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SURVIVAL TO ORAL CANCER. A STUDY OF CLINICAL RISK MARKERS WITH INDEPENDENT PROGNOSTIC VALUE

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MOTS CLES: cancer oral, survivance, pronostic, ploidie

RESUME

Bases: les buts de cette étude ont été de décrire la survivance du cancer oral et d´identifier les variables cliniques avec une influence indépendante dans le pronostic préalable au traitement
Méthodes: 94 patients du cancer oral traités pendant la période 1991-1999 ont participé dans cette etude. Les variables considérées ont été: Âge, sexe, localisation de la lesión, présentation clinique, symptômes, classification, TNM, temps écoulé après traitement, et patron de ploidie. On a realise une etude descriptive des données accopmpagnée dune analyse de survivance employant les courbes de Kaplan-Meier et l´uni et multivariante regression de Cox.
Résultats: l´analyse multivariante a reconnu la valeur de pronostic de l´âge du patient et la taille de la tumeur. On n´a pas trouvé de différences significatives de survivance dans les autres variables de l´étude.
Conclusions: Cette étude suggère le besoin de considerer l´ âge et la taille de la tumeur comme les variables cliniques les plus relevantes pour prédire la survivance du cancer oral au moment du diagnostic.

ABSTRACT

Background: The aims of this study have been to describe survival to oral cancer and to identify clinical variables with independent influence on its prognosis before treatment. Methods: 94 oral cancer patients treated during 1991-99 entered the study. The variables considered were: age, sex, location of the lesion, clinical presentation, symptoms, TNM classification, months elapsed since treatment and ploidy pattern. A descriptive study of the data was performed, along with a survival analysis using Kaplan-Meier curves (log rank test for comparison among curves) and single and multivariate Cox regression. Results: Multivariate analysis recognized a prognostic value for the age of the patient (OR=1.06; CI95%:1.02 -1.09) and also for tumour size. Tumour stage resulted also selected, but its predictive value was lower than size's, so it was excluded from the predictive model. No statistically significant differences in terms of survival were identified on the rest of variables considered in the study. Conclusions: This study suggests the need for considering age and tumour size as the most relevant clinical variables for predicting survival to oral cancer at the time of diagnosis.

INTRODUCTION

Oral squamous cell carcinoma is the sixth malignancy by frequency in the world, and its prevalence has remained constant or decreased during 70's and 80's to increase afterwards (Hindle et al. 1994). Certain characteristics of this disorder, like its bad prognosis, morbidity, age of onset, and the need for aggressive and

extensive treatments with important sequelae amplify the social relevance of this disease.

The high mortality rate associated to oral cancer (50-60% five years after treatment in those cases with localised disease) has risen the interest for identifying possible prognostic indicators of its behaviour (Ildstad et al 1989). Variables like age, sex, nutritional or immunological status, location and size of the tumour, stage of the disease, lymph node status, several histopathological parameters, oncogene expression, proliferation makers, ploidy pattern or response to treatment (Tytor et al. 1990) have been suggested, but no agreement has been reached on its importance and usefulness. The aims of this study have been to describe survival to oral cancer and to identify clinical variables with an independent influence on the prognosis to oral cancer before treatment.

PATIENTS AND METHODS

Ninety four oral cancer patients treated and the Galician Oncology Centre during 1991-99 entered the study. This centre is the reference hospital for radiotherapy for all 5 general hospitals in the north of Galicia (NW Spain).

A survival study was performed in which the entry was defined as the day when cancer treatment starts and the exit as exitus by oral cancer, by other cause, or survival after the follow-up period. The variables studied were: age, sex, location of the lesion, clinical presentation, symptoms, TNM classification, months elapsed since treatment and ploidy pattern.

Hedley's method for ploidy pattern determination was employed for analysis of paraffin embedded tumours using propidium idodide as fluorochrome (Seoane et al. 1999) in a representative sample of 25 patients. The histograms that recovered less than 5000 events, showed a variation coefficient higher than 10% in the G0G1 peak, or showed an excessive amount of debris were classified as non-evaluable.

A descriptive analysis of the data was performed, along with a survival analysis using Kaplan-Meier curves (log rank test for comparison among curves) and single and multivariate Cox regression. The signification level chosen for all tests was 0,05.

RESULTS

Mean age at diagnosis was 60.29 (SD ± 11.96) ranging between 36 and 88. Most patients (82.5%) were males. Oral squamous cell carcinomas were more frequently found on the tongue (48.9%; CI95%: 38.6 - 51.9), followed by the floor of the mouth (19.1%; CI95%: 14.8 - 32.2). The tumour spread over more than one location on 22.4% of the patients.

Most patients (41.5%; CI95%: 31.7 - 51.9) showed a T2 tumour at diagnosis. Up to 58.8% (CI95%: 48.1 - 68.7) of the patients showed clinically negative necks. N1 nodes were found on 14.1% (CI95%: 8 - 23.1) of the sample; N2a nodes on the 11.8% (CI95%: 6.3 – 20.4) of the patients; N2b on the 10.6% (CI95%: 5.4 - 19) of the patients and N2c on the 3.5% (CI95%: 0.9 – 10.1). N3 nodes were identified on the 1.2% (CI95%: 0 - 6.8) of the patients investigated. No distant metastasis could be identified at the time of diagnosis. Most patients (51.1%; CI95%: 40.8 – 61.3) showed an advanced disease defined as stages III and IV, the latter being more frequent (35.1%; CI95%: 28.8 - 45.5), followed by stage II (33%; CI95%: 23.9 - 43.3), stage III (16%; CI95%: 9.6 – 25.1) and stage I (15.9%; CI95%: 7.9 - 22.6).

A 67.9% (CI95%: 47.6 - 83.4) of the tumours studied had a diploid DNA pattern, for a 32.1% (CI95%: 16.5 - 52.3) of aneuploid ones.

Five-year survival (60 months) was 44% in our series with 43 exitus and 47 survivors at the end of the follow-up period.

The age of the patient was identified as a prognostic variable ($p<0.05$), as the risk of death increases a 6.02% by each year of age. Tumour stage has also proved prognostic value for survival ($p<0.05$). Tumour size has arisen as an important prognostic indicator ($p<0.05$) in the Kaplan-Meier test, and this result was confirmed by both single and multivariate Cox regression (Fig. 1, Tabs. 1-2).

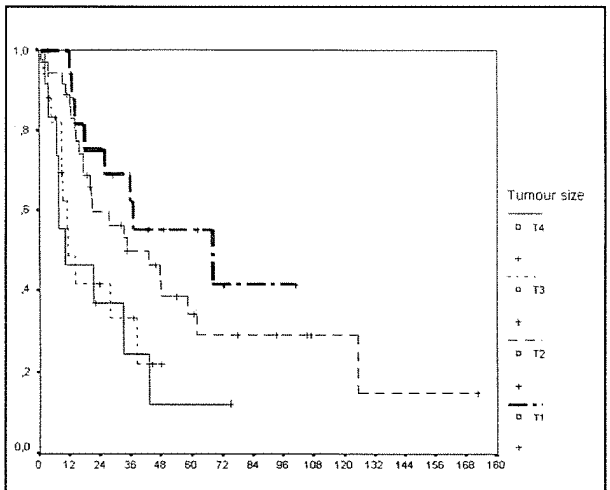

Fig. 1: Survival function for tumour size.

Single variable Cox regression acknowledges prognostic value to the age of the patient at the time of diagnosis, to the size of the tumour grouped under the headings described in the TNM classification and also to the stage of the tumour before treatment (Tab. 1).

Tab. 1: Single variable Cox regression análisis

Variable	Exp(Q)	p	CI 95%	
			Lower	Upper
Age	1,0602	**0,007**	1,0251	1,0965
Tumour size				
T1		**0,0129**		
T2	1,4509	0,4374	0,5672	3,7114
T3	3,4009	**0,0221**	1,192	9,703
T4	4,1131	**0,0092**	1,4186	11,9259
Neck nodes				
N0		0,1709		
N1	1,7197	0,2435	0,6915	4,2772
N2	1,0755	0,8599	0,4796	2,4114
N3	8,5114	**0,0444**	1,0549	68,6715
Tumour stage				
I		**0,0394**		
II	0,829	0,7083	0,3104	2,2143
III	2,698	0,0689	0,9259	7,8615
IV	1,8679	0,1972	0,7227	4,8278
Ploidy pattern	2,1321	0,1981	0,6731	6,7541

Multivariate analysis (Tab. 2) recognized a prognostic value for the age of the patient (OR=1.06; CI95%:1.02 -1.09) and also for tumour size. Tumour stage resulted also selected, but its predictive value was lower than size's, so it was excluded from the predictive model, as tumour stage includes tumour size values.

No statistically significant differences in terms of survival were identified on the rest of variables considered in the study.

Patients with diploid tumours (Fig 2) showed a survival rate of 61.43% after 3 years for 33.33% of those with aneuploid tumours. After 5 years, all patients with aneuploid tumours had died whereas 51.19% of the patients with diploid cancers survived. The classification of the patients by its DNA ploidy pattern results on markedly different survival functions (Fig 3).

Tab. 2: Multi-variate Cox regression análisis

Variable	Exp (Q)	p	CI 95%	
			Lower	Upper
Age	1,0561	**0,0018**	1,0205	1,0929
Tumour size		**0,0065**		
T2	1,5502	0,3617	0,6043	3,9771
T3	4,5423	0,0052	1,5714	13,1300
T4	3,7838	0,0149	1,2957	11,0498

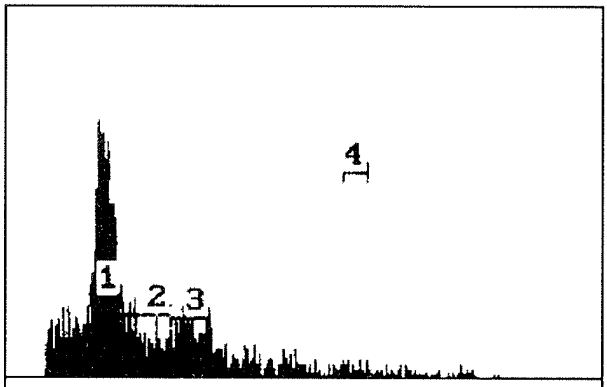

Fig 2: DNA ploidy histogram of a diploid tumour

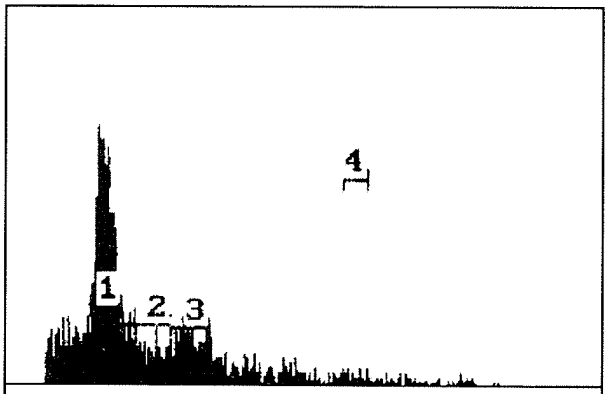

Fig 3: Survival function for ploidy pattern

DISCUSSION

Mean follow-up period in our series (34.54 months; range 0.83 - 197) falls about the 3 years described as necessary, as longer follow-up periods do not alter significantly the results of survival to oral cancer (Boysen et al. 1992). The survival rate of the patients in our series was 44% after 5 years, which is within the range described in other reports (La Vecchia et al. 1997).

Other research groups found age as a relevant prognostic factor (Ildstad et al. 1989; Stell, 1990; Olszewski & Semczuk, 1991), with longer survival for younger patients (Ildstad et al. 1989; Shiltoe et al. 1986; Urist et al. 1987; Evans et al. 1982) which agrees with our results, although this finding could not be always confirmed (Tab. 3). It is possible that the better behaviour of younger patients may be due to confounding factors, affecting survival because of the influence of age on the response to treatment or because the increment of the risk of dying by other causes in older patients (Stell, 1992).

Tab. 3: Age as a prognostic factor for survival

Authors	Year	Location of the tumour	Prognostic value
Evans et al	1982	Oral	Yes
Hibbert et al	1983	Oral	No
Shilltoe et al	1986	oral	Yes
Urist et al	1987	oral mucosa	Yes
Ildstad et al	1989	Head and neck	Yes
Tytor et al	1990	oral	Yes
Stell	1990	larynx	Yes
Olszewski et al	1991	larynx	Yes
Wolfensberg et al	1992	Upper aerodigestive tract	No
Stell	1992	oral	Yes
Krishnan et al	1992	oral	No
Milián et al	1993	oral	No
Boffetta et al	1994	oropharynx	No
Faye-Lund et al	1996	Head and neck	Yes

An inverse correlation between survival and tumour size has been described in scientific literature (Krishnan Nair et al. 1992). Some investigations find this relationship valid only for certain categories (Milián Masanet et al. 1993) or invalid at all (Faye Lund, 1996). The results of multivariate analysis showed tumour size is the most relevant independent prognostic factor for survival (along with age) amongst all variables considered, which agrees with previous reports (Milián Masanet et al. 1993; Platz et al. 1986; Hemmer et al. 1999) although there is no agreement in scientific literature (Faye Lund, 1996; Hibbert et al. 1983) probably due to the use of heterogeneous procedures by different research groups.

Tumour stage had a significant influence on the survival of the patients studied, in agreement with previous research (Ildstad et al. 1989; Milián Masanet et al. 1993; Faye Lund, 1996; Hemmer et al. 1999). This variable has been excluded from the final multivariate predictive model because it has less predictive value than tumour size.

DNA ploidy pattern has been recognized as a predictive variable in oral cancer (Tytor et al. 1989), as patients with aneuploid tumours showed lower survival rates (Tytor et al. 1990; Hemmer et al. 1998; Hemmer et al. 1990; Holm, 1982; Chen et al. 1993; Goldsmith et al. 1987; Burgio et al. 1992; Balsara et al. 1994; Rubio Bueno et al. 1998; Melchiorri et al. 1996; Kokal et al. 1988) and shorter periods free form disease than patients with diploid tumours (Rubio Bueno et al. 1998; Melchiorri et al. 1996; Kokal et al. 1988). However, some research reports find this associations equivocal (Mohr et al. 1992; Syms et al. 1995; Wolfsensberg, 1992) (Tab 4). Our results did not recognize prognostic value for the DNA ploidy pattern in terms of survival to oral cancer.This study suggests the need for considering age and tumour size as the most relevant clinical variables for predicting survival to oral cancer at the time of histopathological and extension diagnosis of oral cancer.

Tab. 4: Ploidy pattern as a prognostic factor for survival

Author	Year	Location	No of cases	Fresh / Paraffined	% non diploid	Prognost value
Holm *	1982	Head and neck	45	P	75.63	Yes
Goldsmith et al	1987	Head and neck	69	P	74	Yes
Kokal et al	1988	Head and neck	76	P	67	Yes
Tytor et al	1989	Oral	140	P	50	Yes
Tytor et al **	1990	Oral	176	P	50	Yes
Hemmer et al	1990	Oral	110	P	72.7	Yes
Mohr et al	1992	Head and neck	142	F	36.8	No
Burgio et al	1992	Head and neck	497	F	66	Yes
Chen et al	1993	Oral	40	F	58	Yes
Balsara et al	1994	Oral	68	P	42	Yes
Barettion et al	1995	Oral	106	P	68	No
Syms et al	1995	Oral	94	P	47	No
Melchiorri et al	1996	Oral & maxillof	25	P	32	Yes
Rubio Bueno et al	1998	Oral	109	P	54	Yes
Hemmer et al	1998	Oral	116	F	59.48	Yes
Hemmer et al	1999	Oral	429	F	88.89	Yes

*Static Cytometry **Image Cytometry. P:paraffin embedded F: fresh

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