Determinants of outcome following surgery for oral squamous cell carcinoma

Abstract summary

The recent changes in incidence and prevalence of oral squamous cell carcinoma in relation to gender and age mirror the changing patterns of exposure to tobacco and alcohol, the main aetiological agents. Most cases of oral cancer are managed by surgery, often combined with radiotherapy. Histopathological assessment of the resection specimen provides information vital for post-operative management and prognosis. This review considers the full range of histological determinants of outcome in relation to the primary oral tumour and any metastatic involvement of the cervical lymphatic system, together with an outline of more general patient factors that may also impact on morbidity and mortality rates.

Key words

Oral cavity cancer
Squamous cell carcinoma
Histopathology
Prognosticators
Outcome following surgery

Introduction

The incidence of oral squamous cell carcinoma (SCC) varies worldwide and rates for the UK and the USA are increasing, and currently estimated as 10 cases per 100,000 population per annum [201]. The highest age standardised rates (over 20 per 100,000 population) are reported in parts of Europe and south central Asia [201]. In high-incidence countries such as Sri Lanka, India, Pakistan and Bangladesh, oral cancer is the most common cancer in men and may account for up to 30% of all new cases of cancer compared to 3% in the UK and 6% in France [201].

The 5-year disease specific survival has improved slightly but still remains around 50% [202]. Surgery is the favoured treatment option for most patients [1] and has the advantage of providing a surgical specimen for detailed pathological staging on which the decisions on the need for adjuvant therapy (usually radiotherapy) and more accurate prognostication can be made. In recent years, reconstructive surgery has improved morbidity but survivors still face aesthetic [2] and functional problems [3]. This review considers the factors that determine outcome following surgery for oral cavity tumours, UICC ICD-O C00, C02-C06 [4]. General and clinical factors related to survival will be outlined first, followed by an account of histopathological factors which are, by far, the more important. Surgical treatment involves neck dissection in most patients and hence, the account considers features of both primary and metastatic disease. All the data discussed concerns patients who were managed by primary surgery without prior chemotherapy, radiotherapy or chemoradiation.

1 General and clinical factors

1.1 Age

In a comprehensive analysis of survival reported by a regional maxillofacial surgery unit in the North-West region of England [5], patients aged 75 years or over were found to have a worse overall and disease specific 5-year survival probably due to increased co-morbidity and inability to withstand major surgery and radiotherapy. Several studies [6, 7] have shown an improved survival in patients < 65 years but there was no evidence of better survival in stage-matched younger (50-69) and older (>70 yrs) patient groups in the study of Bhattacharyya [8]. Current evidence [9-12] suggests that young age at presentation (<40 years) is not an adverse prognostic factor.

1.2 Gender

Until recently, females were thought to have a better prognosis than males [13, 14] but gender was not a significant factor in the study of Rogers *et al* [5] and there were no prognostic differences in a recent case-matched study by Garavello *et al* [15].

1.3 Race

Controlling for stage and treatment, black patients demonstrate poorer overall and disease-specific survival [16, 17]. One study [7] has suggested advanced stage at presentation accounts for poorer outcomes among black patients. Other studies have, however, shown that lower survival amongst Blacks may

be associated with less access to, and underutilisation of, healthcare resources [18, 19].

1.4 Co-morbidity

Alcohol and tobacco smoking, the primary aetiological agents for oral cancer [20, 21], cause other chronic conditions and may contribute to the high prevalence of co-morbidity and poor survival of patients [21-27]. Additionally, co-morbidities may have consequences for reconstruction and rehabilitation by affecting the success of vascularised free-flaps [28, 29]. Around one-fifth of head and neck cancer patients suffer moderate to severe co-morbidity [5, 26] with a significant effect on survival rates [23, 27] even when controlled for age and stage [26].

1.5 Risk factors/lifestyle

Cancer-free survival is worse in cases not related to smoking or alcohol exposure [10, 30] and this may reflect dietary [31], genetic and immunological differences [32-34]. Continued use of aetiological agents including tobacco, betel quid and alcohol is related to the development of second primary tumours [9]. HPV is widely reported to be an aetiological factor in a proportion of oropharyngeal squamous cell carcinomas and appears to be associated with a more favourable prognosis [35-37]. At oral cavity sites, firm conclusions have yet to be drawn regarding the importance of HPV in both pathogenesis and prognosis [38].

1.6 Socio-economic

Increased incidence of, and mortality from, oral cancer is related to material deprivation, particularly in males [39]. Whether social deprivation *per se* or behavioural differences in terms of smoking and alcohol use and poor diet are to blame is uncertain [40]. In terms of delayed presentation, Rogers *et al* [41] found no correlation with deprivation whereas others [7] report advanced stage at presentation in patients with low income.

1.7 Psychological factors including support

Single / divorced / widowed patients and those who do not have religious beliefs reportedly have lower survival [42].

2 Histopathological factors

2.1 Primary tumour

2.1.1 Site

More posteriorly located tumours have a lower 5 year survival [43]. Possible explanations include later stage at presentation, increased difficulty in achieving clear surgical margins and increased metastases that frequently involve multiple anatomical levels and may be bilateral [44, 45]. In tongue, retromolar and oropharyngeal tumours, 59-64% had nodal metastasis at initial surgery compared to only 22% of buccal tumours [46]. The same study [46] also shows different survival patterns with 38-41% of retromolar, oropharyngeal and lateral tongue patients dying of / with oral SCC compared to only 10-17% of patients with floor-of-mouth / buccal tumours.

2.1.2 Clinical and pathological T stage and tumour dimensions

Clinical and pathological TNM staging (TNM and pTNM, respectively) [4] uses the same criteria for categorising T stage based on tumour greatest surface dimension for categories T1-T3, and involvement of specific structures (such as bone and skin) for T4, and are major determinants of outcome [5, 47, 48]. The pT stage is the more accurate prognosticator as the clinical measurement frequently underestimates the true extent since tumour often undermines intact mucosa and satellites nodules cannot be detected by palpation or current routine imaging procedures. Distinction between dysplasia and invasive carcinoma at the mucosal periphery, and the occurrence of multifocal invasive carcinoma, are further potential sources of error [49]. In addition, differentiating between hyperplastic high-grade dysplastic lesions and microinvasive carcinoma is a continuing diagnostic challenge and discussed by Woolgar and Triantafyllou [50]. Reliance on an intact basement membrane is problematic as this can be disrupted by the subepithelial inflammatory reaction that may accompany dysplasia. Cross-cutting of irregularly hyperplastic rete processes can also lead to a false impression of invasive islands. However, despite the practical difficulties in accurately measuring the T diameter, it is well established that T stage at presentation is correlated with local recurrence, lymph node metastasis and poor survival [44, 46, 47, 51]. Recent studies [48, 52-56] show that tumour thickness is a more significant prognosticator on multivariate analysis than tumour T stage / surface dimension, particularly in T1 and T2 tumours [53]. Although the risk of nodal metastasis is a function of thickness as a continuum rather than an all-or-nothing phenomenon, the concept of a critical thickness is a useful one and overall in the oral cavity, a tumour 4 mm thick has a fourfold increased risk

[57]. However, regional differences within the oral cavity exist and in the floor of mouth, depth of 1.5mm may be significant due to the plentiful thin-walled, superficial lymphatic vessels [58].

2.1.3 Histological grade

The current UICC and WHO recommended tumour grading system [4, 59] is based on Broders' original classification [60] and defines three categories: well, moderate and poorly differentiated. Tumour heterogeneity and inter-observer variability are well known problems and may explain the lack of correlation of grade with outcome in many studies [52, 53]. In addition, grading is poorly discriminating since the vast majority of tumours are Grade 2 (moderately differentiated) [59].

2.1.4 Multifactorial and invasive front histological grading

Systems in which various histological features are assigned a numerical score [61-63] have been devised in an attempt to overcome the deficiencies in UICC / WHO grading. Problems of tumour heterogeneity and sampling still exist but the intention here is to grade the most severely atypical areas at the deepest aspect of the tumour using more strictly defined criteria. Several workers [44, 62, 64, 65] have found invasive front multifactorial grading to be predictive of recurrence, metastasis and survival although inter-observer variability remains an important shortcoming [63]. The single most important factor is pattern of invasion [56, 63, 64, 66, 67] with a tumour having a poorly-defined invasive front composed of small islands and cords of keratinocytes more likely to metastasise than a circumscribed tumour with bulbous islands and broad cords. In an attempt to improve standardisation, the Royal College of Pathologists, UK, (RCPath) Guidelines [68] suggest two categories: cohesive

and non-cohesive comprising patterns 1 / 2 and 3 / 4, respectively, in the original description of Anneroth *et al* [61] and Bryne *et al* [62].

2.1.5 Lymphovascular invasion

When strict criteria are applied – isolated, or clusters of, tumour cells within endothelial-lined channels or invasion of the media of a vessel with ulceration of the lumen – several studies [44-46] have demonstrated a positive correlation with multiple adverse histological features (tumour site, diameter, thickness, perineural invasion, pattern at invasive front) and also with nodal metastasis, the status (closeness) of the resection margin and recurrence. Lymphovascular invasion is a factor influencing survival on univariate analysis [46, 69].

2.1.6 Perineural invasion

Studies [5, 40-42, 56, 67, 70, 71] have repeatedly shown infiltration of nerve or perineurium at the advancing front of tumours relates not only to size and depth of the primary tumour but also to marginal status, presence of nodal metastasis, and survival. When present, the 5-year disease specific survival dropped from 81% to 55% on univariate analysis in a recent study [5]. Lip cancer generally has a much better prognosis than intra-oral cancer [202]. However, it is significant that perineural invasion in lip tumours is highly predictive of lymph node metastasis, aggressive clinical course and reduced survival [202].

2.1.7 Bone involvement

Distinguishing between the erosive and invasive types [72] is important in the histological appraisal of bone involvement since the latter is predictive of recurrence and survival even after taking into account other soft tissue

prognosticators. The current pTNM staging [4] does not consider the type of involvement with erosive tumours still classified as pT4, pstage IVA. This is unfortunate since gingival / alveolar carcinomas frequently show bone erosion by virtue of their position yet metastasise infrequently, and, hence, as independent studies have shown [72, 73], do not deserve their pT4 status and implied poor prognosis. The high proportion of gingival / alveolar carcinomas may explain the lack of an association between bone invasion and prognosis in the two studies by O'Brien *et al* [74, 75].

2.1.8 Skin involvement

This is a particularly adverse finding with reports of median survival of only seven months in a study by Cole and McGuirt [76].

2.1.9 Histological subtypes of squamous cell carcinoma

These are reviewed in an article by Pereira *et al* [77] and listed in Table 1. Verrucous carcinoma is a well-differentiated subtype that involves connective tissue on a broad, pushing (compressive) front and rarely leads to lymph node metastasis [59]. When arising in close proximity to bone, erosion is more likely than invasion. Approximately one-fifth of verrucous carcinomas are found to harbour foci of conventional squamous cell carcinoma. The prognosis is then comparable to that of the higher grade or conventional tumour [59]. Two subtypes of SCC reported to have a particularly poor prognosis are basaloid SCC and adenosquamous carcinoma [78, 79]. Extensive local spread and frequent early lymph node metastasis are likely reasons as well as a tendency, particularly for the basaloid variant, to arise in more posterior locations [80].

2.1.10 Status of the surgical resection margins

In one recent study [5], the status of the surgical resection margins together with the pN status were the strongest predictors of outcome in a logistic regression model based on 489 patients (Figure 1). Univariate analysis showed a marked difference in 5-year disease-specific survival for clear, close and involved margins (92%, 68% and 48%, respectively). Assessment of the resection margins should consider separately the mucosal margins, the submucosal / deep margin and the bone margins [68]. Involved or close mucosal margins may be more amenable to further surgery compared with involved submucosal / deep and bone margins, and mucosal margins are more easily observed during post-operative review. The current RCPath guidelines and minimum dataset [68] advises recording of margins of <1 mm as involved, 1-5 mm as close and > 5mm as clear. “Involved” margins are recorded as showing histological cut-through when tumour is detected at the actual margin.

Since inadequate resection margins have such a profound effect on outcome, a detailed consideration of some of the pathological findings is worthwhile and may serve to alert surgeons and pathologists of potential high-risk sites and features. Inadequate mucosal margins are rare compared to close / involved submucosal / deep margins. In a study of 301 surgical resection specimens [81], only eleven cases showed an involved mucosal margin compared to 61 cases with involved submucosal / deep soft tissue margins. Furthermore, there was a histological explanation for the inadequate mucosal margin in nine of the eleven cases. In six of these, cut-through of superficially invasive carcinoma that was not visible macroscopically was present. These tumours often showed a multifocal surface origin within a wider area of dysplasia. In a

248 further three cases, a second synchronous primary tumour, not suspected
249 clinically, was evident at the histological mucosal margin separated from the
250 index tumour by non-dysplastic epithelium. Involved submucosal / deep
251 margins were more frequent in the oropharynx and buccal mucosa (33% of
252 cases) compared to floor of mouth and oral tongue (20% and 11%,
253 respectively). The most frequent histological explanation of the involved soft
254 tissue margin (seen in 39 of the 61 cases) was a non-cohesive growth pattern
255 with individual tumour cells or tiny islands or cords forming the advancing
256 front. A single streak of tumour or isolated satellite nodule accounted for
257 eleven and six cases, respectively, with lymphovascular invasion and neural
258 invasion accounting for three of the remaining five cases. The tumour had a
259 circumscribed edge – growth pattern 2 [54, 55] – in only a single case. An
260 involved bone margin was seen in 10 of the 100 cases with pT4 status on
261 account of bone involvement. Most of these cases also had an involved soft
262 tissue / mucosal margins, and, hence, the involved bone margin was further
263 evidence of the tumour's unfavourable growth pattern.
264 Guidelines are essential for accurate standardised reporting and the criteria
265 for assessment recommended by the RCPath [68] are simple to use yet
266 generally robust. Nevertheless, our experience suggests that a 5mm margin
267 may still be inadequate in the case of a highly infiltrative tumour in which the
268 tumour islands and individual cells are widely dispersed. Conversely, a 2-3mm
269 margin may be adequate in a verrucous carcinoma with its characteristic
270 pushing front or a conventional SCC with a cohesive, circumscribed growth
271 pattern. Hence, decisions on post-operative management may need to
272 consider some cases on an individual basis rather than apply a single, across-

the-board protocol. Brandwein-Gensler *et al* [67] concur with this view and state that a 5mm margin may not be effective in the presence of high risk histological features, namely pattern of invasion, perineural spread and minimal lymphocytic response. Tissue shrinkage during fixation and processing, which may be as high as 47% and varies depending on the type and consistency of the resected tissue [81, 82], is not taken into account, and this is an inherent weakness of the present recommendations.

2.2 Lymph node metastases

The UICC clinical and pathological N staging [4] is based on the number, laterality and size of nodal deposits. The RCPath minimum dataset [68] records these features, together with anatomical level(s) and extracapsular (extranodal) spread (ECS). The clinical, and in particular, the pathological N stage are major determinants of outcome [47, 48, 54, 69, 71, 73, 83]. As mentioned above, pN status was one of the two predictive factors in the best-fit logistic regression model in one recent study [5] (Figure 1). Traditionally, lymph node metastasis was said to reduce survival by 50% [84]. However, evidence that ECS not metastasis *per se* accounts for the predictive value is accumulating from independent studies [5, 85-89]. Difficulties with defining and standardising the reporting of ECS need to be resolved before its inclusion in the UICC pathological staging procedure but several potential systems have been suggested [50]. Moreover, it appears that it is the presence of ECS, however minor, rather than the extent, that imparts the poor prognosis [85, 86]. Patients with more extensive (macroscopic) ECS tend to die within the first year after surgery while patients with ECS only detectable

histologically tend to die within the second post-operative year [85]. Post operative radiotherapy to the neck may not improve the long-term survival [90] since many patients with ECS have multiple unfavourable histological features of their primary tumour and are highly likely to suffer intra-oral relapse [85]. Our current opinion is that ECS is a simple histological marker of an aggressive tumour. The fact that ECS can be present in association with small metastatic deposits of only 1mm (undetectable by palpation and current routine radiological imaging procedures) makes it a more powerful prognosticator than traditional markers such as size and number of nodal deposits which indicate tumour extent rather than aggressive behaviour.

The prognostic importance of isolated tumour cells (<0.2mm), micrometastases (<2mm) and established metastases [4, 91] confined to the lymph node is uncertain. Woolgar [92] reported no differences in survival between patients with only micrometastasis and those with pN0 necks. In a further study [93] in which cytokeratin immunohistochemistry was utilised on all lymph nodes from dissections that were negative on routine staining, tumour cells were identified in one or more nodes in 50% of patients. Although neck recurrence was seen with increased frequency in the pN0 (mi) group [4], there were no overall differences in survival [93]. Serial sectioning and immunohistochemical staining are used in the setting of sentinel node biopsy procedures in an attempt to increase the probability of identifying positive nodes before proceeding to selective neck dissection. However, since the prognostic significance of micrometastases is uncertain, step-serial sectioning and the use of immunohistochemistry are not currently recommended in the pathological examination of routine neck dissection specimens [94].

2.3 Distant (systemic) metastases

Around 2-3% of oral cancer patients have clinically detectable distant systemic metastases at presentation [95]. Lung is the favoured site followed by bone (spine and ribs) and liver. A synchronous lung primary tumour should be considered in the differential diagnosis of an isolated lung metastasis. Surgery may be performed for palliative intent in patients with distant metastases. Even with chemoradiation, the prognosis remains poor.

2.4 Pathological TNM stage

This is a powerful prognosticator with a gradual decline in the 5-year disease specific survival for stages I-III followed by a steep drop for stage IV [5, 43, 47, 71, 96, 97]. For example, in one recent oral cancer study [5], 5-year disease specific survival for stages I-III fell from 96-78% but survival for pstage IV was only 57%. Pathological N2/3 rather than pT4 accounted for the pstage IV status in the majority of cases.

2.5 Field cancerisation, serial tumours

Multiple primaries at the time of initial surgery or sequential in the post-operative period are challenging problems especially in relation to clinical and pathological diagnosis, surgical planning and staging. It has long been recognised that oral cancer patients frequently develop multiple aetiologically-related primary tumours mainly affecting the aerodigestive tract [98]. Second primary head and neck tumours occur in around 7-15% of patients [5, 99] and this risk appears cumulative with a 20-year risk and as high as 36% [100].

Survival from these is worse than for a comparable first primary [101] since treatment options are limited by the anatomical and physiological effects of the initial therapy. Histological evidence of dysplasia of mucosa peripheral to the index tumour in surgical resection specimens is a useful prognosticator particularly if smoking and drinking habits continue post-operatively.

3 Post-surgical course including peri-operative complications, adjuvant treatment, local and regional and systemic relapse

3.1 General considerations

The post-operative course is related to multiple and varied factors ranging from age, co-morbidity, extent and length of surgery, type of reconstruction, and post-operative adjuvant therapy [102-106].

Death intra or peri-operatively (<2 weeks from surgery) is reported in 3-4% of patients [102, 104, 106]. Alcoholism and peri-operative hypotension are two predictive factors for sudden death in the peri-operative period [106]. Other complications include wound dehiscence and infection which are reported in 20% of cases [104]. Contributing factors for all complications including death are pre-existing co-morbidity, in particular, cardiovascular and respiratory disease; stage of disease; extent and timing of surgery, in particular if bilateral neck dissection is performed; alcoholism; tracheostomy; poor differentiation of tumour; and ECS [102-106]. In general, the factors reflect either a high-risk patient or a high-risk, that is, aggressive, tumour.

Patients receiving post-operative radiotherapy have poorer overall and disease specific survival [5, 107], again reflecting adverse tumour characteristics.

3.2 Local and regional relapse

In the recent study by Rogers *et al* [5], the local recurrence rate was 10% and loco-regional recurrence rate 21%. Relapse in the neck tends to present earlier than an intra-oral recurrence [46] and may be due to growth of residual tumour in the operated field, or disease presenting in nodes outside the treated area. The former imparts a worse prognosis and is almost always associated with ECS at the time of original surgery.

3.3 Distant (systemic) relapse

As local and regional control of oral cancer has improved, distant metastases have been increasingly diagnosed with 5-25% and up to 50% of patients, respectively, having clinical and autopsy evidence of distant spread [108, 109]. They are more commonly associated with increasing T, and, in particular N classification, developing in 17-51% of patients staged N2/3 at initial surgery [1109]. ECS and bilateral nodal metastases are particularly good predictors [108-110]. Most distant metastases are diagnosed within two years and affect the lungs, bone and liver in decreasing frequency. They are preceded by locoregional relapse in a high proportion of cases [110, 111] with around 20% appearing to represent slow growth of tumour disseminated early in the disease course and left behind after successful locoregional control.

4 Molecular markers

Studies have identified regions of genetic loss common to the vast majority of OSCC and also report a high incidence of LOH in aggressive tumours [112]. LOH at 2q, 3p, 8p, 9p, 11p and 18q have been correlated with poor outcome, particularly recurrence and decreased survival [112-114]. Aberrant p53 expression as determined by immunohistochemistry and mutation has been correlated with larger number of metastases as well as decreased recurrence-free and overall survival [115-117].

Although of interest and of potential use in identifying more aggressive tumours, the aberrations themselves represent alterations in complex signalling pathways (cell cycle, proliferation, apoptosis) and as such are not amenable to targeted treatment.

5 Recent trends

Evaluation of outcome over a ten year period [5] has shown a significant improvement in both overall and disease-specific survival in patients treated between 2000-02 compared to 1992-5 (81% and 63% compared to 64% and 46%, respectively). Small tumours at presentation, more favourable histological features, less extensive surgery with reduced use of free-flap reconstruction and neck dissection likely contributed to the improved outcome. In addition, more patients received a higher dosage of post-operative radiotherapy in the later period. It is likely that advances in anaesthesia and post-operative management have also contributed to the improved mortality rates. It is too early to assess the impact of the recent trend [118] to use induction chemotherapy prior to surgery.

6 Future perspectives

Further improvements in the outcome for patients with oral SCC almost certainly lie in the identification of molecular aberrations that are amenable to targeted therapy which will complement the currently available treatment options and in particular deal with the problem of microscopic residual disease. Epidermal growth factor receptor (EGFR) is the most promising candidate for therapeutic targeting due to its over expression in more than 90% of tumours [119]. To date, clinical trials of anti-EGFR monoclonal antibodies including cetuximab have been largely confined to patients with advanced stage disease but some shown a satisfactory and consistent improvement in outcome [120]. Nevertheless, a retrospective, single institution review of 29 patients treated with cetuximab and radiotherapy compared with 103 patients treated by conventional chemoradiotherapy showed no differences in survival although the authors comment that the optimal treatment regime has not yet been defined. [121].

Additional ways of utilising molecular biology are to look for tumour specific changes around the periphery of a tumour in an attempt to identify minimal residual disease that is beyond even histological detection. Studies have correlated the presence of mutant p53 [122] and methylation of p16 and cytoglobin [123] in histologically clear marginal tissue with local recurrence. Identification of minimal residual disease at the molecular level may assist in planning adjuvant post-operative treatment, both conventional chemotherapy / radiotherapy and novel targeted therapy [124] as this becomes translated into routine clinical practice.

Executive summary

Oral Cancer

- Rising incidence
- 5-year disease-specific survival of around 50%
- Pathological staging of surgical resection specimens influences post-operative management

In surgically managed patients, outcome is determined by

- General and clinical factors
- Histopathological features of the surgical resection specimen

General and clinical determinants of outcome include

- Age
- Gender
- Race
- Co-morbidity
- Risk factors / lifestyle
- Socio-economic circumstances
- Psychological factors including support
- Post-operative course

Histopathological features are of over-riding importance and include features of the primary tumour, neck dissection(s), systemic (distant) metastases, pTNM stage, evidence of field cancerisation

- Primary tumour site, T stage, pT stage, tumour dimensions, histological grade and invasive front characteristics, lymphovascular invasion, perineural invasion, skin involvement, histological sub-type, status of resection margins
- Presence of cervical lymph node metastasis; number, laterality and size of metastatic deposits, extracapsular spread; N and pN stage

Relapse may be local (intra-oral), regional (neck), locoregional, systemic (distant)

Future developments will likely identify molecular aberrations for targeted therapy and the detection of “sub-microscopic” residual disease

Table 1
Histological subtypes of oral / oropharyngeal squamous cell carcinoma

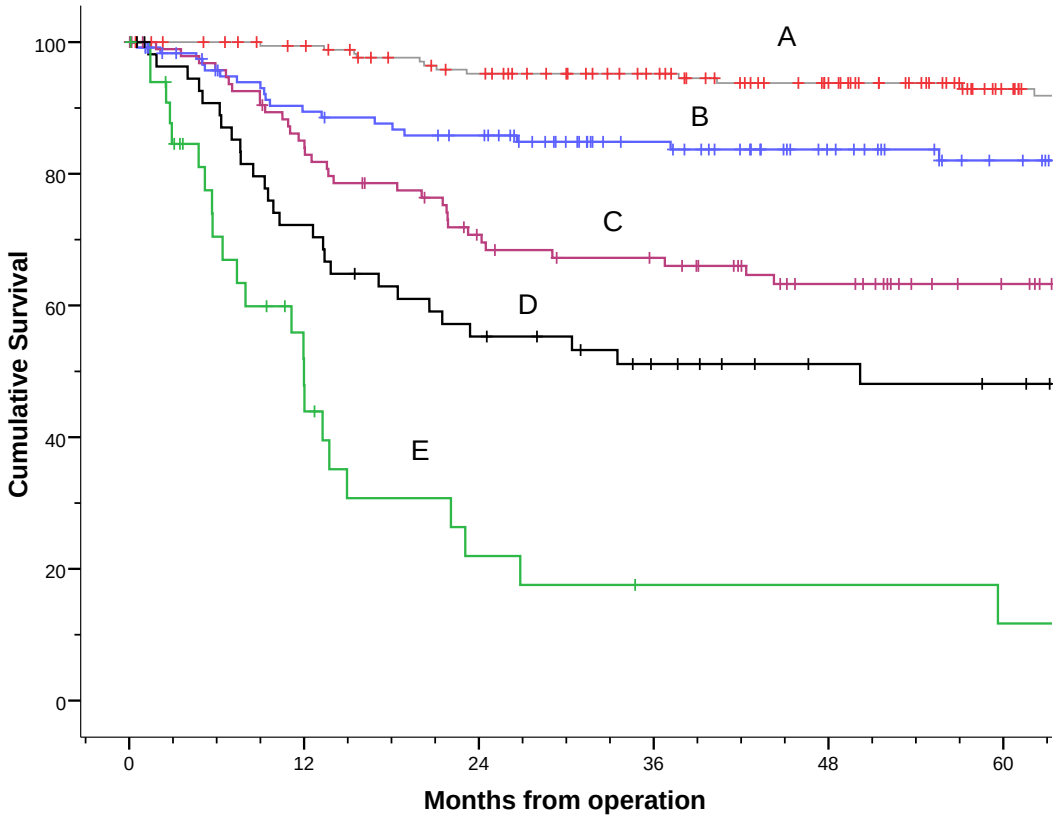
1. Verrucous carcinoma
2. Carcinoma cuniculatum
3. Papillary squamous cell carcinoma
4. Adenoid (acantholytic) squamous cell carcinoma
5. Adenosquamous carcinoma
6. Basaloid squamous cell carcinoma
7. Spindle cell carcinoma
8. Giant cell (pleomorphic) carcinoma
9. Undifferentiated carcinoma

Figure 1

Disease specific survival for 489 patients with oral SCC by pN status and closeness of resection margins. [This figure was published in Oral Oncology, in press, doi:10.1016/j.oraloncology.2008.05.008, Rogers SN, Brown JS, Woolgar JA *et al*, Survival following primary surgery for oral cancer, Copyright Elsevier (2008)].

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



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** A good summary of current knowledge

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