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Papers

Lateness of Diagnosis of Oral and Oropharyngeal Carcinoma: Factors Related to the Tumour, the Patient and Health Professionals

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The risk of presenting with advanced stage vs. early stage disease was evaluated in a prospective study of 336 consecutive patients with oral and oropharyngeal carcinomas referred to three head and neck surgery services in Sao Paulo, Curitiba and Goiania during the period from February 1986 to December 1988. Income and educational levels were not associated with stage distribution. The risk of having advanced disease was dependent upon male gender. Another important determinant of advanced stage was tumour location on the less visible surfaces of the oral cavity and oropharynx. Although there was a clear increase in delay of referral among cases who were seen by more than one health professional, duration of symptoms and patient and professional delays were not associated with the risk of advanced disease in unifactorial analysis. The following factors were independently associated with the risk of advanced disease for lip carcinoma: a painful ulcer, alcoholism and delay caused by a non-specialist medical doctor. The risk factors associated to advanced oral carcinoma were: type of lesion, odynophagia/dysphagia, delay caused by a dentist and delay caused by a non-specialist medical doctor. Two of the most important immediate consequences of advanced stage were a conspicuous increase in treatment costs and a longer hospital stay.
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INTRODUCTION

MORTALITY RATES for carcinoma of the mouth and oropharynx in some areas in Brazil are among the highest in the world [1]. The most important determinant of poor prognosis is advanced disease stage at diagnosis. The best available oncological treatments for stage I oral carcinoma yield an overall survival rate as high as 86%, whereas survival does not exceed 26% for stage IV disease [2–5].

Two of the universally accepted prognostic factors, T-stage and histological status of regional lymph nodes, are clearly interrelated and dependent not only on tumour aggressiveness, site and host factors, but also on the time of chronology of unarrested tumour growth evolution [3, 6, 7]. The importance of lateness of referral cannot be overemphasized and its implication on patient survival has been documented in breast cancer and retinoblastoma [8, 9].

The main reason for diagnostic delay has traditionally been attributed to the patient's ignorance about the disease; mostly due to poor socio-economic status [10, 11]. Patients frequently neglect the importance of early symptoms, sometimes for several months. On the other hand, many patients who seek dental or medical care for early symptoms are frequently misdiagnosed as having benign conditions. As a consequence, they remain without proper diagnosis and adequate treatment for long periods of time. Such delays result not only in an increase in patient suffering due to major disabilities and disfigurement, but also in increasing treatment costs, social rejection and poor survival.

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The present study analyses the importance of various pre-treatment factors such as demographic and socio-economic factors and lateness of case referral, that could explain risk of advanced disease. A multivariate analyses technique was used to allow interpretation of the relationship between those factors by controlling for factors that could potentially influence the results.

PATIENTS AND METHODS

All patients with newly diagnosed carcinomas of the oral cavity and oropharynx referred to three head and neck surgery services in Sao Paulo (Heliopolis Hospital), Curitiba (Erasto Gaertner Hospital) and Goiania (Araujo Jorge Hospital) during the period from 1 February 1986 to 30 December 1988 were considered eligible for the study. Only 336 cases of lesions that could be accessible to self examination (lip, other parts of the oral cavity, tonsillar fossa and posterior wall of the oropharynx) were considered eligible for the study. All diagnoses were confirmed histopathologically and the anatomic site was ascertained by clinical examination prior to treatment. Patients with malignant neoplasms of minor salivary glands, related structures such as bone and soft parts or cases of base of the tongue and vallecula were not included in the study.

Prior to any medical treatment all patients were submitted to a 40–60-min structured questionnaire-based, standardised interview. Interviews elicited detailed information on socio-economic and demographic variables, history of tobacco smoking and alcoholic beverage consumption. Quantities of tobacco and alcohol consumption were summarised on the base of cumulative exposure using pack-year equivalents of cigarette smoking and the sum over all beverage types of kilograms of ethanol consumption. Interviews were immediately interrupted if patients had difficulty in communication due to pain or speech problems. Such cases were not included in the study. Information on the first sign or symptom and the interval between recognition of it and the consultation to a drug store clerk or to a pharmacist (this is a cultural habit still in existence in many geographic areas of the country), dentist, and/or a medical doctor (most commonly a general practitioner or an otolaryngologist) was recorded in the standardised admission questionnaire. The interval between recognition of the signs or symptoms, the consultation with the first health professional and the subsequent admission at one of the head and neck services were taken as time variables considered for the analysis. Patient delay was defined on the basis of median site-specific time interval between the perception of the first sign or symptom and initial consultation with a pharmacy clerk, pharmacist, dentist or physician. Delay was considered if the patient's value for this variable exceeded that of the median. On the other hand, health professional delay was considered present whenever time interval between the first consultation and the admission to a head-and-neck service was greater than 1 month.

There were 291 male (86.6%) and 45 female (13.4%) patients. Ages ranged from 15 to 82 years (median 57 years). There were 55 (16.4%) cases of cancer of the lip, 71 (21.1%) of the mobile tongue, 62 (18.5%) of the floor of the mouth or lower gum, 16 (4.8%) of the hard palate or upper gum, 14 (4.2%) of the soft palate, 30 (8.9%) of the retromolar area, 67 (19.9%) of the tonsillar fossa, and 21 (6.3%) of other parts of the oral cavity or oropharynx. Staging of disease was categorised using the 1978 revision of the Union Internationale Contre le Cancer's tumour-nodes-metastasis (TNM) staging system.

Table 1. *Frequencies of tumours by site and clinical stage according to TNM system*

Site of primary tumour	Clinical stage I	II	III	IV	Total
Lip	22	18	10	5	55
Oral tongue	8	13	24	26	71
Floor of mouth/lower gum	3	7	17	35	62
Hard palate/upper gum	0	5	2	9	16
Soft palate	3	3	3	5	14
Retromolar area	1	1	12	16	30
Tonsillar fossa	0	7	24	36	67
Other	1	3	5	12	21

For the purpose of statistical analysis cases were considered as: (a) early lesions [T1 or T2 N0 clinically and/or histologically (pN−)], or (b) advanced lesions [all T3, T4, and cases with clinically or histologically positive nodes (pN+)]. The odds ratio was the measure of association used to estimate the relative risk (RR) of advanced stage vs. early disease due to selected study factors. Point and interval estimates for the RR were obtained by multiple logistic regression using unconditional maximum likelihood estimations [12]. Significance was based on the statistic representing the ratio of the estimated coefficient to its standard error assuming a standard normal distribution. All statistical inference was based on a 2-sided alternative hypotheses.

RESULTS

The distribution of patients according to clinical stage and site of primary tumours is shown in Table 1. The proportion of patients with clinical stage I and II lip carcinoma was higher than in patients with primary tumours of other parts of the mouth or oropharynx. 245 cases (72.9%) had tumours classified as advanced stage (T3 − T4 or pN+) and 91 (27.1%) as early stage (T1 − T2, pN−). Only 10 patients (3.0%) were examined at a head and neck service less than a month after perception of first signs or symptoms (2 of them were completely asymptomatic and were diagnosed during a routine clinical examination). In all other patients this time interval varied from 1 to 81 months: 1 month, 31 cases (9.2%); 2 months, 54 cases (16.1%); 3 months, 49 cases (14.6%); 4–6 months, 96 cases (28.5%); 7–12 months, 61 cases (18.2%); 13–81 months, 31 cases (10.4%). In 212 patients (63.1%) the first symptom was a painful ulcer in the mouth or oropharynx. Odynophagia and/or dysphagia, and the presence of a neck node were seen in 74 cases each (22%). Only 2 patients were not seen by a health professional before the first consultation in a head and neck service. A drug store clerk or a pharmacist were sought by 47 (14%) of the patients. A dentist or a physician was sought in consultation by the remaining patients: 63 (18.7%) and 319 (94.9%), respectively. The characteristics of the lesions at first examination in a head and neck service were exophytic in 140 (41.7%) and infiltrative in 196 (58.3%).

There was no delay on the referral to a head and neck service of 59 patients (17.6%). The patient was only responsible for

Table 2. Crude RR estimates for advanced stage of oral and oropharyngeal carcinoma according to selected demographic and socio-ecconomical characteristics

Variable	Category	Early/ advanced	RR	95% C.I.
Age (years)	≤50	18/67	1.00	Ref.
	51–65	47/126	0.72	0.39–1.34
	≥65	26/52	0.54	0.27–1.08
Sex	Male	72/219	1.00	Ref.
	Female	19/26	0.45	0.24–0.86
Race	White	80/207	1.00	Ref.
	Non-white	11/38	1.34	0.65–2.74
Study site	Sao Paulo	26/91	1.00	Ref.
	Curitiba	48/96	0.57	0.33–1.00
	Goiania	17/58	0.98	0.49–1.95
Area of residence	Rural	65/177	1.00	Ref.
	Urban	26/68	0.96	0.56–1.64
Monthly income (U.S. dollars)	0–100	57/146	1.00	Ref.
	101–500	30/85	1.10	0.66–1.85
	>500	4/14	1.37	0.43–4.33
Schooling level	Illiterate	31/77	1.00	Ref.
	Grammer school	52/146	1.13	0.67–1.91
	High school	5/21	1.69	0.59–4.88
	College	3/1	0.13	0.01–1.34

RR = risk ratio; CI = confidence interval.

Table 3. Crude RR estimates for advanced stage of oral and oropharyngeal carcinoma according to tobacco and alcohol consumption

Variable	Category	Early/ advanced	RR	95% C.I.
Tobacco consumption (pack/years)	0–9	12/17	1.00	Ref.
	10–50	38/111	2.06	0.90–4.71
	51–99	16/60	2.64	1.05–6.66
	≥100	25/57	1.61	0.67–3.86
Alcohol consumption (kg alcohol)	0	7/17	1.00	Ref.
	1–99	24/23	0.40	0.13–1.13
	100–1499	48/150	1.29	0.50–3.29
	≥1500	12/55	1.89	0.64–5.55

RR = risk ratio; CI = confidence interval.

the delay in reaching a head and neck service in 196 cases (58.3%) varying from 1 to 81 months (median 4.2 months). A medical doctor delayed the referral from 2 to 20 months (median 12.3 months) in 19 cases (5.7%); a dentist delayed the referral from 2 to 23 months (median 6.5 months) in 11 cases (3.3%). A pharmacist or a drug store clerk were involved in delay of referral from 2 to 26 months (median 3.5 months) in 13 cases (3.9%). In 38 cases (11.3%) the interval between the onset of first symptom and referral to a head and neck service was delayed from 3 to 36 months (median 8.5 months) because the patient and a doctor, a dentist, a pharmacist or a drug store clerk were involved in the delay.

Table 2 shows a summary of the crude RR estimates by selected demographic and socio-economic characteristics with frequencies of early and advanced stage cases. There was a moderate risk reduction associated with female gender and a marginally significant reduction in older patients. The distribution of patients according to race, area of residence and study site presented comparable distributions of early or advanced cases. Socio-economic status, as assessed by monthly household income categories and schooling level, was not associated with stage distribution.

Analysis showed a positive and dose–response-like relationship for the cumulative consumption of tobacco and disease status. Use of alcohol was marginally associated with the risk of advanced disease. Differences in magnitude of risk due to the various levels of alcohol consumption were not substantial (Table 3).

Table 4 shows the RR estimates by clinical and pathological characteristics. Significant relationships were seen with these variables in analysis. Infiltrative tumours were more likely to be advanced than exophytic tumours. A significant reduction in risk was seen when a painful ulcer was the first symptom. On the other hand, a substantial increase in risk was observed in

Table 4. Crude RR estimates for advanced stage of oral and oropharyngeal carcinoma according to selected clinical and pathological characteristics

Variable	Category	Early/ advanced	RR	95% C.I.
Type of lesion	Exophytic	57/83	1.00	Ref.
	Infiltrative	34/162	3.27	1.98–5.40
Symptoms				
(a) Painful ulcer	No	15/109	1.00	Ref.
	Yes	76/136	0.24	0.13–0.45
(b) Odynophagia/dysphagia	No	84/178	1.00	Ref.
	Yes	7/67	4.52	1.99–10.26
Site of primary tumour	Lip	40/15	1.00	Ref.
	To/FM/LG*	28/105	10.00	4.84–20.65
	HP/SP†	10/20	5.33	2.04–13.98
	RA/TF‡	9/88	26.07	10.53–64.58
	Other	4/17	11.33	3.28–39.18
Histological differentiation	I	37/73	1.00	Ref.
	II	48/139	1.47	0.88–2.45
	III	6/33	2.79	1.07–7.25

*Tongue, floor of mouth, and lower gum; †hard palate and soft palate; ‡retromolar area and tonsillar fossa. RR = risk ratio; C.I. = confidence interval.

Table 5. Crude RR estimates for advanced stage of oral and oropharyngeal carcinoma according to characteristics of referral delay

Variable	Category	Early/ advanced	RR	95% C.I.
Responsibility for patient's delay	No delay	14/45	1.00	Ref.
	Patient	60/136	0.71	0.36–1.38
	Health prof.	6/37	1.92	0.67–5.49
	Combined	11/27	0.76	0.30–1.92
(a) Patient	No	20/82	1.00	Ref.
	Yes	71/163	0.56	0.32–0.98
(b) Doctor	No	77/196	1.00	Ref.
	Yes	10/36	1.41	0.67–2.99
	Not consulted	4/13	1.28	0.40–4.04
(c) Dentist	No	8/40	1.00	Ref.
	Yes	1/14	2.80	0.32–24.43
	Not consulted	82/191	0.47	0.21–1.04
(d) Pharmacist/drug store clerk	No	6/17	1.00	Ref.
	Yes	6/18	1.06	0.29–3.93
	Not consulted	79/210	0.94	0.36–3.47
Total delay	No	14/45	1.00	Ref.
	1–3 months	17/67	1.23	0.55–2.73
	4–6 months	22/60	0.85	0.39–1.84
	>6 months	38/73	0.60	0.29–1.22

RR = risk ratio; C.I. = confidence interval.

cases with odynophagia and/or dysphagia. Analysis of RRs for site of primary tumour displayed a tendency for the tumour on less visible surfaces of oral cavity or oropharynx to be advanced at the time of diagnosis. There was also a significant increase in risk associated with histological grade III carcinomas.

Table 5 displays patient distribution, the RRs and their 95% confidence interval associated with the risk of having advanced disease as a function of referral characteristics. Except for a moderate risk reduction associated with cases, the patient was the responsible for delay in referral and cases of early and advanced stage presented comparable distributions.

In a subsequent step of analysis, a model containing variables associated with the risk of advanced disease for all cases, and two specific models for lip carcinomas and oral carcinoma (except lip and oropharynx) were built using multiple logistic regression (Table 6). Addition to these baseline combinations of variables showing univariate associ-

Table 6. Multifactorial models for RR estimates for advanced stage of oral and oropharyngeal carcinoma

Variable	Category	RR	95% C.I.	P
(A) Complete model:				
Site of primary tumour	To/FM/LG*	7.05	3.30–15.03	<0.001
	HP/SP†	3.75	1.37–10.26	
	RA/TF‡	17.21	6.75–43.86	
	Other	10.03	2.80–35.94	
Odyno./dysphagia	Yes	3.00	1.25–7.19	0.007
Type of lesion	Infiltrative	2.38	1.34–4.23	0.003
(B) Lip carcinoma model:				
Painful ulcer	Yes	0.08	0.05–1.06	0.038
Alcohol consumption	1–99	0.25	0.06–10.40	0.058
(kg alcohol)	100–1499	3.75	0.26–54.37	
	⩾1500	1.78	0.04–71.06	
Delay attributable to a doctor	Yes	3.02	0.42–21.97	0.074
	Not consulted	12.00	0.88–164.67	
(C) Oral carcinoma (excluding lip and oropharynx carcinoma) model:				
Type of lesion	Infiltrative	3.28	1.52–7.08	0.006
Odyno./dysphagia	Yes	3.26	1.04–10.17	0.025
Delay attributable to a dentist	Yes	0.58	0.05–6.38	0.099
	Not consulted	0.25	0.07–0.86	
Delay attributable to a doctor	Yes	4.22	0.92–13.40	0.074
	Not consulted	0.44	0.07–2.84	

*Tongue, floor of mouth, and lower gum; †hard palate and soft palate; ‡retromolar area and tonsillar fossa. RR = risk ratio; C.I. = confidence interval.

ations with advanced disease did not provide different parameter estimates for these factors.

Treatment decisions were based on the clinical and pathological characteristics of the tumour and patient's individual health condition. Surgery, radiotherapy or an association of both were used with curative intent in 220 patients (65.5%). In 94 patients (27.9%) radiotherapy alone or associated with chemotherapy was used with palliative intention. 22 patients (6.6%) either refused treatment or the advanced stage of disease precluded any kind of oncological treatment. Overall treatment costs including hospital radiation therapy, chemotherapy and professional services charges varied from 275 to 6567 U.S. dollars (median 850 dollars). The relationship between costs by site of primary tumour and stage are presented in Fig. 1. There was a clear positive trend in increasing hospital costs and professional fees according to stage of disease. Treatment duration (days) was computed including hospitalisation for surgical treatment and duration of radiotherapy and chemotherapy (either as inpatient or outpatient) and hospitalisation due to complications varied from 4 to 168 days (median 30 days). The duration of treatment for all sites of primary tumours increased with increasing stage (Fig. 2).

DISCUSSION

The prognosis of oral and oropharyngeal carcinoma diagnosed at early stages (stages I or II) is considered excellent when treated either with surgery or irradiation. On the other hand, for the more advanced cases (stages III or IV) the outlook for the patient is considerably worse [2, 4–6, 13–15]. Furthermore, the potential benefits of modern therapies for

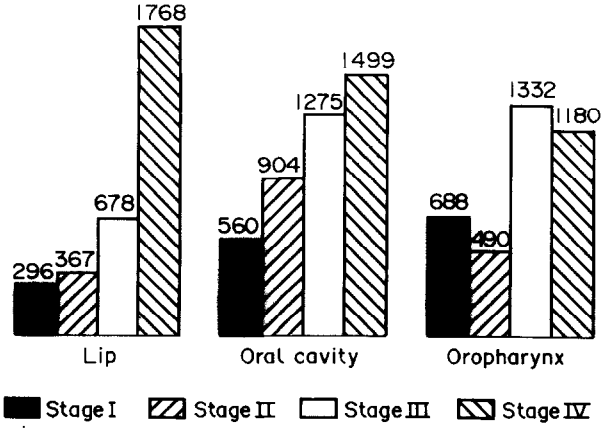

Fig. 1. Distribution of cost (mean) of treatment in U.S. dollars according to site and stage of oral or oropharyngeal carcinoma.

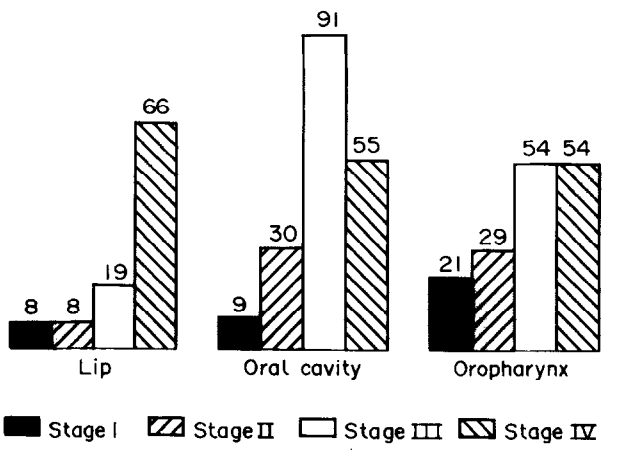

Fig. 2. Duration in days (mean) of treatment according to site and stage of oral or oropharyngeal carcinoma.

the more advanced cases can create several serious problems such as dry mouth, dysphagia, shoulder pain, osteoradionecrosis, disfigurement, prolonged hospitalisation, social rejection and profound modifications in life-style [16, 17]. So, early detection is the most rational method of reducing mortality and morbidity rates of oral and oropharyngeal carcinoma. Unfortunately, in the present study only 28.3% of the patients presented with stage I or II disease. If lip carcinoma was excluded from analysis, only 19.6% of the cases could be classified as early stage. These figures are considerably worse than those reported in developed countries [10, 18].

In spite of including in this series sites of the oral cavity and oropharynx accessible for self and clinical examination without need of any special equipment, only 3.0% were examined at a head and neck service less than 1 month after onset of symptoms. The vast majority of cases were symptomatic for a longer period of time. The most common first symptoms were a painful ulcer in the mouth or oropharynx, followed by odynophagia and/or dysphagia. The interval between the time when a new case is detected and the time the case becomes symptomatic varies according to the site of primary tumour. The most common characteristics related to tumours sited on less visible surfaces of the oral cavity and oropharynx (infiltrative pattern, odynophagia/dysphagia and grade III carcinoma) were all significant risk factors of advanced disease. The interpretation is very complex since clearly stage I disease detected after a long period of time must have a better prognosis than a stage IV detected after a short period. But, considering the imprevisibility in tumour evolution, there is a risk in delaying diagnosis. Therefore, early detection should be beneficial in terms of prognosis with a better cost-benefit ratio.

Unfortunately, the most aggressive tumours such as grade III oropharyngeal carcinoma are oligosymptomatic at early phases of evolution and, as a rule, are detected in advanced stages. Similar to Elwood and Gallagher [8] and Guggenheimer *et al.* [18], we did not find association between the clinically symptomatic period and disease stage at diagnosis. However, Kaufman *et al.* [19] reported that later stages of head and neck cancer had shorter intervals between the onset of first symptom and diagnosis. However, the preclinical phase of disease can be a long period of time [20]. These arguments strongly suggest that screening examination of high risk patients is the most reasonable method for early detection. The effect of a health education campaign for the earlier diagnosis of oral and oropharyngeal carcinoma could be efficient, however, many of them resulted in poor yields, perhaps because of inadequate targeting [20].

All patients, but 2 were seen by at least one health professional prior to their first consultation in a head and neck service. Only 17.6% were seen in a tertiary service without delay. The majority of cases were seen after a considerable period of time. In most cases (58.7%) the patients neglected their symptoms and did not seek professional attention until several months after onset of the symptoms. No patient attributable responsibility of delay was seen in 11.9% of cases. A non-specialist medical doctor was involved in the delay of 5.7% of the cases. A possible explanation for these figures was that our cases were more easily diagnosed by health professionals because of the advanced stages of the disease. When the entire series was analysed, patient and professional delays were not related to stage of disease. It is possible that early tumours are asymptomatic and so they could be detected only during a routine examination of high risk individuals. Other studies also failed to find an association between professional delay and stage of oral and oropharyngeal carcinoma at diagnosis [18].

On the other hand, the site-specific analysis for lip and other oral carcinomas showed the importance of the delay caused by medical doctors and dentists. The failure in recognising early lesions is a major cause for concern. The importance of professional training in early diagnosis cannot be overemphasised. In a study of hospital mortality rates, Hartz *et al.* [21] had observed significant differences according to the percentage of physicians who were board-certified specialists and registered nurses. This means that health campaigns must bear in mind not only public education but also professional training, otherwise several patients with an early lesion will certainly be misdiagnosed. In our experience, patients see medical doctors more frequently than dentists and both should be trained equally since symptomatic patients will see a doctor but the asymptomatic can be diagnosed in a routine dental consultation. Planning an efficient system of reference for the population must be a priority in terms of public health. This should consider that cases diagnosed or highly suspected of oral or oropharyngeal carcinoma should be referred to a head and neck specialist without delay because of unnecessary intermediate consultations to dentists or non-specialist doctors.

The risk of having advanced disease was lower in females and not dependent upon family income and educational levels. This social profile is apparently different at first sight to the main features of poverty that affect the problems of early detection and survival rates of cancer in the U.S.A.: unemployment, inadequate education, substandard housing, chronic malnutrition and diminished access to medical care [11]. The absence of correlation between income and educational levels in the present series is probably because it includes few patients of high income and educational levels and the effect of these variables could not be fully appreciated.

Epidemiological investigations have shown that tobacco and alcohol consumption are the two most important risk factors for oral carcinoma [22], but are not associated with delay on diagnosis [10]. Alcoholism was not associated with the stage of disease at diagnosis in this series, except for an association with late diagnosis of lip cancer.

Our data documented higher costs and longer stay either as outpatient or inpatient for cases with the more advanced diseases. These consequences may be catastrophic especially for socio-economically disadvantaged people.

1. Mirra AP, Franco EL. *Cancer Mortality in Sao Paulo, Brazil.* Sao Paulo, LICR Epidemiological monograph series, 1987.
2. Shah JP, Cendon RA, Farr HW, Strong EW. Carcinoma of the oral cavity: factors affecting treatment failure at the primary site and neck. *Am J Surg* 1976, **132**, 504–507.
3. Rich AM, Radden BG. Prognostic indicators for oral squamous cell carcinoma: a comparison betwee the TNM and STNMP systems. *Br J Oral Maxillofac Surg* 1984, **22**, 30–36.
4. Carvalho MB, Kowalski LP, Andrade-Sobrinho J, *et al.* La radiothérapie exclusive et l'association radiothérapie–chimiothérapie intra-artérielle dans le traitement du cancer étendu de l'oropharynx: étude rétrospective de 126 cas. *Rev Laryngol* 1986, **107**, 119–125.
5. Parsons JT, Mendenhall WM, Cassisi NJ, Isaacs Jr, JH, Million

RR. Hyperfractionation for head and neck cancer. *Int J Radiat Oncol Biol Phys* 1988, **14**, 649–658.
6. Spiro RH, Huvos AG, Wong GY, Spiro JD, Gnecco CA, Strong EW. Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. *Am J Surg* 1986, **152**, 345–350.
7. Brown B, Barnes L, Mazariegos J, Taylor F, Johnson J, Wagner RL. Prognostic factors in mobile tongue and floor of mouth carcinoma. *Cancer* 1989, **64**, 1195–1202.
8. Elwood JM, Moorehead WP. Delay in dagnosis and long-term survival in breast cancer. *Br Med J* 1980, **280**, 1291–1294.
9. Erwenne CM, Franco ELF. Age and lateness of referral as determinants of extra-ocular retinoblastoma. *Opthal Paediatr Genetics* 1989, **10**, 179–184.
10. Elwood JM, Gallagher RP. Factors influencing early diagnosis of cancer of cancer of the oral cavity. *Can Med Assoc J* 1985, **133**, 651–656.
11. Freeman HP. Cancer in the socioeconomically disadvantaged. *CA* 1989, **39**, 266–288.
12. Campos-Filho N, Franco EL. A microcomputer program for multiple logistic regression by unconditional and conditional maximum likelihood methods. *Am J Epidemiol* 1989, **129**, 439–444.
13. Berktold RE. Carcinoma of the oral cavity: selective management according to site and stage. *Otolaryngol Clin N Am* 1985, **18**, 445–450.
14. Carter RL, Barr LC, O'Brien CJ, Soo DC, Shaw HJ. Transcapsular spread of metastatic squamous cell carcinoma from cervical lymph nodes. *Am J Surg* 1985, **150**, 495–499.
15. Mohit-Tabatai MA, Sobel HJ, Rush BF, Mashberg A. Relation of thickness of floor of mouth stage I and II cancers to regional metastasis. *Am J Surg* 1986, **152**, 351–353.
16. Smith K, Lesko LM. Psychosocial problems in cancer survivors. *Oncology* 1988, **2**, 33–44.
17. Frank HA, Davidson TM. Ethical dilemmas in head and neck cancer. *Head Neck* 1989, **11**, 22–26.
18. Guggenheimer J, Verbin RS, Johnson JT, Horkowitz CA, Myers EN. Factors delaying the diagnosis of oral and oropharyngeal carcinomas. *Cancer* 1989, **64**, 932–935.
19. Kaufman S, Grabau JC, Lore JM. Symptomatology in head and neck cancer: a quantitative review of 385 cases. *Am J Public Health* 1980, **70**, 520–522.
20. Mashberg A, Samit AM. Early detection, diagnosis, and management of oral and oropharyngeal cancer. *CA* 1989, **39**, 67–88.
21. Hartz AJ, Krakauer H, Kuhn EM, *et al.* Hospital characteristics and mortality rates. *N Engl J Med* 1989, **321**, 1720–1725.
22. Franco EL, Kowalski LP, Oliveira BV, *et al.* Risk factors for oral cancer in Brazil: a case-control study. *Int J Cancer* 1989, **43**, 992–1000.

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