Pergamon

Oral Oncol, Eur J Cancer, Vol. 30B, No. 6, pp. 369–373, 1994

0964–1955/94 $7.00 + 0.00

0964-1955(94)E0005-N

A Population-based Study of Prognostic Factors in Oral and Oropharyngeal Cancer

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Cases of oral cavity and oropharynx cancer diagnosed among the residents of Torino, Italy, between 1982 and 1984 ($n=143$) were followed up to June 1990. During this period, 97 subjects (67.8%) died, 69 from oral or oropharyngeal cancer. 10 more cases died from causes possibly related to oral cancer. The overall relative 5-year survival rate was 37.2%. Men experienced a worse survival than women. No difference was shown according to age, education or occupation. Patients with smooth lesions had a poorer prognosis than those with fissured or granular lesions; no association between survival and colour, elevation, induration or bleeding from the lesion was found. Extension of the tumour and nodal involvement were strong and independent predictors of survival, but no difference was found between T1 and T2 lesions. Patients who reported a 2–3-month interval between onset of symptoms and diagnosis experienced a better survival than those with shorter or longer interval. Oropharynx cases had a better prognosis than cancers of the oral cavity.

Keywords: oral cavity cancer, oropharyngeal cancer, survival, prognostic factors

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INTRODUCTION

THE INCIDENCE of cancer of the oral cavity and the oropharynx is high in Italy, particularly in the northern regions, as compared with other European countries [1]. It caused over 12 000 deaths among Italian men between 1980 and 1984, representing 3.2% of all cancer deaths [2]. To date, no population-based analysis of determinants of survival of oral cancer patients in Italy has been published. This paper presents the survival experience of 143 cases of cancer of the oral cavity and oropharynx enrolled in a population-based case–control study in Torino, north-western Italy.

Subjects and methods

Cancers at the following sites were considered (typographical code according to ICD-9): mucosa of lip (140.3, 140.4, 140.5), tongue (141), gum (143), floor of the mouth (144), other and unspecified parts of the mouth (145) and oropharynx (146).

Incident histologically confirmed cases among residents of the city of Torino and diagnosed between 1 July 1982 and 31 December 1984, were identified in all 14 stomatology, otorhinolaryngology, radio- or chemotherapy units operating in the city of Torino or its outskirts, as well as through a survey of the files of all public and private pathology services operating in the same area [3]. Patients who were not residents of Torino were excluded from the study. Throughout the period covered by the study, eligible cases were 103 men and 40 women, corresponding to annual incidence rates (age-standardised on the world population based on 1981 census figures) of 5.76 and 1.72×10^{-5}.

The clinical form used in a previous U.S. study of oral cancer [4] was adapted to describe the lesions and their locations. Colour, size (greatest diameter in centimetres), location, surface texture (granular, smooth) and degree of elevation of each lesion were recorded, as well as the presence or absence of induration, bleeding, ulceration and cervical lymphadenopathy. Additional information was collected on interval between first appearance of symptoms or signs and diagnosis. No information was collected on treatment of the patients. Clinical data were collected for 120 patients [5].

Place of birth and educational title were collected for all cases from the files of residents in the city of Torino. 122 cases were interviewed on their life-long smoking, dietary, including alcohol, and occupational histories, with a questionnaire derived from a multicentric study of larynx cancer [6].

Active follow-up to 30 June 1990 was carried out by checking the files of residents in the city of Torino. Information on vital status of subjects who migrated was obtained by

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Received 5 Feb. 1994; provisionally accepted 15 Feb. 1994; revised manuscript received 25 Mar. 1994.

writing to the new municipality of residence. A copy of death certificate was obtained for deceased subjects. Underlying causes of death were coded according to the International Classification of Diseases, 9th revision [7].

Relative survival was calculated using 1986 age- and sex-specific national mortality rates for all causes. Regional mortality rates were very similar to national ones, but were less stable, particularly for young age groups.

Univariate analysis was carried out by estimating crude 5-year survival rates: proportions were compared using the χ^2 test. In addition, the log-rank test was applied using the SAS LIFETEST procedure [8]. Multivariate survival analysis was carried out according to Cox's regression model [9] using programme 2L of the BMDP package [10]. Sex, age, T and N stages and site were the variables included in all models. Two sets of analyses were carried out, considering all deaths and only deaths caused by oral and oropharyngeal cancer deaths. In the latter analysis, subjects dying from other causes were censored at the date of death.

RESULTS

Vital status was ascertained for all 143 subjects: 97 (67.8%) of them died before the end of follow-up. Copy of the death certificate was obtained for 95. Distribution of causes of death is given in Table 1. Figure 1 describes the survival rates for males and females, respectively. The differences between the two sexes is not statistically significant (P value, 0.11).

Tables 2 and 3 report results, respectively, of the univariate and Cox regression analysis. In the former, variables found to be significantly ($P<0.05$) associated with 5-year survival rate were T and N stages, site of origin (poorest prognosis for cancer of the posterior pillar and best prognosis for cancer of oral tongue and oropharynx) and diagnostic delay (without a trend). These findings did not change repeating the univariate analysis by considering deaths from causes other than oral cancer as censored observations.

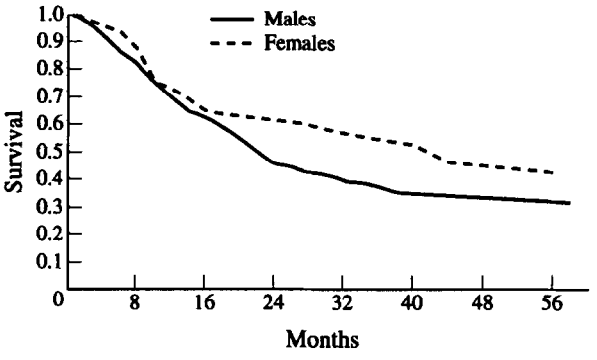

Fig. 1

The same findings were observed in Cox's regression analysis which, in addition, suggested a worse prognosis for lesions with smooth texture vs. all others. Both T and N stages showed a positive trend with mortality, only the former being statistically significant (P values 0.02 and 0.08, respectively). Relative risks were consistent with N and T stages in the analyses considering exclusively deaths caused by oral cancer (P values for trend 0.07 and 0.04, respectively). Another interesting result was a non-significant increase in survival among smokers, when compared to non-smokers (RR for ever versus never smoker 0.8; 95% CI 0.3–1.7): this effect was stronger among current and light smokers.

Patients who were not interviewed on lifestyle factors ($n=21$) experienced a non-significant poorer survival than other patients (RR 1.6; 95% CI 0.9–2.9).

Table 1. *Causes of death of deceased subjects* (n=97)

Cause of death	ICD-9 code	*n*
Cancer of tongue	141	20
Cancer of salivary gland	142	2
Cancer of gum	143	6
Cancer of floor of mouth	144	6
Cancer of other and unspecified parts of mouth	145	17
Cancer of oropharynx	146	14
Cancer of hypopharynx	148	1
Cancer of other and ill-defined sites within the lip, oral cavity and pharynx	149	6
Cancer of oesophagus	150	1
Cancer of larynx	161	6
Other malignant neoplasms*	151–160, 162–239	4
Diseases of circulatory system	390–459	8
Other diseases†	1–139, 240–389, 460–999	4
Unknown causes of death	—	2

*Including cancer of the colon (ICD 153, $n=1$), cancer of liver (ICD 155, $n=1$), cancer of pancreas (ICD 157, $n=1$), cancer of kidney (ICD 189, $n=1$). †Including liver cirrhosis (ICD 571.5, $n=2$), undefined cause of death (ICD 799, $n=1$), burns (ICD 948, $n=1$).

DISCUSSION

The 5-year survival rate in the present series (37%) was similar to these recently reported from France and Switzerland, and worse than those reported from other population-based series. Table 4 reports these data broken down by site of origin. Similarities among the Latin countries might reflect similarities in health care systems.

In the present study, survival was not associated with age, birthplace, education and occupation. As for age, a better survival of young patients was reported in three hospital-based studies in the U.S.A. [11–13], which nevertheless were not analysed in multivariate models. A multivariate analysis of a hospital series of oropharyngeal cancer cases in the same country suggested that better survival of younger patients may result from confounding by other predictors [14]. In our study, however, there was no effect of age even in the univariate analysis (Table 2).

Women had a better survival than men in our study as well as in a study on oropharyngeal cancer [14], whereas another study on patients with cancer of the buccal mucosa did not find a difference in survival between sexes [12]. A study from the U.S.A. showed patients from private clinics experienced a better survival from oral cancer than patients from public hospitals [15]. In the present study, only years of education could be used as a possible surrogate of income: it did not show consistent results.

In contrast with previous studies suggesting a poorer survival of patients with thick lesions [12, 16–18], the present

Table 2. Crude 5-year survival by selected variables

Variable	Total* n	5-year survival n	%	Log rank statistics χ^2	df	P value
Sex						
Male	103	33	32.0	2.52	1	0.11
Female	40	17	42.5			
Age (years)						
≤44	7	3	42.9	6.52	7	0.48
45–54	17	6	35.3			
55–59	29	11	37.9			
60–64	31	11	35.5			
65–69	14	7	50.0			
70–74	19	5	26.3			
75–84	18	6	33.3			
85+	8	1	12.5			
Birthplace						
Torino region	70	25	35.7	2.71	2	0.26
Northern Italy	48	13	27.1			
Southern Italy†	25	12	48.0			
Years of schooling						
≤5	95	33	34.7	0.16	2	0.92
6–8	28	10	35.7			
9+	20	7	35.0			
Occupation						
Manual unskilled	44	18	40.9	4.46	3	0.22
Manual skilled	31	12	38.7			
Craft	13	3	23.1			
Office, professionals	31	12	38.7			
Histology						
Squamous cell carcinoma	109	33	30.3	0.01	1	0.91
Other	11	2	18.2			
Colour of the lesion						
Red	78	24	30.8	3.46	2	0.18
Mixed	12	5	41.7			
White	19	3	15.8			
Surface texture of the lesion						
Smooth	9	2	22.2	4.10	3	0.25
Granular	65	18	27.7			
Fissured	20	3	15.0			
Granular and fissured	17	9	52.9			
Surface integrity						
Continuous	19	8	42.1	1.42	1	0.23
Not continuous	89	23	25.8			
Elevation of the lesion						
<1 mm	57	17	29.8	0.30	1	0.58
≥1 mm	57	16	28.6			
Induration of the lesion						
Yes	100	28	28.0	<0.01	1	1.00
No	13	4	30.8			
Bleeding						
Yes	46	13	28.3	0.28	1	0.60
No	67	20	29.9			
Mobility of the tongue						
Modified	50	12	24.0	2.38	1	0.12
Not modified	60	19	31.7			
T						
T1	18	6	33.3	16.80	3	<0.01
T2	59	23	39.0			
T3	26	3	11.5			
T4	15	2	13.3			
N						
N0	63	21	33.3	8.54	2	0.01
N1	33	11	33.3			
N2, N3	21	2	9.5			
Time lapse between symptoms and diagnosis						
0–1 month	25	6	24.0	8.34	2	0.02
2–3 months	42	19	45.2			
4+ months	41	7	17.1			
Site of origin						
Other sites of oral cavity‡	23	5	21.7	12.01	5	0.03
Floor of the mouth	26	6	23.1			
Oral tongue	30	12	40.0			
Anterior pillar	13	3	23.1			
Posterior pillar	10	1	10.0			
Oropharynx§	18	8	44.4			
Alcohol consumption‖						
Non drinker	9	4	44.4	10.73	5	0.06
1–20 g/day	14	2	14.3			
21–40 g/day	22	9	40.9			
41–80 g/day	37	20	54.1			
81–120 g/day	18	7	38.9			
121+g/day	22	3	13.6			
Tobacco smoking						
Never smoker	18	6	33.3	1.45	2	0.49
Current smoker	86	30	34.9			
Ex-smoker	18	9	50.0			
Type of product						
Never smoker	18	6	33.3	0.47	2	0.79
Cigarette only	92	36	39.1			
Cigar/pipe¶	12	3	25.0			
Amount of smoking**						
Never smoker	18	6	33.3	2.26	4	0.69
1–7 g/day	13	6	46.2			
8–15 g/day	35	14	40.0			
16–25 g/day	42	15	35.7			
26+g/day	14	4	28.6			

*Not all totals sum up to 143 due to missing information. †Including subjects born abroad. ‡Labial mucosa ($n=4$), buccal mucosa ($n=6$), alveolar ridge ($n=7$), hard palate ($n=1$), soft palate ($n=5$), lingual aspect of retromolar trigone ($n=3$). §Basis of tongue ($n=8$), lateral and posterior wall ($n=10$). ‖Average lifetime alcohol intake (g/day). ¶With or without cigarette smoking, 3 subjects were pure cigar/pipe smokers. **Average lifetime amount of smoking (g of tobacco/day).

analysis did not show any association between thickness of the lesion and prognosis. This might reflect a chance result, as well as inaccuracies in measurement in our study, or confounding by surface texture of the lesion, a variable which was not considered in the previous studies and was strongly associated with survival in our study. Our results on the prognostic value of T and N indexes are totally consistent with previous findings [12, 14, 16, 18–21].

Our results on the correlation between diagnostic delay and survival are consistent with the hypothesis of a higher malignancy of lesions that are diagnosed soon after onset of symptoms. One study [19] analysed velocity of tumour growth by combining area of the lesion and delay: velocity was significantly associated with survival, but delay was not (*P* value 0.16).

In the multivariate analysis, none of the differences in

*Table 3. Relative risk (RR) and 95% confidence interval (CI) of dying by selected and cause of death—results of Cox model regression analysis**

Variable	All deaths RR	95% CI	Only oral cancer deaths RR	95% CI	Variable	All deaths RR	95% CI	Only oral cancer deaths RR	95% CI
Sex					Mobility of tongue				
Men†	1.0	—	1.0	—	Modified†	1.0	—	1.0	—
Women	0.8	0.4, 1.4	0.8	0.4, 1.6	Not modified	0.9	0.5, 1.5	0.9	0.5, 1.6
Age (years)					T				
⩽54	1.0	—	1.0	—	T1†	1.0	—	1.0	—
55–64	0.8	0.4, 1.7	0.7	0.3, 1.4	T2	0.9	0.4, 1.7	1.0	0.5, 2.3
65–74	0.6	0.3, 1.3	0.5	0.2, 1.1	T3	1.5	0.7, 3.3	1.3	0.5, 3.2
75+	1.1	0.5, 2.5	0.7	0.3, 1.6	T4	2.2	0.9, 5.3	2.3	0.8, 6.4
Birthplace					N				
Torino region†	1.0	—	1.0	—	N0†	1.0	—	1.0	—
Northern Italy	1.0	0.6, 1.8	1.2	0.7, 2.1	N1	1.2	0.7, 2.1	1.4	0.8, 2.6
Southern Italy‡	0.7	0.3, 1.4	0.9	0.4, 1.8	N2, N3	1.8	1.0, 3.5	2.1	1.0, 4.3
Years of schooling					Time lapse between symptoms				
⩽5†	1.0	—	1.0	—	and diagnosis				
6–8	1.2	0.7, 2.3	1.7	0.8, 3.3	0–1 month†	1.0	—	1.0	—
9+	1.4	0.7, 3.0	1.4	0.6, 3.1	2–3 months	0.4	0.2, 0.9	0.4	0.2, 1.0
Occupation					4+ months	0.8	0.4, 1.7	0.9	0.4, 1.9
Manual unskilled	1.0	—	1.0	—	Site of origin				
Manual skilled	1.0	0.5, 1.9	1.0	0.5, 2.1	Other sites of oral cavity†§	1.0	—	1.0	—
Craft	2.0	0.9, 4.6	1.7	0.7, 4.3	Floor of mouth	1.0	0.5, 1.7	1.0	0.5, 1.8
Office, professionals	1.4	0.7, 2.9	1.2	0.5, 2.8	Oral tongue	0.8	0.4, 1.5	0.9	0.4, 1.8
Histology					Oropharynx‖	0.6	0.3, 1.2	0.6	0.3, 1.5
Squamous cell carcinoma†	1.0	—	1.0	—	Alcohol consumption¶				
Other	1.2	0.5, 2.8	1.3	0.5, 3.3	Non drinker and 1–20 g/day†	1.0	—	1.0	—
Colour of the lesion					21–40 g/day	1.0	0.4, 2.3	0.9	0.4, 2.2
Red†	1.0	—	1.0	—	41–80 g/day	0.9	0.4, 1.8	0.9	0.4, 2.0
Mixed	0.6	0.3, 1.5	0.5	0.2, 1.4	81–120 g/day	1.0	0.4, 2.3	0.7	0.2, 1.9
White	1.7	0.9, 3.3	1.2	0.6, 2.6	121+g/day	1.4	0.6, 3.1	1.1	0.5, 2.6
Surface texture of the lesion					Tobacco smoking				
Smooth†	1.0	—	1.0	—	Never smoker†	1.0	—	1.0	—
Granular	0.4	0.2, 1.2	0.4	0.1, 1.1	Current smoker	0.9	0.4, 1.9	0.7	0.3, 1.7
Fissured	0.5	0.2, 1.5	0.3	0.1, 1.1	Ex-smoker	1.2	0.4, 3.4	1.3	0.5, 3.9
Granular and fissured	0.2	0.06, 0.7	0.2	0.05, 0.7	Type of product				
Surface integrity					Never smoker†	1.0	—	1.0	—
Continuous†	1.0	—	1.0	—	Cigarette only	0.9	0.4, 2.0	0.8	0.4, 1.8
Not continuous	1.1	0.5, 2.2	1.0	0.5, 2.3	Cigar/pipe**	0.9	0.3, 2.4	0.7	0.2, 2.1
Elevation of the lesion					Amount of smoking††				
⩽1 mm†	1.0	—	1.0	—	Never smoker†	1.0	—	1.0	—
⩾1 mm	0.8	0.5, 1.4	0.9	0.5, 1.6	1–7 g/day	0.6	0.2, 1.8	0.5	0.1, 1.7
Induration of the lesion					8–15 g/day	1.0	0.4, 2.4	0.8	0.3, 2.1
Yes†	1.0	—	1.0	—	16–25 g/day	1.3	0.5, 3.4	1.1	0.4, 2.9
No	1.4	0.7, 3.1	1.2	0.5, 2.9	26++ g/day	1.0	0.3, 2.9	0.9	0.3, 2.8
Bleeding									
Yes†	1.0	—	1.0	—					
No	1.1	0.7, 1.8	1.3	0.7, 2.2					

*All models included sex, age, T, N, site—26 individuals were excluded because of missing data. †Reference category. ‡Including subjects born abroad. §Labial mucosa, buccal mucosa, alveolar ridge, hard palate, soft palate lingual aspect of retromolar trigone anterior and posterior pillars. ‖Basis of tongue, lateral and posterior wall. ¶Average lifetime alcohol intake (g/day). **With or without cigarette smoking, 3 subjects were pure cigar/pipe smokers. ††Average lifetime amount of smoking (g of tobacco/day).

survival rates for site or origin was statistically significant, but this might reflect the low number of observations. The apparent relatively good prognosis of cancer of the oral tongue contrasts with previous results [21] which, nevertheless, were estimated on hospital series and might be biased.

Results from population-based series are not consistent with respect to prognosis of oral tongue cancer (Table 4). On the other hand, in the population-based series, oropharyngeal cancer has a consistently worse prognosis than cancers of the oral cavity (Table 4): our discordant result may reflect a different level of accuracy in the identification of the site of origin of the lesion.

To our knowledge, this is the first study that analysed survival of oral cancer in relation to smoking history and alcohol drinking: smokers and drinkers have a very small improvement in their prognosis when only oral cancer deaths were considered; this result is similar to that found in a recent study among lung cancer patients [28].

Table 4. Five-year relative survival in selected population-based series of oral cavity or oropharynx cancer, by sex

Country/calendar period [ref.]	Sites (ICD-8)	5-year survival Male	Female
Norway 1968–1975 [22]	141	36	45
	143	27	43
	144–145	58	62
	146	20	47
Finland 1953–1974 [23]	141	43	51
	143–145	47	53
	146	39	47
Geneva, Switzerland 1970–1983 [24]	143–145	23	—
	140–149	37	34
France*1975–1981 [25]	141	27	39
	143	33	39
	144	34	44
	145	34	39
	146	23	44
South Australia 1977–1986 [26]	141	50	66
	143–145	53	61
	146	35	42
US-selected areas of SEER Program 1981–1986 [27]	140–149	52	56
Torino, Italy 1982–1984 (our study)	141	45	40
	144	27	0†
	146	44	53
	141, 143–146, 148	34	45

*Nationwide hospital based survey in 20 large hospitals. †Based on 2 cases.

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Acknowledgements—This study was supported by Consiglio Nazionale delle Ricerche, Rome (Progetto Finalizzato Oncologia, Contracts 85.02391.44 and 86.00595.44), Associazione Italiana per la Ricerca sul Cancro and the Italian Ministry of Education. We wish to thank Dr R. Zanetti from the Cancer Registry in Turin for helping with the definition of the study population, Dr A. Mashberg for providing the clinical form used in the study, Mr G. Ferro and Ms M. Nonnato for technical help and Ms A. Hanss-Cousseau for secretarial support.