

# Oral Cancer

## Advanced Information for Patients and Carers

### 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)<sup>1</sup>. 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.<sup>1:2</sup>

### Incidence/prevalence

Oral cancer is the sixth most common cancer in the world and is largely preventable.<sup>3:4</sup> It accounts for approximately 4% of all cancers and 2% of all cancer deaths world-wide.<sup>5</sup> In India it is the commonest malignant neoplasm, accounting for 20-30% of all cancers.<sup>6</sup> 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.<sup>2:7</sup> The mean UK annual incidence rate for both sexes is approximately 4.5:100,000.<sup>8:9</sup> 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.<sup>2:10</sup> 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.<sup>11 12-16</sup> The incidence of oral cancer in young adults ranges between 0.4% and 3.6%.<sup>17</sup> 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.<sup>18:19</sup> Metastases to the mouth are rare (1%).<sup>20</sup>

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.<sup>21</sup> Adjunctive use of 1% Toulidine Blue mouthwash can assist in the identification of high-risk patients/lesions.<sup>22</sup> Although up to 90% of oral lesions can be easily visualised<sup>23</sup> 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.<sup>24</sup> 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%.<sup>25</sup>

### 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.<sup>26-28</sup> 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.<sup>29</sup> 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.<sup>1:30</sup> The malignant transformation rate of potentially malignant lesions is stated to vary between 3 and 6%,<sup>1</sup> although the actual rate may be as high as 15%<sup>31</sup> 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.<sup>32</sup> 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<sup>33:34</sup> 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.<sup>35</sup> Quitting smoking for 10 years or more reduces the odds ratio for developing oral cancer almost to unity.<sup>36</sup> Oral cancer is rare in non-smokers.<sup>37</sup> Alcohol is an independent risk factor for oral cancer and also acts synergistically with tobacco in an additive or multiplicative fashion.<sup>27</sup> 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.<sup>38</sup> Approximately 15% of oral and oropharyngeal cancers can be attributed to dietary deficiencies or imbalances.<sup>34</sup> Frequent consumption of fresh fruit and vegetables reduces the risk (0.5-0.7) of developing oral and oropharyngeal cancer<sup>39</sup> and  $\beta$ -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.<sup>40:41</sup> 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.<sup>42</sup> There are some data implicating Herpes simplex viruses (HSV) and the Human papillomaviruses (HPV) in the aetiology of oral cancer<sup>1</sup> although, if they do have an oncogenic role it is likely to be small.<sup>43</sup> Lower socio-economic status is positively linked with a higher incidence of oral cancer.<sup>44</sup> 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.<sup>19</sup>

## Prognosis

Approximately 12,000 people in the US<sup>5</sup> and 900 in the UK die of oral cancer each year.<sup>7</sup> 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).<sup>1</sup> 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.<sup>45-49</sup> 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.<sup>2;50</sup> The status of the cervical nodes is the single most important prognostic indicator of survival for patients with oral cancer.<sup>51</sup> The development of nodal metastases halves the 5-year survival rate.<sup>25</sup> 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%.<sup>52;53</sup> 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.<sup>53</sup>

## Summary Statement

There are 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.<sup>54</sup>

## Benefits

Diagnosing oral cancer at an early stage is crucial to reducing morbidity and mortality.<sup>2</sup> Currently, there is a lack of evidence to support the introduction of a national screening programme.<sup>55</sup> 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.<sup>55</sup>

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.<sup>56</sup> There is 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  $p < 0.005$ )<sup>57</sup> as well as significantly longer overall survival times ( $p = 0.001$ , relative death rate = 0.24; 95% CI 0.01-0.59).<sup>58;59</sup> 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.<sup>60;61</sup>

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.<sup>51; 61</sup> There is 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)<sup>49</sup> (64% v 47% at 22 months)<sup>62</sup> (80.5% v 44.8% 5-year determinate, logrank 10.58, p=0.001).<sup>63</sup> 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.<sup>62</sup> 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.<sup>60</sup>

For T1 and early T2 squamous cell carcinomas confined to the lining mucosa, surgery and radiotherapy alone offer an equal chance of cure.<sup>35; 64; 65</sup> 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.<sup>66</sup> There is no evidence that tumour response to radiotherapy can be predicted by the severity of normal tissue reactions.<sup>67</sup>

Improved local control rates have been demonstrated in patients where hyperfractionated<sup>68; 69</sup> and continuous hyperfractionated accelerated radiation therapy (CHART) regimes have been used<sup>65</sup> 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.<sup>70</sup>

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).<sup>71</sup> A 40-50% complete response rate is necessary before improved survival rates are seen.<sup>72</sup> 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.<sup>73</sup> Two recent RCT's have demonstrated improved disease-free survival times (87% v 45% p<0.04 12-48 months post treatment<sup>74</sup> 61% v 43% p=0.03 12-96 months post treatment)<sup>75</sup> 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/m<sup>2</sup> on the 3<sup>rd</sup>, 10<sup>th</sup> and 17<sup>th</sup> postoperative day) compared to those who did not. Survival rates were 71% v 45% at 12 months (p<0.01)<sup>76</sup> and 61% v 37% at 24 months (p<0.01)<sup>71</sup> 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.<sup>71</sup> 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.<sup>77</sup> A metaanalysis of 51 published trials revealed a survival advantage if chemotherapy was used as a single agent synchronously with radiotherapy.<sup>78</sup> 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.<sup>58</sup> There is evidence suggesting that adjuvant immunotherapy does not reduce recurrence rates or improve survival in patients with oral cancer.<sup>79-82</sup>

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.<sup>83</sup> There is 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.<sup>84</sup> An RCT comparing radical surgery with radiotherapy found that both treatments resulted in similar swallowing problems but fewer primary radiation patients had articulation difficulties.<sup>85</sup>

## Harms

### a) Surgery

#### (i) Morbidity and mortality common to all major operations

#### (ii) Procedure specific morbidity and mortality<sup>86</sup>

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

**Flap failure** rates vary between 4% and 7%.<sup>90; 91</sup>

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

**Dysphagia** Over 25% of patients experience difficulty in swallowing following major head and neck resections.<sup>93</sup> 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.<sup>94</sup> Swallowing difficulties can be minimised by adequate and appropriate reconstructive procedures and the use of fine bore nasogastric and/or gastrostomy feeding tubes.<sup>95</sup>

### 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.<sup>96</sup> 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.<sup>97</sup>

**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.<sup>98; 99</sup> When severe it may force treatment breaks and limit the total radiotherapy/chemotherapy dose that can be delivered thereby adversely affecting prognosis.<sup>100</sup> 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.<sup>100; 101</sup>

**Xerostomia** Salivary flow from irradiated salivary glands diminishes a few days after starting radiotherapy, ceases after 5-weeks and never fully recovers.<sup>102</sup> Xerostomia interferes with speech, mastication, taste and swallowing, increases oral pain and the risk of dental decay.<sup>61</sup> Saliva substitutes offer symptomatic though short-lived relief.<sup>103</sup> There is evidence that administration of oral Pilocarpine significantly reduces the severity of post-irradiation oral xerostomia compared to saliva substitutes and placebo.<sup>104</sup> 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.<sup>105-107</sup> Enhanced Pilocarpine efficacy has been shown if therapy is commenced during radiotherapy.<sup>108; 109</sup>

**Dental caries** particularly adjacent to the amelocemental junction of mandibular teeth (radiation caries) occurs secondary to post-irradiation xerostomia.<sup>110</sup> 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.<sup>25</sup> One RCT demonstrated a 38% reduction in dental caries following the daily application of a 1% sodium fluoride gel.<sup>111</sup> 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.<sup>112-114</sup> It occurs in 2%-20% of patients, and is 3 times more common in dentate than edentulous patients.<sup>115-117</sup> There is evidence for an increased incidence of osteoradionecrosis following dental extractions but conflicting evidence as to the optimal timing of extractions (pre or post-radiotherapy).<sup>116</sup> Meticulous oral/dental care<sup>111</sup> and possibly oral tetracycline prophylaxis for dental extractions<sup>118</sup> reduces the incidence of osteoradionecrosis. There is evidence for the efficacy of both hyperbaric oxygen<sup>119</sup> and ultrasound in the management of established osteoradionecrosis.<sup>115; 120</sup>

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