Pergamon

Oral Oncol, Eur J Cancer, Vol. 30B, No. 1, pp. 8–15, 1994
Elsevier Science Ltd
Printed in Great Britain
0964–1955/94 $6.00 + 0.00

Prognosis in Mouth Cancer: Tumour Factors

A.S. Jones

524 patients with histologically proven squamous cell carcinoma of the oral cavity who were previously untreated are studied for prognostic factors. There were various associations between T stage and site; T_2 being more common in buccal cancer, T_1 in tongue cancer, T_4 in floor of mouth tumours and T_2 in the roof of the mouth. Floor of mouth cancer tended to be more frequently associated with positive cervical lymph nodes than were other sites (45%). Well-differentiated tumours tended not to be associated with nodal disease (66%). Small tumours tended not to be associated with nodal metastases whereas large ones were. Univariate analysis of observed survival showed that well differentiated tumours had a slightly better survival than poorly-differentiated tumours (a difference of 8%). Survival fell with increasing T stage and with increasing pT stage. Positive resection margins and advanced pT stage in particular had a dismal prognosis. Survival also fell with increasing N stage and with increasing pathological N stage and extranodal rupture adversely affected prognosis. When the data were analysed by Cox's multivariate regression only two factors were found to be significant. These were T stage and N stage. Both were highly significant predictors of survival; survival falling with increasing stage.
Oral Oncol, Eur J Cancer, Vol. 30B, No. 1, pp. 8–15, 1994.

INTRODUCTION

FEW STUDIES have been carried out on the prognostic indicators of survival in oral cancer. The studies that have been completed are small, e.g. containing 103 and 194 patients [1, 2]. The largest study, from the Christie Hospital Holt Radium Institute, included 8500 patients registered since 1932 [3]. No studies used multivariate analysis and thus the conclusions drawn from such studies must be interpreted with caution.

Most of the large American series are concerned with the results of treatment and usually have a very heavy bias on surgical treatment. They concentrate little attention on prognostic factors per se.

Site

Henk and Langdon [2] state that carcinomas of the buccal mucosa have the best survival followed by carcinoma of the tongue, floor of mouth and mandibular alveolus. Maxillary tumours did worst. According to Easson and Palmer [3] patients with carcinoma of the buccal mucosa have the best outlook followed by carcinoma of the palate, floor of mouth, alveolus and tongue. These figures are in broad agreement with Hibbert *et al.* [1]. Other studies not specifically looking at prognosis are in broad agreement. For example, carcinoma of the buccal mucosa does best with a 5-year survival varying between 70% [4] and 50% [5] whereas the 5-year survival for floor of mouth cancer is 55% [6], and rates for carcinoma of the tongue in the region of 41% [7] and 44% [8].

Correspondence to A.S. Jones, Department of Otorhinolaryngology, University of Liverpool, Royal Liverpool Hospital, PO Box 147, Liverpool L69 3BX, U.K.
Received 24 Feb. 1993; accepted 19 Mar. 1993.

T stage

Although in Henk and Langdon's series [2] 73% of oral cancers were chronologically early, only 30.6% were stage I or II in the TNM classification of the day. Observed 5-year survival for stage I disease was 50% compared with 20% for stage IV lesions. Easson and Palmer [3] state that prognosis rapidly worsens from stage I to stage IV disease. The observed 5-year survival for stage I disease is approximately 50% whereas the figure was around 35% for stage II disease. Hibbert *et al.* [1] quotes an actuarial 5-year survival of 73% for stage I disease, 65% for stage II disease, 57% for stage III disease and 17% for stage IV disease. There was no significant difference between stages I, II and III, but there was between all stages and stage IV using the log rank test. Callery and his colleagues [8] quoted a 71% 5-year survival for stage I and II cancer of the tongue dropping to 31% for stages III and IV. The 5-year survival rates for lesions of the floor of mouth are quoted for stage I and II disease at 80 and 88%, respectively, fell to 66% for stage III disease, and to 32% for stage IV disease [6]. For buccal mucosa the 5-year survival was 77% for stage I disease, and 65, 27 and 18% for stages II, III and IV, respectively [9].

N stage

Most surgical series results quote stage groupings. Stage I and II disease do not have lymph node metastases, whereas stage III disease may be associated with small nodes (N_1) and

stage IV disease may include massive local disease. It is probable that the nodal disease is a much more significant factor than the T stage. Henk and Langdon [2] quote observed survivals of 38% for no nodes, 21% for mobile homolateral nodes, and 25% for mobile contralateral or bilateral nodes. 29% of patients in their series presented with no nodal metastases. Hibbert and colleagues [1] noted a 65% actuarial 5-year survival for no nodes, 52% for small single nodes falling to 17% in patients with more than one node. Many series have noted that the presence of neck nodes is an ominous sign [10, 11]. It is almost certain that the drastically worse prognosis for patients with stage grouping III and IV compared with I and II is mainly due to increased nodal involvement [2, 3, 6, 8, 9]. In general, patients presenting with neck node metastases do half as well as do patients who present with a primary tumour only.

Node level

Since 1964 [12] it has been felt that node level affected survival; the lower in the neck the node affected the worse the survival. Spiro and his colleagues [13] suggested five levels. Level I is the submandibular region, levels II, III and IV are upper middle and lower deep cervical, and level V is posterior triangle/supra clavicular fossa. The 5-year survival fell from 45% for level I to 18% for level IV. No patient with level V nodes survived for 5 years [13]. Several clinical studies have confirmed this trend [13, 14].

Second primary tumours

To be classed as a second primary tumour the second tumour must be [15]:

1. A histologically proven malignancy.
2. Geographically separate from the first primary, not connected by submucosal or intra-epithelial neoplastic change.
3. The possibility of this being a secondary neoplasm must be excluded.

Although some authorities state that a second primary tumour is not necessarily an unfavourable prognostic marker no study allows definite conclusions to be made [15]. Vikram *et al.* [16] state that the occurrence of a second primary frequently negates a successful treatment of the original cancer. Shikhani *et al.* [17] states that the risk of a second cancer in the head and neck region, of a patient who has had carcinoma of the oral cavity is six times that of a person who has not had a previous oral cancer. Hibbert *et al.* [1] noted that multiple lesions in a different site occurred in 12 of their series of 103 patients with oral cancer, and most occurred in those with stage II disease. Multicentric oral cancer was first described by Slaughter [18] and he suggested that this was probably a function of a tissue being exposed to the same carcinogenic stimulus; the concept of field change. Multiple primary tumours reduced the 5-year survival by at least 10%. Metastatic tumours do worst because initial primary treatment limits subsequent treatment, particularly radiotherapy [19].

Histology

Early this century two separate histological classification systems were developed for the purpose of correlating histological differentiation with clinical parameters, particularly prognosis. Broders [20, 21] divided carcinomas into four grades mainly depending on the proportion of anaplastic cells in the section. Thomson [22] favoured a simple three-stage system: well differentiated, moderately differentiated, and poorly differentiated tumours and it is this system which is in wide use today, although there are two main variations. Firstly, the pathologist forms an overall view of the histological section and assigns a grade to the section on the basis of the most undifferentiated part of the section. Secondly, the histologist may try to get an overall idea of the section and (for example) in a poorly differentiated tumour a reasonable "amount of the section must contain a poorly differentiated area and this must occur on more than one section". There is no question that this is a very subjective method of classifying a tumour. In an attempt to overcome this problem Jacobsson and his associates devised a highly complex scoring system based on eight factors. Four of these are tumour factors, and four are related to histological changes within the host tissues [23, 24]. This scoring system is difficult to use and does not correlate well with prognosis [25]. Hibbert *et al.* [1] found that patients with well differentiated carcinomas tended to have neck node metastases less often than those patients with moderately or poorly differentiated carcinomas. However, these differences were not significant. Henk and Langdon [2] quoted a crude 5-year survival of 40% for well differentiated carcinomas, 26% for moderately differentiated, and 12% for poorly differentiated tumours. Crissman and his colleagues noted that of all the histological parameters only the number of mitoses and the thickness of the primary tumour correlated with prognosis [25]. Recent work confirms the importance of the depth of infiltration of the tumour on prognosis in mouth cancer [26–28].

Margins of resection

Lee [29] states that 15% of all oral carcinomas are incompletely resected. Between 50 and 80% of patients with positive margins will either get a recurrence of the tumour or require a re-excision. Conversely only 15–30% of patients with negative margins will get a recurrence [29–32]. In those patients with positive margins who do not get a recurrence the residual carcinoma is perhaps destroyed by local immunity. In some cases the tumour is presumably adjacent to the resection margin, but does not cross the margin.

Pathology—N stage

This is an important concept as it is well known that clinical staging of the neck is extremely inaccurate. Snow and his colleagues [33] found both the number of metastatically involved nodes and the presence or absence of extracapsular rupture to be of great importance. Those patients with increasing numbers of nodes and with rupture of the capsule have a reduced prognosis. Extracapsular rupture has also been shown to be important in other studies [11].

Ploidy—cell kinetics and cell adhesion molecules

In most head and neck sites the ploidy of the cancer does not affect the prognosis. The oral cavity is the exception with non-diploid tumours being associated with a poor prognosis [34].

The cell kinetic profile of the tumour has been widely stated to have prognostic significance. In cell kinetic studies the potential doubling time of the tumour is calculated by various

methods and all rely on labelling of the cancer cells at some time in the cell cycle with a substance such as bromodeoxyuridine. In oesophageal cancer the greater the potential doubling time the worse is the prognosis [35], but this has not yet been proved for oral cancer.

Proliferating cells express an antigen which may be detected using an antibody, Ki67. This allows the proportion of the actively dividing cells in a specimen of tumour to be determined [36].

Various cell adhesion molecules are known to exist and one of these termed E-cadherin has been studied and shown to be a prognostic marker in colon cancer and may be important in head and neck carcinomas [37]. Cell adhesion molecules are thought to be important in metastasis; tumours that have metastasied have little or no expression of this molecule.

PATIENTS AND METHODS

Patients

Between 1963 and 1990, 807 patients with tumours of the oral cavity (excluding the lips) were seen in Liverpool by Professor Stell. The relationship between host and tumour factors and between tumour factors and survival was calculated on 524 of these patients who had histologically proven squamous carcinoma and who had not been previously treated (Table 1).

These patients were treated throughout using a standard policy: radiotherapy for favourable lesions, e.g. T_{1-2} and surgery for patients with palpable lymph node metastases or advanced tumours. 220 patients (42%) were treated initially by radiotherapy (27 with palliative intent) and 210 (40%) by surgery. 94 patients (18%) for a variety of reasons were not treated, usually a combination of advanced age, poor general condition, and advanced tumour.

7 patients (1.3%) had a distant metastasis at the time of presentation, and 36 (7%) had a previous tumour.

Table 1. Patients data

Sex and age			
363 men	(mean age 62.1 years)		
161 women	(mean age 65.4 years)		
General condition (ECOG status)			
0	331		
1	116		
2	35		
3	10		
4	15		
Not recorded	17		
Site			
Buccal mucosa (and RMT)			78
Tongue			170
Floor of mouth/lower alveolus			232
Hard palate/upper alveolus			44
Histological grade			
Well differentiated			226
Moderately differentiated			160
Poorly differentiated			61
Ungraded			77
T and N stage			
T_1	163	N_0	320
T_2	153	N_1	92
T_3	88	N_2	62
T_4	120	N_3	38
		N_X	12

RMT = retromolar trigone, N_X = unclassified.

Methods

Since 1963 Stell recorded patient information on a standardised database. Each patient had information on the same parameters entered, and this was initially on a punch card system and for the past 12 years on a microcomputer database. The database is updated from information obtained from the regular follow-up clinics, and from information from general practitioners, the Mersey Regional Cancer Registry, or the National Health register. 2 patients in the series were lost to follow-up. The median potential period of follow-up was 8 years.

All patients were staged or restaged by the latest UICC method (1987) [38]. The data on node status was insufficient on 12 patients for reclassification. The patient's general condition was likewise recorded and reclassified on a 0–4 scale using the ECOG method [39]. The data on 17 patients were insufficient for regrading. The histological grading was performed by a variety of pathologists, the grading of the first pathologist giving an opinion on the histological sections was taken. There was no attempt to review the histology.

Analysis of the data

Qualitative data are displayed in contingency tables and analysed by χ^2. Survival curves were constructed using the life table method [40]. Differences between observed (crude) survival were analysed by the log rank test [41] with allowance for trend where a natural order occurred such as in T stage. Where appropriate, the survival of treated patients was studied separately. Adjusted actuarial survivals of such patients are quoted and in this case only deaths from oral cavity cancer are of interest.

Of necessity pathological T and N stage are only considered on surgically treated patients.

Survival was further analysed using the multivariate technique devised by Cox [42].

RESULTS

Correlation between tumour factors

Site and histological grade. At all sites about half the tumours where a grade was given were well differentiated (Table 2), with the exception of tumours of the roof of the mouth, almost two thirds of which were well differentiated, although this difference was not significant ($X^2_6 = 7.9$).

Table 2. Site and histological grade

	Well diff.	Mod diff.	Poorly diff.	Ungraded
Buccal mucosa (inc RMT*)	29	21	12	16
Tongue	76	53	18	23
Floor of mouth/lower alveolus	98	79	24	31
Hard palate/upper alveolus	23	7	7	7

*Retromolar trigone.

Table 3. Site and T stage

	T_1	T_2	T_3	T_4
Buccal mucosa	22	30	13	13
Tongue	61	38	39	32
Floor of mouth	67	67	30	68
Roof of mouth	13	18	6	7

Table 4. Site and N stage

	N_0	N_1	N_2	N_3	N_X
Buccal mucosa	56	8	7	6	1
Tongue	101	33	20	11	5
Floor of mouth	128	47	32	20	5
Roof of mouth	35	4	3	1	1

Table 5. Histological grade and T stage

	Well diff.	Mod diff.	Poorly diff.	Ungraded
T_1	71	49	25	33
T_2	66	52	15	24
T_3	35	25	13	14
T_4	54	34	8	6

Table 6. Histological grade and N stage

	Well diff.	Mod diff.	Poorly diff.	Ungraded
N_0	150	88	33	60
N_1	37	36	8	8
N_2	23	25	10	1
N_3	12	6	9	1
N_X	4	5	1	7

Site and T stage. The commonest T stage for tumours of the buccal mucosa was T_2, for tumours of the tongue was T_1, for tumours of the floor of the mouth was T_4 and for tumours of the roof of the mouth was T_2. These differences were statistically significant ($X_9^2 = 229.0$, $P < 0.0001$) (Table 3).

Site and N stage. There were large differences in the proportion of patients with palpable nodes at the various sites (Table 4) varying from 20% for tumours of the roof of the mouth to 45% for tumours of the floor of the mouth ($X_3^2 = 13.73$, $P < 0.01$).

Histological grade and T and N stage. There was no significant relation between histological grade and T stage (Table 5) ($X_6^2 = 6.26$). However, there was a relation between histological grade and N status ($X_6^2 = 17.4$, $P < 0.01$). Well differentiated tumours tended not to be associated with neck node metastases (Table 6).

Table 7. T and N stage

	T_1	T_2	T_3	T_4
N_0	130	108	34	48
N_1	16	27	25	24
N_2	9	12	15	26
N_3	4	4	9	21
N_X	4	2	5	1

T and N stage. There was a significant relation between T and N stage: only 23% of early (T_{1-2}) tumours having nodal metastases compared with 59% of advanced (T_{3-4}) tumours ($X_9^2 = 86.93$, $P < 0.0001$) (Table 7).

Survival

The crude 5-year survival for all patients was 34% (95% confidence interval 29–38%) and for treated patients was 40% (35–45%). The corresponding adjusted survival figures were 47% (41–52%) and 58% (51–63%) (Fig. 1). The crude median survival for untreated patients was 7 months (5–8 months).

Site. The observed survival, recurrence rate at the primary site, and the recurrence rate in the cervical lymph nodes are shown in Table 8. It can be seen that as regards both survival and primary recurrence rate the patients with tumours of the buccal mucosa fared best and those with tumours of the roof of the mouth fared worst. However, these differences were not significant. Tumours of the tongue had a significantly higher later node recurrence rate than tumours at other sites.

The findings for treated patients were similar.

Histological grade. Observed survival fell from 38% for well differentiated tumours to 30% for poorly differentiated tumours. This difference was not quite significant, but the trend in survival with lessening grade of differentiation was. There was no significant relation between recurrence rate at the primary recurrence site or in the cervical nodes and histological grade—indeed the primary recurrence rate was lower for poorly differentiated than for well differentiated tumours (Table 9).

The 5-year survival (adjusted) for treated patients with well differentiated tumours was 61% (52–69%), for moderately

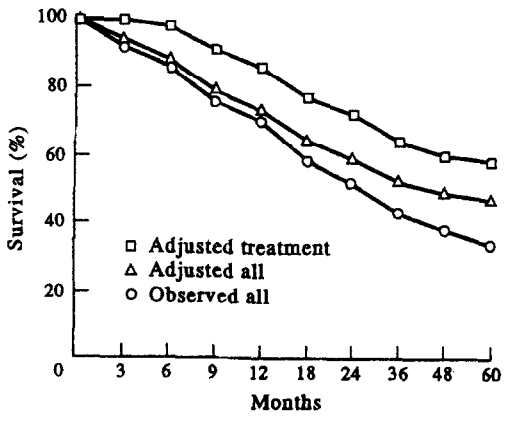

Fig. 1. Observed and adjusted survival of 524 patients with oral cancer and adjusted survival of 430 treated patients.

Table 8. Site

	Observed 5-year survival	Primary recurrence at 5-years	Node recurrence at 5-years
Buccal mucosa	45% (31–56%)	18% (9–34%)	32% (13–39%)
Tongue	35% (26–42%)	23% (16–36%)	46% (36–58%)
Floor of mouth	34% (27–40%)	24% (17–36%)	30% (21–42%)
Roof of mouth	30% (16–43%)	29% (14–55%)	30% (14–50%)
X^2 (d.f.)	4.72 (3)	2.24 (3)	10.52 (3)
P	N.S.	N.S.	<0.025

Table 9. Histological grade

	Observed 5-year survival	Primary recurrence at 5-years	Node recurrence at 5-years
Well diff.	38% (31–44%)	21% (15–31%)	34% (27–44%)
Mod. diff.	32% (24–40%)	31% (21–46%)	39% (27–55%)
Poorly diff.	30% (18–43%)	15% (6–40%)	44% (27–68%)
X_1^2 for trend	5.86	3.39	0.04
P	<0.025	N.S.	N.S.

Table 10. Clinical T-stage

	Observed survival (5 years)	Primary recurrence	Survival after primary recurrence (rT stage)
T_1	50% (41–57%)	12% (7–23%)	29% (16–43%)
T_2	41% (32–48%)	30% (22–42%)	37% (16–57%)
T_3^*	25% (15–35%)	25% (13–45%)	21% (8–36%)
T_4^*	17% (10–24%)	36% (13–79%)	
X^2 (d.f.)	101.0 (3)	17.7 (3)	17.60 (3)
P	<0.0001	>0.001	<0.001
X_1^2 for trend	30.82	2.37	7.08
P	<0.0001	N.S.	<0.01

*1 year survival.

differentiated tumours 50% (37–60%) and for poorly differentiated tumours 58% (37–74%). The difference was not significant ($X_2^2=5.22$).

Clinical T stage. Survival fell significantly with increasing T stage, as did survival after a primary recurrence (survival at 1 year only is quoted for T_{3-4} as the number in this category is small) (Table 10). The primary recurrence rate for treated patients increased with increasing T stage, but the differences were neither as marked nor as significant; furthermore the trend was not significant.

The 5-year adjusted survival for treated patients with T_1 tumours was 69% (58–77%) and for T_4 tumours was 29% (15–43%) (Fig. 2). The difference in survival by T stage was significant ($X_3^2=35.31$, $P<0.001$) (X_1^2 for trend $=14.48$, $P<0.001$).

Pathological T stage. The observed survival also fell dramatically and significantly with increasing pathological stage (pT) from 45% to 19%, and both the difference and the trend were significant (Table 11). There was a difference also between those with and without positive margins: there were few survivors of those with positive margins (median survival 8 months) whereas the 5-year survival for those with clear margins was 31% (median survival 27 months). This difference was significant. The recurrence rate at the primary site also increased with increasing T stage, but not significantly so. However, the difference in recurrence rates at the primary site for those with and without positive margins was significant.

Survival after a primary recurrence was also highly dependent on pathological stage—those with a pT_3 or pT_4 tumour and those with positive margins did not survive. Surprisingly these differences were not significant, perhaps because the numbers were small.

Clinical N stage. Observed 5-year survival fell from 44% for N_0 tumours to 11% for N_3 tumours, and this difference and the trend of falling survival were both highly significant (Table 12). The recurrence rate in the cervical nodes also increased with increasing N stage but the difference was not statistically significant, although the trend was. The survival after a nodal recurrence was poor—it was only about 25% after a N_1 recurrence and nil at 5 years after a N_3 recurrence. These differences were highly significant.

The survival fell the lower in the neck a palpable node lay, but the differences were not significant (Table 13).

The adjusted 5 year survival for treated patients with N_0 tumours was 65% (58–71%) and for N_2 was 38% (18–57%). The number of N_3 tumours was too small to calculate the adjusted survival (Fig. 3). The difference in survival for the various N stages was significant ($X_3^2=31.06$, $P<0.001$) (X_1^2 for trend $=18.58$, $P<0.001$).

Pathological node stage. The survival fell sharply when more than one lymph node was invaded: this difference and the trend were both highly significant. Indeed, the falling survival with increasing number of nodes invaded did not differ significantly from a linear trend ($X_3^2=4.18$) (Table 14).

The survival rate was lower and the nodal recurrence higher

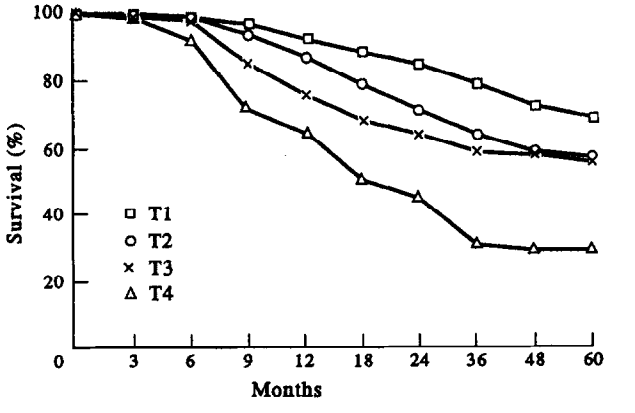

Fig. 2. Adjusted survival of 430 treated patients with oral cancer by T stage.

Table 11. *Pathological T stage*

pT	Observed survival 5-years	Time to recurrence (3-years)	Survival primary recurrence (rT stage)
1	45% (23–63%)	5% (1–35%)	41% (24–56%)
2	25% (9–45%)	27% (11–59%)	
3, 4	19% (6–36%)	39% (19–70%)	0%
X_1^2 for trend	6.11	5.73	2.09
P	<0.02	<0.02	N.S.
Negative margins	31% (21–40%) Median survival 27 months (17–38)	18% (9–36%)	51% (34–66%)
Positive margins	Median survival 8 months (8–12)	41% (17–81%)	
X_1^2	8.73	5.85	2.92
P	<0.005	>0.02	N.S.

Table 12. *Clinical N stage*

N stage	Observed survival (5-years)	Nodal recurrence rate (2-years)	5-year survival after nodal recurrence (rN stage)
N_0	44% (37–49%)	24% (19–31%)	N.A.
N_1	29% (18–39%)	30% (21–45%)	25% (15–38%)
N_2	18% (8–30%)	41% (25–65%)	21% (10–33%)
N_3	11% (3–22%)	43% (13–91%)	0%
X_1^2 for trend	108.1	6.14	6.77
P	<0.0001	<0.025	<0.01

Table 13. *Node level in neck*

Level in neck	Observed survival (3-years)
I	35% (24–45%)
II	23% (14–32%)
III, IV	14% (2–35%)
X_1^2 for trend	3.21
P	N.S.

in those patients with extranodal disease. The former was significant, the latter not.

Multivariate analysis of survival

Cox's regression demonstrated that only T stage and N stage were predictors of (observed) survival ($P<0.0001$, $z=-3.75$ and $P=0.0011$, $z=-1.94$). When adjusted, survival was studied the respective figures were similar ($P<0.0001$, $z=-2.05$, and $P<0.0001$, $z=-0.34$).

Cell kinetics and other parameters

Only 16 tumours in this series have been studied in relation to these parameters. Ploidy and labelling index have been measured by flow cytometry and S phase fraction and potential doubling time calculated. In addition Ki67 and E-cadherin expression have been studied on these specimens. Although the numbers are small, none of these parameters appear to be indicators of survival.

DISCUSSION

In a previous paper, Stell [43] showed that the only relationship between host factors was that between age and performance status. He also found that patients with advanced tumours (stage III and IV) were more likely to be men in poor general condition. As regards survival he found that when adjusted survival was studied on treated patients none of the host factors had any effect.

The present study demonstrates an association between T_2 tumours in the buccal site, T_1 tumours and tongue, T_4 tumours and the floor of the mouth, and T_2 tumours and the roof of the mouth. Regarding N stage and site, tumours of the roof of the

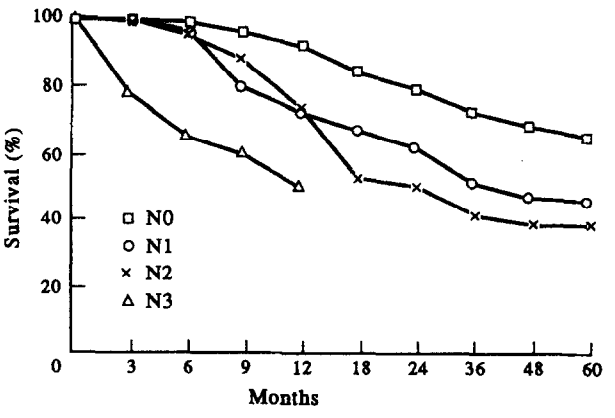

Fig. 3. Adjusted survival of 430 treated patients with oral cancer by N stage.

Table 14. Pathological N stage

Number of nodes	Observed 3-year survival	Nodal recurrence (2-years)
0	49% (33–62%)	19% (11–33%)
1	46% (23–65%)	48% (30–70%)
2	27% (6–53%)	67% (38–93%)
3+	11% (1–30%)	
X^2 (d.f.)	28.95 (4)	15.43 (4)
P	<0.001	0.0005
X_1^2 for trend	24.77	11.46
P	<0.0001	<0.001
ECR		
−ve	32% (17–48%) Median survival 19 months (13–38)	44% (28–66%)
+ve	Median survival 10 months (7–17)	65% (38–91%)
X_1^2	5.73	0.70
P	<0.025	N.S.

mouth tended not to produce nodes whereas tumours of the floor of the mouth had nodes at presentation in 45% of cases. T_{1-2} tumours tended not to produce neck node metastases. Advanced tumours, however, were frequently associated with this event.

When studying survival by univariate analysis tumours of the tongue tended to produce late neck node recurrences and reduced survival. Worsening histological grade had a slight adverse affect on survival. Univariate analysis showed that survival fell with increasing T stage as did survival after a primary recurrence. Positive margins on histological examination of a resected specimen adversely affected survival with advanced pathological T stage (Pt3 and Pt4) and positive resection margins heralding a dismal prognosis. Increasing N stage adversely affected survival and this finding was maintained when studying pathological N stage. Extranodal spread also adversely affected survival.

Whilst univariate analysis studies the observed events the conclusions that may be drawn are limited. The present paper studies 524 patients; a large enough number to allow multivariate analysis to be used. A large series of patients such as that presented allows meaningful deductions to be made from the results of such an analysis. Cox's multivariate regression was carried out on both observed (crude) survival and on survival adjusted to take into account only oral cancer deaths. Only two parameters significantly affected survival and these were T stage and N stage. Both were highly significant both for the observed and adjusted figures and demonstrated (as one might expect) that advancing T and N stage adversely affect survival.

The present study, then, supports the commonsense view that patients with oral cancer should be treated as early as possible and every effort should be made to identify such disease.

1. Hibbert J, Marks NJ, Winter PJH, Shaheen OH. Prognostic factors in oral carcinoma and their relation to clinical staging. *Clin Otolaryng* 1983, **8**, 197–203.
2. Henk and Langdon. *Malignant Tumours of the Oral Cavity*. London, Edward Arnold, 1985.
3. Easson EC, Palmer MK. Prognostic factors in oral cancer. *Clin Oncol* 1976, **2**, 191–202.
4. MacComb WS, Fletcher GH. *Cancer of the Head and Neck*. Baltimore, Williams and Wilkins, 1967.
5. O'Brien PH, Catlin D. Cancer of the cheek (mucosa). *Cancer* 1965, **18**, 1392–1398.
6. Shaha AR, Spiro RH, Shah JP, Strong EW. Squamous carcinoma of the floor of the mouth. *Am J Surg* 1984, **148**, 455–459.
7. Frazell EL, Lucas JC Jr. Cancer of the tongue: report of the management of 1554 patients. *Cancer* 1962, **15**, 1085–1099.
8. Callery CD, Spiro RH, Strong EW. Changing trends in the management of squamous carcinoma of the tongue. *Am J Surg* 1984, **148**, 449–454.
9. Bloom ND, Spiro RH. Carcinoma of the cheek mucosa: a retrospective analysis. *Am J Surg* 1980, **140**, 556–559.
10. 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.
11. Grandi C, Alloisio M, Moglia E, *et al.* Prognostic significance of lymphatic spread in head and neck carcinomas: therapeutic implications. *Head Neck Surg* 1985, **8**, 67–73.
12. Trible WM, Dias A. Cervical node metastases: prognosis related to level and distribution. *Arch Otolaryngol* 1964, **79**, 247–249.
13. Spiro RH, Alfonso AE, Farr HW, Strong EW. Cervical node metastases from epidermoid carcinoma of the oral cavity or oropharynx: a critical assessment of current staging. *Am J Surg* 1974, **128**, 562–567.
14. Warren S, Gates O. Multiple primary malignant tumours: a survey of the literature and statistical study. *Am J Cancer* 1932, **16**, 1358–1414.
15. Kleinsasser O. *Tumoren des Larynx und des Hypopharynx*. Stuttgart, Thieme Verlag, 1987, 191.
16. Vikram B, Strong EW, Shah JP, Spiro RH. Second malignant neoplasms in patients successfully treated with multimodality treatment with advanced head and neck cancer. *Head Neck Surg* 1984, **6**, 734–737.
17. Shikhani AH, Matanoski GM, Jones MM, Kashima HK, Johns ME. Multiple primary malignancies in head and neck cancer. *Arch Otolaryngol Head Neck Surg* 1986, **112**, 1172–1179.
18. Slaughter DP. Multicentric origin or intraoral carcinoma. *Surgery* 1946, **20**, 133–146.
19. Davis RK. Prognostic variables in head and neck cancer: tumour site, stage, nodal status, differentiation and immune status. *The Otolaryngologic Clinics of North America* 1985, **18**, 411–419.
20. Broders AC. Squamous-cell epithelioma of the lip. *J Am Med Ass* 1920, **74**, 656–662.
21. Broders AC. Carcinoma grading and practical application. *Arch Path (Chicago)* 1926, **2**, 576–581.
22. Thomson St Cl. The history of cancer of the larynx. *J Laryngol* 1939, **54**, 61–87.
23. Jacobson PA. Histologic grading of malignancy and prognosis in glottic carcinoma of the larynx. In Alberti PN, Bryce DP, eds. *Centennial Conference on Laryngeal Cancer*. East Norwalk, CT Appleton-Century-Crofts. 1976, 847.
24. Lund C, Sogaard H, Elbrond O, Jorgensen K, Andersen AP. Epidermoid carcinoma of the tongue: histologic grading in the clinical evaluation. *Acta Radiol* 1975, **14**, 513–521.
25. Crissman JA, Gluckman J, Hiteley J, Quenelle D. Squamous-cell carcinoma of the floor of the mouth. *Head Neck Surg*. 1980, **3**, 2–7.
26. Spiro RH, Huvos AG, Wong GY, Spiro JD, Gnecco CA, Strong EW. Predictive value of tumor thickness of squamous carcinoma confined to the tongue and floor of the mouth. *Am J Surg* 1986, **152**, 345–350.
27. Mohit-Tabatabai MA, Sobel HJ, Rush BJ, Mashberg A. Relationship of thickness of floor of mouth stage I and II cancers to regional metastasis. *Am J Surg* 1986, **152**, 351–353.
28. Moore C, Kuhns JG, Greenberg RA. Thickness as prognostic aid in upper aerodigestive tract cancer. *Arch Surg* 1986, **121**, 1410–1414.
29. Lee JG. Detection of residual carcinoma of the oral cavity, oropharynx, hypopharynx and larynx: a study of surgical margins. *Trans Am Acad Ophthalmol Otolaryngol* 1974, **78**, 49–53.
30. Byers RM, Bland KI, Borlase B, Luna M. The prognostic and therapeutic value of frozen section determinations in the surgical

treatment of squamous carcinoma of the head and neck. *Am J Surg* 1978, **136**, 525–528.
31. Looser KG, Shah JP, Strong EW. The significance of "positive" margins in surgically resected epidermoid carcinomas. *Head Neck Surg* 1978, **1**, 107–111.
32. Chen TY, Emrich LJ, Driscoll DL. The clinical significance of pathological findings in surgically resected margins of the primary tumor in head and neck carcinoma. *Int J Radiat Oncol Biol Phys* 1987, 13, 833–837.
33. Snow GB, Annyas AA, Van Slooten EA, Bartelink H, Hart AAM. Prognostic factors of neck node metastasis. *Clin Otolaryngol* 1982, 7, 185–192.
34. Tytor M, Franzen G, Olofsson J. DNA ploidy in oral cavity carcinomas with special reference to prognosis. *Head Neck* 1989, **11**, 257–263.
35. Kaketani K, Saito T, Kobayashi M. Flow cytometric analysis of nuclear DNA content in oesophageal cancer. *Cancer* 1989, **64**, 887–891.
36. Kearsley JH, Furlong KC, Cook RA, Waters MJ. An immunohistochemical assessment of cellular proliferation markers in head and neck squamous cell cancers. *Br J Cancer* 1990, **61**, 821–827.
37. Schipper JH, Frixen UH, Behrens J, Unger A, Gahnke K, Birchmeier W. E-cadherin expression in squamous cell carcinomas of the head and neck: inverse correlation with tumour dedifferentiation and lymph node metastases. *Cancer Res* 1991, **51**, 6328–6337.
38. Hermanek P, Sobin LH. *TNM Classification of Malignant Tumours*. Berlin, Springer, 1987.
39. Beahrs OH, Henson DE, Hutter RVP, Myers MH. eds. American Joint Committee for Cancer Staging and End Result Reporting. *Manual for Staging of Cancer* 3rd edition. Philadelphia, JB Lippincott Company, 1988.
40. Armitage P, Berry G. In *Statistical Methods in Medical Research* 2nd ed. London, Blackwell Scientific Publication, 1987, 436–437.
41. Peto R, Pike MC, Armitage P, *et al.* Design and analysis of randomised clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1976, **34**, 585–612, and **35**, 1–34.
42. Cox DR. Regression models and life-tables. *J R Stat Soc* 1972, **B34**, 187–220.
43. Stell PM. Prognosis in mouth cancer: host factors. *J Laryngol Otol* 1992, **106**, 399–402.

Acknowledgements—The author wishes to acknowledge Professor Stell for building up the database over many years, the North West Cancer Research Committee for technical support and to Mrs Brenda Cowley for typing the manuscript.