

Oral Cancer

Definition

The term “oral” includes the lips and all intra-oral sites corresponding to the ICD9 codes 140 (lip), 141 (tongue), 143 (gum), 144 (floor of mouth) and 145 (other non-specific sites), but excludes sites 142 (major salivary glands), 146 (oropharynx), 147 (nasopharynx), 148 (hypopharynx) and 149 (ill defined oral/oropharynx)¹. Approximately 90% of oral cancers are primary squamous cell carcinomas arising from the lining mucosa of the mouth, most commonly the tongue and the floor of the mouth.^{1; 2}

Incidence/prevalence

Oral cancer is the sixth most common cancer in the world and is largely preventable.^{3; 4} It accounts for approximately 4% of all cancers and 2% of all cancer deaths world-wide.⁵ In India it is the commonest malignant neoplasm, accounting for 20-30% of all cancers.⁶ Incidence rates show marked geographic variation with the Bas-Rhin region in France having the highest recorded incidence of oral cancer in the world. Approximately 30,000 persons in the US and 2000 persons in the UK develop oral cancer annually.^{2; 7} The mean UK annual incidence rate for both sexes is approximately 4.5:100,000.^{8; 9} Ninety five percent of patients with oral cancer are over 40 years of age at diagnosis, and the mean age at diagnosis is 60 years (males 63.5 years females 60.6 years) with a male: female ratio between 1.3:1 and 2:1.^{2; 10} After a steady decline since the turn of the century oral cancer incidence rates in the UK and US are now rising particularly in women.^{11 12-16} The incidence of oral cancer in young adults ranges between 0.4% and 3.6%.¹⁷ Between 10-30% of persons with primary oral cancer develop second primary tumours of the aerodigestive tract at a rate of 3.7% per year.^{18; 19} Metastases to the mouth are rare (1%).²⁰

Early signs and symptoms of oral cancer include persistent mouth ulcers (frequently painless), warty lumps and nodules, white, red, speckled or pigmented lesions, recent onset of difficulty with speaking or swallowing and enlarged neck nodes. Any new oral lesion that persists longer than 3-weeks should be referred for an urgent specialist opinion and possible biopsy.²¹ Adjunctive use of 1% Toulidine Blue mouthwash can assist in the identification of high-risk patients/lesions.²² Although up to 90% of oral lesions can be easily visualised²³ many changes may go unnoticed by both patient and practitioner. Approximately 6% of patients with oral cancer present with an enlarged cervical node as their only symptom.²⁴ All such neck lumps require fine needle aspiration cytological (FNAC) examination before formal excision is considered which in expert hands FNAC has diagnostic accuracy of over 94%.²⁵

Aetiology/risk factors

Globally, tobacco consumption in all its various forms (smoking, chewing & snuff dipping etc.) is the commonest aetiological risk factor for the subsequent development of oral cancer.²⁶⁻²⁸ In developing countries the use of tobacco and /or the areca (betel) nut produces chronic, potentially malignant lesions (leucoplakia, erythroplakia & submucous fibrosis) from which the majority of oral cancers arise.²⁹ Conversely, in developed countries, potentially malignant lesions are identifiable in only a minority of cases and the majority of oral cancers arise *de novo* from clinically normal mucosa. These cancers are more aggressive and have a poorer prognosis than those arising within areas of tobacco induced leucoplakia.^{1; 30} The malignant transformation rate of potentially malignant lesions is stated to vary between 3 and 6%,¹ although the actual rate may be as high as 15%³¹ especially for the nodular or speckled leucoplakias. The malignant transformation rate for untreated dysplastic potentially malignant lesions is 15.4% compared to 6.2% for those that are excised.³² In the Western world cigarette smoking is responsible for the majority of all tobacco related oral cancers. The risk of developing oral cancer is directly related to the intensity of tobacco usage^{33; 34} with heavy smokers (over 20 cigarettes or 5 cigars per day) having a six fold increased risk of developing the disease compared to non-smokers.³⁵ Quitting smoking for 10 years or more reduces the odds ratio for developing oral cancer almost to unity.³⁶ Oral cancer is rare in non-smokers.³⁷ Alcohol is an independent risk factor for oral cancer and also acts synergistically with tobacco in an additive or multiplicative fashion.²⁷ Heavy drinkers (>30 drinks per week) and heavy smokers have a relative risk for developing oral cancer 24

times greater than non-drinkers and non-smokers.³⁸ Approximately 15% of oral and oropharyngeal cancers can be attributed to dietary deficiencies or imbalances.³⁴ Frequent consumption of fresh fruit and vegetables reduces the risk (0.5-0.7) of developing oral and oropharyngeal cancer³⁹ and β -Carotene and vitamin E can produce regression of oral leucoplakia. Prolonged and heavy consumption of foods rich in nitrites and nitrosamines such as preserved meats and fish significantly increases lifetime risk for the development of oral cancer as may diets low in carotenoids.^{40; 41} Of the many viruses that are potential candidates for oral carcinogenesis there is little or no evidence at the present time for either the retroviruses, adenoviruses or the Epstein-Barr virus being involved either directly or indirectly.⁴² There are some data implicating Herpes simplex viruses (HSV) and the Human papillomaviruses (HPV) in the aetiology of oral cancer¹ although, if they do have an oncogenic role it is likely to be small.⁴³ Lower socio-economic status is positively linked with a higher incidence of oral cancer.⁴⁴ First degree relatives of persons with squamous cell carcinoma of the head and neck have a significantly increased relative risk (3.79) for developing head and neck cancer.¹⁹

Prognosis

Approximately 12,000 people in the US⁵ and 900 in the UK die of oral cancer each year.⁷ With a death:registration ratio of 0.45 it is a disease of high lethality, comparable to that of carcinoma of the cervix (0.48) and greater than that of malignant melanoma (0.38).¹ Large tumours with evidence of metastatic spread and tumours thicker than 4mm have a poorer prognosis than those that remain localised to the primary site or are less than 4mm thick.⁴⁵⁻⁴⁹ 5-year survival rates are over 80% for persons with early stage disease, over 40% for those with regional disease and less than 20% for patients with metastatic disease.^{2; 50} The status of the cervical nodes is the single most important prognostic indicator of survival for patients with oral cancer.⁵¹ The development of nodal metastases halves the 5-year survival rate.²⁵ Two recent studies have demonstrated that clinical examination of the neck is imprecise. There is a false negative rate of between 27% and 34%, and a false positive rate of between 31% and 40%.^{52; 53} Preoperative CT/MRI imaging may not improve the accuracy of clinical examination as many occult nodal metastases are only detectable by thorough post-resection histological examination.⁵³

Aims

Where treatment is with curative intent:

- To remove all known risk factors
- To improve survival
- To prevent local, regional and distant recurrence
- To maximise quality of life

Where treatment is with palliative intent:

- To remove all known risk factors
- To reduce tumour size
- To prevent fungation
- To maximise quality of life

Outcomes

Disease-free survival time

Quality of life

Summary Statement

We found few systematic reviews and RCT's that satisfied the inclusion criteria for this section and most of these were chemotherapy/radiotherapy trials. The majority of data on this subject, particularly concerning aetiology, diagnosis and surgical management are derived from observational studies often on small patient groups. However, we were able to find evidence supporting the following conclusions. Smoking and alcohol are the major risk factors for developing oral cancer the incidence of which is increasing, especially in females. Prognosis ultimately depends on the stage of disease at presentation. Large and/or thick tumours and cervical lymph node metastases are significant adverse prognostic indicators. National screening programs are unlikely to be of benefit but targeted screening of high-risk

populations would be. Surgery and radiotherapy are equally effective in treating early stage disease. Surgery plus postoperative radiotherapy produces better local control rates and disease-free survival times than surgery or radiotherapy alone in late stage disease. Adjuvant chemotherapy may decrease local recurrence rates and extend disease-free survival times. Regional nodal metastases should be treated by radical neck dissection. Elective neck dissections increase disease-free survival times for patients with T1/T2N0 disease especially for patients with thick tumours and those subsequently shown to have occult nodal metastases. Where there is no evidence for a survival advantage for one treatment modality over another, any differences in morbidity profiles and quality of life measures as well as patient preferences should be considered when discussing treatment options with patients and their relatives/carers. All patients with oral cancer should be managed by a multi-disciplinary team consisting of site-specialised surgeons, oncologists and paramedical support staff working in cancer centres or cancer units.⁵⁴

Benefits

Diagnosing oral cancer at an early stage is crucial to reducing morbidity and mortality.² Currently, there is a lack of evidence to support the introduction of a national screening programme.⁵⁵ Opportunistic and targeted screening of high risk groups could be expected to produce a health gain of 312 QALYs and save 15 lives for every 100,000 subjects screened.⁵⁵

Surgery, radiotherapy and chemotherapy either alone or in combination are the main treatment modalities. Cure rates are related to the adequacy of surgical excision. In stage 3 and 4 disease local failure rates increase from 39% to 73% where surgical margins are less than 5mm.⁵⁶ We found evidence that patients treated by surgery and postoperative radiotherapy have significantly longer disease-free survival times in comparison to patients treated by surgery alone (68% v 38% at 3 years $p < 0.005$)⁵⁷ as well as significantly longer overall survival times ($p = 0.001$, relative death rate = 0.24; 95% CI 0.01-0.59).^{58; 59} Patients with nodal disease should have a radical neck dissection. If multiple nodes are involved and/or there is evidence of extracapsular spread this should be followed by radiotherapy.^{60; 61}

The optimal management of patients without clinical evidence of nodal disease is more controversial. Diverse data exist which support radiotherapy alone, elective neck dissection as well as a “watch and wait” policy only treating nodes if and when they become clinically apparent.^{51; 61} We found evidence that for patients with T1/T2N0 disease elective neck dissection as opposed to therapeutic neck dissection results in improved disease-free survival times (72% v 49% at 3.5 years)⁴⁹ (64% v 47% at 22 months)⁶² (80.5% v 44.8% 5-year determinate, logrank 10.58, $p = 0.001$).⁶³ In addition, patients with occult cervical node metastases who receive an elective neck dissection have been shown to have disease-free survival times twice as long as those who undergo a subsequent therapeutic neck dissection.⁶² A US study found an overall determinate 5-year survival rate of 65% (82% for stages 1 and 2, 49% for stages 3 and 4) for patients with tongue carcinoma following the introduction of a treatment protocol comprising elective neck dissections for N0 disease and postoperative radiotherapy for inadequate resection margins, high stage disease, unfavourable histological factors or occult nodal disease.⁶⁰

For T1 and early T2 squamous cell carcinomas confined to the lining mucosa, surgery and radiotherapy alone offer an equal chance of cure.^{35; 64; 65} Large tumours are seldom eradicated by radiotherapy alone. Where radiotherapy is the sole treatment modality local control rates are 90% and 10% for T1 and T4 tumours respectively.⁶⁶ We found no evidence that tumour response to radiotherapy can be predicted by the severity of normal tissue reactions.⁶⁷

Improved local control rates have been demonstrated in patients where hyperfractionated^{68; 69} and continuous hyperfractionated accelerated radiation therapy (CHART) regimes have been used⁶⁵ although an earlier (1987) Phase 3 study failed to show any benefit for hyperfractionation over the standard schedule of 5 fractions per week and demonstrated increased acute normal tissue reactions in the hyperfractionation group.⁷⁰

Oral squamous cell carcinoma responds well to chemotherapy with combinations of cisplatin and 5-fluorouracil (5-FU) giving the best results (93% response rate and 54% complete remission rate).⁷¹ A 40-50% complete response rate is necessary before improved survival rates are seen.⁷² One RCT demonstrated postoperative chemotherapy (methotrexate, bleomycin and vincristine) resulted in a better survival rate than postoperative radiotherapy (65% v 29% at 3 years $p = 0.051$) for patients with T3NxM0 oral carcinoma.⁷³ Two recent RCT's have demonstrated improved disease-free survival times (87% v 45% $p < 0.04$ 12-48 months post treatment⁷⁴ 61% v 43% $p = 0.03$ 12-96 months post treatment)⁷⁵ in patients with T2-T3/N0-N2 oral cavity and tonsil carcinoma given carboplatin/5-FU prior to

surgery and radiotherapy. A prospective RCT demonstrated improved disease-free survival rates in patients receiving perioperative chemotherapy (methotrexate 50mg/m² on the 3rd, 10th and 17th postoperative day) compared to those who did not. Survival rates were 71% v 45% at 12 months (p<0.01)⁷⁶ and 61% v 37% at 24 months (p<0.01)⁷¹ in the chemotherapy patients and non-chemotherapy patients respectively. A significant reduction (p= 0.002) was observed in the local recurrence rate in the first 6 postoperative months.⁷¹ The randomised EORTC Head and Neck Co-operative Group reported an estimated median survival of 7 years in patients with floor of mouth cancer given preoperative vincristine and bleomycin compared to 3 years in those treated by surgery alone.⁷⁷ A metaanalysis of 51 published trials revealed a survival advantage if chemotherapy was used as a single agent synchronously with radiotherapy.⁷⁸ Three year survival rates of 79% and 2 year local recurrence rates of 15% have been reported in patients with advanced (T2-T4/N0-N3/M0) oral cavity carcinomas given simultaneous preoperative cisplatin radiochemotherapy.⁵⁸ We found evidence suggesting that adjuvant immunotherapy does not reduce recurrence rates or improve survival in patients with oral cancer.⁷⁹⁻⁸²

Quality of life following treatment for oral cancer is of paramount importance to the patient and their relatives/carers and provides an important and objective measurement of outcome.⁸³ We found evidence for a trend 12 months post-treatment for improved quality of life scores in females rather than males, patients presenting with early stage disease with anterior tumours where primary closure or laser treatment was employed rather than late stage disease requiring flap reconstruction and in patients who did not receive radiotherapy.⁸⁴ An RCT comparing radical surgery with radiotherapy found that both treatments resulted in similar swallowing problems but fewer primary radiation patients had articulation difficulties.⁸⁵

Harms

a) Surgery

(i) Morbidity and mortality common to all major operations

(ii) Procedure specific morbidity and mortality⁸⁶

Thoracic duct fistulae occur following 1-2% of radical neck dissections (mainly left sided).⁸⁷ The majority dry up if managed conservatively following dietary manipulation using medium chain triglycerides and/or TPN.⁸⁸ Surgical exploration is reserved for persistent (>30 days) high volume leaks that fail to respond to conservative measures.⁸⁹

Flap failure rates vary between 4% and 7% .^{90; 91}

Oro-cutaneous fistulae following flap failure and/or wound breakdown occurs in approximately 4% of cases.⁹²

Dysphagia Over 25% of patients experience difficulty in swallowing following major head and neck resections.⁹³ T4 lesions, extensive removal of the tongue base, removal of the geniohyoid and mylohyoid muscles, and removal of the lateral pharyngeal wall are significantly related to poor swallowing function.⁹⁴ Swallowing difficulties can be minimised by adequate and appropriate reconstructive procedures and the use of fine bore nasogastric and/or gastrostomy feeding tubes.⁹⁵

b) Radiotherapy/Chemotherapy

Post-treatment morbidity is common. The morbidity attendant to cure by radiotherapy includes at least one significant complication of bone or soft tissue in between 40% and 70% of patients with oral/oropharyngeal carcinoma.⁹⁶ Following radiotherapy patients with oral cancer, especially of the soft palate, are at increased and constant actuarial risk of developing a second head and neck cancer at the rate of 2.7% per year of observation.⁹⁷

Mucositis Radiation mucositis is characterised by erythema, pseudomembranes, and ulceration of mucosa in the irradiated field and is the commonest and frequently the most distressing adverse effect of radiotherapy in this patient group.^{98; 99} When severe it may force treatment breaks and limit the total radiotherapy/chemotherapy dose that can be delivered thereby adversely affecting prognosis.¹⁰⁰ The basis of management is avoidance of irritants including smoking and alcohol, pain relief, prevention of dehydration and adequate nutrition. There is little evidence that most antiseptic mouthwashes and anti-ulcer agents are effective. Simple mechanical cleansing by saline is the most effective traditional measure.^{100; 101}

Xerostomia Salivary flow from irradiated salivary glands diminishes a few days after starting radiotherapy, ceases after 5-weeks and never fully recovers.¹⁰² Xerostomia interferes with speech, mastication, taste and swallowing, increases oral pain and the risk of dental decay.⁶¹ Saliva substitutes offer symptomatic though short-lived relief.¹⁰³ We found evidence that administration of oral Pilocarpine significantly reduces the severity of post-irradiation oral xerostomia compared to saliva substitutes and placebo.¹⁰⁴ Several double-blind, placebo-controlled trials have demonstrated significantly higher salivary flows and reduction in xerostomia-associated symptoms including problems with chewing, speaking and swallowing in patients taking oral Pilocarpine in doses between 2.5mg and 10mg three times daily versus placebo following irradiation (>40cGy) to the head and neck.¹⁰⁵⁻¹⁰⁷ Enhanced Pilocarpine efficacy has been shown if therapy is commenced during radiotherapy.^{108; 109}

Dental caries particularly adjacent to the amelocemental junction of mandibular teeth (radiation caries) occurs secondary to post-irradiation xerostomia.¹¹⁰ Caries rates can be minimised by meticulous oral hygiene and professional dental care. Chlorhexidine gluconate is an effective commercially available antibacterial. Patients should be encouraged to use 5ml of a diluted 0.2% solution morning and night and after each meal.²⁵ One RCT demonstrated a 38% reduction in dental caries following the daily application of a 1% sodium fluoride gel.¹¹¹ Patients (dentate and edentulous) require frequent (at least twice yearly) dental examinations.

Osteoradionecrosis of the jaws is caused by radiation-induced hypoxia, hypocellularity and hypovascularity and is dose and volume dependent.¹¹²⁻¹¹⁴ It occurs in 2%-20% of patients, and is 3 times more common in dentate than edentulous patients.¹¹⁵⁻¹¹⁷ We found evidence for an increased incidence of osteoradionecrosis following dental extractions but conflicting evidence as to the optimal timing of extractions (pre or post-radiotherapy).¹¹⁶ Meticulous oral/dental care¹¹¹ and possibly oral tetracycline prophylaxis for dental extractions¹¹⁸ reduces the incidence of osteoradionecrosis. We found evidence for the efficacy of both hyperbaric oxygen¹¹⁹ and ultrasound in the management of established osteoradionecrosis.^{115; 120}

Reference List

1. Johnson NW, Ranasinghe AW, Warnakulasuriya KAA. Epidemiology of oral cancer in the United Kingdom. *Community Dental Health* 1993;**10 (Suppl 1)**:13-29.
2. Park BZ, Kohn WG, Malvitz DM. Preventing and controlling oral and pharyngeal cancer - recommendations from a national strategic planning conference. *Morbidity & Mortality Weekly Report* 1998;**47**:1-12.
3. Parkin SM, Laara E, Muir CS. Estimates of the worldwide frequency of sixteen major cancers. *International Journal of Cancer* 1988;**41**:184-197.
4. Raubenheimer EJ, De Villiers PIA. Clinical manifestations of oral precancer and cancer. *Journal of the Dental Association of South Africa* 1989;11-14.
5. Boring CC, Squires TS, Tong T. Cancer Statistics, 1993. *Californian Journal of Clinical Cancer* 1993;**43**:7-26.

6. Nair UJ, Friesen M, Richard I, MacClennan R, Thomas S, Bartsch H. Effect of lime composition on the formation of reactive oxygen species from the areca nut extract in vitro. *Carcinogenesis* 1990;**11**:2145-2148.
7. Johnson NW, Warnakulasuriya KAA. Oral Cancer: Is it more common than cervical? *British Dental Journal* 1991;**170**:170-171.
8. Blot, W. J., Devesa, S. S., McLaughlin, J. K., and Fraumeni Jr, J. F. Oral and pharyngeal cancers. 1994. Cold Spring Harbor, CSHL Press.
9. Waterhouse, J., Muir, C., and Correa, P. Cancer incidence in five continents. 1976. Lyon, IARC Scientific Publications.
10. Langdon JD, Harvey PW, Johnson NW, Patel MF. Oral cancer: the behaviour and response to treatment of 194 cases. *Journal of Maxillofacial Surgery* 1977;**5**:221-237.
11. Binnie, W. H., Cawson, R. A., Hill, G. B., and Soaper, A. E. Oral Cancer Incidence in England and Wales. A national study of morbidity, mortality, curability and related factors. 1972. London, HMSO.
12. Devesa SS, Silverman DT, Young Jr JL, et al. Cancer incidence and mortality trends among whites in the United States, 1947-84. *Journal of the National Cancer Institute* 1987;**79**:701-770.
13. Hindle I, Nally F. Oral cancer: a comparative study between 1962-67 and 1980-84 in England and Wales. *British Dental Journal* 1991;**170**:15-20.
14. Hindle I, Downer MC, Speight PM. The epidemiology of oral cancer. *British Journal of Oral and Maxillofacial Surgery* 1996;**34**:471-476.
15. Worrall SF. Oral cancer incidence between 1971 and 1989. *British Journal of Oral and Maxillofacial Surgery* 1995;**33**:195
16. Zakrzewska JM. Oral cancer and precancer - our responsibility. *British Dental Journal* 1994;**176**:286-287.
17. Friedlander PL, Schantz SP, Shaha AR, Yu G, Shah JP. Squamous cell carcinoma of the tongue in young patients: a matched-pair analysis. *Head & Neck* 1988;**20**:363-368.
18. Day GL, Blot WJ. Second primary tumours in patients with oral cancer. *Cancer* 1992;**70**:14-19.
19. Foulkes WD, Brunet J-S, Sieh W, Black MJ, Shenouda G, Narod SA. Familial risks of squamous cell carcinoma of the head and neck: retrospective case control study. *Cancer* 1996;**313**:716-721.
20. Smith CJ. Epidemiology and aetiology. In: Langdon JD, Henk JM, eds. *Malignant Tumours of the Mouth Jaws, and Salivary Glands*. London: Edward Arnold, 1995;1-13.
21. British Association of Oral and Maxillofacial Surgeons. Oral cancer: a professional guide for doctors, dentists, nurses and pharmacists. 1995.
22. Johnson N. Diagnosing oral cancer: can Toluidine Blue mouthwash help? *FDI World* 1998;**2**:22-27.

23. Smart CR. Screening for cancer of the aerodigestive tract. *Cancer Supplement* 1993;**72**:1060-1065.
24. Clark A. Oral cancer prevention and early detection. *Nursing Standard* 1999;**13**:43-47.
25. Langdon JD, Henk JM. *Malignant Tumours of the Mouth, Jaws and Salivary Glands*. London: Edward Arnold, 1995;1-278
26. Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Research* 1988;**48**:3282-3287.
27. Elwood JM, Pearson JCG, Skippen DH, Jackson SM. Alcohol, smoking, social and occupational factors in the aetiology of cancer of the oral cavity, pharynx and larynx. *International Journal of Cancer* 1984;**34**:603-612.
28. International Agency for Research on Cancer. Tobacco habits other than smoking, betel quid and areca-nut chewing; and some related nitrosamines. 1985. Lyon, IARC.
29. Daftary DK, Murti PR, Bhonsle RB, Gupta PC, Mehta FS, Pindborg JJ. *Oral precancerous lesions and conditions of tropical interest*. Oxford: Oxford Medical Publications, 1992;
30. Langdon JD. Epidemiology and Aetiology. In: Henk JM, Langdon JD, eds. *Malignant Tumours of the Oral Cavity*. London: Edward Arnold, 1985;1-13.
31. Tradati N, Grigolat R, Calabrese L, et al. Oral leukoplakias: to treat or not? *Oral Oncology* 1997;**33**:317-321.
32. Lumerman H, Freedman P, Kerpel S. Oral epithelial dysplasia and the development of invasive squamous cell carcinoma. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, & Endodontics* 1995;**79**:321-329.
33. Graham S, Dayal H, Rohrer T. Dentition, diet, tobacco and alcohol in the epidemiology of oral cancer. *Journal of the National Cancer Institute* 1977;**59**:1611-1618.
34. La Vecchia C, Tavani A, Franceschi S, Levi F, Corrao G, Negri E. Epidemiology and prevention of oral cancer. *Oral Oncology* 1997;**33**:302-312.
35. Cawson RA, Langdon JD, Eveson JW. *Surgical Pathology of the Mouth and Jaws*. Oxford: Wright, 1996;
36. Franceschi S, Talameni R, Barra S, et al. Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx and esophagus in Northern Italy. *Cancer Research* 1990;**50**:6507
37. Lemon FR, Walden RT, Woods RW. Cancer of the lung and mouth in Seventh Day Adventists. Preliminary report on a population study. *Cancer* 1964;**17**:1891-1896.
38. McCoy GD, Wynder EL. Etiological and preventive implications in alcoholic carcinogens. *Cancer Research* 1979;**39**:2844-2850.
39. La Vecchia C, Franceschi S, Levi F, Negri E. Diet and human oral carcinoma in Europe. *Oral Oncology, European Journal of Cancer* 1993;**29B**:17-22.

40. Johnson NW, Warnakulasuriya KAA, Tavassoli M. Hereditary and environmental risk factors; clinical and laboratory risk markers for head and neck, especially oral cancer and precancer. *European Journal of Cancer Prevention* 1996;**5**:5-17.
41. Garewal HS, Schantz S. Emerging role of B-Carotene and antioxidant nutrients in prevention of oral cancer. *Archives of Otolaryngology and Head and Neck Surgery* 1995;**121**:141-144.
42. Cox MF, Scully C, Maitland N. Viruses in the aetiology of oral carcinoma? Examination of the evidence. *British Journal of Oral and Maxillofacial Surgery* 1991;**29**:381-387.
43. Scully C, Maitland N. Papillomaviruses: their possible role in oral disease. *Oral Surgery* 1985;**59**:166-174.
44. Graham S, Levin M, Lilienfield A. The socio-economic distribution of cancer at various sites in Buffalo, N.Y., 1948-1952. *Cancer* 1960;**13**:180-191.
45. Hibbert J, Marks NJ, Winter PJ, Shaheen OH. Prognostic factors in oral squamous cell carcinoma and their relation to clinical staging. *Clinics in Otolaryngology* 1983;**8**:197-203.
46. Davis RK. Prognostic variables in head and neck cancer - tumour site, stage, nodal status, differentiation, and immune status. *Otolaryngology Clinics of North America* 1985;**18**:411-419.
47. Fakhri AR, Rao RS, Borges AM, Patel AR. Elective versus therapeutic neck dissection in early carcinoma of the oral tongue. *American Journal of Surgery* 1989;**158**:309-313.
48. Zatterstrom UK, Wennerberg J, Ewers S-B, Willen R, Attewell R. Prognostic factors in head and neck cancer: histological grading, DNA ploidy and nodal status. *Head & Neck* 1991; **13**:477-487.
49. Kligerman J, Lima RA, Soares JR, et al. Supraomohyoid neck dissection in the treatment of T1/T2 squamous cell carcinoma of oral cavity. *American Journal of Surgery* 1994;**168**:391-394.
50. Beenken SW, Krontiras H, Maddox WA, Peters GE, Soong S, Urist MM. T1 and T2 squamous cell carcinoma of the oral tongue: prognostic factors and the role of elective lymph node dissection. *Head & Neck* 1999;**21**:124-130.
51. Persky MS, Lagmay VM. Treatment of the clinically negative neck in oral squamous cell carcinoma. *Laryngoscope* 1999;**109**:1160-1164.
52. Shah J, Candela FC, Poddar AK. The patterns of cervical lymph node metastases from squamous carcinoma of the oral cavity. *Cancer* 1990;**66**:109-113.
53. Woolgar JA, Scott J, Vaughan ED, Brown JS. Pathological findings in clinically false-negative and false positive neck dissections for oral carcinoma. *Annals of the Royal College of Surgeons of England* 1994;**76**:237-244.
54. Calman, K. and Hine, D. A Policy Framework for Commissioning Cancer Services. 1-33. 1995. Department of Health.
55. Downer MC, Jullien JA, Speight PM. An interim determination of health gain from oral cancer and precancer screening: 3. Preselecting high risk individuals. *Community Dental Health* 1998;**15**:72-76.

56. Looser KG, Shah JP, Strong EW. The significance of 'positive' margins in surgically resected epidermoid carcinomas. *Head and Neck Surgery* 1978;**1**:107-111.
57. Mishra RC, Singh DN, Mishra TK. Post-operative radiotherapy in carcinoma of buccal mucosa, a prospective randomized trial. *European Journal of Surgical Oncology* 1996;**22**:502-504.
58. Muller RP, Staar S, Samek M, Pape HD. Simultaneous preoperative radiochemotherapy with cisplatin in advanced oral cavity carcinomas: acute response and follow-up. *Recent Results in Cancer Research* 1994;**134**:165-172.
59. Robertson AG, Soutar DS, Paul J, et al. Early closure of a randomized trial: surgery and postoperative radiotherapy versus radiotherapy in the management of intra-oral tumours. *Clinical Oncology (Royal College of Radiologists)* 1998;**10**:155-160.
60. Franceschi D, Gupta R, Spiro RH, Shah JP. Improved Survival in the Treatment of Squamous Carcinoma of the Oral Tongue. *The American Journal of Surgery* 1993;**166**:360-365.
61. Soutar DS, Taggart I. Surgery. In: Langdon JD, Henk JM, eds. *Malignant tumours of the mouth, jaws and salivary glands*. London: Edward Arnold, 1995;67-101.
62. Fakhri AR, Rao RS, Patel AR. Prophylactic neck dissection in squamous cell carcinoma of oral tongue: a prospective randomized study. *Seminars in Surgical Oncology* 1989;**5**:327-330.
63. Haddadin KJ, Soutar DS, Oliver RJ, Webster MH, Robertson AG, MacDonald DG. Improved survival for patients with clinically T1/T2, N0 tongue tumors undergoing a prophylactic neck dissection. *Head & Neck* 1999;**21**:517-525.
64. Hintz B, Charyulu K, Chandler JR, Sudarsanam A, Garciga C. Randomized study of local control and survival following radical surgery or radiation therapy in oral and laryngeal carcinomas. *Journal of Surgical Oncology* 1979;**12**:61-74.
65. Goodchild K, Hoskin P, Dische S, Pigott K, Powell M, Saunders M. A feasibility study of continuous hyperfractionated accelerated radiotherapy (CHART) and brachytherapy in patients with early oral or oropharyngeal carcinomas. *Radiotherapy & Oncology* 1999;**50**:29-31.
66. Henk JM, Langdon JD. Radiotherapy. In: Langdon JD, Henk JM, eds. *Malignant tumours of the mouth, jaws and salivary glands*. London: Edward Arnold, 1995;102-122.
67. Bernier J, Thames HD, Smith CD, Horiot JC. Tumor response, mucosal reactions and late effects after conventional and hyperfractionated radiotherapy. *Radiother Oncol* 1998;**47**:137-143.
68. Horiot JC, leFur R, N'Guyen C, et al. Hyperfractionation compared with conventional radiotherapy in oropharyngeal cancer - an EORTC randomised trial. *European Journal of Cancer Prevention* 1990;**26**:779-780.
69. Cox JD, Pajak TF, Marcial VA, et al. Dose-response for local control with hyperfractionated radiation therapy in advanced carcinomas of the upper aerodigestive tracts: preliminary report of radiation therapy oncology group protocol 83-13. *International Journal of Radiation Oncology, Biology, Physics* 1990;**18**:515-521.
70. Marcial VA, Pajak TF, Chang C, Tupchong L, Stetz J. Hyperfractionated photon radiation therapy in the treatment of advanced squamous cell carcinoma of the oral cavity,

pharynx, larynx, and sinuses, using radiation therapy as the only planned modality: (preliminary report) by the Radiation Therapy Oncology Group (RTOG). *International Journal of Radiation Oncology, Biology, Physics* 1987;**13**:41-47.

71. Rao RS, Parikh DM, Parikh HK, Bhansali MB, Deshmane VH, Fakhri AR. Perioperative chemotherapy in patients with oral cancer. *American Journal of Surgery* 1994;**168**:262-267.
72. Frei III E, Clark JR, Fallon BG. Guidelines, regulations and clinical research. *Journal of Clinical Oncology* 1986;**4**:1026-1030.
73. Bitter K. Postoperative chemotherapy versus postoperative cobalt 60 radiation in patients with advanced oral carcinoma. Report on a randomized study. *Head & Neck Surgery* 1981;**3**:264
74. Volling P, Schroder M. Preliminary results of a prospective randomized study of primary chemotherapy in carcinoma of the oral cavity and pharynx. *HNO* 1995;**43**:58-64.
75. Volling P, Schroder M, Eckel H, Ebeling O, Stennert E. Results of a prospective randomized trial with induction chemotherapy for cancer of the oral cavity and tonsils. *HNO* 1999;**47**:899-906.
76. Rao RS, Parikh DM, Parikh HK, Bhansali MB, Fakhri AR. Perioperative chemotherapy in oral cancer. *Journal of Surgical Oncology* 1991;**47**:21-26.
77. Richard JM, Kramar A, Molinari R, et al. Randomised EORTC head and neck cooperative group trial of preoperative intra-arterial chemotherapy in oral cavity and oropharynx carcinoma. *European Journal of Cancer* 1991;**27**:821-827.
78. Munro AJ. An overview of randomised controlled trials of adjuvant chemotherapy in head and neck cancer. *British Journal of Cancer* 1995;**71**:83-91.
79. Szpirglas H, Chastang C, Bertrand JC. Adjuvant treatment of tongue and floor of the mouth cancers. *Recent Results in Cancer Research* 1978;**68**:309-317.
80. Szpirglas H, Chastang C, Bertrand JC. Adjuvant treatment of tongue and floor of the mouth cancers. *Recent Results in Cancer Research* 1979;309-317.
81. Neifeld JP, Terz JJ, Kaplan AM, Lawrence WJr. Adjuvant *Corynebacterium parvum* immunotherapy for squamous cell epitheliomas of the oral cavity, pharynx, and larynx. *Journal of Surgical Oncology* 1985;**28**:137-145.
82. Padmanabhan TK, Balaram P, Vasudevan DM. Role of levamisole immunotherapy as an adjuvant to radiotherapy in oral cancer. I. A three-year clinical follow up. *Neoplasma* 1987;**34**:627-632.
83. Rogers SN, Fisher SE, Woolgar JA. A review of quality of life assessment in oral cancer. *International Journal of Oral & Maxillofacial Surgery* 1999;**28**:99-117.
84. Rogers SN, Lowe D, Brown JS, Vaughan ED. The University of Washington head and neck cancer measure as a predictor of outcome following primary surgery for oral cancer. *Head & Neck* 1999;**21**:394-401.
85. Hintz B, Charyulu K, Chandler JR, Sudarsanam A, Garciga C. Randomized study of local control and survival following radical surgery or radiation therapy in oral and laryngeal carcinomas. *Journal of Surgical Oncology* 1979;**12**:61-74.

86. McGregor IA, McGregor FM. General Management and Complications. In: McGregor IA, McGregor FM, eds. *Cancer of the Face and Mouth*. Edinburgh: Churchill Livingstone, 1986;321-340.
87. Crumley RL, Smith JD. Postoperative chylous fistula prevention and management. *Laryngoscope* 1976;**86**:804-813.
88. Lucente FE, Diktaban T, Lawson W, Biller HF. Chyle fistula management. *Otolaryngology - Head & Neck Surgery* 1981;**89**:575-578.
89. de Gier HH, Balm AJ, Bruning PF, Gregor RT, Hilgers FJ. Systematic approach to the treatment of chylous leakage after neck dissection. *Head & Neck* 1996;**18**:347-351.
90. Bhatena HM, Savant DN, Kavarana NM, Parikh DM, Sanghvi VD. Reconstruction with different free flaps in oro-facial cancer patients. *Acta Chirurgiae Plasticae* 1996;**38**:43-49.
91. Ord RA. The pectoralis major myocutaneous flap in oral and maxillofacial reconstruction: a retrospective analysis of 50 cases. *Journal of Oral & Maxillofacial Surgery* 1996;**54**:1292-1295.
92. O'Brien CJ, Lee KK, Stern HS, et al. Evaluation of 250 free-flap reconstructions after resection of tumours of the head and neck. *Australian & New Zealand Journal of Surgery* 1998;**68**:698-701.
93. Vaughan ED. An analysis of morbidity following major head and neck surgery with particular reference to mouth function. *Journal of Maxillofacial Surgery* 1982;**10**:129-134.
94. Hirano M, Kuroiwa Y, Tanaka S, Matsuoka H, Sato K, Yoshida T. Dysphagia following various degrees of surgical resection for oral cancer. *Annals of Otolaryngology, Rhinology & Laryngology* 1992;**101**:138-141.
95. Langton SG, Bradley PF. The management of dysphagia after surgery for oral malignancy. *British Journal of Oral & Maxillofacial Surgery* 1992;**30**:8-13.
96. Larson DL, Lindberg RD, Lane E, Goepfert H. Major complications of radiotherapy in cancer of the oral cavity and oropharynx. A 10 year retrospective study. *American Journal of Surgery* 1983;**146**:531-536.
97. Fijuth J, Mazon JJ, Le Pechoux C, et al. Second head and neck cancers following radiation therapy of T1 and T2 cancers of the oral cavity and oropharynx. *International Journal of Radiation Oncology, Biology, Physics* 1992;**24**:59-64.
98. Epstein JB, Van der Meij EH. Complicating mucosal reactions in patients receiving radiation therapy for head and neck cancer. *Special Care in Dentistry* 1997;**17**:88-93.
99. Scully C, Epstein JB. Oral health care for the cancer patient. *European Journal of Cancer* 1996;
Part B, Oral Oncology. 32B:281-292.
100. Symonds RP. Treatment-induced mucositis: an old problem with new remedies. *British Journal of Cancer* 1998;**77**:1689-1695.
101. Verdi CJ. Cancer therapy and oral mucositis. An appraisal of drug prophylaxis. *Drug Safety* 1993;**9**:185-195.

102. Mira JG, Westcott WB, Starcke EN, Shannon IL. Some factors influencing salivary function when treating with radiotherapy. *International Journal of Radiation Oncology, Biology, Physics* 1981;**7**:535-541.
103. Shannon IL, McGarry BR, Starcke EN. A saliva substitute for use by xerostomic patients undergoing radiotherapy to the head and neck. *Oral Surgery* 1977;**44**:656-661.
104. Davies AN, Singer J. A comparison of artificial saliva and pilocarpine in radiation-induced xerostomia. *Journal of Laryngology & Otology* 1994;**108**:663-665.
105. Davies AN, Daniels C, Pugh R, Sharma K. A comparison of artificial saliva and pilocarpine in the management of xerostomia in patients with advanced cancer. *Palliative Medicine* 1998;**12**:105-111.
106. Johnson JT, Ferretti GA, Nethery WJ, et al. Oral pilocarpine for post-irradiation xerostomia in patients with head and neck cancer. *New England Journal of Medicine* 1993;**329**:390-395.
107. LeVeque FG, Montgomery M, Potter D, et al. A multicenter, randomized, double-blind, placebo-controlled, dose-titration study of oral pilocarpine for treatment of radiation-induced xerostomia in head and neck cancer patients. *Journal of Clinical Oncology* 1993;**11**:1124-1131.
108. Taylor SE, Miller EG. Preemptive pharmacologic intervention in radiation-induced salivary dysfunction. *Proceedings of the Society for Experimental Biology & Medicine* 1999;**221**:14-26.
109. Valdez IH, Wolff A, Atkinson JC, Macynski AA, Fox PC. Use of pilocarpine during head and neck radiation therapy to reduce xerostomia and salivary dysfunction. *Cancer* 1993;**71**:1848-1851.
110. Garg AK, Malo M. Manifestations and treatment of xerostomia and associated oral effects secondary to head and neck radiation therapy. *Journal of the American Dental Association* 1997;**128**:1128-1133.
111. Daly TE, Drane JB, MacComb WS. Management of problems of the teeth and jaws in patients undergoing irradiation. *American Journal of Surgery* 1972;**124**:539-542.
112. Bedwinek JM, Shukovsky LJ, Fletcher GH, Daly TE. Osteonecrosis in patients treated with definitive radiotherapy for squamous cell carcinoma of the oral cavity and naso and oropharynx. *Radiology* 1976;**119**:665-667.
113. Beumer J, Harrison R, Sanders B, Kurrasch M. Preradiation dental extractions and the incidence of bone necrosis. *Head & Neck Surgery* 1983;**5**:514-521.
114. Marx RE. Osteoradionecrosis: A new concept of its physiology. *Journal of Oral and Maxillofacial Surgery* 1983;**41**:283-288.
115. Harris M. The conservative management of osteoradionecrosis of the mandible with ultrasound therapy. *British Journal of Oral & Maxillofacial Surgery* 1992;**30**:313-318.
116. Morton ME. Osteoradionecrosis: a study of the incidence in the North West of England. *British Journal of Oral & Maxillofacial Surgery* 1986;**24**:323-331.

117. Murray CG, Herson J, Daly TE, Zimmerman S. Radiation necrosis of the mandible: a 10-year study. Part 1, factors influencing the onset of necrosis. *International Journal of Radiation Oncology, Biology, Physics* 1980;**6**:543-548.
118. Alexander R, Elzay RP, Dettman P, King ER. Tetracyclines for controlling osteoradionecrosis in rat mandibles. *Journal of Oral Surgery* 1967;**25**:503
119. Marx RE. A new concept in the treatment of osteoradionecrosis. *Journal of Oral and Maxillofacial Surgery* 1983;**41**:351-357.
120. Reher P, Doan N, Bradnock B, Meghji S, Harris M. Therapeutic ultrasound for osteoradionecrosis: an in vitro comparison between 1 Mhz and 454kHz machines. *European Journal of Cancer* 1998;**34**:1962-1968.