

1 **Determinants of outcome following surgery for oral**
2 **squamous cell carcinoma**

3

4 **Abstract summary**

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

15

16

17 **Key words**

18 Oral cavity cancer

19 Squamous cell carcinoma

20 Histopathology

21 Prognosticators

22 Outcome following surgery

23

24

25 **Introduction**

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

34 The 5-year disease specific survival has improved slightly but still remains
35 around 50% [202]. Surgery is the favoured treatment option for most patients
36 [1] and has the advantage of providing a surgical specimen for detailed
37 pathological staging on which the decisions on the need for adjuvant therapy
38 (usually radiotherapy) and more accurate prognostication can be made. In
39 recent years, reconstructive surgery has improved morbidity but survivors still
40 face aesthetic [2] and functional problems [3]. This review considers the
41 factors that determine outcome following surgery for oral cavity tumours,
42 UICC ICD-O C00, C02-C06 [4]. General and clinical factors related to survival
43 will be outlined first, followed by an account of histopathological factors which
44 are, by far, the more important. Surgical treatment involves neck dissection in
45 most patients and hence, the account considers features of both primary and
46 metastatic disease. All the data discussed concerns patients who were
47 managed by primary surgery without prior chemotherapy, radiotherapy or
48 chemoradiation.

49

50 **1 General and clinical factors**

51 **1.1 Age**

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

61

62 **1.2 Gender**

63 Until recently, females were thought to have a better prognosis than males
64 [13, 14] but gender was not a significant factor in the study of Rogers *et al* [5]
65 and there were no prognostic differences in a recent case-matched study by
66 Garavello *et al* [15].

67

68 **1.3 Race**

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

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

75

76 **1.4 Co-morbidity**

77 Alcohol and tobacco smoking, the primary aetiological agents for oral cancer
78 [20, 21], cause other chronic conditions and may contribute to the high
79 prevalence of co-morbidity and poor survival of patients [21-27]. Additionally,
80 co-morbidities may have consequences for reconstruction and rehabilitation
81 by affecting the success of vascularised free-flaps [28, 29]. Around one-fifth of
82 head and neck cancer patients suffer moderate to severe co-morbidity [5, 26]
83 with a significant effect on survival rates [23, 27] even when controlled for age
84 and stage [26].

85

86 **1.5 Risk factors/lifestyle**

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

96

97

98 **1.6 Socio-economic**

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

105

106 **1.7 Psychological factors including support**

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

109

110 **2 Histopathological factors**

111 **2.1 Primary tumour**

112 **2.1.1 Site**

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

122 **2.1.2 Clinical and pathological T stage and tumour dimensions**

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

148 [57]. However, regional differences within the oral cavity exist and in the floor
149 of mouth, depth of 1.5mm may be significant due to the plentiful thin-walled,
150 superficial lymphatic vessels [58].

151 **2.1.3 Histological grade**

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

159 **2.1.4 Multifactorial and invasive front histological grading**

160 Systems in which various histological features are assigned a numerical score
161 [61-63] have been devised in an attempt to overcome the deficiencies in UICC
162 / WHO grading. Problems of tumour heterogeneity and sampling still exist but
163 the intention here is to grade the most severely atypical areas at the deepest
164 aspect of the tumour using more strictly defined criteria. Several workers [44,
165 62, 64, 65] have found invasive front multifactorial grading to be predictive of
166 recurrence, metastasis and survival although inter-observer variability remains
167 an important shortcoming [63]. The single most important factor is pattern of
168 invasion [56, 63, 64, 66, 67] with a tumour having a poorly-defined invasive
169 front composed of small islands and cords of keratinocytes more likely to
170 metastasise than a circumscribed tumour with bulbous islands and broad
171 cords. In an attempt to improve standardisation, the Royal College of
172 Pathologists, UK, (RCPath) Guidelines [68] suggest two categories: cohesive

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

175 **2.1.5 Lymphovascular invasion**

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

182 Lymphovascular invasion is a factor influencing survival on univariate analysis
183 [46, 69].

184 **2.1.6 Perineural invasion**

185 Studies [5, 40-42, 56, 67, 70, 71] have repeatedly shown infiltration of nerve
186 or perineurium at the advancing front of tumours relates not only to size and
187 depth of the primary tumour but also to marginal status, presence of nodal
188 metastasis, and survival. When present, the 5-year disease specific survival
189 dropped from 81% to 55% on univariate analysis in a recent study [5]. Lip
190 cancer generally has a much better prognosis than intra-oral cancer [202].

191 However, it is significant that perineural invasion in lip tumours is highly
192 predictive of lymph node metastasis, aggressive clinical course and reduced
193 survival [202].

194 **2.1.7 Bone involvement**

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

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

206 **2.1.8 Skin involvement**

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

209 **2.1.9 Histological subtypes of squamous cell carcinoma**

210 These are reviewed in an article by Pereira *et al* [77] and listed in Table 1.

211 Verrucous carcinoma is a well-differentiated subtype that involves connective
212 tissue on a broad, pushing (compressive) front and rarely leads to lymph node
213 metastasis [59]. When arising in close proximity to bone, erosion is more likely
214 than invasion. Approximately one-fifth of verrucous carcinomas are found to
215 harbour foci of conventional squamous cell carcinoma. The prognosis is then
216 comparable to that of the higher grade or conventional tumour [59]. Two
217 subtypes of SCC reported to have a particularly poor prognosis are basaloid
218 SCC and adenosquamous carcinoma [78, 79]. Extensive local spread and
219 frequent early lymph node metastasis are likely reasons as well as a
220 tendency, particularly for the basaloid variant, to arise in more posterior
221 locations [80].

222 **2.1.10 Status of the surgical resection margins**

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

237 Since inadequate resection margins have such a profound effect on outcome,
238 a detailed consideration of some of the pathological findings is worthwhile and
239 may serve to alert surgeons and pathologists of potential high-risk sites and
240 features. Inadequate mucosal margins are rare compared to close / involved
241 submucosal / deep margins. In a study of 301 surgical resection specimens
242 [81], only eleven cases showed an involved mucosal margin compared to 61
243 cases with involved submucosal / deep soft tissue margins. Furthermore,
244 there was a histological explanation for the inadequate mucosal margin in
245 nine of the eleven cases. In six of these, cut-through of superficially invasive
246 carcinoma that was not visible macroscopically was present. These tumours
247 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-

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

280

281 **2.2 Lymph node metastases**

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

298 histologically tend to die within the second post-operative year [85]. Post
299 operative radiotherapy to the neck may not improve the long-term survival [90]
300 since many patients with ECS have multiple unfavourable histological features
301 of their primary tumour and are highly likely to suffer intra-oral relapse [85].
302 Our current opinion is that ECS is a simple histological marker of an
303 aggressive tumour. The fact that ECS can be present in association with small
304 metastatic deposits of only 1mm (undetectable by palpation and current
305 routine radiological imaging procedures) makes it a more powerful
306 prognosticator than traditional markers such as size and number of nodal
307 deposits which indicate tumour extent rather than aggressive behaviour.
308 The prognostic importance of isolated tumour cells (<0.2mm),
309 micrometastases (<2mm) and established metastases [4, 91] confined to the
310 lymph node is uncertain. Woolgar [92] reported no differences in survival
311 between patients with only micrometastasis and those with pN0 necks. In a
312 further study [93] in which cytokeratin immunohistochemistry was utilised on
313 all lymph nodes from dissections that were negative on routine staining,
314 tumour cells were identified in one or more nodes in 50% of patients. Although
315 neck recurrence was seen with increased frequency in the pN0 (mi) group [4],
316 there were no overall differences in survival [93]. Serial sectioning and
317 immunohistochemical staining are used in the setting of sentinel node biopsy
318 procedures in an attempt to increase the probability of identifying positive
319 nodes before proceeding to selective neck dissection. However, since the
320 prognostic significance of micrometastases is uncertain, step-serial sectioning
321 and the use of immunohistochemistry are not currently recommended in the
322 pathological examination of routine neck dissection specimens [94].

323

324 **2.3 Distant (systemic) metastases**

325 Around 2-3% of oral cancer patients have clinically detectable distant
326 systemic metastases at presentation [95]. Lung is the favoured site followed
327 by bone (spine and ribs) and liver. A synchronous lung primary tumour should
328 be considered in the differential diagnosis of an isolated lung metastasis.

329 Surgery may be performed for palliative intent in patients with distant
330 metastases. Even with chemoradiation, the prognosis remains poor.

331

332 **2.4 Pathological TNM stage**

333 This is a powerful prognosticator with a gradual decline in the 5-year disease
334 specific survival for stages I-III followed by a steep drop for stage IV [5, 43, 47,
335 71, 96, 97]. For example, in one recent oral cancer study [5], 5-year disease
336 specific survival for stages I-III fell from 96-78% but survival for pstage IV was
337 only 57%. Pathological N2/3 rather than pT4 accounted for the pstage IV
338 status in the majority of cases.

339

340 **2.5 Field cancerisation, serial tumours**

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

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

353

354 **3 Post-surgical course including peri-operative** 355 **complications, adjuvant treatment, local and regional** 356 **and systemic relapse**

357 **3.1 General considerations**

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

361 Death intra or peri-operatively (<2 weeks from surgery) is reported in 3-4% of
362 patients [102, 104, 106]. Alcoholism and peri-operative hypotension are two
363 predictive factors for sudden death in the peri-operative period [106]. Other
364 complications include wound dehiscence and infection which are reported in
365 20% of cases [104]. Contributing factors for all complications including death
366 are pre-existing co-morbidity, in particular, cardiovascular and respiratory
367 disease; stage of disease; extent and timing of surgery, in particular if bilateral
368 neck dissection is performed; alcoholism; tracheostomy; poor differentiation of
369 tumour; and ECS [102-106]. In general, the factors reflect either a high-risk
370 patient or a high-risk, that is, aggressive, tumour.

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

374

375 **3.2 Local and regional relapse**

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

382

383 **3.3 Distant (systemic) relapse**

384 As local and regional control of oral cancer has improved, distant metastases
385 have been increasingly diagnosed with 5-25% and up to 50% of patients,
386 respectively, having clinical and autopsy evidence of distant spread [108,
387 109]. They are more commonly associated with increasing T, and, in particular
388 N classification, developing in 17-51% of patients staged N2/3 at initial
389 surgery [1109]. ECS and bilateral nodal metastases are particularly good
390 predictors [108-110]. Most distant metastases are diagnosed within two years
391 and affect the lungs, bone and liver in decreasing frequency. They are
392 preceded by locoregional relapse in a high proportion of cases [110, 111] with
393 around 20% appearing to represent slow growth of tumour disseminated early
394 in the disease course and left behind after successful locoregional control.

395

396 **4 Molecular markers**

397 Studies have identified regions of genetic loss common to the vast majority of
398 OSCC and also report a high incidence of LOH in aggressive tumours [112].
399 LOH at 2q, 3p, 8p, 9p, 11p and 18q have been correlated with poor outcome,
400 particularly recurrence and decreased survival [112-114]. Aberrant p53
401 expression as determined by immunohistochemistry and mutation has been
402 correlated with larger number of metastases as well as decreased recurrence-
403 free and overall survival [115-117].
404 Although of interest and of potential use in identifying more aggressive
405 tumours, the aberrations themselves represent alterations in complex
406 signalling pathways (cell cycle, proliferation, apoptosis) and as such are not
407 amenable to targeted treatment.

408

409 **5 Recent trends**

410 Evaluation of outcome over a ten year period [5] has shown a significant
411 improvement in both overall and disease-specific survival in patients treated
412 between 2000-02 compared to 1992-5 (81% and 63% compared to 64% and
413 46%, respectively). Small tumours at presentation, more favourable
414 histological features, less extensive surgery with reduced use of free-flap
415 reconstruction and neck dissection likely contributed to the improved outcome.
416 In addition, more patients received a higher dosage of post-operative
417 radiotherapy in the later period. It is likely that advances in anaesthesia and
418 post-operative management have also contributed to the improved mortality
419 rates. It is too early to assess the impact of the recent trend [118] to use
420 induction chemotherapy prior to surgery.

421

422 **6 Future perspectives**

423 Further improvements in the outcome for patients with oral SCC almost
424 certainly lie in the identification of molecular aberrations that are amenable to
425 targeted therapy which will complement the currently available treatment
426 options and in particular deal with the problem of microscopic residual
427 disease. Epidermal growth factor receptor (EGFR) is the most promising
428 candidate for therapeutic targeting due to its over expression in more than
429 90% of tumours [119]. To date, clinical trials of anti-EGFR monoclonal
430 antibodies including cetuximab have been largely confined to patients with
431 advanced stage disease but some shown a satisfactory and consistent
432 improvement in outcome [120]. Nevertheless, a retrospective, single institution
433 review of 29 patients treated with cetuximab and radiotherapy compared with
434 103 patients treated by conventional chemoradiotherapy showed no
435 differences in survival although the authors comment that the optimal
436 treatment regime has not yet been defined. [121].

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

446 **Executive summary**

447 **Oral Cancer**

- 448 • Rising incidence
- 449 • 5-year disease-specific survival of around 50%
- 450 • Pathological staging of surgical resection specimens influences post-
- 451 operative management

452

453 **In surgically managed patients, outcome is determined by**

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

456

457 **General and clinical determinants of outcome include**

- 458 • Age
- 459 • Gender
- 460 • Race
- 461 • Co-morbidity
- 462 • Risk factors / lifestyle
- 463 • Socio-economic circumstances
- 464 • Psychological factors including support
- 465 • Post-operative course

466

467 **Histopathological features are of over-riding importance and include**

468 **features of the primary tumour, neck dissection(s), systemic (distant)**

469 **metastases, pTNM stage, evidence of field cancerisation**

470 • Primary tumour site, T stage, pT stage, tumour dimensions, histological
471 grade and invasive front characteristics, lymphovascular invasion,
472 perineural invasion, skin involvement, histological sub-type, status of
473 resection margins

474 • Presence of cervical lymph node metastasis; number, laterality and
475 size of metastatic deposits, extracapsular spread; N and pN stage

476

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

479

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

483

484

485

486

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

487

488

489 Figure 1

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

495

496

497 **Groups (patients in cohort)**

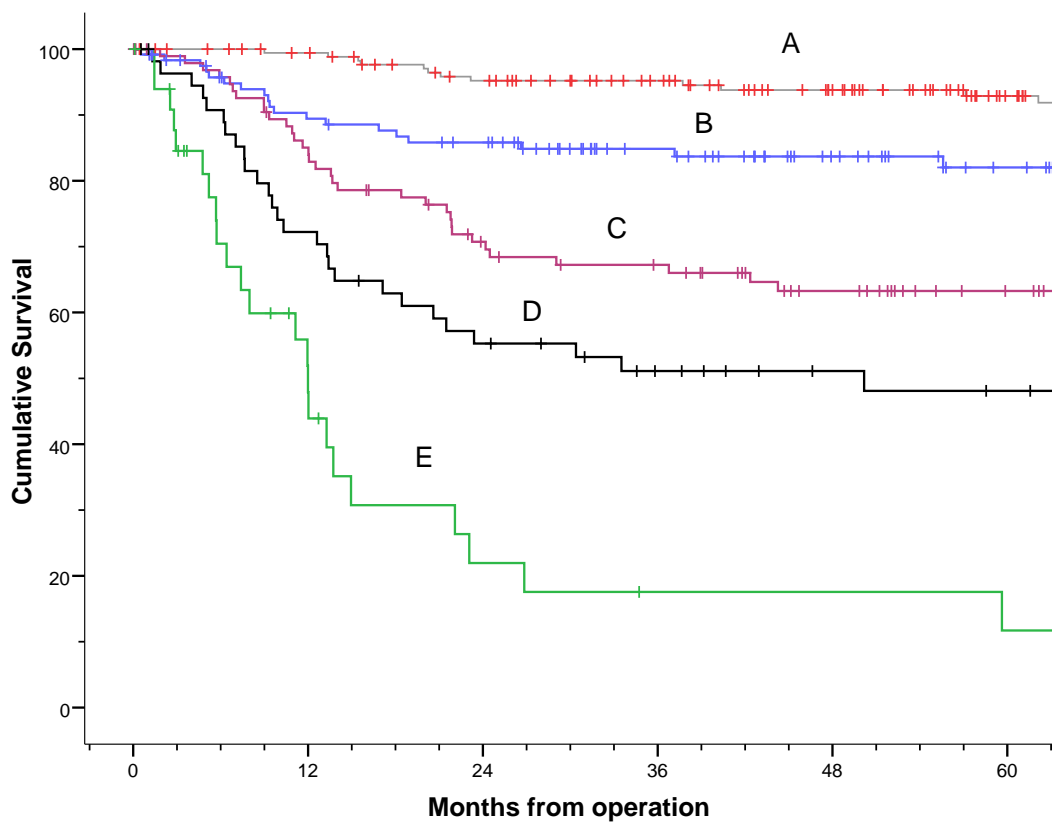
498 A (n=180): Clear Margins & pN0

499 B (n=122): Clear margins & pN1 OR close margins & pN0

500 C (n=97): Clear margins & pN2-3 OR close margins & pN1 OR involved margins & pN0

501 D (n=56): Close margins & pN2-3 OR involved margins & pN1

502 E (n=34): Involved margins & pN2-3



503

504

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888 ** A good summary of current knowledge

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