Pergamon

Oral Oncol, Eur J Cancer, Vol. 32B, No. 2, pp. 83–90, 1996

Printed in Great Britain
0964–1955/96 $15.00+0.00

0964–1955(95)00073–9

Prognostic Factors of Survival in a Cohort of Head and Neck Cancer Patients in Oslo

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A cohort of 433 Oslo patients with head and neck (H/N) carcinomas was analysed for prognostic factors of survival. Mean observation time was 635 days, the distribution of men and women was 2:1 and the mean age was 64.5 years. Tumour localisations were: oral cavity 32.1%, oro/hypopharynx 19.3%, larynx 22.6% and others 25.2%. Stage distribution was: stage I: 21.0%, stage II: 22.6%, stage III: 18.7% and stage IV: 37.4%. Pragmatic strategy showed independent prognostic factors of survival to be gender, age, tumour localisation and stage. A model of predicting 3 year survival was generated. An explanatory approach showed that female patients had a 38% lower risk of mortality compared to male patients after controlling for age, stage and tumour localisation. Comparing observed to expected mortality of the age and gender matched Norwegian population, showed excess risk of death among male compared to female patients when also adjusted for demographic confounders.

Keywords: head and neck cancer, survival, prognostic factors

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INTRODUCTION

In Oslo, the consumption of pure ethanol (10 l per year per person over the age of 15 years) is double the average consumption in Norway. The incidences of oral, pharyngeal and laryngeal carcinomas in Oslo are double that of the average Norwegian incidences. Thus, the present material is expected to be comparable to material from most of Europe. In spite of better irradiation and more sophisticated surgery, the overall 5 year survival in head and neck (H/N) cancer is 50–60% for local disease, and 30% for patients with regional involvement [1–5]. Several studies have demonstrated the significance of the clinical profile of the patients at the time of diagnosis [1, 6–12] (Table 1). Because of differences in populations and difficulties in extrapolating results from one population to another, it was mandatory to pinpoint the risk factors of mortality for the Oslo cohort. Another aim was to compare the observed survival estimates of the cohort with the expected survival of the Norwegian population of the same age and gender.

PATIENTS AND METHODS

A dynamic cohort consisting of 433 patients with H/N cancer was consecutively admitted to Ullevaal Hospital between 1 January 1988 and 1 September 1994. Ullevaal Hospital is the only oncological centre treating the inhabitants of Oslo for H/N cancer. The criterion for inclusion in the cohort was an undisputable positive biopsy (429 patients) or a positive fine needle aspiration (3 patients) from a carcinoma in the head and neck. In one patient, laryngectomised in Spain, the specimen was not available. Patients with skin carcinomas were excluded. Thus, the study includes the ICD9 diagnoses 140–148, 160, 161, 171 and 193. Data from the time of diagnosis, treatment and from follow-ups were recorded; 26 parameters were included for each patient. For the postulated prognostic factors age, gender, tumour site and stage of disease, a preliminary analysis for survival with univariate methods was performed [13]. The strategy of the analysis was pragmatic [14]. Comparisons of survival curves with Breslow and Mantel–Cox test statistics were conducted [15, 16]. Predictors of mortality (total mortality) were analysed in a multivariate mode using the Cox regressional model [17]. Continuous variables, such as age, were tested for trend before being introduced in the model as such. A predictive model taking into consideration the major prognostic factors was generated. The observed survival in the cohort was compared to the expected survival in a reference population (the national population) of the same age and gender distribution [18]. This method consists of comparing age and gender specific rates of death (expected deaths, E) of a standard population, the total Norwegian population, to the observed deaths (O) in the population of interest, the present cohort. Tables giving the incidents of deaths per 100 000 inhabitants per year among women and men in different age groups were used. The

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Received 3 July 1995; accepted 30 Oct. 1995.

Table 1. Pretreatment prognostic factors found in other studies

References	Prognostic factors					
	Gender	Age	Stage	Site	Symptom dur.	Karnofsky
Oreggia *et al.*, 1983 [6]	×		×			
Kramer *et al.*, 1986 [7]			×	×		×
Bataini *et al.*, 1988 [8]			×	×		
Ildstad *et al.*, 1988 [1]		×	×	×		
Buisset *et al.*, 1989 [9]			×			
Eiband *et al.*, 1989 [10]	×		×			
Wiernik *et al.*, 1990 [11]		×	×	×		
Wolfensberger, 1992 [12]		×	×	×		

method used was to estimate the standardised mortality ratio (SMR) [19]: $SMR = Ei/Oi = E/O$ $i = 1 - K$ at age and gender strata.

$$SE(SMR) = SMR/\sqrt{Oi}.$$

The 95% confidence interval $(SMR \pm 1.96 \times SMR/\sqrt{O})$, where SE = standard crror, Ei = summation of the expected deaths, Oi = summation of the observed deaths.

If SMR is bigger than 1 it means that more deaths are observed in the cohort than expected (on the basis of rates) in the larger national Norwegian population. If SMR is less than 1, fewer deaths are observed than expected. The estimation of SMR should be viewed with caution when the expected value is less than 2, except when the disease is very rare as in H/N cancer. The SMR method of adjustment merely controls for gender, age and geographical area. The statistic programmes used were EPI-INFO and BMDP.

RESULTS

Clinical profile

The clinical profile of the cohort is shown in Table 2. The eastern parts of the centre of Oslo were over-represented with approximately double the number of patients expected, controlled for age. Tumour localisations are shown in Tables 3 and 4. The stages of the disease, T-stages, N-stages and M-stages are shown in Table 5. The histological evaluation of the specimens showed the following: squamous cell carcinoma, 79.9%; adenocarcinoma, 4.2%; and "other", 15.2%. This last group includes carcinomas of the thyroid, adenoid cystic, merkelcell, mucoepidermoid, acinarcell, nasopharyngeal and non-differentiated carcinomas. The Karnofsky index showed Karnofsky 1, 52.7%; 2, 21.2%; 3, 7.6%; 4, 2.5%; 5, 2.5%; 6, 7.2%; and unknown, 6.2%.

Survival

The median observation time was 635 days with a range between 13 and 2415 days and the cumulative follow-up time was 797 patient years. For the total cohort of 433 patients 3 year survival was $52.8 \pm 3.3\%$ (Fig. 1). For the male patients, the 3 year survival was $50.8 \pm 3.2\%$ and for the female $58.4 \pm 4.7\%$. This difference was statistically significant with a P value of 0.032 for Breslow test and 0.027 for Mantel–Cox (Fig. 2). Multivariate analysis adjusted for age, tumour site and stage (age 60, oral tumour, stage I) confirmed the difference (Fig. 3). Univariate analysis on age divided in quartiles and 3 year survival are shown in Fig. 4. The youngest quartile had survival of $62.5 \pm 7.3\%$, followed by the patients between the ages of 58 and 65 years who had survival of $47.4 \pm 7.4\%$, the patients between the ages of 66 and 74 years had survival of $43.2 \pm 7.4\%$ and the oldest quartile had survival of $43.8 \pm 7.7\%$. The differences are borderline statistically significant with Breslow test giving $P = 0.06$ and Mantel–Cox $P = 0.09$. Multivariate analysis adjusted for gender, tumour site and stage (male, oral tumour, stage II), confirmed the tendency (Fig. 5). Survival for the different tumour localisations are shown in Table 6. Because of heterogeneity and small groups, no statistical tests were performed. Figure 6 represents survival stratified for the stage of the disease using univariate analysis. The 3 year survivals were for disease in stage I, $73.9 \pm 5.1\%$; stage II, $73.0 \pm 5.0\%$; stage III, $64.8 \pm 5.7\%$ and stage IV, $22.3 \pm 3.8\%$. The results showed a significant difference between the stages of the disease, with Breslow test giving $P = 0.032$ and Mantel–Cox, $P = 0.027$. Multivariate analysis adjusted for age, gender and tumour site (age 60, male, pharynx tumour), confirmed the results (Fig. 7).

In a predictive approach [14], a multivariate analysis using a manual backword, elimination procedures showed that gender, age and stage of disease were all significant predictors of survival (Figs 3, 5, 7 and Table 7). We used this model to generate a prognostic forecast for a specific patient with a specific subset of prognostic variables. Consider 2 patients with the following profiles: (A) male, aged 60, tumour localised in the oral cavity, stage I, had a predictive 3 year survival of 80%. Patient (B) with the same gender, age and tumour localisation but stage III, had a predictive 3 year survival of 40%.

In an explanatory approach, this strategy describes the interrelationship between gender and mortality [14]. The other risk factors are considered to be confounders of this association. The result shows a gender difference regarding mortality. Female patients have a relative risk of mortality of 0.62 compared to male patients, which means 38% less risk of mortality. This result is adjusted for the confounding effect of age, tumour site and stage of the disease (Table 7).

Table 2. Clinical profile of the cohort

Variables	No.	Male/female ratio
Number of patients in the cohort	433	
Male/female	294/139	2/1
Age range and mean (years)	18–92, 64.5	
Symptom duration mean (months)	9	

Table 3. Subsites and male/female ratio of oral and pharyngeal tumours

Subsites	No.	%	Male/female ratio
Lip			
Upper lip, external	1	0.2	
Inferior lip, external	11	2.5	
Inferior lip, internal	2	0.5	
Unspecified	15	3.4	8.5/1
Tongue			
Base	9	2.1	
Dorsum	7	1.6	
Side/apex	32	7.4	
Inferior	4	0.9	
Unspecified	3	0.7	
	55	12.7	1/1
Gingiva			
Upper jaw	2	0.5	
Lower jaw	10	2.3	
	12	2.8	1/2
Floor of mouth			
Outer part	19	4.4	
Lateral part	5	1.2	
	24	5.6	1.7/1
Other localisations			
Bucca	3	0.7	
Vestibulum	2	0.5	
Hard palate	4	0.9	
Soft palate	8	1.8	
Retromolar	16	3.7	
	33	7.6	2.3/1
Oral tumours	**139**	**32.1**	**1.5/1**
Oropharynx			
Tonsillae	31	7.2	
Arcus tonsillae	3	0.7	
Vallecula	2	0.5	
Epiglottis	3	0.7	
Lateral wall	5	1.2	
Posterior wall	3	0.7	
	47	11.0	2.5/1
Hypopharynx			
Postcricoidal	6	1.4	
Fossa piriformis	22	5.1	
Epiglottic fold	6	1.4	
Posterior wall	1	0.2	
Multiple localisations	1	0.2	
	36	8.3	2.7/1
Oro/hypopharyngeal tumours	**83**	**19.3**	**2.6/1**

Table 4. The subsites and male/female ratio of laryngeal/various tumours

Site	No.	%	Male/female ratio
Glottis	68	15.7	
Supraglottic	25	6.2	
Subglottic	3	0.7	
Laryngeal tumours	**96**	**22.6**	**4.6/1**
Nose	14	3.2	
Ear	4	1.0	
Maxillar sinus	6	1.4	
Ethmoidal sinus	1	0.2	
Unspecified	2	0.5	
	27	6.3	2/1
Nasopharynx			
Ceiling	8	1.8	
Side wall	5	1.0	
	13	2.8	12/1
Salivary glands			
Parotid gland	22	5.1	
Submandibular gland	2	0.5	
	24	5.6	2/1
Thyroid gland	31	7.0	1/2
Unknown primary	20	3.5	1.5/1
Various tumours	**115**	**25.2**	

Table 5. TNM classification and stage of disease

The stage of the disease	
Stage I	21.0%
Stage II	22.6%
Stage III	18.7%
Stage IV	37.4%
The T-stage of the tumours	
T1	22.4%
T2	29.6%
T3	16.4%
T4	27.7%
Unknown primary	3.5%
Unknown T-stage	0.2%
The N-stage of the tumours	
N0	66.7%
N1	14.5%
N2	13.6%
N3	5.1%
The M-stage of the tumours	
M0	98.8%
M1	1.2%

Comparing the survival with the survival in the Norwegian population

Tables 8 and 9 show the events of death in the subcohorts of female and male patients, respectively stratified on subgroups of 4 years of age, except in the youngest and oldest subgroups. Table 8 shows 53 observed events of death for female patients and an expected death rate of 10.07. This gives a SMR of 5.26 with a standard error of 0.71. Table 9 shows 143 observed events of death for male patients and an expected death rate of 20.77. This yields a SMR of 6.89, with a standard error of 0.57. The female patients from the cohort have a 5.26 times greater risk of death as women from the Norwegian population not diseased and having the same age distribution, and the male patients have a 6.89 times greater risk of death as men from the Norwegian population with the same age and not diseased. It is worth noting that after having adjusted for demographic confounders, men still have an excess risk of death compared to women.

DISCUSSION

Socioeconomical conditions

Approximately 75% of carcinomas of the head and neck (oral cavity, oro/hypopharynx and larynx) are due to an

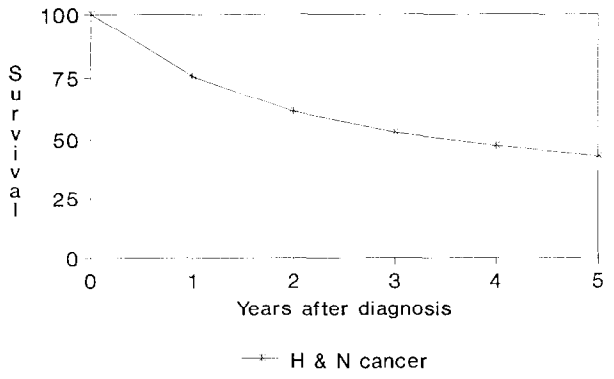
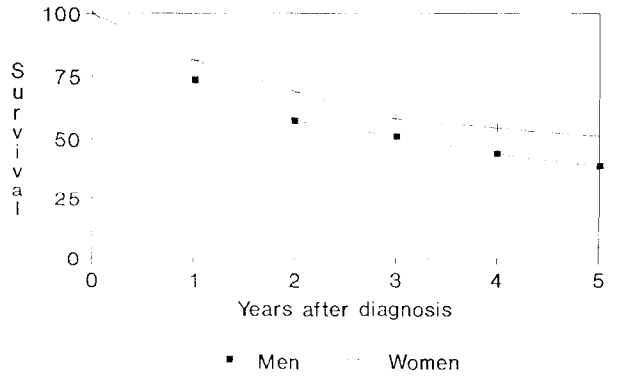


Fig. 1. Survival rates for the cohort.



Breslow p=0.032 & Mantel-Cox p=0.027

Fig. 2. Survival rates stratified for gender.

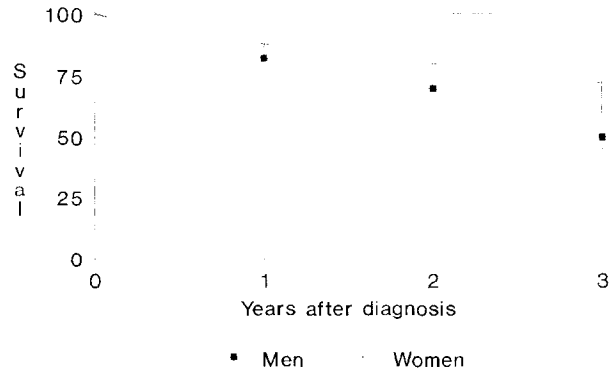
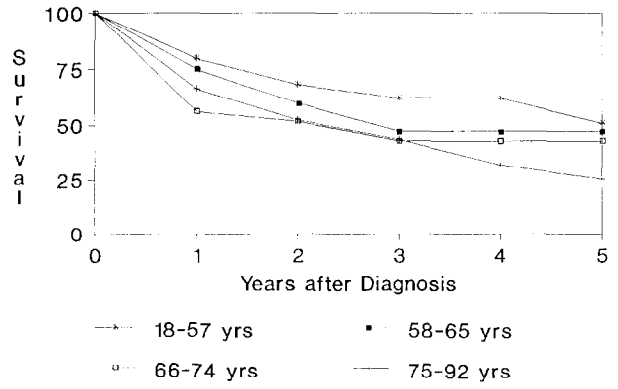


Fig. 3. Survival rates for the cohort stratified for gender, adjusted for age, stage, localisation.

excessive use of tobacco and alcohol [20–23]. A pilot study in Ullevaal Hospital, Norway among H/N patients with carcinomas indicated that 70% had an excessive use of alcohol compared to 27% in patients without malignancies. Correspondingly, an overrepresentation of H/N cancer of approximately double that expected was found when controlled for



Breslow p=0.06 & Mantel-Cox p=0.09

Fig. 4. Survival rates stratified for age.

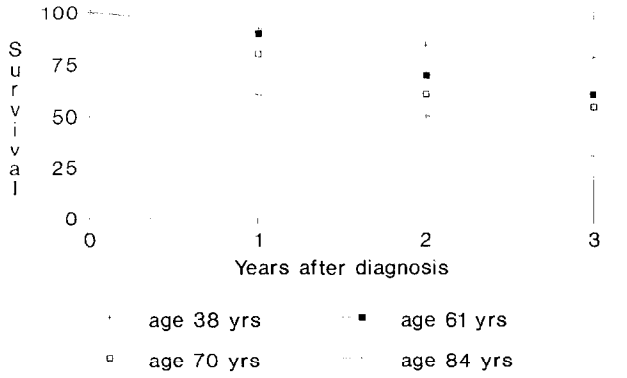
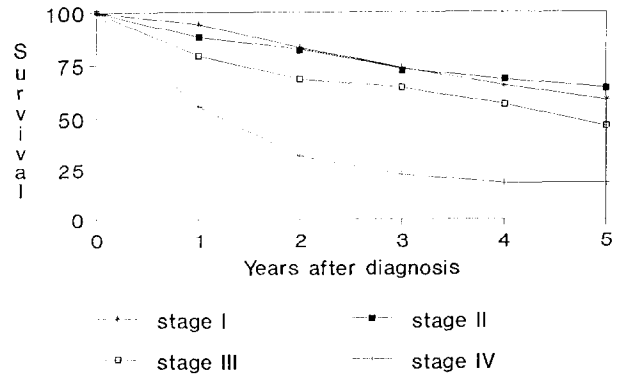


Fig. 5. Survival rates stratified for age, adjusted for gender, stage, localisation.

Table 6. Tumour localisation and 1, 2 and 3 year survival, univariate analysis

Site	1 year	2 years	3 years
Hypopharynx	52.8±8.3%	24.8±7.4%	17.7±6.8%
Floor of mouth	60.8±10.2%	42.2±10.5%	26.3±9.7%
Oropharynx	57.8±7.3%	42.3±7.6%	38.8±7.8%
Unknown primary	83.7±8.5%	56.9±12.5%	40.6±13.2%
Oral cavity	65.6±8.4%	51.0±9.2%	46.6±9.3%
Tongue	69.5±6.3%	58.6±6.9%	47.7±7.5%
Gingiva	80.9±12.1%	80.9±12.1%	53.9±23.4%
Lips	88.9±7.4%	82.5±9.2%	75.3±10.8%
Nasopharynx	66.7±13.6%	55.5±5.2%	55.5±15.2%
Nose/sinus/ears	87.7±6.6%	69.2±9.7%	63.2±10.5%
Larynx	89.3±3.2%	73.4±4.7%	65.3±5.4%
Salivary glands	86.9±7.1%	86.9±7.1%	75.7±9.6%
Thyroid gland	92.8±4.8%	88.9±6.1%	88.9±6.1%



Breslow p=0.032 & Mantel-Cox p=0.027

Fig. 6. Survival rates stratified for stage.

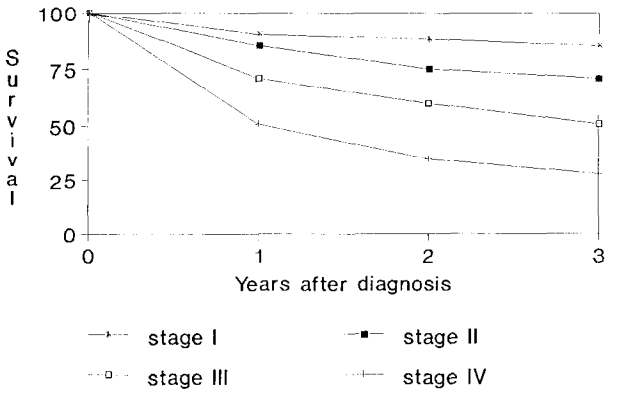


Fig. 7. Survival rates stratified for stage, adjusted for gender, age, localisation.

age in parts of Oslo where the inhabitants belong to lower socio-economical levels.

Gender

Approximately two-thirds of patients in the present study were male and one-third female. The ratio varies with tumour sites (Tables 3, 4). In Denmark, the distribution of men and women in H/N carcinomas is approaching equality [24]. Most studies show a more pronounced difference in incidence between males and females [3, 12, 21]. Why Scandinavian women seem to be more prone to H/N cancer relative to men, may be the result of early activity of female liberation in this part of the world. A consequence of this was a higher prevalence of daily smoking and more alcohol consumption among Scandinavian women than among women in the rest of Europe.

Age

The high average age of the patients corresponds to other materials and may be explained by the long latency of the aetiological factors (tobacco and alcohol) needed to develop H/N carcinoma [1, 12].

Duration of symptoms

The long duration of symptoms in the present material, 9 months, is caused by a few patients claiming to have had symptoms for years. This parameter, therefore, was often set arbitrarily. Symptom duration was less than 4 months for 50% of the patients.

Tumour localisation

Carcinomas of the oral cavity, oro/hypopharynx and larynx account for about 75% of cases. This is in accordance with other findings [4], but in contradiction to others [1, 12] and depends on which diagnoses are included in the material.

Stage of disease

A high number of patients, 37.4%, were presenting disease in stage IV. This is in accordance with the findings of some [3], but in contradiction to others [25] and coincides with the long symptom duration in the present study. The advanced stage (IV) was mostly due to a large primary tumour, not usually the presence of metastasis.

Metastasis

In spite of a high percentage of advanced primary tumours, regional metastases based on palpation and CT scan occurred in only 33.3% of the patients and only 5.1% had advanced adenopathy, N3. The prevalence of a positive neck ranged from 40 to 75% [6–8, 10, 12, 25, 26]. The high numbers in some studies may depend on the use of ultrasound in the fine needle aspiration. Only 5 (1.2%) patients had distant metastases and all were pulmonal [12, 25]. The tendency to develop distant metastases is a consequence of the location and stage of the adenopathy [27] and correspondingly, regional and distant metastases tend to occur late in the development of the disease in the present cohort.

Histology and differentiation

The majority (79.9%) of the histology was squamous cell carcinomas. In the literature, the rates vary between 82% [28] and 96.9% [21]. When excluding the thyroid tumours from the present material, the number of squamous cell carcinomas was raised to 86%.

Karnofsky index

According to the Karnofsky index found in the present cohort, 74% of the patients claimed to live normal or almost normal lives (Karnofsky 1 and 2). This is not in accordance with the high percentage of advanced tumours and might be a demonstration of the patient's tendency to neglect symptoms, the doctor's inability to penetrate the patient's everyday life, or the Norwegian may be a tough customer!

Prognostic factors

By uni- and multivariate analysis it was found that gender, age, tumour site and stage of the disease were independent prognostic factors and could be used as such in a predictive model. When stratifying for the various factors, however, the groups of patients were too small for 5 year survival studies, thus only 3 year survival was evaluated and discussed for accuracy. Longer than 3 year follow-up does not change

Table 7. Independent prognostic factors of survival using Cox hazard model

Variable	Coefficient	Standard error (S.E.)	Coefficient/S.E.	*P* value
Tumour site	0.3116	0.0853	−3.6527	0.0003
Age	0.0287	0.0061	4.6823	0.00001
Stage	0.6441	0.0717	8.9791	0.0001
Gender	−0.4662	0.1661	−2.8070	0.0050

Exponential function of $(-0.4662)=0.62=$ RR (relative risk). Women have a RR of death of 0.62 compared to men. In other words, a risk of $(1-0.62)=38\%$ of the risk of men when adjusted for age, stage of disease and tumour localisation.

Table 8. Mortality rates for women

Age	Number	Mors (O*i*)	Follow-up (patient/year)	Mors incidence/100 000/year Norwegian population	E*i*
18–29	3	0	11.36	31	0.0035
30–34	2	1	5.26	61	0.0032
35–39	2	0	10.60	87	0.0092
40–44	6	1	13.80	122	0.0168
45–49	5	1	10.21	193	0.0197
50–54	11	3	37.30	309	0.1152
55–59	6	3	15.00	475	0.0712
60–64	16	8	28.00	768	0.2150
65–69	22	2	60.70	1299	0.7884
70–74	15	6	28.30	2126	0.6016
75–79	18	11	44.70	4008	1.7900
80–84	19	10	6.38	7236	0.4616
85–92	15	7	33.10	18 000	5.9800
	140	53			10.0700

$SMR = Oi/Ei = 53/10.07 = 5.26$.
$SE(SMR) = SMR/\sqrt{Oi} = 5.26/\sqrt{53} = 0.71$.
$SMR = 5.26 \pm 0.71$.
E*i*, summation of expected deaths; O*i*, summation of observed deaths; SMR, standardised mortality rate; Mors, death.

Table 9. Mortality rates for men

Age	Number	Mors (O*i*)	Follow-up (patient/year)	Mors incidence/100 000/year Norwegian population	E*i*
18–29	9	1	24.80	96	0.0230
30–34	4	0	12.98	107	0.0138
35–39	4	1	6.64	164	0.0108
40–44	9	1	26.50	200	0.0530
45–49	13	6	82.90	342	0.2835
50–54	22	9	55.46	560	0.3105
55–59	26	15	66.13	985	0.6513
60–64	52	25	92.10	1614	1.4800
65–69	56	30	115.80	2692	3.1100
70–74	40	22	82.50	4254	3.5000
75–79	37	25	65.90	7114	4.6800
80–84	15	6	25.30	11 524	2.9100
85–92	6	2	17.00	22 000	3.7400
	293	143			20.7650

$SMR = Oi/Ei = 143/20.7 = 6.89$.
$SE(SMR) = SMR/\sqrt{Oi} = 6.89/\sqrt{143} = 0.57$.
$SMR = 6.89 \pm 0.57$.
For abbreviations see legend to Table 8.

survival very much, thus a longer observation time is of limited value [6, 8, 29].

The 3 year survival for the whole study was 52.8%. This corresponds to the findings of others [1, 12]. Results vary concerning age as a risk factor. Ildstad *et al.* [1] found advanced age to be a risk factor, but otherwise of little importance. In the present study, age was found to be a predictor for prognosis, but of borderline significance. The risk of a bad outcome was naturally highest in the oldest age group (Figs 4, 5). The localisation of the primary tumour is of importance as a risk factor, but its significance in the different sites varies between studies. Primary tumours in the tonsillae have both been associated with an inferior and a superior survival, and while a tumour in the larynx predicts an optimistic prognosis, a tumour in the hypopharynx predicts a bad prognosis [1, 12]. A significantly better prognosis is found when the tumour is localised in the glottic larynx than in the oropharynx, and in the supraglottic larynx and nasopharynx than in the hypopharynx [7]. In the present study, a primary tumour in the hypopharynx had the lowest (17.7%) and in the thyroid gland the highest (88.9%) survival. Multivariate analysis makes no sense with patient groups of these small sizes. Of 36 patients with hypopharynx carcinoma, 32 were in stage IV, while of 31 patients with cancer of the thyroid, only 5 were in stage IV. Thus, larger cohorts are required to eliminate the effect of different staging of the tumours. Univariate analysis demonstrated significant difference in survival between stages (Fig. 6). The significance of the involvement of the neck is demonstrated by the different survivals for stages II and III in a male patient, aged 60, with a pharynx carcinoma (Fig. 7). Gender as a prognostic factor for H/N cancer has not been established [1, 6, 10, 11, 14]. The contrasting results may reflect the different composition of populations as regards for instance, socioeconomic factors, different stages of the disease, age or observation time [6, 10, 11]. In the present study we found the risk of death for women to be 38% less than for men, confirmed when adjusted for other variables (Figs 2, 3, Table 7). To control for the "normal" difference between survival of men and women in different age cohorts, the observed survival was compared to the expected survival in the Norwegian population of the same age and gender. A male H/N cancer patient had 6.9 times and a female patients 5.2 times the rate of death as a "normal" Norwegian. The explanation for the difference in survival of men and women with H/N cancer (adjusted for age, tumour localisation, stage and demographic confounders), must be found in the different physical (pathophysiological), socioeconomical and/or psychological conditions in the genders. Many pathological conditions, owing to hormonal and biochemical differences, behave differently in men and women. One might speculate whether the malignant pathology is obtained after a lower exposure to the aetiological factors in women than in men. Thus, female patients would have avoided the detrimental social effects of long-term alcohol consumption, and consequently cope better with the disease. To what extent the patient copes with the disease may also depend on his/her socioeconomic status. Proper accommodation and the possibility of cooking a hot meal is always of importance, especially for patients with difficulties in chewing and swallowing. Women still have the advantage of a certain skill and interest in cooking, even if their physical condition is bad. The psychological state of women may be different from men. Women are perhaps more likely to submit themselves to restrictions imposed by medical expertise. It is also claimed that women have a better developed social network than men. The impression is that the female H/N cancer patient to a greater extent is taken care of by a husband, son or daughter. The present findings could be a Norwegian phenomenon and not applicable to other cohorts, but nevertheless, warrants further investigation.

CONCLUSION

Comparison of a cohort of 433 patients with H/N carcinomas from Oslo with other cohorts found that the men/women ratio was lower and stage IV more prevalent than in most studies. Age, gender, stage and tumour localisation were significantly independent prognostic factors. Female patients had a higher survival than men controlled for age, stage, tumour localisation and demographic confounders.

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