# Survival following primary surgery for oral cancer: A regional units experience in the UK

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Submission to Oral Oncology

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**Abstract**

The main aims of this article are to report the overall and disease-specific survival of a consecutive series of patients presenting with oral cancer from 1992 to 2002 and relate survival to clinical and pathological factors. The article uses population-based age-sex mortality rates in the North-West of England to highlight differences in overall and disease-specific survival.

541 patients with oral squamous cell carcinoma presented to the Regional Maxillofacial Unit from 1992 to 2002. Curative treatment favoured radical primary surgery, 10% (52) received primary radiotherapy. These patients were on average 8 years older with more advanced tumours and overall poorer survival at 5 years, 23% (SE 7%). The remainder of the results refer to 489 patients who had primary curative surgery, 40% (194) of whom received adjuvant radiotherapy. The overall survival (OS) was 56% (SE 2%) and the disease-specific survival (DSS) was 74% (SE 2%). There was local recurrence rate of 10% (50) and the loco-regional recurrence rate was 21% (103). The second primary rate was 7% (35). Survival figures had improved over the 10-year period from 63% DSS for the first 4 years of the study (1992-1995) compared to 81% for the last 3 years (2000-2002). In stepwise Cox regression the two predictors selected for disease specific survival were pN status and margins (both $p<0.001$). Age-sex mortality rates for the North-West indicate that 15.0% of the 489 primary surgery patients might have been expected to die within 5 years if they were typical of the general population and the observed difference between all causes and oral-cancer specific survival was 18.3%.

These data emphasise the value of disease-specific survival as an indicator of successful treatment in a cohort that tends to be elderly, from social deprived backgrounds, with life styles and comorbidity that influence overall survival.

Word count for abstract 295

## Introduction

UK cancer rates for melanoma, oral cavity, uterus and kidney are increasing. [1] From 1995 to 2004 the number of new diagnoses of oral cancer rose from 3696 to 4769, (i.e. from about 64 to 80 cases per million UK population), an increase in age standardised incidence of 23%. Since the 1970s survival rates for oral cancer have remained constant whilst incidence has increased among younger people. [2]

Relatively few institutions have reported survival data of their patients with oral cancer and this probably in part reflects the diligence required in collecting accurate data. Some older papers pre-date the widespread introduction of microvascular reconstructive techniques.[3-6] Reports exist from within other countries such as Australia,[7] Denmark,[8,9,] Taiwan,[10] USA[11-14] Norway,[15] Japan,[16] South Korea,[17] Germany [18] but there is a paucity of data from the UK.

The Regional Maxillofacial Unit in Liverpool has previously published survival data on oral and oropharyngeal squamous cell carcinoma [19-21] and about the influence of pathological features on prognosis.[22,23] Survival data have also been published in relation to blood transfusion and free tissue transfer,[24] for patients with mandibular invasion [25] and in respect to adjuvant radiotherapy for patients at an intermediate risk of recurrence.[26] This is the first paper from this Unit to report overall experience in the management of oral cancer including primary radiotherapy and primary surgery.

The Unit has advocated radical primary surgery with free tissue transfer reconstruction where indicated in the management of oral cancer.[27] A selective neck dissection is performed when depth of tumour invasion exceeds 3 to 4 mm. Operations are performed with intention to cure by resection of in excess of a one centimetre margin of normal tissue. Post-operative radiotherapy is given as adjuvant treatment based on the histopathology of the resection specimen. [26] Megavoltage external beam radiotherapy is employed, directed at the primary site and draining lymphatic apparatus in the neck. The typical regimen uses a three-field method including bilateral parallel opposed fields to the primary site and upper neck and, when prescribed, a low single anterior neck field. X-rays (5MV) were used in 2 Gray daily fractions 5 days per week, with typical doses of 50 to 60 Gray

Cure and survival is of primary concern for patients [28,29] however there are several problems with basing outcome exclusively on overall survival. Patients are relatively elderly and often have associated comorbidity associated with their life style and background. Therefore following oral cancer treatment they can die of other causes and have life expectancy of less than five years (5-year survival). From an Oral Oncology perspective, successful treatment can be defined by the absence of further disease. Overall survival is relatively easy to measure particularly with the assistance of national hospital data or links with outside agencies such as the Office for National Statistics. However disease specific survival is much more difficult to record accurately. It is difficult to maintain accurate follow-up data to confirm the absence of oral cancer at the time of death. Death certification is problematic with a tendency once diagnosed with oral cancer to record the demise of the patient as an oral cancer death.[21] In addition although loco-regional recurrence or second primary oral tumours are usually easily identifiable, it is difficult to completely exclude disseminated spread or to account for treatment associated affects which may have had a bearing on outcome such as silent aspiration leading to pneumonia. Because of the importance of disease specific survival as an outcome parameter the main aim of this article is to report the overall and disease-specific survival of a consecutive series of patients presenting with oral cancer from 1992 to 2002 and to relate survival to clinical and pathological factors. Importantly the paper also uses population-based age-sex mortality rates in the North-West to help put differences in overall and disease-specific survival into perspective.

## Methods

Since 1992 all patients diagnosed or treated with Head and Neck cancer in the Regional Maxillofacial Unit have routinely had their details entered onto a computerised Head and Neck database. This database includes details of demography, clinical status (TNM)) of the tumour, treatment (surgical and radiotherapy), pathological stage (pTNM), [30] recurrence (local, regional, locoregional), subsequent management and disease status at last visit.

The preferred method of treatment was primary surgery to eradicate the tumour and in patients with tumours of thickness of more than 3 to 4 millimetres also underwent selective neck dissection to appropriately stage the tumour and aid the decision to add RT to the treatment plan. . Patients were considered for radiotherapy if they had involved margins, extracapsular spread or close margins with nodal metastasis. Over the time period of the study there was a shift in dosage from 50 Gy to 60 Gy .Radiotherapy details were corroborated with the computerised patient records at Clatterbridge Centre for Oncology.

The Office of National Statistics supplied death certification details comprising the immediate cause of death plus associated factors. Patient follow-up was until January 1st 2005 with at least 2 years follow-up for each patient. Four clinicians independently attributed cause of death to oral cancer or other causes and a consensus was taken. In 10 cases (4% of deaths) there was a 50:50 judgement and further discussion between clinicians was required to reach a verdict based on the most recent follow-up record and the medical status of the patient.

Recurrence was defined as local (arising only in the oral cavity relative to the primary tumour), regional (arising only in the neck) and loco-regional (arising in both primary site and neck). The preferred method of confirming recurrence was by biopsy and this was done for all patients treated, with a further attempt at cure. Other acceptable ways to confirm recurrence were by scanning or by fine needle aspiration cytology.

Statistical method

Office for National Statistics age-sex mortality rates for 2000 for the North-West were used to estimate naturally occurring mortality over a 5 year period in the patient cohort from the time of surgery. The age groups used were 16-24, 25-34, 35-44, 45-54, 65-75, 75-84 and 85+ years. Rates were applied year by year to patients so as to account for the ageing cohort effect.

Kaplan-Meier methods were used to estimate the disease-specific (DSS) and overall survival (OS) by patient groups and the log-rank test was used to compare survival curves. Cox regression methods were used to investigate the main independent

predictors of survival and linear predictor scores from the regression model were used to place patients into five risk groups based on margins and pN status. Because of the multitude of testing we regarded $p<0.01$ as statistically significant.

The link with the Office of National Statistic has ethical approval from the Multi-Research Ethical Committee (MREC) and the data collection on the Liverpool Oncology Database has approval from the Sefton Research Ethics Committee,

**Results**

The 1992 to 2002 cohort comprised 541 patients with oral squamous cell carcinoma. A total of 489 had primary surgery, 40% (194) with adjuvant radiotherapy, while 52 had primary radiotherapy. Primary radiotherapy patients were older (median 70 Vs 62 years), with more advanced tumours (>=4cm: 48% Vs 29%; Clinical T3-4: 50% Vs 40%; Clinical tN2-3: 16% Vs 6%). Their overall survival rate at 5 years was 23% (SE 7%). The rest of this paper relates to the 489 patients with primary surgery. Overall survival at 5 years was 56% (SE 2%), while disease specific survival was 74% (SE 2%)and loco-regional recurrence-free survival was 76% (SE 2%), Table 1, Figure 1. There was local recurrence for 10% of patients (50) and loco-regional recurrence in 21% of patients (103). The second primary rate was 7% (35). Most (82%, 400/489) of these patients had a neck dissection, 268 unilateral, 129 bilateral and 3 radical/modified radical. Three-quarters (76%, 373) were treated by free-flap surgery, with 260 soft tissue and 113 composite flaps, while one-quarter were treated mainly by laser or primary closure including the 89 without neck dissection. Other characteristics of the sample are shown in Table 2.

Age-sex mortality rates for the North-West 2000 were applied to the 489 patients to estimate the expected naturally occurring mortality within 5 years from surgery. As rates for oral cancer mortality in the general population are negligible relative to total mortality this expected mortality was assumed to be for deaths other than from oral cancer. The calculated expected mortality of these 489 patients within 5 years of surgery was 15.0%. The difference between the Kaplan-Meier all-causes and oral-cancer specific survival at 5 years was 18.3%.

The patient factors listed in Table 2 were analysed as to how well they predicted survival, and the results of univariate Kaplan-Meier analyses to compare survival curves are also shown in Table 2. The strongest univariate predictors of oral cancer specific survival were pathological features of the tumour, in particular extra-capsular spread and pN status which were strongly inter-related. Age and clinical appearance of the tumour were also predictive, as was free-flap surgery and use of adjuvant radiotherapy.

In Cox regression modelling (with $p<0.01$ for entry) to predict disease specific survival the first predictor into the regression was extra-capsular spread (at $p<0.001$), and then tumour margins ($p<0.001$ for its extra contribution to the model, $\chi2=26.7$), pN status ($p<0.001$ for extra, $\chi2=16.9$), age group ($p=0.003$ for extra, $\chi2=14.00$), pstage ($p=0.002$ for extra, $\chi2=15.2$) and tumour differentiation ($p=0.006$ for extra, $\chi2=10.3$) before extra capsular spread was then forced out of the regression model. The final model from these regression analyses is summarised in Table 3. In modelling the three initial main predictors only, pN status added significantly ($p<0.001$) to the model comprising extra capsular spread and margins whilst margins added significantly ($p<0.001$) to the model comprising extra capsular spread and pN status. However extra capsular spread did not add significantly ($p=0.02$) to the model comprising margins and pN status.

Linear predictor scores from the regression model involving pN and margins were used to place patients into five risk groups for the purpose of illustrating the amount of discrimination in outcome being achieved by these variables (Figure 2). There is a certain logic to these 5 groups if we were to score margins as 0=clear, 1=close, 2=involved and score pN as 0=pN0, 1=pN1, 2=pN2 as then the 5 risk groups represent a combined score of 0, 1, 2, 3 and 4 respectively. When the regression was re-run using the five risk groups the same three additional variables of age group, p stage and tumour differentiation were selected into the regression model. Survival by p stage alone is shown in Figure 3, ~~whilst~~ survival by ECS and margins is shown in Figure 4 whilst survival by ECS alone, margins alone and pN status alone are shown in Figures 5 to7. .

Cox regression modelling (with $p<0.01$ for entry) to predict all causes survival the first variable into the regression was extra-capsular spread (at $p<0.001$), and then age group ($p<0.001$ for its extra contribution to the model, $\chi 2=25.0$), perineural status ($p<0.001$ for extra, $\chi 2=15.5$) and margins ($p=0.002$ for extra, $\chi 2=12.9$).

Age per se was predictive of disease-specific survival (Table 1) and was notably worse in those aged 75 years or older. These older patients comprised more female patients (57%, 48/84 Vs 34%, 139/405) and more graded as ASA III or IV (41%, 31/75 Vs 18%, 66/359). There were more pT3-4 tumours (51%, 43/84 Vs 37%, 150/405), and extra-capsular spread (27%, 23/84 Vs 19%, 78/405) but fewer N positive tumours (18%, 15/84 Vs 29%, 119/404). Otherwise those aged 75 and over were quite similar to younger patients in regard to the other variables described in Table 1 except that fewer had free flap surgery (64%, 54/84 Vs 79%, 319/405), neck dissection (71%, 60/84 Vs 84%, 340/405) and adjuvant radiotherapy (30%, 25/84 Vs 42%, 169/405).

Year group (1992-5, 1996-9, 2000-2) was also predictive of disease-specific survival at $p<0.001$ ($\chi 2=19.2$) after adjusting for the variables in Table 2, indicating a halving in mortality from 1992-5, with a hazard ratio (relative risk of death) of 0.4 (95% CI 0.3 to 0.7) for both 1996-9 and 2000-2 relative to 1992-5. The rate of local-only recurrence also fell (17%, 27/156 Vs 7%, 14/196 Vs 7%, 9/137) as did the rate of any loco-regional recurrence (30%, 47/156 Vs 18%, 35/196 Vs 15%, 21/137). Clinically, there was a progressive increase in patients presenting with smaller tumours under 2cm (14%, 25%, 37%), this also being reflected in more clinical T1 (17%, 25%, 35%), pT1 (21%, 28%, 35%) and Pstage 1 tumours (19%, 24%, 32%). Fewer had perineural invasion (33%, 24%, 20%) or positive nodes (41%, 35%, 31%). The groups were more similar in regard to other variables in Table 2 except for an increase towards treating by laser/primary closure (13%, 22%, 38%) and for not doing a neck dissection (11%, 18%, 27%). The percentage having radiotherapy changed little over time (46%, 37%, 37%) but of those receiving radiotherapy the percentage having 60Gy or more did increase (15%, 50%, 82%). Five-year disease specific survival for less than 60Gy was 59% (SE 5%) and for 60Gy and more was 63% (SE 6%).

Though both free-flap surgery and adjuvant radiotherapy were predictive of worse outcome in univariate analyses both these reflect the underlying pathology of the patient condition and neither variable was a significant predictor when added to the model described in Table 3 (free-flap: p=0.84, hazard ratio 0.9 (95%CI 0.5 – 1.9); radiotherapy: p=0.31, hazard ratio 0.8 (95%CI 0.5 – 1.3).

## Discussion

This is the first paper from this Unit to focus exclusively on oral cancer and compare survival outcome with age-sex mortality rates for the North-West. Our experience in oropharyngeal cancer will be reported in a separate article (in preparation). The findings are strengthened by the consecutive nature of the cohort and an intention throughout the study period for curative primary surgery. It is a larger series than we have previously published (*all our references in introduction*) with longer patient follow-up. In recognition of the need for close follow-up [31] and limitations of using Cancer Registry data,[2] there has been very careful documentation of disease specific status. Using our oncology database we were able to take note of last clinic appointments and of recurrence status throughout each patient's follow-up. The link with the Office of National Statistic allowed for cross-reference between hospital records and official date and cause of death. Four clinicians independently ascribed the cause of death and consensus was achieved in the relatively few cases where there was disagreement. The comparison with age-sex mortality rates for the North-West of England has allowed for closer inspection as to the difference between all cause and disease specific mortality. It is recognised that the data only represents the experience of one regional unit in the North-West of England. This may not be typical because the immediate catchment population live in a particularly deprived area of the UK. [32] In this article we report on all oral cancer sites and it is intended that further work will include in-depth analyses of particular sub-sites such as the cheek (buccal carinoma).

Although it is often stated that survival figures for oral cancer are not improving our data shows that the disease-specific survival following primary surgery was 74%. There was an improvement in survival figures over the 10 year period of the study from 63% DSS for the first 4 years of the study (1992-1995) compared to 81% for the

last 3 years (2000-2002). The overall 5-year survival was 56% improving from the first 4 years of the study (46%) to the last 3 years (64%). The difference in DSS and overall survival reflects issues around associated co-morbidity and comparison with age-sex mortality rates for the North-West of England has shown that a substantial proportion of non oral cancer deaths would be expected by 5 years in this cohort.

It is difficult in a retrospective study to clearly identify reasons for the improvement in survival over time in our cohort. The earlier group had similar characteristics in terms of gender, age site and pathology. However the earlier patients in the series tended to have larger tumours (reflected in pT stage) and have free tissue reconstruction. There were similar clear margin rates yet the earlier group were more prone to local recurrence. The indication that a higher proportion of patients were being seen with earlier disease since 1996 is encouraging and might reflect better oral cancer awareness and faster referral processes. It is unlikely to reflect a change in referral patterns from clinicians in the Mersey Region as here is a long established referral process to the Regional Unit base on a hub and spoke configuration with all oral cancers being referred from the spokes on diagnosis. Another factor behind improved survival might be better medical management with improvements in managing comorbidity, in comorbidity however sufficient data for a robust comment is unfortunately lacking in this retrospective analysis. Inclusion of cormorbidity indices such as the ACE-27 in the future will perhaps allow a better indication of the changes in associated illness over time of patients with oral cancer. It was notable that patients aged 75 and over had a worse overall and disease specific survival. There are many issues potentially associated with this such as worse comorbidity and their ability to withstand radical treatment including adjuvant radiotherapy. In our cohort, patients 75 or over were less likely to have adjuvant radiotherapy.

Several features of the primary tumour had significant bearing on outcome. The main clinical predicators were margins, pattern of invasion, tumour differentiation, pTstage, perineural invasion, presence positive nodes and of extracapsular spread. Our results confirm the well-established relationship between cervical node metatasis and reduced rates of survival. In our series the proportion of those having a neck dissection has decreased over time and mostly reflects a change in practice in favour of less free flap reconstructions in selected patients. Although primary closure or laser

was used more frequently in recent years we have not noticed an increase in involved margins, local or regional recurrence rates, nor a fall in our survival rates.

We postulate that 15.0% of patients would be expected to die within 5 years if they were typical of the general population and this compares to the observed difference between all-causes and oral-cancer specific survival for the 489 oral cancer patients of 18.3%. This emphasises the risk of death in oral cancer of recurrence in the first 12 to 24 months and emphasises the poor prognosis, recurrence confers following 'radical' primary treatment. Of those patients who do not get recurrence their life expectancy at 5 years is similar to their unaffected counterparts and this reflects geographical and life style factors.

It is difficult to compare our outcomes directly with others because of variations in case mix, selection for treatment and presentation of outcome data. An indication of how our cohort compares to published literature is given in Table 5. If one looks at the figures from the UK, the results for the patients treated with primary radiotherapy had DSS of 64% and 55% and OS of 37% and 43% respectively. In a series reported by Langdon et al[3] in which the majority of patients were treated with primary radiotherapy (73% of the cohort) the OS was as low as 33% with no figures reported for DSS. It is also interesting to note that the more up to date reports show better survival figures. Memorial Sloan Kettering have reported their improving oral cancer survival figures which very much reflect our reported experience in this study. [33] (Shaw et al 1999) 33

These survival figures represent the standard practice in the Regional Maxillofacial Unit in Liverpool. The improved survival figures and better local and regional control of the disease are welcome and confirm the benefit in the management of this disease by primary surgery compared to primary radiotherapy. We have shown that a more conservative approach to the primary site and the neck has not compromised our results and leave more options for the effective management of recurrence and further options for the high percentage of second head and neck primary tumours.

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Table 1. Recurrence-free, disease-specific and all-causes 5 year Kaplan-Meier survival for 489 oral cancer patients by P stage

| | N of patients | 5 year Kaplan-Meier % survival (SE) | | |
|---|---|---|---|---|
| | | Loco-regional Recurrence-free | Disease-specific | All-causes |
| P stage 1 | 121 | 92 (3) | 96 (2) | 76 (4) |
| P stage 2 | 91 | 80 (4) | 82 (4) | 68 (5) |
| P stage 3 | 56 | 78 (6) | 78 (6) | 65 (7) |
| P stage 4 | 21 | 65 (4) | 57 (4) | 37 (4) |
| TOTAL | 489 | 76 (2) | 74 (2) | 56 (2) |

Table 2. Kaplan-Meier survival analyses for 489 oral cancer patients

Table gives 2 and 5 year Kaplan-Meier survival rates (SE) .

| | | | Disease-specific survival | | | Overall survival | | |
|---|---|---|---|---|---|---|---|---|
| | | Patients | 2yr | 5yr | Log rank test | 2yr | 5yr | Log rank test |
| | TOTAL | 489 | 79 (2) | 74 (2) | | 70 (2) | 56 (2) | |
| Year | 1992-5 | 156 | 69 (4) | 63 (4) | $\chi^2$=12.7 p=0.002 | 59 (4) | 46 (4) | $\chi^2$=13.7 p=0.001 |
| | 1996-9 | 196 | 84 (3) | 79 (3) | | 76 (3) | 60 (4) | |
| | 2000-2 | 137 | 84 (4) | 81 (4) | | 74 (4) | 64 (5) | |
| Gender | Male | 302 | 81 (2) | 77 (3) | $\chi^2$=1.5 p=0.23 | 72 (3) | 45 (3) | $\chi^2$=0.5 p=0.50 |
| | Female | 187 | 76 (3) | 70 (4) | | 67 (3) | 58 (4) | |
| Age | <55 | 140 | 84 (3) | 79 (4) | | 79 (4) | 67 (4) | |
| | 55-64 | 138 | 80 (4) | 75 (4) | $\chi^2$=13.9 p=0.003 | 74 (4) | 60 (4) | $\chi^2$=33.2 p<0.0001 |
| | 65-74 | 127 | 81 (4) | 79 (4) | | 69 (4) | 52 (5) | |
| | 75+ | 84 | 64 (6) | 56 (6) | | 51 (6) | 37 (6) | |
| Tumour site | Buccal | 93 | 75 (5) | 68 (5) | | 69 (5) | 50 (5) | |
| | Lower gum | 56 | 82 (6) | 76 (6) | $\chi^2$=4.9 p=0.30 | 71 (6) | 52 (7) | $\chi^2$=5.2 p=0.27 |
| | Tongue (ant 2/3) | 144 | 81 (3) | 78 (4) | | 72 (4) | 64 (4) | |
| | Floor of Mouth | 162 | 81 (3) | 77 (4) | | 70 (4) | 56 (4) | |
| | Other | 34 | 68 (8) | 63 (9) | | 62 (8) | 44 (9) | |
| Tumour size | <2 cm | 116 | 95 (2) | 93 (2) | $\chi^2$=31.9 p<0.0001 | 87 (3) | 74 (4) | $\chi^2$=26.0 p<0.0001 |
| | 2-3 cm | 224 | 77 (3) | 73 (4) | | 69 (3) | 54 (3) | |
| | 4+ cm | 137 | 69 (4) | 61 (4) | | 58 (4) | 44 (4) | |
| Clinical T stage | Tis/1 | 123 | 95 (2) | 93 (2) | | 88 (3) | 76 (4) | |
| | 2 | 175 | 77 (3) | 74 (4) | $\chi^2$=34.1 p<0.0001 | 68 (4) | 57 (4) | $\chi^2$=32.2 p<0.0001 |
| | 3 | 47 | 72 (7) | 66 (8) | | 60 (7) | 48 (7) | |
| | 4 | 144 | 70 (4) | 61 (5) | | 61 (4) | 41 (4) | |
| Clinical N stage | 0 | 354 | 84 (2) | 80 (2) | $\chi^2$=23.6 p<0.0001 | 76 (2) | 62 (3) | $\chi^2$=24.2 p<0.0001 |
| | 1 | 103 | 69 (5) | 62 (5) | | 57 (5) | 40 (5) | |
| | 2+ | 31 | 58 (9) | 53 (10) | | 52 (9) | 37 (9) | |
| ASA | I | 115 | 86 (3) | 84 (4) | | 80 (4) | 77 (4) | |
| | II | 222 | 77 (3) | 71 (3) | $\chi^2$=5.1 p=0.17 | 70 (3) | 52 (4) | $\chi^2$=30.5 p<0.0001 |
| | III/IV | 97 | 76 (5) | 71 (5) | | 61 (5) | 39 (5) | |
| | Unknown | 55 | 77 (6) | 72 (7) | | 66 (6) | 54 (8) | |
| Free-flap surgery | Yes | 373 | 75 (2) | 70 (3) | $\chi^2$=15.9 p<0.0001 | 66 (2) | 51 (3) | $\chi^2$=10.4 p=0.001 |
| | No | 116 | 93 (3) | 88 (4) | | 82 (4) | 72 (5) | |
| Neck dissection | Yes | 400 | 76 (2) | 70 (2) | $\chi^2$=14.0 p<0.0001 | 68 (2) | 52 (3) | $\chi^2$=9.7 p=0.002 |
| | No | 89 | 93 (3) | 91 (3) | | 82 (4) | 76 (5) | |
| Adjuvant radiotherapy | Yes | 194 | 68 (4) | 59 (4) | $\chi^2$=34.4 p<0.0001 | 61 (4) | 42 (4) | $\chi^2$=26.3 p<0.0001 |
| | No | 295 | 87 (2) | 84 (2) | | 76 (2) | 65 (3) | |
| Tumour differentiation | Poor | 49 | 57 (7) | 48 (8) | $\chi^2$=34.0 p<0.0001 | 53 (7) | 29 (7) | $\chi^2$=24.6 p<0.0001 |
| | Moderate | 286 | 76 (3) | 70 (3) | | 66 (3) | 53 (3) | |
| | Well | 139 | 92 (2) | 89 (3) | | 81 (3) | 68 (4) | |
| Pattern of invasion | Favourable | 146 | 94 (2) | 91 (3) | $\chi^2$=28.4 p<0.0001 | 83 (3) | 72 (4) | $\chi^2$=17.5 p<0.0001 |
| | Unfavourable | 327 | 71 (3) | 65 (3) | | 63 (3) | 47 (3) | |
| Margins | Clear >5mm | 237 | 91 (2) | 88 (2) | $\chi^2$=50.9 p<0.0001 | 82 (2) | 66 (3) | $\chi^2$=34.2 p<0.0001 |
| | Close <5mm | 170 | 72 (4) | 66 (4) | | 65 (4) | 53 (4) | |
| | Involved | 82 | 58 (6) | 49 (6) | | 45 (6) | 35 (5) | |
| pT stage | Tis,1 | 134 | 96 (2) | 95 (2) | | 89 (3) | 75 (4) | |
| | 2 | 162 | 78 (3) | 73 (4) | $\chi^2$=47.8 p<0.0001 | 70 (4) | 59 (4) | $\chi^2$=39.8 p<0.0001 |
| | 3 | 30 | 67 (9) | 58 (10) | | 57 (9) | 46 (10) | |
| | 4 | 163 | 67 (4) | 61 (4) | | 57 (4) | 39 (4) | |
| pN | 0 | 310 | 91 (2) | 87 (2) | $\chi^2$=104.7 p<0.0001 | 81 (2) | 68 (3) | $\chi^2$=72.4 p<0.0001 |
| | 1 | 72 | 73 (6) | 68 (6) | | 65 (6) | 49 (6) | |
| | 2-3 | 107 | 48 (5) | 40 (5) | | 42 (5) | 26 (5) | |
| P stage | 1 | 121 | 97 (2) | 96 (2) | | 89 (3) | 76 (4) | |
| | 2 | 91 | 86 (4) | 82 (4) | $\chi^2$=71.0 p<0.0001 | 79 (4) | 68 (5) | $\chi^2$=62.4 p<0.0001 |
| | 3 | 56 | 85 (5) | 78 (6) | | 77 (6) | 65 (7) | |
| | 4 | 221 | 64 (3) | 57 (4) | | 54 (3) | 37 (4) | |
| Perineural invasion | No | 364 | 85 (2) | 81 (3) | $\chi^2$=33.1 p<0.0001 | 76 (2) | 63 (3) | $\chi^2$=33.1 p<0.0001 |
| | Yes | 125 | 61 (5) | 55 (5) | | 52 (4) | 35 (4) | |
| Extra capsular spread | No ECS | 388 | 87 (2) | 83 (2) | $\chi^2$=100.7 p<0.0001 | 79 (2) | 64 (3) | $\chi^2$=84.4 p<0.0001 |
| | ECS | 101 | 45 (5) | 37 (6) | | 37 (5) | 24 (4) | |
| Positive nodes | No | 314 | 90 (2) | 87 (2) | $\chi^2$=76.0 p<0.0001 | 80 (2) | 67 (3) | $\chi^2$=52.3 p<0.0001 |
| | Yes | 175 | 58 (4) | 52 (4) | | 52 (4) | 36 (4) | |

Table 3. Final model of independent predictors of disease specific survival for 489 patients with neck dissection using multi-variable Cox regression

| | Hazard ratio (relative risk of death) | 95% CI of Hazard ratio |
|---|---|---|
| pN status: | | |
| pN0 | Relative to 'pN0' | |
| pN1 | 2.5 | 1.2 - 5.1 |
| pN2-3 | 3.4 | 2.0 - 5.8 |
| Margins: | | |
| Clear | Relative to 'clear' | |
| Close | 2.3 | 1.5 - 3.6 |
| Involved | 2.8 | 1.7 - 4.7 |
| Age group: | | |
| <55 | Relative to '<55 years' | |
| 55-64 | 1.5 | 0.9 - 2.5 |
| 65-74 | 1.6 | 0.9 - 2.6 |
| 75+ | 3.4 | 2.0 - 5.8 |
| Pstage | | |
| 1 | Relative to 'stage 1' | |
| 2 | 3.7 | 1.4 - 10.2 |
| 3 | 1.5 | 0.4 - 5.0 |
| 4 | 3.8 | 1.4 -10.1 |
| Tumour differentiation: | | |
| Well | Relative to 'Well' | |
| Moderate | 2.8 | 1.4 - 5.5 |
| Poor | 1.4 | 0.8 - 2.4 |

Table 4. Recurrence by Tumour site

| | | Local only | | Regional only | | Local and regional | | Any loco-regional* | | Distant | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | n | % | n | % | n | % | n | % | n |
| Buccal | 93 | 19 | 18 | 3 | 3 | 6 | 6 | 29 | 27 | 1 | 1 |
| Lower gum | 56 | 11 | 6 | 2 | 1 | 5 | 3 | 18 | 10 | 4 | 2 |
| Tongue anterior 2/3rds | 144 | 6 | 8 | 8 | 11 | 3 | 4 | 16 | 23 | 4 | 6 |
| Floor of Mouth | 162 | 6 | 10 | 9 | 15 | 2 | 4 | 18 | 29 | 5 | 8 |
| Other | 34 | 24 | 8 | 18 | 6 | 0 | 0 | 41 | 14 | 0 | 0 |
| TOTAL | 489 | 10 | 50 | 7 | 36 | 3 | 17 | 21 | 103 | 3 | 17 |

* P=0.004, Chi-squared=15.4, 4 df.

Table 5 Survival data for oral cancer

| Author | Year | Institute | No Patients | % patients treated with surgery | % DSS (5 years) | % OS (5 years) |
|---|---|---|---|---|---|---|
| Langdon | 1977 | London, UK | 131 | 27 | - | 33 |
| Wildt | 1989 | Arrhus, Denmark | 267 | 60 | - | 44 |
| Lindelov | 1990 | Copenhagen, Denmark | 304 | 26 | 41 | |
| Loree | 1990 | Memorial Sloan Kettering, USA | 398 | 100 | - | 57 |
| Tytor | 1990 | Bergen, Norway | 176 | 76 | 53 | 28 |
| Jones | 1993 | Liverpool, UK | 126 | 0 | 64 | 37 |
| Shingaki | 1995 | Niigata, Japan | 61* | 100 | 87 | 80 |
| Turner | 1996 | Manchester, UK | 333 | 0 | 55 | 43 |
| Chen | 1999 | Southern Taiwan | 496 | 65 | - | 32 |
| Koo | 2006 | Soeul, South Korea | 127 | 100 | 76 | 71 |
| Kessler | 2008 | Erlangen, Germany | 128 | 100 | 83 | 69 |
| Current paper | 2008 | Liverpool, UK | 489 | 100 | 74 | 56 |

NB * denotes stage I and II only

Figure 1. All causes and disease specific survival

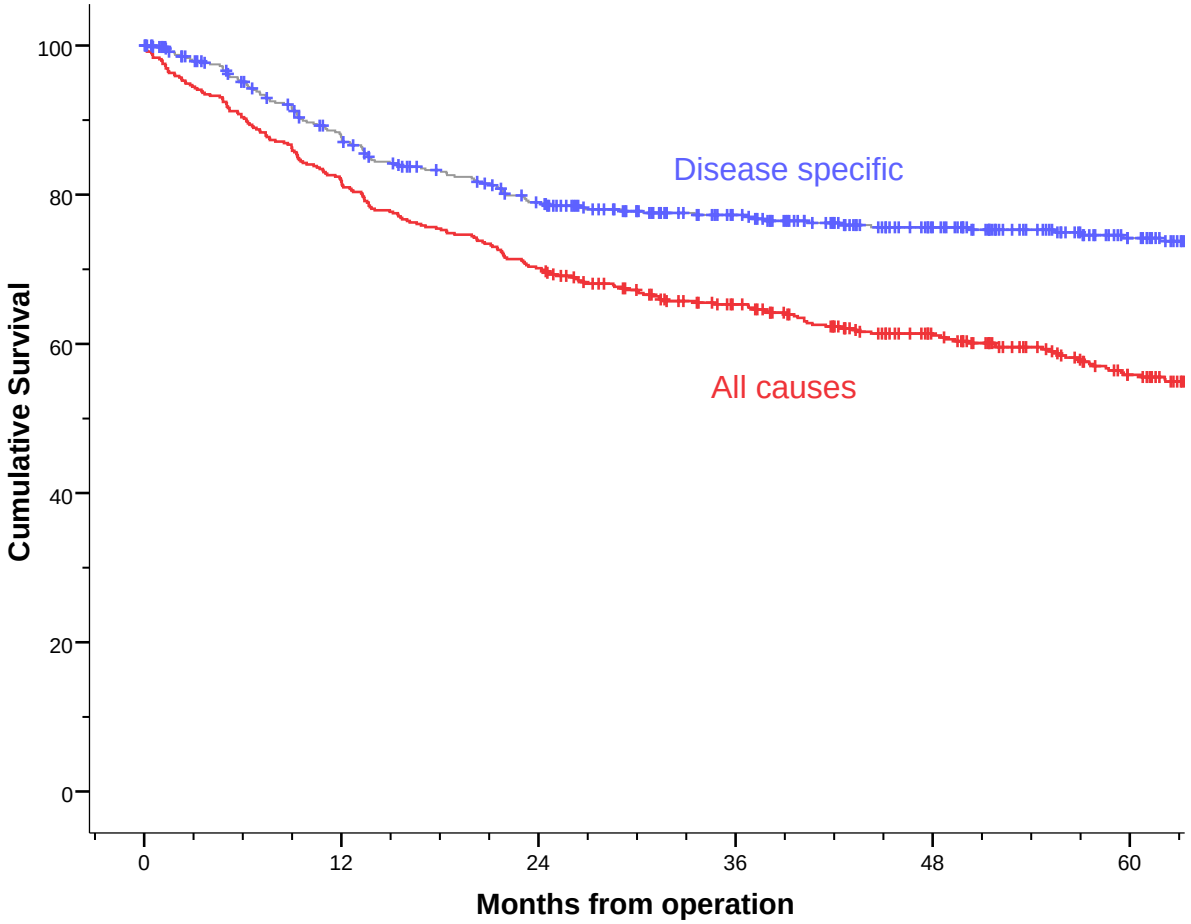
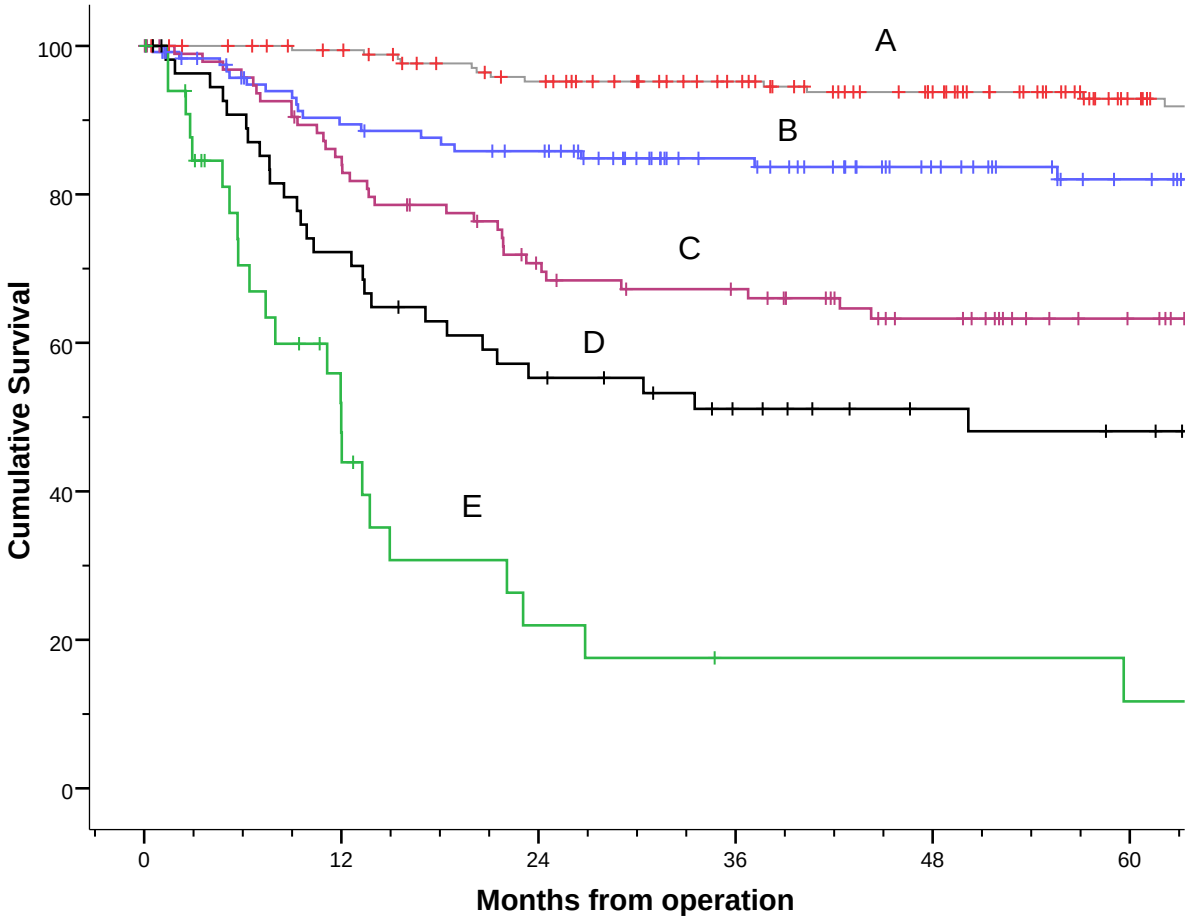


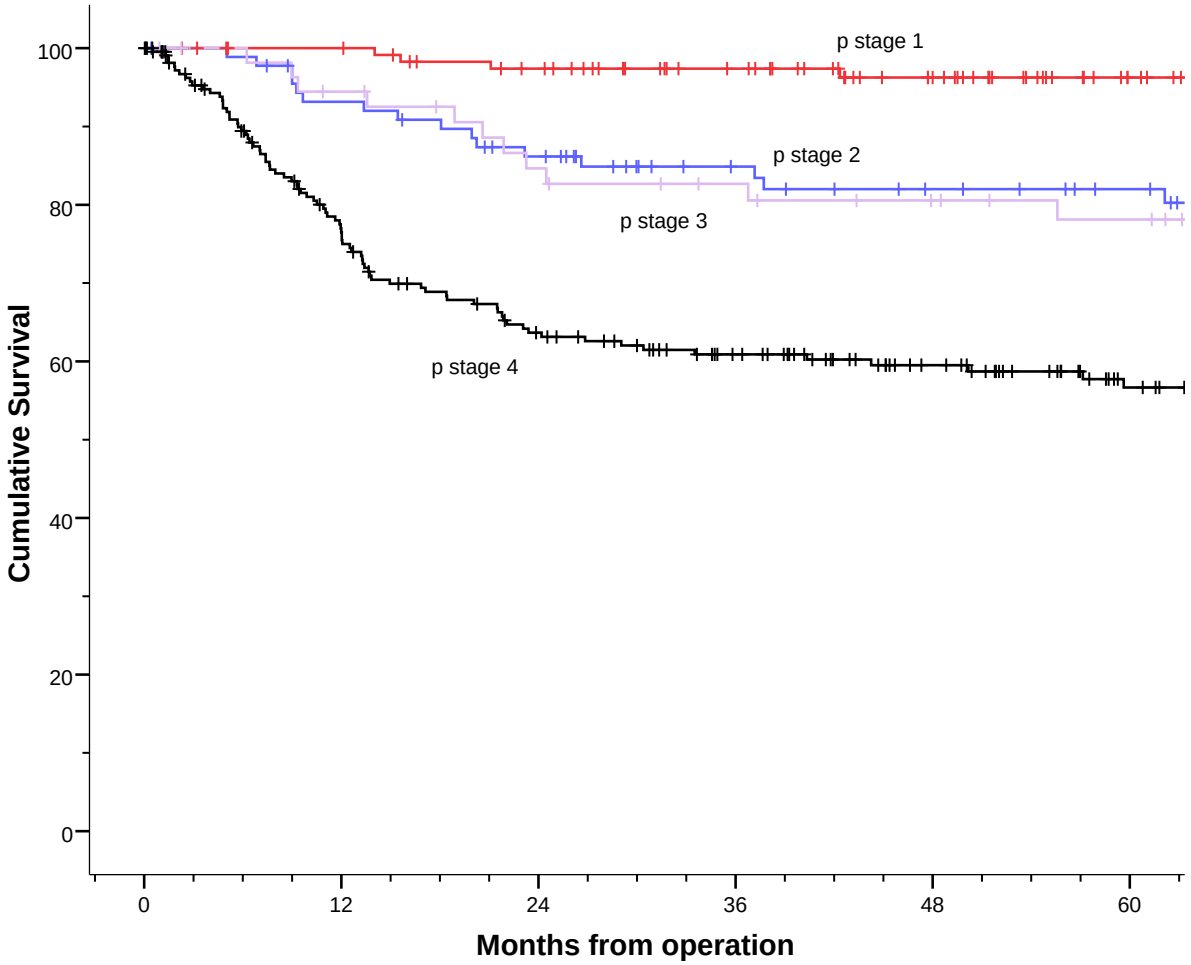
Figure 2 Disease specific survival for 489 patients with oral tumours by pN status and closeness of margins.




**Groups (patients in cohort)**

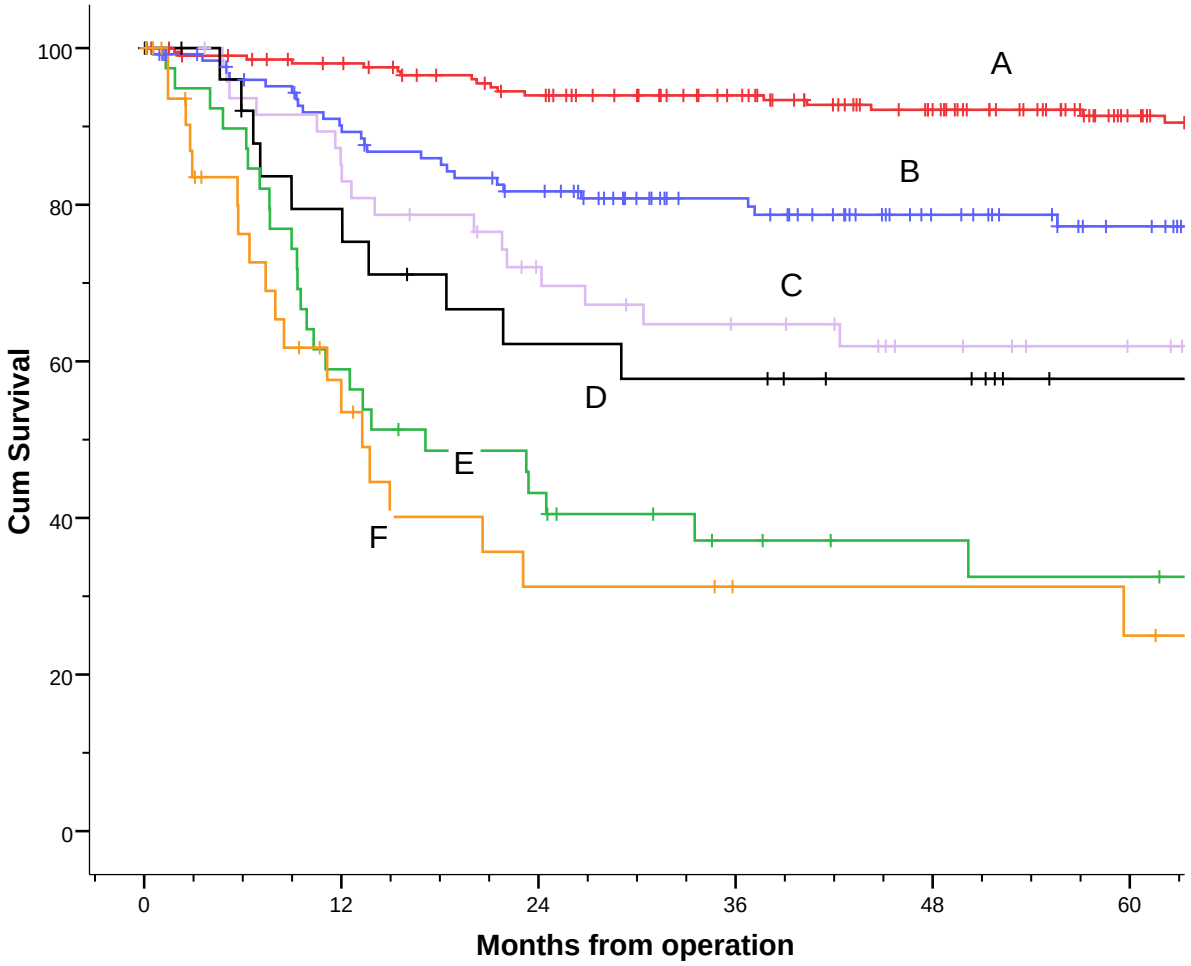
A (n=180): Clear Margins & pN0
B (n=122): Clear margins & pN1 OR close margins & pN0
C (n=97) : Clear margins & pN2-3 OR close margins & pN1 OR involved margins & pN0
D (n=56) : Close margins & pN2-3 OR involved margins & pN1
E (n=34) : Involved margins & pN2-3

Figure 3 Disease specific survival for 489 patients with oral tumours by p stage




**Groups (patients in cohort)**
P stage 1 (n=121), P stage 2 (n=91), P stage 3 (n=56), P stage 4 (n=221)

Figure 4 Disease specific survival for 489 patients with oral tumours by extra-capsular spread and margins.




**Groups (patients in cohort)**

A (n=210): Clear Margins & no ECS
B (n=130): Close Margins & no ECS
C (n=48): Involved Margins & no ECS
D (n=27): Clear Margins & ECS
E (n=40: Close Margins & ECS
F (n=34): Involved Margins & ECS

Figure 5 Disease specific survival for 489 patients with oral tumours by extra-capsular spread.

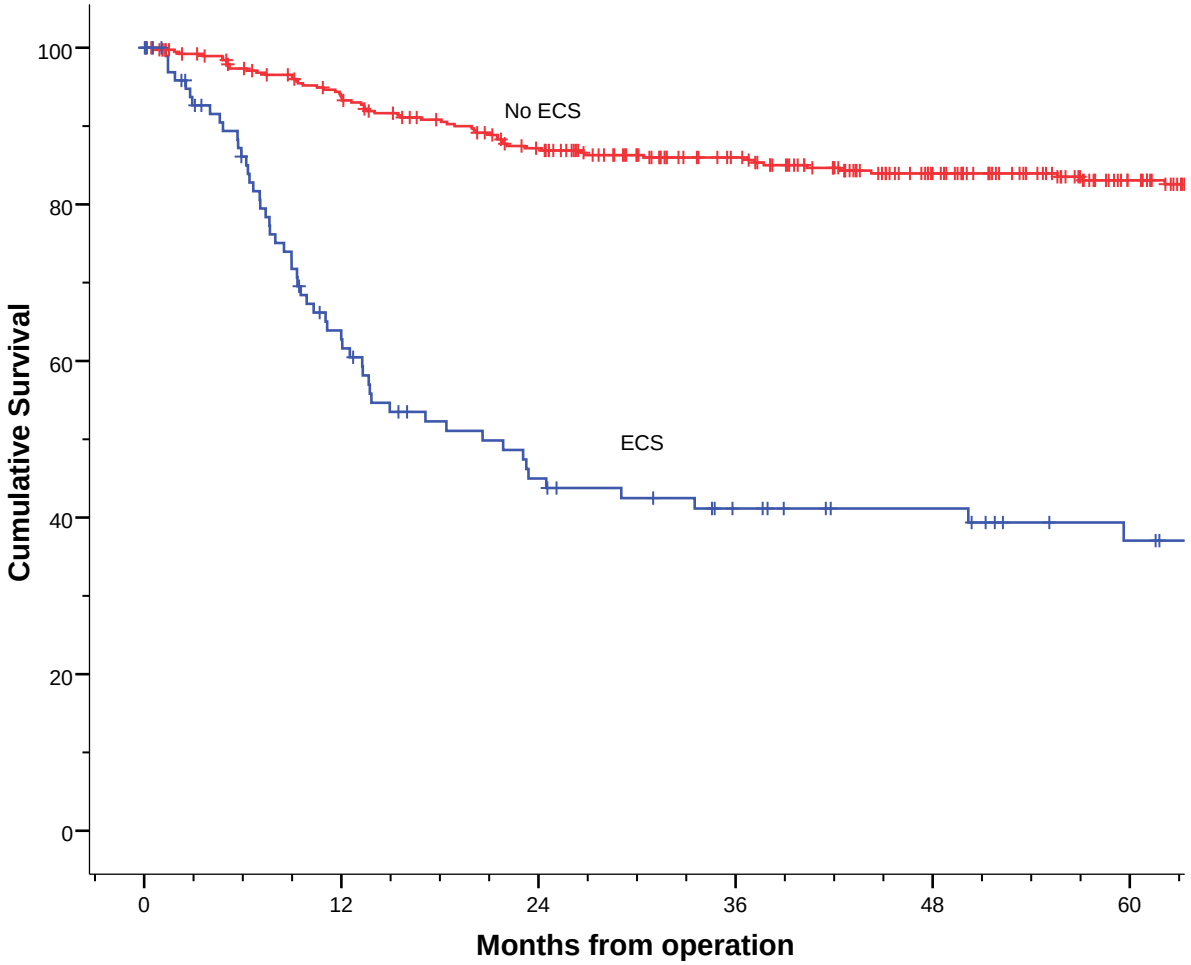


Figure 6 Disease specific survival for 489 patients with oral tumours by involvement of margins.

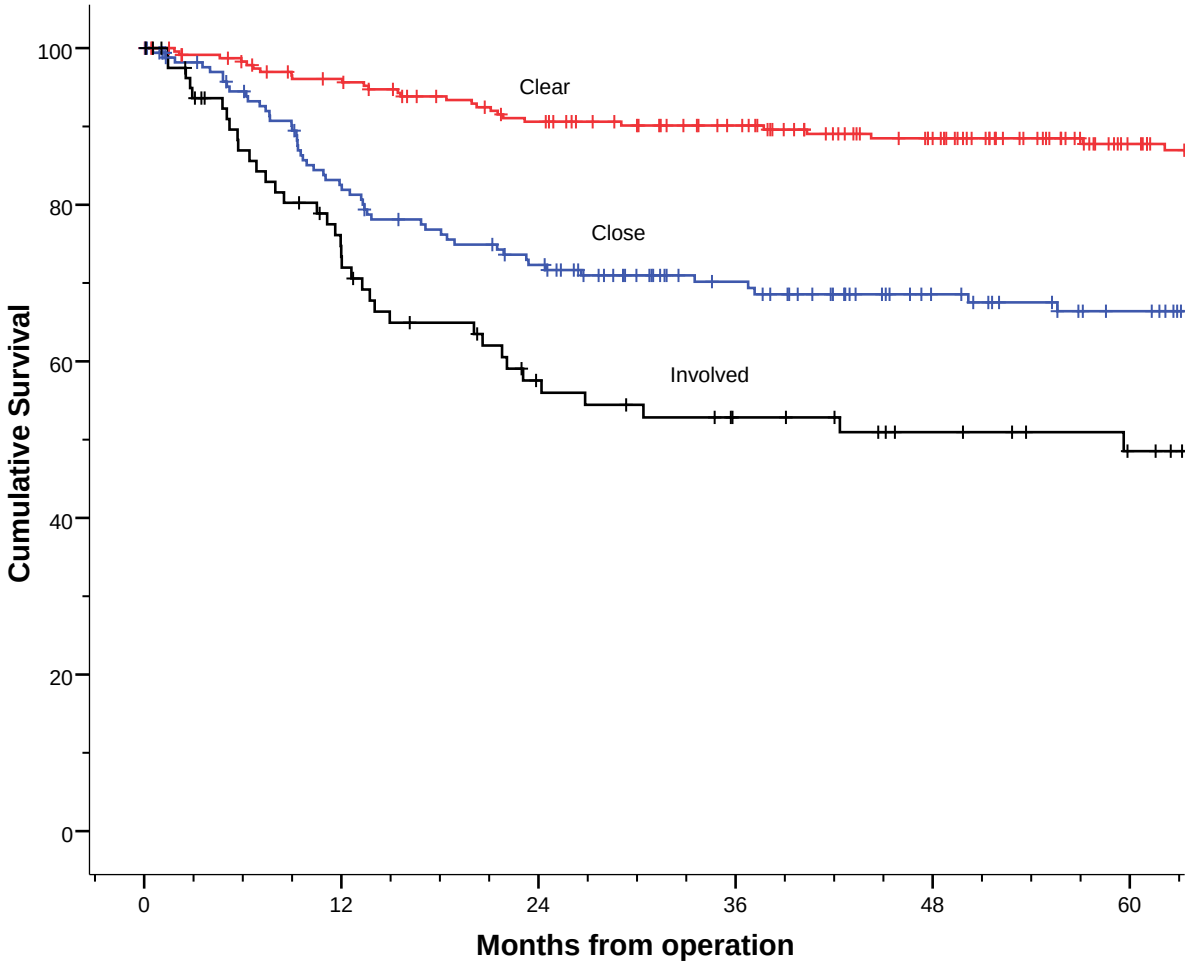


Figure 7 Disease specific survival for 489 patients with oral tumours by pN status