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Prognostic Factors for Local Control, Regional Control and Survival in Oropharyngeal Squamous Cell Carcinoma

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We have performed univariate and multivariate analysis to identify the clinical and treatment-related prognostic factors in a series of 254 patients with newly diagnosed, histologically proven, oropharyngeal squamous cell carcinoma treated with radical radiation therapy. The probabilities of local control, regional control, disease-free survival (DFS) and adjusted survival (AS) were calculated using the Kaplan–Meier method and differences between curves were evaluated by the Mantel–Cox test. The obtained significant variables in the univariate analysis were analysed using the Cox proportional hazards model. In the Cox multivariate analysis, four variables significantly influenced local control probability in the following order: tumour diameter, N stage, alcohol intake and weight loss. N stage significantly influenced the probability of regional control. Five variables influenced both DFS and AS: N stage, tumour diameter, weight loss, alcohol intake and tumour origin within the posterior oropharyngeal wall.

Key words: oropharynx, carcinoma, prognostic factors, alcohol, weight loss
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INTRODUCTION

THE EXTENT of the primary tumour and the absence, presence and extent of lymph node metastases are considered the most important factors determining prognosis of oropharyngeal squamous cell carcinoma. Treatment selection is usually based on these factors. Other factors may also influence the outcome of patients with oropharyngeal carcinoma. The influence of primary site [1], histological grade [2], patients gender [3], performance score [4, 5] and haemoglobin value [3] have been reported.

An analysis of the influence of clinical and therapeutical factors on prognosis should evaluate their possible impact on local control and regional control, as well as on tumour lethality, since locoregional relapses represent the most frequent cause of failure, and current treatment modalities treat locoregional disease.

This study attempts to identify, by means of a multivariate analysis, the clinical and treatment-related factors significantly associated with outcome in a series of patients with oropharyngeal carcinoma treated with curative intent at one department of radiotherapy.

PATIENTS AND METHODS

Patients

Between July 1964 and December 1989, 344 patients with histologically proven diagnosis of squamous cell carcinoma of the oropharynx were admitted at the Department of Radiation Oncology of Clinica Puerta de Hierro (Madrid, Spain). Those patients with newly diagnosed carcinomas and without previous irradiation of the oropharynx, whose radical radiation therapy

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treatment was given entirely at our department, were considered eligible for this study. 254 patients met these criteria and are included in the analysis. Patients with relapsed oropharyngeal carcinoma after treatment at other institutions (36 cases), those who were treated for palliation (8 cases, 6 with metastases at presentation), those who had been given part of their radiotherapy treatment elsewhere and were referred to us for implant boost (9 cases), those treated with surgery and postoperative irradiation (20 cases, including one who had also received previous irradiation), those with previous irradiation of the oropharynx (15 cases), and patients who voluntarily did not finish the prescribed treatment course (3 cases) were excluded from the analysis. 3 patients scheduled for radical radiotherapy who died of cancer during their treatment were excluded from the analysis of therapeutical factors and were included in the analysis of clinical factors.

The initial tumour site was the base of the tongue in 92 cases, the valleculae in 20 cases, the tonsil in 77 cases, the anterior faucial pillar in 19 cases, the posterior faucial pillar in 4 cases, the soft palate in 24 cases and the posterior oropharyngeal wall in 18 cases. The mean age was 57.6 years (range 15–93), and the male to female ratio 12:1 (235 men and 19 women). Information on smoking history and alcohol intake was available in 239 clinical records. Five per cent of women (1 of 19) and 99% of men (217 of 220) were smokers. None of the women admitted to drinking alcohol, but regular alcohol intake was declared by 90% of men (197 of 220). 11 patients had had previous carcinomas and 14 patients had simultaneous tumours. Histological diagnosis was differentiated squamous cell carcinoma in 234 cases (92%), lymphoepithelioma in 9 cases (4%) and undifferentiated squamous cell carcinoma in 11 cases (4%). Information on histopathological grade was available in 148 cases; there were 53 (36%) G1 carcinomas, 34 (23%) G2 carcinomas, 41 (28%) G3 carcinomas and 20 (14%) G4 carcinomas.

Each patient's disease was retrospectively restaged according to the unified recommendations of the American Joint Committee on Cancer [6] and International Union Against Cancer [7] on the basis of descriptions and drawings made at the initial presentation. Patient distribution by T stage and N stage is demonstrated in Table 1. Overall, stage I occurred in 17 patients (7%), stage II in 48 patients (19%), stage III in 59 patients (23%) and stage IV in 130 patients (51%).

Treatment

All eligible patients in the present series were treated with curative intent; however, because this is a retrospective study, treatment policies varied slightly over this period.

The main treatment approaches for treating the primary tumour were external-beam irradiation alone and external-beam irradiation plus brachytherapy boost with ^{192}Ir wire. 160 patients (63%) were treated with external beam radiotherapy (EBRT) alone, 80 patients (31%) with EBRT plus brachytherapy boost, and brachytherapy alone was used to treat 11 patients (4%). 3 patients (1%) scheduled for treatment with radiotherapy died during treatment.

External beam irradiation was delivered with megavoltage equipment. Patients were irradiated through two opposing lateral fields and, in most cases, a lower neck anterior field. After a 50-Gy tumour dose, a boost dose was delivered to the primary, either with external beam irradiation through an ipsilateral or two lateral reduced portals, or with brachytherapy using ^{192}Ir wire. Brachytherapy boost was usually administered with ^{192}Ir hairpins (84 patients, 92%), but the loop technique was used in some cases (7 patients, 8%).

The total tumour doses given to patients treated with EBRT alone varied from 48.4 to 82 Gy (mean 70.2 Gy). 137 patients (86%) had total doses between 60 and 75 Gy. The mean duration of the treatments with EBRT alone was 55.4 days (range 30–86). Sixty-two per cent of patients completed the treatment course of radiation therapy within 46–60 days. 137 patients (86%) were treated using a conventional fractionation schedule, 13 patients (8%) using a hyperfractionated schedule and the remaining patients were treated once a day using 150 cGy fractions in 6 cases, 220 cGy fractions in 3 cases and 165 cGy fractions in 1 case. In patients treated with opposed beams, the tumour doses were prescribed at the point midway between the entrance of the beams on the central axis. When an ipsilateral boost was used, the dose was prescribed at the maximum tumour depth.

The total tumour doses given to patients treated with EBRT plus brachytherapy boost varied from 49 to 99 Gy (mean 77.4 Gy). 63 patients (79%) had total doses between 65 and 85 Gy. The doses delivered by EBRT varied from 27 to 56 Gy, with a mean dose of 49 Gy; and those delivered by interstitial implant varied from 4 to 48.9 Gy, with a mean dose of 27.5 Gy. In 72 patients (90% of cases), the doses delivered by EBRT ranged from 45 to 55 Gy, and in 60 patients (75% of cases) the doses delivered by implant ranged from 20 to 35 Gy. The dose rates varied from 20 to 112 cGy/h (mean 57.6 cGy/h). 79 patients (99%) were treated using a conventional fractionation schedule. Since 1982, computer dosimetry using the implant anteroposterior and lateral radiographs has been used, and all interstitial implants performed prior to 1982 have been recalculated using computer dosimetry and the implant radiographs. The minimum target absorbed doses have been used for dose prescription in brachytherapy.

11 patients with early tumours, arising in the soft palate in 6 cases, in the base of the tongue in 3 cases, in the anterior faucial pillar in 1 patient and in the valleculae in another patient were treated by interstitial implant alone.

103 (92%) N0-staged patients received elective treatment of the neck, which was administered using radiotherapy alone and the neck was observed in 9 patients. One N0-staged patient died during treatment. The mean radiation dose delivered to the neck

Table 1. T and N stage distribution in 254 patients (AJCC and UICC unified TNM system [6, 7])

	N0 (%)	N1 (%)	N2 (%)	N3 (%)	Total (%)
T1	17 (59% of T1)	3	7	2	29 (11%)
T2	48 (53% of T2)	15	18	9	90 (35%)
T3	28 (39% of T3)	13	25	6	72 (28%)
T4	20 (32% of T4)	12	27	4	63 (25%)
Total	113 (44%)	43 (17%)	77 (30%)	21 (8%)	254

in N0-staged patients was 49.3 Gy and 81% of these patients received doses between 45 and 51 Gy. Patients with clinically positive lymph nodes were treated in most cases with radiotherapy alone (116 patients, 83%), however, some patients were treated with neck dissection plus radiotherapy (22 patients, 16%) and 1 patient was treated with surgery alone. 2 patients with clinically positive nodes died during treatment. The total nodal doses given to N positive patients treated with radiotherapy alone ranged from 44 to 89 Gy (mean 68.1 Gy).

Systemic therapy varied considerably during this 25-year period. Chemotherapy was given to 77 patients with advanced tumours. 53 patients were given concomitant chemotherapy, which consisted of bleomycin in 27 patients, tegafur in 24 and methotrexate in 2 patients. Neoadjuvant chemotherapy was given to 24 patients. In 8 cases, neoadjuvant chemotherapy consisted of cisplatin, methotrexate, bleomycin and vincristine; in 10 of cisplatin and 5-fluorouracil, in 5 patients of cisplatin and bleomycin and in 1 patient of cisplatin and tegafur.

Follow-up

11 patients were lost to follow-up. 7 of these patients were lost to follow-up in the first year after treatment, 2 in the second year, 1 in the third year and another in the sixth year after treatment. All remaining patients have been followed for at least 2 years, and 184 patients (72% of the cases) have been followed for at least 5 years.

Statistical methods

Data were stored and analysed in the Department of Biostatistics. BMDP software was used for data analysis [8, 9].

The clinical factors that were analysed were primary tumour site, primary tumour extent (T stage, tumour diameter, trismus and invasion of soft tissues or deep muscle of tongue), extent of nodal disease (N stage, node fixation, number of palpable nodes, diameter of the largest node), overall stage, histological grade and patient-related factors (age, sex, alcohol intake, smoking habits, history of weight loss and haemoglobin level).

The analysed treatment-related parameters were duration of the first part of the radiotherapy treatment (wide field irradiation of the tumour bed and neck nodes); total duration of the treatment and total radiation dose administered to patients treated with external beam radiotherapy alone; total radiation dose given to patients treated with external beam irradiation plus brachytherapy boost and total nodal radiation dose given to patients with palpable nodes.

Various cut-off values were used for grouping continuous variables, including cut-off values reported as significant in previous studies, and cut-off values that were thought to discriminate two clinically different groups of patients. The most significant comparison was selected.

All variables were first analysed independently to assess their effect on the probabilities of local control (LCP), regional control (RCP), disease-free survival (DFS) and adjusted (cause-specific) survival (AS). Probabilities of local control, regional control, disease-free survival and adjusted survival were calculated using the Kaplan–Meier method [10] and differences between curves were evaluated by the Mantel–Cox test [11]. Uncensored recurrence-free time was defined as the interval from the date of treatment initiation to the date of local relapse for local control analysis, to the date of nodal relapse for regional control analysis, to the date of relapse at any site for DFS analysis and to the date of death from oropharyngeal cancer for AS analysis. 11 patients who were eventually lost to follow-up, 10 patients dead of unknown causes and 2 patients dead of complications were considered uncensored for LCP, RCP, DFS and AS analyses. Statistical significance was considered when the P value was less than 0.05 but P values up to 0.10 were also noted.

In the second part of the study, variables with prognostic significance and those which approached the significance level ($P \leq 0.10$) were compared using the Cox proportional hazards model [12]. This model enters those factors that independently influence prognosis in a stepwise fashion, the most significant variable being entered first. We performed various multivariate analyses. In the first multivariate analysis, we compared the significant or nearly significant clinical variables obtained in the univariate analysis. Since information about histological grade was not available in a large number of patients and this factor was not significant in the first multivariate analysis, we excluded this variable and performed another multivariate analysis. The number of patients with complete data included in this analysis was 207. We also performed another multivariate analysis restricted to patients treated with EBRT alone or EBRT plus brachytherapy boost to evaluate the influence of treatment-related factors on the outcome. This analysis included the significant variables obtained in the multivariate analysis of clinical factors and the treatment-related factors with prognostic significance in the univariate analysis. The number of patients included in this analysis was 227.

With these multivariate analyses, four final sets of independent factors were obtained, which were the most useful in predicting the outcome of each patient in relation to the four end points: local control probability, regional control probability, disease-free survival and adjusted survival.

The proportional hazards assumption was checked using the BMDP 2L program [9]. This program produces a plot of the log minus log survival function for each significant variable.

RESULTS

General outcome

Of 254 patients, 63 (25%) remained alive at the closing date of the study, 124 (49%) died of tumour-related causes, 18 (7%) of intercurrent disease, 26 (10%) of second cancer, 2 (0.8%) of treatment complications (one due to granulocytopenia and pneumonia after a chemotherapy course and a second patient due to extensive necrosis and infarction of the base of the tongue), 10 patients (4%) died of unknown causes and 11 patients (4%) were lost to follow-up.

133 patients relapsed. Of these 133 relapses, 70 (53%) were isolated local recurrences, 18 (14%) isolated nodal recurrences, 10 (8%) isolated distant failures, 20 (15%) primary and nodal failures, 4 (3%) primary and distant failures, 6 (5%) nodal and distant failures, 5 (4%) local, nodal and distant failures.

The actuarial 3-year local control probability was 78% for T1, 57% for T2, 41% for T3 and 40% for T4 tumours. The 3-year regional control probability was 82% for N0-staged patients treated electively. The 3-year regional control probability was 58% for N1, 56% for N2 and 46% for N3. Five-year actuarial local control, actuarial regional control and actuarial survival probabilities are shown in Table 2.

The actuarial risk of developing a second tumour was 14.4% (standard error 3.4) at 5 years and 36% (standard error: 8.3) at 10 years. The actuarial risk of developing a second carcinoma in the head and neck, lung or oesophagus was 11.3% (standard error 3.1) at 5 years and 30.2% (standard error 8.2) at 10 years.

Table 2. Univariate analysis of clinical factors

Factors description	No. of patients	5-year rates			
		Adjusted survival (%)	Local control probability (%)	Nodal control probability (%)	Disease-free survival (%)
Primary site					
Base of tongue	92	35	43	63	35
Valleculae	20	51	74	70	47
Anterior pillar	19	53	34	74	26
Posteria pillar	4	0	50	75	50
Tonsil	77	38	49	60	38
Soft palate	24	51	67	73	44
Posterior wall	18	6	9	36	6
		$P < 0.005$	$P < 0.02$	NS	$P < 0.05$
T stage					
T1	29	52	63	62	43
T2	90	43	50	65	39
T3	72	37	41	65	31
T4	63	28	40	60	29
		$P < 0.02$	$P < 0.01$	NS	$P = 0.05$
Tumour diameter					
≤3 cm	78	51	60	—	46
>3 cm	176	33	41	—	30
		$P < 0.002$	$P < 0.0003$		$P < 0.002$
N stage					
N0	113	52	56	75	50
N1	43	36	35	58	23
N2	77	26	42	56	25
N3	21	19	28	34	19
		$P < 0.0003$	$P < 0.05$	$P < 0.0005$	$P < 0.0005$
Stage					
I	17	50	—	—	46
II	48	55	—	—	54
III	59	46	—	—	32
IV	130	28	—	—	28
		$P < 0.001$			$P < 0.005$
Weight loss					
Yes	19	10	12	27	8
No	235	40	49	66	37
		$P < 0.002$	$P < 0.001$	$P = 0.09$	$P < 0.003$
Haemoglobin level					
≤12 g/dl	19	15	28	70	26
>12 g/dl	201	38	45	62	33
		$P < 0.03$	$P = 0.08$	NS	NS
Alcohol intake					
≤40 g per day	74	46	58	72	39
>40 g per day	165	36	41	59	33
		NS	$P < 0.05$	NS	NS

NS, non-significant. There were trends toward statistically significant differences in the probability of local control in relation to histological grade ($P = 0.09$), in the probability of regional control in relation to diameter of the largest node ($P = 0.06$) and in the probability of survival according to number of palpable nodes ($P = 0.06$). Differences were not significant in relation to other variables analysed: age, sex, level of smoking (≤10 cigarettes per day versus >10 cigarettes per day), node fixation, presence of trismus and presence or absence of tumour invasion into the deep musculature of the tongue or soft tissues.

Univariate analysis

The clinical factors associated with statistically significant differences in the univariate analysis are summarised in Table 2.

T-stage, tumour diameter, primary site and weight loss significantly influenced LCP, DFS and AS. N-stage significantly influenced RCP, DFS, AS and LCP. Overall stage was associated with statistically significant differences in DFS and AS. Other factors associated with statistically significant differences were haemoglobin level (AS) and alcohol intake (LCP). There were trends toward significant differences (P value up to 0.10) in the probability of local control in relation to histological grade and haemoglobin level, in the probability of regional control in

relation to diameter of the largest node and weight loss, and in the probability of survival in relation to the number of palpable nodes.

Total radiation dose and total duration of treatment in patients treated with EBRT alone and total radiation dose given to patients treated with external beam irradiation plus brachytherapy boost were not associated with statistically significant differences in LCP, DFS and AS (Table 3). The total duration of the initial wide field irradiation, to a dose of approximately 50 Gy, was associated with significant differences in the probabilities of local control, DFS and AS.

Multivariate analysis

Four independent clinical variables were found to significantly influence local control probability, in the following order: tumour diameter, N stage, alcohol intake, weight loss.

There was a trend toward statistical significance in relation to primary tumour site: base of tongue, valleculae, faucial pillars, tonsillar fossa and soft palate versus posterior wall ($P = 0.052$; relative risk: 1.83; 95% confidence interval: 0.99–3.38). The therapeutical factors analysed did not significantly influence the probability of local control (data not shown). Table 4 gives the coefficients, standard errors, P values, relative risks and 95% confidence intervals of relative risk for each prognostic factor.

Only N stage was found to independently influence the probability of regional control. Table 5 gives coefficient, P value and relative risk.

Five independent clinical variables were found to significantly influence disease-free survival in the following order: N stage, tumour diameter, weight loss, alcohol intake, primary site. These variables influenced adjusted survival in the following order: N stage, tumour diameter, primary site, weight loss, alcohol intake.

In the multivariate analysis of predictors for adjusted survival, which included treatment-related factors, there was a trend toward statistical significance in relation to duration of the initial wide field irradiation ($P = 0.055$; relative risk 1.43; 95% confidence interval 0.99–2.06). The therapeutic factors analysed did not significantly influence the probability of disease-free survival (data not shown). Table 6 shows the significant variables influencing disease-free survival and Table 7 those influencing adjusted survival. Their respective coefficients, P values and relative risks are also shown.

DISCUSSION

General outcome

Local relapse was the main cause of failure in the present series. Our actuarial local control rates are difficult to compare with those reported by other authors because our series includes tumours of all oropharyngeal subsites, and most studies report the actuarial local control probabilities for patients with tumours of one of the oropharyngeal subsites. The local control probabilities calculated for T1 tumours were lower than those reported by other authors for T1-staged tumours of one of the oropharyngeal subsites [1, 13–16]. This might be due to the method used for calculation, since we considered patients lost to

Table 3. Univariate analysis of treatment-related factors

Factors description	No. of patients	5-year rates: Adjusted survival (%)	Local control probability (%)	Nodal control probability (%)	Disease-free survival (%)
Duration of the initial "wide field" RT*					
≤40 days	143	46	53	—	42
>40 days	97	28	36	—	26
		$P < 0.005$	$P < 0.03$		$P < 0.02$
Total radiation dose (EBRT alone)					
≤6500 cGy	18	29	27	—	24
6501–7500 cGy	123	34	44	—	34
>7500 cGy	19	45	62	—	45
		NS	NS		NS
Treatment duration (EBRT alone)					
≤45 days	20	24	42	—	25
46–55 days	62	49	59	—	46
>55 days	78	26	33	—	24
		NS	NS		NS
Total radiation dose (EBRT + ^{192}Ir)					
≤7000 cGy	12	42	44	—	31
>7000 cGy	68	46	51	—	43
		NS	NS		NS
Total nodal radiation dose (RT alone, N+)					
≤6000 cGy	22	19	—	47	25
6001–7000 cGy	42	28	—	61	27
>7000 cGy	52	26	—	51	21
		NS		NS	NS

NS, non-significant; RT, radiotherapy. *Includes patients treated with external beam radiotherapy (EBRT) alone and patients treated with EBRT plus brachytherapy. EBRT + ^{192}Ir: patients treated with external beam radiotherapy plus brachytherapy boost. RT alone, N+: patients with clinically positive lymph nodes treated with radiotherapy alone.

Table 4. Cox proportional hazards analysis: independent factors influencing local control

Factors and subgroups	Regression coefficient (β) ± S.E.	*P* value	Relative risk e^{β}	Relative risk (95% confidence interval)
Tumour diameter				
≤3 cm	0.78 ± 0.25	0.002	2.17	1.33–3.55
>3 cm				
N-stage				
N0	0.39 ± 0.16	0.014	1.48	1.07–2.03
N1, N2 and N3				
Alcohol intake				
≤40 g/day	0.63 ± 0.22	0.005	1.88	1.21–2.92
>40 g/day				
Weight loss				
No	0.84 ± 0.30	0.006	2.31	1.27–4.22
Yes				

There was a trend toward statistical significance according to primary site, base of tongue, valleculae, faucial pillars, tonsillar fossa and soft palate versus posterior wall ($P = 0.52$, relative risk 1.83, 95% confidence interval 0.99–3.38).

Table 5. Cox proportional hazards analysis: independent factors influencing regional control

Factors and subgroups	Regression coefficient (β) ± S.E.	*P* value	Relative risk e^{β}	Relative risk (95% confidence interval)
N stage				
N0	0.64 ± 0.2	0.002	1.9	1.27–2.85
N1, N2 and N3				

Table 6. Cox proportional hazards analysis: independent factors influencing disease-free survival

Factors and subgroups	Regression coefficient (β) ± S.E.	*P* value	Relative risk e^{β}	Relative risk (95% confidence interval)
N stage				
N0	0.64 ± 0.19	0.001	1.9	1.31–2.76
N1, N2 and N3				
Tumour diameter				
≤3 cm	0.45 ± 0.21	0.032	1.57	1.03–2.38
>3 cm				
Weight loss				
No	0.71 ± 0.28	0.013	2.03	1.15–3.59
Yes				
Alcohol intake				
≤40 g/day	0.37 ± 0.18	0.045	1.45	1.003–2.10
>40 g/day				
Primary site				
BT, V, FP, T, SP	0.59 ± 0.28	0.033	1.81	1.04–3.15
Posterior wall				

BT, Base of tongue; V, valleculae; FP, faucial pillars; T, tonsillar fossa; SP, soft palate.

follow-up and patients dead of unknown causes as failures for local control, regional control and survival analyses. Of 29 patients with T1 tumours, 2 patients failed at the primary site, 1 patient developed a primary and distant failure, 2 patients were lost to follow-up (1 during the first year and 1 in the second year) and 2 died of unknown causes (1 in the first year after treatment and 1 in the fourth year after treatment). Although this limits the accuracy of the calculation of local control probabilities, these probabilities might be similar to those reported. When patients lost to follow-up were considered as "lost" in the actuarial calculations, the 3-year local control probability was 85% for T1 and 59% for T2 tumours. Our local control rates for

Table 7. Cox proportional hazards analysis: independent factors influencing adjusted survival

Factors and subgroups	Regression coefficient (β) ± S.E.	*P* value	Relative risk e^{β}	Relative risk (95% confidence interval)
N stage				
N0	0.56 ± 0.14	0.0002	1.75	1.31–2.33
N1, N2 and N3				
Tumour diameter				
≤3 cm	0.51 ± 0.21	0.016	1.67	1.09–2.53
>3 cm				
Primary site				
BT, V, FP, T, SP	0.68 ± 0.28	0.017	1.98	1.12–3.49
Posterior wall				
Weight loss				
No	0.83 ± 0.30	0.006	2.29	1.27–4.14
Yes				
Alcohol intake				
≤40 g/day	0.44 ± 0.19	0.02	1.56	1.06–2.29
>40 g/day				

BT, Base of tongue; V, valleculae; FP, faucial pillars; T, tonsillar fossa; SP, soft palate. In the multivariate analysis of treatment-related factors there was a trend toward statistical significance in relation to duration of the initial wide field irradiation ($P = 0.055$; relative risk 1.43; 95% confidence interval 0.99–2.06).

T2, T3 and T4 staged tumours were consistent with those reported by other authors for oropharyngeal carcinomas [17] and base of tongue carcinomas [13, 15], but lower than the control probabilities reported for T2-staged carcinomas of the tonsillar fossa [1, 16].

Clinical prognostic factors

Only a few studies on prognostic factors for local control and survival in oropharyngeal carcinoma have been performed using multivariate analyses. Multivariate analyses allow the identification of those variables that independently influence the prognosis and eliminate the confounding variables that are significant in the univariate analyses due to their relationship with an independent prognostic factor.

As expected, the probability of local control was influenced by primary tumour extent, i.e. tumour diameter, the probability of regional control was influenced by N stage and disease-free survival and adjusted survival were influenced by both N stage and primary tumour extent. N stage predominated over primary tumour extent as predictor for disease-free survival and for adjusted survival.

Bentzen and colleagues [2] found an inverse relationship between tumour size and local control. Various reports confirm the influence of T stage on local control [1, 5, 13, 16, 18, 19] and the influence of N stage on regional control [16, 17, 20]. In addition, various reports confirm the influence of N stage [21–24] and T stage [21–24] on survival. The predominance of N stage over T stage as predictor for survival in patients with head and neck cancer has also been reported [25].

Apart from the influence of N stage on regional control and survival, this factor was a prognosticator for local control in the present study. Similar findings have been reported by Griffin and associates [5] for patients with head and neck carcinoma. Also, Cerezo and colleagues [25] reported that node fixation increased the probability of local relapse for head and neck cancers with clinically positive nodes. These data and our results differ from those reported by Freeman and associates [18], who were unable to demonstrate such a relationship for patients with oropharyngeal carcinomas.

We must emphasise that factors other than primary tumour extent and N-stage are strong predictors for both the probability of local control and the probability of adjusted survival. Patients who drank more than 40 g of alcohol per day had a higher probability of local relapse, and a higher probability of cancer-related death. Mick and colleagues [26] reported that alcohol abuse was a predictor for observed survival in head and neck cancer.

Weight loss was a very strong independent predictor for local control, for disease-free survival and for adjusted survival. Weight loss is a health status measure which is not usually reported in studies on oropharyngeal and other head and neck carcinomas, but our data suggest that this could be one of the strongest prognostic factors. Mick and associates reported that weight loss was a predictor for observed survival in patients with advanced head and neck carcinomas [26]. Weight loss was also a stronger predictor than Karnofsky performance status in their series [26]. Karnofsky performance status has been shown to be a predictor for the outcome in patients with carcinoma of the head and neck [5] and tonsillar region [4]. Information on Karnofsky performance status was not available in most of our clinical records and we were unable to determine if weight loss and Karnofsky performance status were independent predictors. In our opinion, unexplained weight loss might be a cause of, rather than a consequence of, low Karnofsky performance status.

Patients with tumours of the posterior oropharyngeal wall were associated with a poor prognosis. These results have also been reported by other authors for tumours of the posterior oropharyngeal wall together with tumours of the posterior hypopharyngeal wall [27].

Treatment-related factors

According to the results of the univariate analysis, those patients whose initial wide field irradiation was accomplished in

40 days or less had a lower risk of local relapse and tumour-related death, but we were unable to demonstrate a relationship between total duration of the treatment with external beam radiotherapy alone and the outcome. This finding could be explained if we take into account that the dose administered to the initial wide field and the expected duration of this part of the treatment scheme is almost constant, thus variations in its duration reflect treatment interruptions. In contrast, variations in the total duration of the treatment might result from changes in the total dose, and total dose varies according to tumour size and is frequently modified to compensate treatment interruptions or according to tumour response. The deleterious effect of treatment interruptions has been previously reported for carcinomas of the oropharynx [2, 28, 29] and for carcinomas of the tonsillar region [1, 30].

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