and pharyngeal cancers. Additionally, tobacco smoking and alcohol drinking accounted for a higher portion of head and neck cancer among males than females [11].

In addition to traditional risk factors like tobacco and alcohol, high-risk human papilloma virus (HPV) and in particular HPV-16 was recognized to be an individual risk factor. HPV-16 seropositivity, is associated with an increased risk of developing HPV-positive oropharyngeal cancers as well as a weaker association with OSCC [6]. HPV-positive OSCCs are associated with a risk factor profile related to sexual history and exposure to marijuana, but not with cumulative tobacco smoking, alcohol or poor oral hygiene [12]. Tobacco and alcohol seemed to be responsible for a smaller proportion of head and neck cancers in individuals who were younger (<45 years) compared to the older age groups. It is possible that other risk factors, such as genetic susceptibility,

HPV infections, or some nutritional factors, are more important in the younger age groups [11]. Functional inactivation of the tumor suppressor gene p16 by deletion or methylation is known to be a common event in HNSCC. In a study evaluating alterations of p16 in HNSCCs, in relation to age, site and human papillomavirus (HPV) status they found that p16 methylation is a more common event in those younger than 40 years in contrast to p16 deletions, which are more common in those older than 40 years. This study also concluded that it is unlikely that HPV-16 is a primary causative agent of HNSCCs in young adults [13].

A meta-analysis of the impact of human papilloma virus (HPV) on cancer risk and overall survival in HNSCCs concluded that a positive HPV status gave an increased risk for HNSCCs, but overall survival was improved in HPV-positive patient versus HPV-negative patients. HPV-positive tumors also were more responsive to radiotherapy and chemotherapy, but the optimal treatment for this subgroup of patients remains unclear. Growing data supports the theory that these tumors should be treated differently than HPV-negative tumors [14]. A retrospective study published in 2010 analyzed the association between tumor HPV status and favorable survival among patients with stage III and IV HNSCCs enrolled in a randomized trial. The result showed strong evidence that patients with a HPV-positive cancer had better survival rate than HPV-negative cancer. The 3-year survival rate was 82.4 % for HPV-positive and 57.1 % for HPV-negative. The 5-year survival rate was 75-80 % for HPV-positive cancer and 45-50 % for HPV-negative cancer. Their conclusion is that HPV status is a strong and independent prognostic factor for survival among patients with HNSCCs [15].

It is known that incidence and risk factors associated with oral cancer differ around the world. The aim of this study was to assess the incidence and survival rate of oropharyngeal cancer in a Northern Norwegian population from 1986-2002, and to analyze if factors such as TNM stage at diagnosis, age, tobacco and alcohol consumption, as well as different treatment regimens affected survival.

To study this, a database of information collected from medical records of 162 patients from Nordland, Troms and Finnmark treated for oropharyngeal SCCs from 1986 to 2002 was used. Among the information recorded was tumor localization, TNM stage (at diagnosis), gender and age of patients, overall and disease specific death, tobacco and alcohol habits, treatment regime and whether or not the tumor recurred.

3.0 Material and methods

3.1 The material:

From the archives of the University Hospital of Northern Norway (UNN) patients diagnosed with OSCCs in the period from 1986 until 2002 were selected for this study. The group was followed up until 2009. An ear-nose and throat specialist at UNN was responsible for collecting information from the patient records. Patients with tumors in the mobile tongue, the base of the tongue, the floor of the mouth, the palatal arches, the tonsils, the buccal mucosa, the alveolar process and oral cavity not further specified were included. The archive contain most of the patients who got these diagnoses in the three most northern regions of Norway (Nordland, Troms, Finnmark), since treatment is mainly done at UNN. Patients who had recurrence (who had been treated for a primary tumor in the same region before 1986) were excluded from the study as well as those who were misdiagnosed or misreported.

From the patients that were alive, informed written consent had been given, and in the database all patients were anonymous. The material that forms the basis for this project was approved by the Regional Ethics Committee.

The database contained information collected from the patients' hospital records. In order to get more robust statistics, some of the variables had to be re-categorized into larger groups. Since this was a retrospective study, some medical records lacked information, because all patients were not asked specifically about the variables analyzed. The amount of alcohol and tobacco given in the medical records of the patients was the patient's own perception of consumption. So we don't have exact amount of daily consumption of cigarettes, nor number of units of alcohol, but only the patient's own subjective view of his or hers consumption.

All tumors were recorded according to the TNM-classification system, see appendix 1.

In the original database, cause of death was not reported for most patients. To be able to study disease specific survival, information about cause of death was retrieved from The Norwegian Institute of Public Health.

3.2 Methodes/Statistics:

This was an epidemiological study with descriptive as well as analytical statistics in the form of Kaplan Meier analysis. We have used SPSS 20 (software package for statistical calculations) for graphics and statistical analyses.

First univariate analyses were performed, looking at each variable separately in relation to survival. For doing this we conducted a Kaplan-Meier survival analysis and a log-rank test. The Kaplan-Meier test shows the proportion of subjects surviving a certain amount of time after diagnosis. The study period of a patient ends when death occurs, and graphically this is marked as a step down in the Kaplan-Meier curve. Therefore, the Kaplan-Meier procedure is a method of estimating time-to-event models in the presence of censored cases [16]. In our study we also calculated the 5-year disease specific survival, which means that unspecific deaths where censored. The log-rank test is a method of comparing the survival of groups. The method is used to test the null hypothesis; that there is no difference between subgroups in a variable. The analysis was based on the times of death. For each such time point we calculated the observed number of deaths in each group and the number expected if there were in reality no difference between the groups [17]. *P* values <0.05 were accepted as statistically significant.

4.0 Results

The medical records of the patients were studied to look at risk factors and to evaluate any differences from the rest of the country and other countries. The patients recorded were diagnosed between 1986 and 2002, and followed up until 2009. Descriptive statistics and 5-years overall and disease specific survival data of the 162 patients included in the study are summarized in Table 3.

4.1 Descriptive:

Incidence:

As seen in table 1the incidence of OSCC in this population tended to increase from 1986-2002, with most often minor variations from year to year, but larger increases were seen in 1996 and 2002 (Table 1). The incidence of patients diagnosed with lymph node metastases (N1-N3) was also increasing (Table 2). Incidence for the period 2001-02 is not calculated since this is not a full five year period and can't be compared to previous five year periods.

Table 1: Change in incidence of OSSCs in the period 1986-2002 per 100000 inhabitants in Northern Norway.

Year	-86	-87	-88	-89	-90	-91	-92	-93	-94	-95	-96	-97	-98	-99	-00	-01	-02
Incidence	1,29	1,52	1,09	1,96	1,52	0,87	1,73	1,72	1,71	2,77	4,91	1,07	2,15	2,80	1,72	1,94	4,10

Table 2: Increased incidence over five-year-periods for stage N0 and stage N1-N3 at diagnosis.

	Numbers of patients diagnosed with primary OSCC according to N-stage (incidence per 100,000 inhabitant calculated for the time period in NN)			
	1986-90	1991-95	1996-00	2001-02
N0	**34**(7,4)	**41**(8,8)	**59**(12,7)	**28**
Primary tumor diagnosed N1-N3	**6**(1,3)	**13**(2,8)	**21**(4,5)	**14**

The age at diagnosis ranged from 27 to 93 years, where the average (mean) age at diagnosis was 64.4 years (Figure 1).

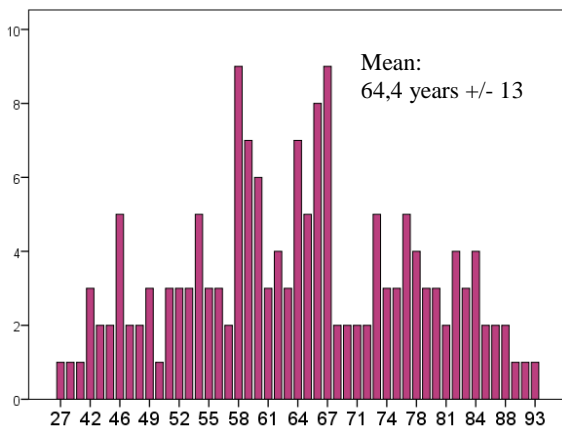Figure 1: Age at diagnosis.

Only 3 (1.9 %) patients were <40 years when they were diagnosed with OSCC. Patients <40years are often defined as young patients with OSCC in literature. The older age group (≥40years) accounted for 98.1 % of the patients (Figure 1). To give a reasonable size of the groups in this study, the younger age group was defined as <60 years and the older age group as ≥60 years.

Of the patients enrolled in the study, 90 (56 %) were males and 72 (44 %) were females. Number of new cases per year for each gender is shown in Figure 2.
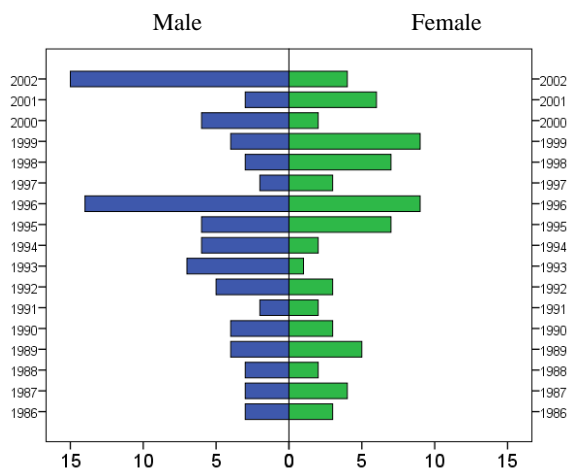

Figure 2: Number of new cases 1986-2002 by gender.

A greater proportion of female patients (59.7%) were diagnosed before they had lymph node metastasis (N0) than males (50%). In males, 41.1 % had lymph node metastases (N1-3) compared to 23.6 % of the females (Table 3 and Figure 3). In Figure 3 the distribution of N- and T- stage by gender is shown.
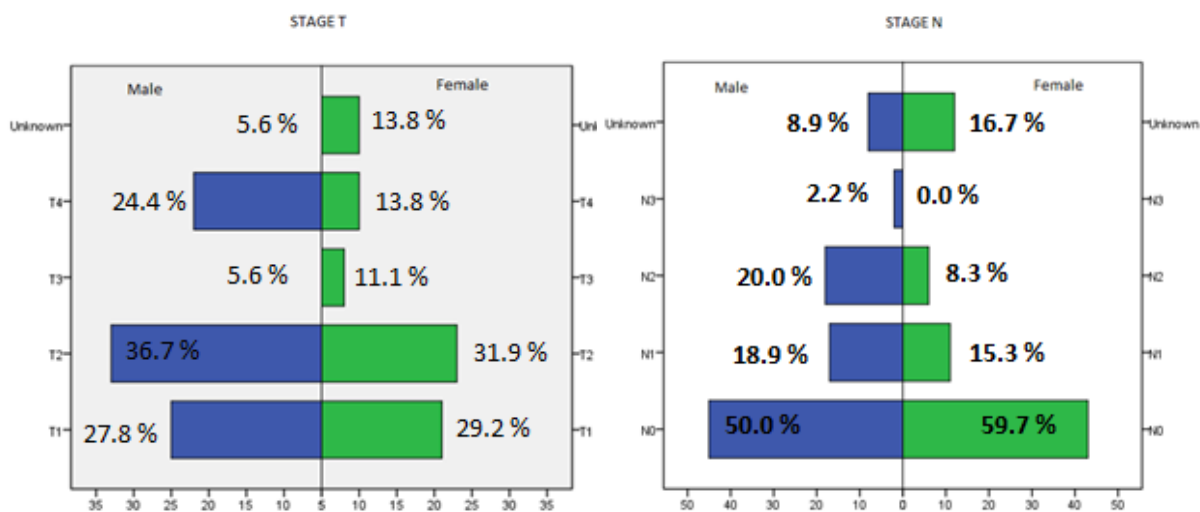

Figure 3: The distribution of N- and T- stage by gender.

The majority of the tumors were located in the mobile tongue (43.8 %), the floor of the mouth (18.5%) or at the alveolar crista (14.8%)(Figure 4).

It seemed to be some gender differences in localization. There were a greater proportion of males with cancer in the floor of the mouth and the tonsils, while there were more females diagnosed with cancer of the bucca and the alveolar crista.
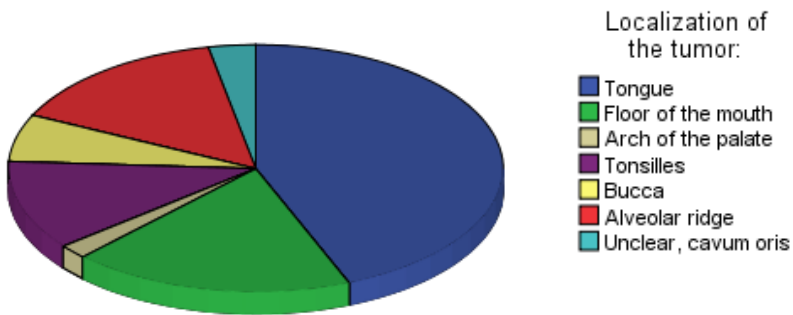
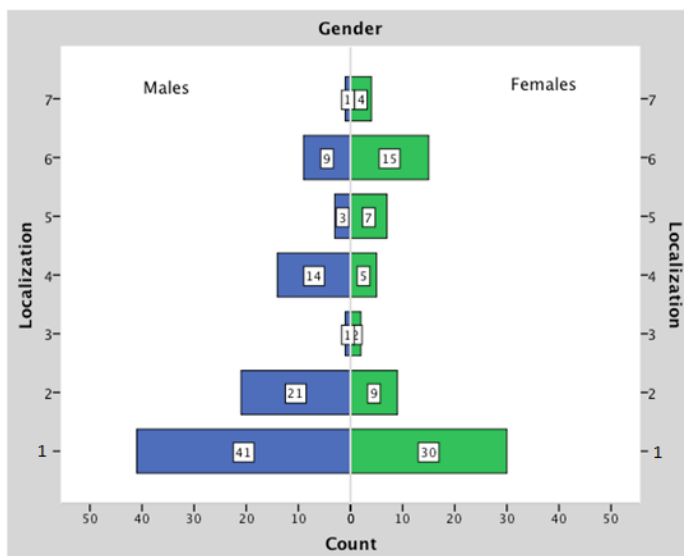Figure 4: Main sites for localization of the tumor in the oral cavity.

Figure 5: Histogram showing counts on localization of tumors for males and females. Localization 1=tongue, 2=floor of the mouth, 3=arch of the palate, 4=tonsils, 5=bucca, 6=alveolar ridge, 7=unknown.

More than half of the patients (60.5%) had reported using or previous use of tobacco, and 31 % consumed alcohol more than once a week. Surprisingly, those who smoked or had high alcohol consumption did not have more advanced disease (higher proportion of lymph node metastasis) than the rest of the sample.

Recurrence was reported in 30.2% of the patients, but the number of patients with unknown recurrence status was high (63%). This was probably because many of the patients were followed up at local hospitals which did not always report recurrences to UNN. Due to the large group of unknown, no further investigations regarding recurrences were performed.

Of all the deaths, 35.5 % were of unknown cause, 50.4 % were disease specific mortality (DSM) and 14.1 % were diseases unspecific mortality (DUM). Of the patients with DSM, 60.7 % were males and 39.3 % were females, and of the DUM's 70.6 % were males and 29.4 % were females. The number of unknown deaths was equally distributed among males and females. In 2009 there were 7.4 % more females alive than males diagnosed with OSCC.

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Table 3: Descriptive statistic for 5- year overall survival and disease specific survival.

Variable	Category	Cases total, n (%)	Cases male n (%)	Cases female n (%)	5-yr overall survival, total (%)	5-yr disease specific survival, total (%)
Clinical features of patients diagnosed with HNSCCs						
Age:						
	< 60	61 (37.7)	40(44.4)	21(29.2)	53.3	61.0
	≥ 60	101 (62.3)	50(55.6)	51 (70.8)	41.9	59
Gender:						
	Male	90 (56)			41.9	56.7
	Female	72 (44)			52.2	63.2
Anatomic site:						
	Tongue	71 (43.8)	41(45.6)	30(41.7)	50.7	66.6
	Floor of mouth	30 (18.5)	21(23.4)	9(12.5)	34.5	58.6
	Palate	3 (1.9)	1(1.1)	2(2.8)	0	0
	Tonsil	19 (11.7)	14(15.6)	5(6.9)	61.1	61.1
	Bucca	10 (6.2)	3(3.3)	7(9.7)	44.4	44.4
	Alveolar crista	24 (14.8)	9(10.0)	15(20.8)	42.9	52.4
	Cavum oris (unclear)	5 (3.1)	1(1.1)	4(5.6)	40	60
Tobacco consumption:						
	Non/never smokers	44 (27.2)	14(15.6)	30(41.7)	55.8	66.6
	Previous smokers	25 (15.4)	18(20.0)	7(9,7)	50	59,1
	Smokers	73 (45.1)	51(56.7)	22(30.6)	41.7	52.2
	Habit unknown	20 (12.3)	7(7.8)	13(18.0)	35.7	77.9
Alcohol consumption:						
	≤once a week	90 (55.6)	45(50)	45(62.5)	55.7	64.5
	>once a week	31 (19.1)	22(24.4)	9(12.5)	38.7	48.2
	Habit unknown	41 (25.3)	23(25.6)	18(66.7)	29.4	60.5
Recurrence*:						
	No	7 (4.3)	4(4.4)	3(4.1)	-	-
	Yes	49 (30.3)	24(26.7)	25(34.7)	-	-
	Unknown	103 (63.6)	60(66.7)	43(59.7)	-	-
Histologic differentiation:						
	Well	52 (32.1)	29(32.2)	23(31.9)	57.4	65.6
	Moderately	65 (40.1)	38(42.2)	27(37.5)	34.9	50.8
	Poorly	16 (9.9)	9(10.0)	7(9.7)	42.9	46.4
	Unclear	22 (13.6)	12(13.3)	10(13.8)	45.5	68.8
	Verrucous	7 (4.3)	2(2.2)	5(6.9)	85.7	100

Variable	Category	Cases total, n (%)	Cases male n (%)	Cases female n (%)	5-yr overall survival, total (%)	5-yr disease specific survival, total (%)
Treatment:						
	Surgery	24 (14.8)	13(14.4)	11(15.2)	62.5	85.1
	Surgery –> radiotherapy	77 (47.6)	40(44.4)	37(51.4)	56	71.2
	Radiotherapy –> surgery	20 (12.3)	14(15.6)	6(8.3)	45	45
	Concomitant cytostatica	3 (1.9)	3(3.3)	0(0)	0 (only 3 in the group)	0 (only 3 in the group)
	Palliative treatment	5 (3.1)	2(2.2)	3(4.2)	0 (only 5 in the group)	0 (only 5 in the group)
	Radiotherapy	15 (9.3)	11(12.2)	4(5.6)	14.3	23.8
	No treatment	4 (2.4)	2(2.2)	2(2.7)	0 (only 4 in the group)	0 (only 4 in the group)
	Unknown	14 (8.6)	5 (5.6)	9 (12.5)	40	60
T-stage:						
	T1	46(28.3)	25(27.8)	21(29.2)	67.4	77.7
	T2	56(34.6)	33(36.7)	23(31.9)	50.9	69.5
	T3	13(8.0)	5(5.6)	8(11.1)	30.8	44.4
	T4	32(19.8)	22(24.4)	10(13.8)	12.5	19.4
	Unknown	15(9.3)	5(5.6)	10(13.8)	55.6	77.8
N-stage:						
	N0	88(54.3)	45(50.0)	43(59.7)	53.5	68.3
	N1	28(17.3)	17(18.9)	11(15.3)	28.6	40.1
	N2	24(14.8)	18(20.0)	6(8.3)	43.5	45.9
	N3	2(1.2)	2(2.2)	0(0)	50	0(only 2 in the group)
	Unknown	20(12.4)	8(8.9)	12(16.7)	42.9	85.7
M-stage:						
	M0	142(87.7)	82(91.1)	60(83.3)		
	M+	1(0,6)	1(1.1)	0(0)		
	Unknown	19(11.7)	7(7.8)	12(16.7)		
Death:						
	Alive (2009)	41(25.3)	19(21.1)	22(30.5)		
	[+]DSM	61(37.7)	37(41.1)	24(33.3)		
	[++]DUM	17(10.5)	12(13.3)	5(6.9)		
	Unknown	43(26.5)	22(24.4)	21(29.2)		

[+]DSM: Disease-specific mortality, [++]DUM: Disease-unspecific mortality
*Only 159 recorded patients with recurrence state, 3 patients were not recorded in the system.

4.2 Survival analysis:

4.2.1 Gender and age:

Disease specific survival in our study was 51.7 % for females and 43.7 % for males, but the difference was not statistical significant (p=0.441). Age at diagnosis did not affect survival significantly (Figure 6).
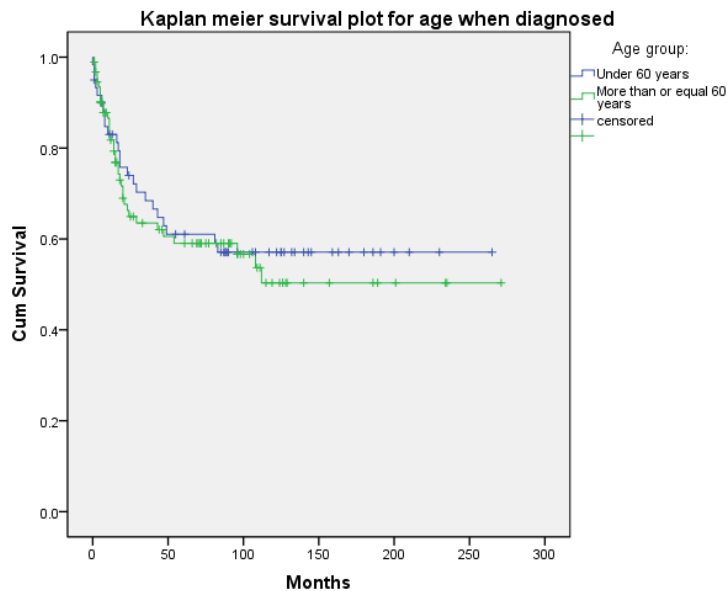

Figure 6: No statistically significant difference in survival between those <60 years (blue line) at diagnosis and those ≥60 years (green line).

4.2.2 TNM-stage:

Survival analysis revealed that females without lymph node metastases (N0) had a much better survival rate than those who had N1 (p= 0.037) and N2 (p=0,018). Surprisingly, the presence of lymph node metastases had much less impact on survival rates for males (Figure 9), mainly because males without lymph node metastases showed a poorer survival rate (44.7 % +/- 9.6 %) than females (62.0 % +/- 7.9 %) in the same group. In the groups with lymph node metastases, females also showed a better survival rate than males (Figure 7 and 8) though the differences were less pronounced than for those without.
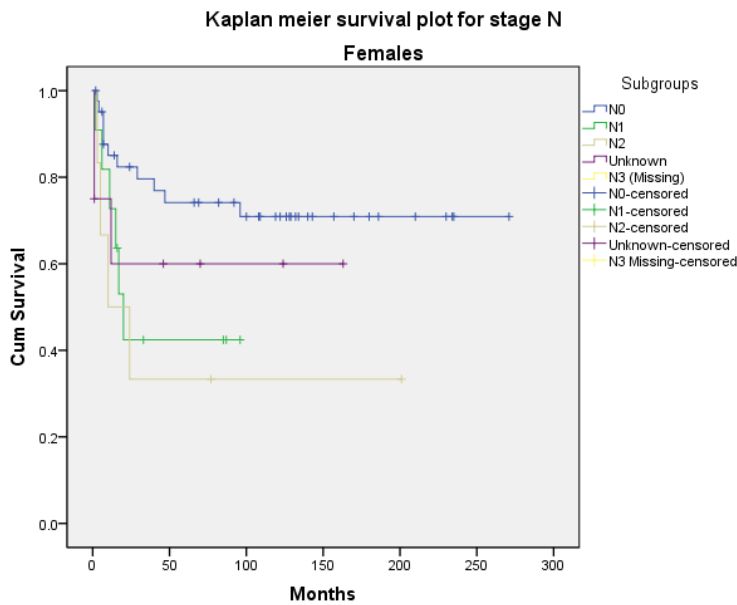
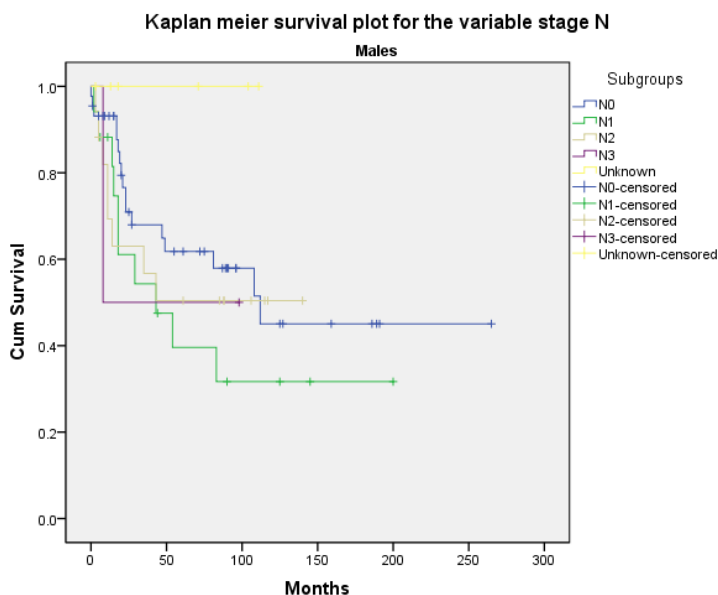Figure 7: Kaplan-Meier curves for the tumor stadium N, females.

Figure 8: Kaplan-Meier curves for tumor stadium N, males

4.2.3 Tobacco and alcohol consumption:

Five-year disease specific survival was poorer for those who smoked (52.2%) compared with non-smokers (66.6%). For the whole observation period the difference was not statistically significant (p=0.063).

Men that consumed alcohol daily had significantly shorter survival (p = 0.018) compared with those who consumed alcohol less than once a week. For women there was a significant difference in survival time for those who never consumed alcohol compared with those who consumed alcohol daily (p = 0.001), were those who never consumed alcohol had longer survival time (Figure 9 and 10).
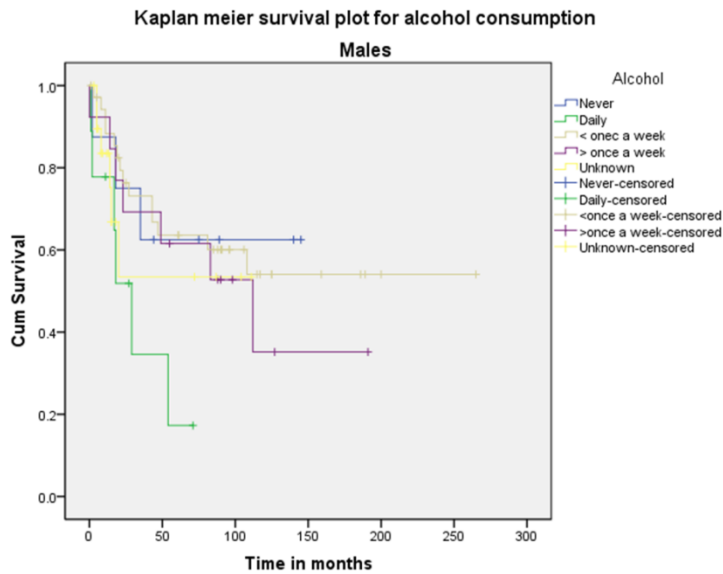
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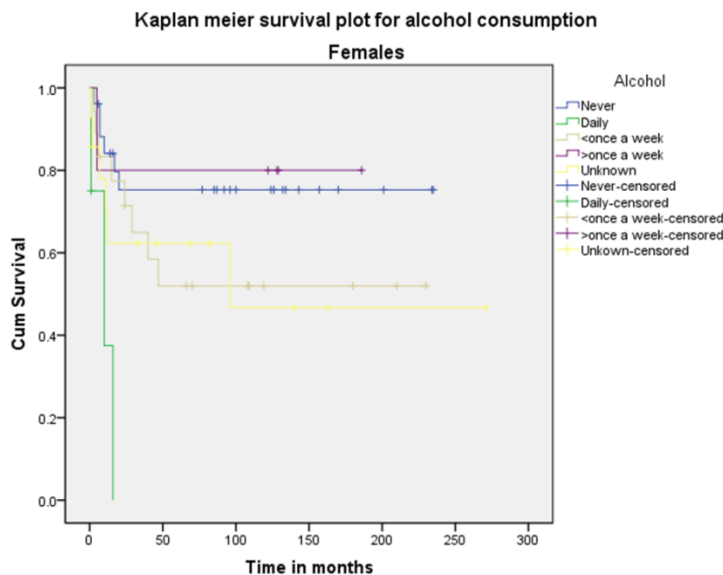Figure 9: Kaplan Meier for alcohol consumption for males.

Figure 10: Kaplan Meier for alcohol consumption for females.

4.2.4 Differentiation:

Only one of the seven patients that were diagnosed with a verrocous tumor died a disease specific death, and the five year disease specific survival was 100 %. Numbers showed that there was a significantly higher survival for women with well differentiated tumors than for those with moderately differentiated tumors (p=0.035). No significant differences were found for males between well, moderate or poorly differentiated tumors.

4.2.5 Localization:

Localization of the tumor had no significant influence on survival, neither in males nor in females.

4.2.6 Treatment:

The effect of treatment method on survival was not analyzed because treatment method was influenced by various factors such as severity and extent of the disease. TNM-stage and age of the patient were also essential for the choice of treatment. Therefore it was not interesting to do a Kaplan Meier survival analysis on the treatment variable.

5.0 Discussion

In the present study we have assessed clinical characteristics and survival data of patients who were diagnosed with OSSCs at UNN from 1986 till 2002. Data of birth, year of diagnosis and death was used to calculate survival time, while factors such as smoking and drinking habits were assessed as possible prognostic factors. Since this material is based on a period of 23 years, the number of patients included in the database is relatively high. This may provide a basis for analyzing prognostic factors for OSCCs in the northern Norwegian population. In the following discussion we compare the results with what is known from national and international studies.

In order to get more robust statistics, some of the variables had to be re-categorized into larger groups. This might have caused some loss of information, but was necessary to be able to see trends and putative statistically significant differences between our variables.

We found an increased incidence of OSCCs in Northern Norway from 1986-2002. When adjusted for population size in the given time periods, our data show increasing numbers of patients diagnosed with both localized OSCCs as well as with lymph node metastases in each of the five year periods (Table 2). From 2001-2005 there were diagnosed more primary tumors that had spread to regional lymph nodes than localized tumors in the oral cavity. Only one of the patients included in the study had distant metastasis (to another tissue) at the time of diagnosis. Also the national average from 1956-2006, showed a minor decrease in incidence of OSCCs for males and a marked increase for females (incidence from 8.0-7.9 and 2.3-4.3 per 100000 inhabitants for men and women respectively)[2].   Worldwide there is a tendency that OSCCs is decreasing. We therefore wonder why there hasn't been the same tendency of decreased incidence of OSCCs in Norway and the rest of the Nordic countries[5] as compared to the rest of the world in general.

The best established risk factors associated with oral cancer are tobacco and alcohol consumption. In a report from SIRIUS, The Norwegian Institute for Alcohol and Drug Research, shows that the annual sales of alcohol in Norway measured in liters of pure alcohol per inhabitant aged 15 years or older was increased from 4.00L in 1967 to 6.75L in 2008 [21]. This increase in alcohol consumption may be involved in the increased incidence of OSCCs nationally and in Northern Norway respectively.

Since the medical records did not tell the exact consumption of cigarettes or alcohol for each patient, analysis of this variables are somewhat uncertain. Some patients may have a subjective view that they aren't heavy smokers or drinkers, but when cigarettes and units of alcohol are counted, an objective view may say that they are. For 25.1 % of the patients alcohol consumption was unknown, and 12.3 % had an unknown smoking habit. These are high numbers and a lot of information is lost since smoking and alcohol habits were not registered. The reason for lack of information about these and several other variables for some of the patients is due to this being a

retrospective study. However, as high alcohol and tobacco consumption are well recognized risk factors for HNSCCs, information about patients smoking and drinking habits should be recorded in the hospital records.

Alcohol consumption appeared to affect survival time negatively. Results from the analysis showed that both males and females who consumed alcohol daily had a shorter survival time. This can be seen in the context of the well-known phenomenon that high alcohol consumption/alcoholism impairs the immune system and is linked to numerous diseases and health problems [20]. Therefore, the poorer survival of those who drank a lot of alcohol may be due to a poor general health status in this group. Alcoholism may also be associated with altered psycho-social behavior and a reduced ability of self-care. Perhaps this may affect the threshold for contacting health services and reduce the ability of self-detection of symptoms that could be associated with OSCCs or premalignant lesion which can develop into OSCCs.

Our expectations that smoking would have a significant impact on survival were not met. There was only a trend of shortened survival time for those who smoked moderate or a lot compared to non-smokers. Literature states that smoking is a significant risk factor for getting OSCCs, but the result of this analysis indicates that smoking habits did not have a significant impact on survival after diagnosis [10]. From 1973 till 2009 the amount of daily smokers in Norway has decreased. In 1973 over 50 % of male inhabitants between 16-74 years smoked daily, and about 30 % of females. In 2009 the amount of daily smokers for both genders was decreased to about 20 %, and in 2011 a further reduction to about 17% were seen. There were only small differences in females and males smoking habits, but among the younger people and females between 35-54 years, the number of daily smokers was higher than in the same groups for males. In our study there were 45.1% smokers and a large amount of female smokers. As the number of smokers were higher in this group than in the general population, our study indicates that smoking predispose to OSCCs. This is also known from literature. While the number of daily smokers was decreasing, the consumption of snuff was increasing among especially the younger age groups [19]. This has occurred during the last decade, and therefore the effect on incidence of OSCCs of this increased snuff consumption is still unknown. We had no information about use of snuff in our study population.

Forty-four percent of the patients in our study were females and 56 % were males. At the national level, the distribution of females and males who were diagnosed with OSCCs in the period 1985-1999 was 32 % and 68 % respectively [2]. This shows that a higher proportion of oral cancer patients in Northern Norway are females compared to the national average.

Numbers from the Norwegian National Statistics' Health survey from 1995 shows that the proportion of daily smokers among females in Northern Norway were similar to the national average (28 % vs. 29 %), whereas the percentage of females reporting relatively high alcohol consumption was a little higher in Northern Norway compared to the national average (16 % vs. 13 %) [18]. This difference is too small to be a probable explanation for the higher proportion of females diagnosed with oral cancer in Northern Norway compared to the national average.

A greater proportion of female patients were diagnosed before they had lymph node metastasis than males. This was interesting and may be caused by a general trend that females go to the doctor / dentist earlier than males. There was also a national trend that more OSSCs were diagnosed after the tumor has metastasized to regional lymph nodes in males[8]. An interesting finding was the big

difference in disease specific survival in females and males without lymph node metastasis, where females had a much higher survival rate (70.9%) then males (45.1%) (Figure 7 and 8).

At diagnosis, 52.2 % of the tumors in males were moderately or poorly differentiated, for females this percentage were 47.4 %. So tumors in females had a slightly higher differentiation status at diagnosis than males. For females there were a significant difference in survival between highly and moderately differentiated tumors (0,035), the same was not seen for males. We were surprised of the weak correlation between differentiation and survival in men since literature states that differentiation has an influence on prognosis, where highly differentiated tumor is set in the context of a better prognosis, while the poorly differentiated tumors indicates a poorer prognosis of survival [1].

Verrucous carcinomas showed a much better 5-year survival rate than the other tumors (85.7 %). The number of cases that had a verrucous lesion was small. Therefore we couldn't draw any conclusion regarding any significant difference between verrucous lesions and tumors showing other differentiation levels. We chose not to add them to any other group, because according to literature, patients with this subgroup of oral SCCs have a better chance of survival, due to these tumors' low grade malignancy [23].

In our study 62 % of the patients were 60 years or older while 38 % were younger than 60. This does not deviate much from the age distribution in the national average for 2005-2009, were 67 % of the patients were 60 years or older , and 33 % were under 60 years [2].

The percentage of patients ≥40 years was 98.1 %. This was a little larger than seen in data collected from SEER, where the age group over forty makes up around 90 % of HNSCC patients [7]. SEER collects data on cancer cases from various locations and sources throughout the United States. The reason for the lower incidence of OSCC in the younger population of Northern Norway compared with SEER, is not known. It might have to do with the small population of Northern Norway, which might not follow expected outcomes based on studies done on a significantly larger population, like the US. In this study the amount of patients in the young age group was too small to give any meaningful statistics when compared to the older age groups. In our study 71 of 162 patients had tongue cancer, 41 males and 30 females. Within the age groups 20-59 years and 60-99 years, 42 % and 45 % respectively, had tongue cancer. A study done at Lund University Hospital in Sweden concluded that there is a persistent trend in the increase of carcinoma of the tongue into the twenty-first century for both genders and all age groups except young males [22]. Numbers from Cancer registry of Norway [2] also shows increased numbers of SCCs of the tongue into the twentieth century. The reason for this increase is unknown.

Our data does not contain information about HPV status in patients diagnosed with HNSCCs. Testing for HPV status has not been standard protocol at the UNN for all the patients with OSCCs, but was done for the patients who were diagnosed with tonsil cancer.

What are the reasons for the low survival of HNSCCs? A master degree paper written in Tromsø in 2010 concluded that there is a suboptimal registration of oral mucosal lesions in Norway. Many oral cancers are discovered very late, which might suggest that general dentists don't do a good enough job examining the oral mucosa [24]. The reason for late diagnosis is often a combination of both doctor's delay and patient's delay. Due to the low incidence of oral cancer it will be difficult to

increase the awareness of this type of cancer in the public, and thereby reducing the patient's delay. However, it should be possible to reduce doctor's delay by increasing the competence regarding diagnostics of oral cancer among general dentists [25]. Resent reviews done on the cause of patient's delay conclude that more research has to be done. A systematic review from 2007, regarding patient delay in oral cancer, concluded that clinical- and tumor factors, socio-demographic variables and patient health related behavior did not influence the duration of patients delay. Healthcare factors and psychosocial factors may play a role, but the research in this area is spears, theoretical and of poor quality [26].

6.0 Conclusions

The results of the clinical data in this study were compared to national data and trends worldwide. Results from this study of the Northern Norwegian population showed that alcohol habits had a significant influence on survival, whereas smoking habits only tended to influence. Women showed longer disease specific survival than men with the same TNM-stage, and generally had less advanced disease at diagnosis than men. Numbers also showed that there was a significant difference in survival between highly and moderately differentiated tumors in females, while tumor differentiation had no significant influence on survival for males. There was no significant influence on survival when it came to the age at diagnosis. Females had a higher incidence rate of OSCCs in Northern Norway than what is reported at a national level. Calculation of incidence shows that there was an increasing incidence of OSCCs in the Northern Norwegian population. The incidence of SCCs in the tongue was considerably increased during the period from 1994-2002.

7.0 References

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8.0 Appendix 1

Presented below is a list over the classifications used for describing tumor size, regional lymph node metastasis and distant metastasis at UNN (Universitetssykehuset Nord-Norge).

TNM-classification:

T0 No evidence of primary tumor

T1 Tumor 2 cm or less in greatest dimension

T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension

T3 Tumor more than 4 cm in greatest dimension.

T4 (Lip) Tumor invades adjacent structures (e.g., through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin)

T4 (Oral cavity) Tumor invades adjacent structures (e.g., through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin)

N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension

*N2 a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than

6 cm in greatest dimension;

*N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension

*N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N3 Metastasis in a lymph node more than 6 cm in greatest dimension

MX Presence of distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

*In this paper we have merged the groups N2a, N2b and N2c into on N2 group. The N2 group is defined as; *metastasis to one or more lymph nodes (bilateral, ipsilateral and bilateral) with >3cm to >6cm in diameter*. We did this to get a larger group, and more significant results, knowing that we would lose some information.