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REVIEW

Recent advances in Oral Oncology

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Summary This paper reviews the main papers related to oral squamous cell carcinoma published in 2006 in *oral oncology* — an international interdisciplinary journal which publishes high quality original research, clinical trials and review articles, and all other scientific articles relating to the aetiopathogenesis, epidemiology, prevention, clinical features, diagnosis, treatment and management of patients with neoplasms in the head and neck, and orofacial disease in patients with malignant disease.

Potentially malignant oral lesions

Oral submucous fibrosis (OSF) has been reviewed.[1] Epidemiological studies show the areca nut to be the main aetiological factor — alkaloids from the nut are the most important factors whilst tannin may contribute. These chemicals appear to interfere with the deposition and/or degradation of extracellular matrix molecules such as collagen. Commercially freeze-dried areca products such as Guthka, pan masala, and mawa (areca and lime) have high concentrates of areca nut per chew and appear to cause OSF more rapidly than does self-prepared conventional betel quid that contain smaller amounts of the nut. *In vitro* studies on human fibroblasts using arecoline or areca extracts support the hypothesis of fibroblast proliferation and increased collagen formation. The copper content of areca nut is high and may contribute to up-regulation of lysyl oxidase. Disturbed equilibrium between matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMP) may cause increased and continuous deposition of extracellular matrix. Collagen-related genes may be involved in the susceptibility to, and pathogenesis of, OSF.[1] Transmission electron microscopic images of collagen fibres from oral subepithelial regions of normal and OSF patients may allow classification of progressive stages of the disease.[2]

The application of strict and rigorous clinical criteria in dysplasia/neoplasia surveillance led one group studying oral lichen planus (OLP) to diagnose most episodes of malignant transformation in early intraepithelial and microinvasive phases, namely stage 0 and I oral cancers (Tis N0M0 or T1N0M0). The 5-year survival rate, where applicable, was 96.7%. Advanced stage oral cancers were diagnosed in six patients, three of whom died.[3] Nevertheless, a small subgroup of OLP patients has been shown not to benefit from such surveillance and to be characterized by a rapid development to advanced-stage oral carcinomas, with consequent poor prognosis.[3]

To assess the histological features of *in vivo* toluidine blue (TB) uptake in potentially malignant oral lesions

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(PML) and to determine whether any were related to clinical dark versus pale royal blue stain and/or to the malignant/dysplastic nature of the lesions, frozen sections were used to evaluate TB extra- and intra-epithelial distribution, depth of penetration and nuclear or extra-nuclear uptake. The results suggested that dark royal blue staining is the true positive outcome of a TB test and showed that royal blue stain-malignant and dark royal blue stained-benign lesions have a different histological pattern of uptake.[4]

A novel binary grading system (high/low risk) for oral epithelial dysplasia (OED) was compared with the WHO classification 2005.[5] Four observers reviewed the same set of H& E stained slides of OED lesions using a two grading system blinded to the clinical outcomes; all pathologists showed satisfactory agreement on the distinction of mild dysplasia from severe dysplasia and from carcinoma *in situ*, but assessment of moderate dysplasia remained problematic. The sensitivity and specificity of the new binary grading system for predicting malignant transformation in OED were 85% and 80%, respectively and the accuracy was 82%.[5]

P57(kip2) expression was decreased in oral leukoplakia with moderate or severe dysplasia, and further decreased in oral squamous cell carcinoma (OSCC).[6] Negative expression of P57(kip2) was significantly associated with advanced tumour size, the occurrence of lymph node metastasis and the advanced clinical stage in OSCC. The overall 5-year survival rate in the P57(kip2) positive group was significantly higher than that in the P57(kip2) negative group. P57(kip2) expression was decreased in oral leukoplakia with moderate or severe dysplasia, and further decreased in OSCC. P57(kip2) appeared to be a progressive and prognostic biomarker in OSCC.[6]

Ki67 immunoexpression was not statistically different between OLP and oral lichenoid lesions (OLL), but, p53 staining showed a significant contrast.[7] The study showed that apparently a diagnosis of OLP or OLL makes no difference for the patient regarding malignant transformation, although, in OLP, p53 showed a higher index of expression.[7]

A retrospective study of a total of 269 lesions in 236 patients in which 94 lesions were surgically removed, 39 lesions (41%) being homogenous and 46 (49%) non-homogenous leukoplakias whereas nine (5%) were erythroplakias, showed 71% of the lesions to have a degree of OED.[8] All patients were encouraged to quit smoking and candidal infections were treated. Following surgical treatment, 11 lesions (12%) developed OSCC after a mean follow-up period of 7.5 years. Non-homogenous leukoplakias accounted for the highest frequency of malignant development, i.e. 20%, whereas only 3% of the homogenous leukoplakias developed carcinomas. Surgically treated lesions with slight, moderate, severe and no OED developed carcinoma with similar frequencies, i.e. 9—11%. Without surgical intervention, 16% of the 175 lesions disappeared whereas seven lesions (4%) developed carcinoma after a mean observation period of 6.6 years. The highest frequency of malignant development (15%) was seen for non-homogenous leukoplakias, the figure being 3% for homogenous leukoplakias. Fourteen percent of lesions with slight OED developed malignancy and 2% of lesions with no OED showed malignant transformation. Logistic regression analysis showed a 7 times increased risk of non-homogenous leukoplakia for malignant development as compared with homogenous leukoplakia and a 5 times increased risk for malignant development for lesions with a size exceeding 200 mm^2. No other examined variables, including presence of OED, site, demarcation, smoking and surgical intervention were statistically significant factors for malignant development.[8]

Oral cancer

Epidemiology

A descriptive epidemiological study of oral cancer in 12 UK cancer registries showed 32,852 oral cancer cases registered (1990—1999). There were statistically significant increases in incidence of 18% and 30% in males and females, respectively ($p < 0.01$). The trend was seen both in younger (<45 years) and older (45+ years) groups — with 3.5% and 2.4% average annual increases, respectively. Incidence remains higher in men than women, in older compared with younger groups, and in northern regions of the UK.[9]

Aetiopathogenesis

Animal models

Several animal models have been used for the *in vivo* investigation of carcinogenesis and the development of diagnostic or therapeutic protocols, employing chemical, transplantation and genetic (knockout and transgenic) animals.[10] Chemically induced (4-nitroquinoline 1-oxide [4NQO]) — tongue cancer in rats was shown to be determined by accumulation of loss of heterozygosity, and methylation of the promoter regions in the $p15^{INK4B}$ and $p16^{INK4A}$ tumour suppressor genes in advanced tumours — suggesting that they may play a role in tongue cancer progression.[11] One animal study found that squamous cell carcinoma antigen 1 was over-expressed in OSCC-bearing mice — suggesting it could be a useful biomarker.[12]

Role of tobacco

Tobacco constituents can cause DNA adduct formation and are implicated in OSCC development. Faulty mitochondrial DNA (mtDNA) repair has also been implicated as having a potential role.[13]

Epidemiological studies on oesophageal cancer and tobacco smoking cessation published before December 2005 were reviewed.[14] The results from at least 10 cohort and 10 case-control studies showed that current smokers had a higher risk of squamous-cell or unspecified oesophageal cancer than former smokers; that the risk of oesophageal cancer remains elevated for many years (at least 10) after cessation of smoking, to decline by about 40% only thereafter; and that, after 10 years since cessation of smoking, ex-smokers still have a twofold increased risk as compared to never smokers.[14] The same workers examined epidemiological studies on laryngeal cancer, and showed that at least four cohort studies and 15 case-control studies reported information on smoking cessation.[15] These studies indicated that the risk of laryngeal cancer is considerably reduced in ex-smokers as compared to current smokers. The relative

risk steeply decreases with time since stopping smoking, with reductions by about 60% after 10—15 years since cessation, and even larger after 20 years. The favourable effect of stopping smoking is already evident within few years after cessation, thus suggesting that smoking has a relevant impact on the late stage of laryngeal carcinogenesis. However, several years after stopping smoking, ex-smokers still have elevated risks of laryngeal cancer as compared to never smokers.[15]

Role of alcohol

Alcohol is a well documented risk factor for upper digestive tract cancers. It has been shown that acetaldehyde, the first metabolite of ethanol, is carcinogenic. The role of microbes in the production of acetaldehyde to the oral cavity has previously been described but one recent study measured the alcohol dehydrogenase (ADH) activity of the viridans group streptococci and showed that *Streptococcus salivarius* produced high amounts of acetaldehyde. The observation supports the concept of a novel mechanism of alcohol in the pathogenesis of oral cancer.[16]

Role of viruses

Human papillomaviruses (HPV) may be found in clinically health oral mucosa, and have been implicated in OSCC. HPV detection using the Hybrid Capture 2 assay (HC2; Digene) and the PCR-based Roche AMPLICOR HPV Test on specimens from the buccal mucosa and lateral border of tongue collected with cervical brushes and brooms from 50 healthy volunteers showed all cases to be high-risk HPV negative using HC2 assay, but the AMPLICOR Test detected four samples with positive results for high-risk HPVs.[17]The role of herpes simplex viruses, HSV-1 and HSV-2, as cofactors in association with tobacco, alcohol, or HPV-16 infection has also been examined.[18] Heavy use of tobacco, alcohol and HPV-16 infection was associated with an increased risk of OSCC but, after adjusting for age, tobacco, alcohol use, and number of sexual partners, the risk of cancer was not significantly increased in those with HSV-1 or HSV-2, though seropositivity to HSV-1 and HSV-2, may modify the risk associated with exposure to tobacco, alcohol, or HPV.[18] In a study using a fuzzy logic (FL) technique, HPV infection showed an association with OSCC TNM (stage II — T2), but not with histological grading. Also, FL seemed to be an additional effective tool in analysing the relationship of HPV infection with correlates of OSCC.[19]

Molecular studies

Although tobacco usage and alcohol consumption are the major risk factors for OSCC, there are individual variations in genetic susceptibility. One factor is the variance in xenobiotic metabolizing enzymes such as glutathione-S-transferase (GST), glutathione peroxidase (GPX), cytochrome p450 (CYP), N-acetyltransferase (NAT), and alcohol dehydrogenase (ADH), which are involved in the detoxification of many carcinogens. NAT2 polymorphism, alone or combined with GSTM3, has been shown to modulate susceptibility to OSCC in one study from Brazil.[20]

A high percentage of the oncogene *Ras* mutations in OSCC have been reported from India. Cyclin D1, a downstream member of the *Ras* pathway, was also shown to be overexpressed in most OSCC and overexpression was shown to be associated with poor prognosis. One recent study evaluated the association of single nucleotide polymorphisms in the H-*Ras* (C81T) and cyclin D1 (CCND1A870G and C1722G) genes and oral cancer risk. In H-*Ras* C81T polymorphism, TC+CC genotype showed a one and half fold increased risk for OSCC. The comparison of the CCND1 A870G and C1722G genotype frequencies in cases and controls did not show any significant association with OSCC risk. Thus the variant 'C' allele of the H-*Ras* (C81T) could be a low penetrance gene predisposition factor for oral carcinoma.[21]

The expression of proteins cyclin D1, Ki-67 LI and activated Extracellular signal-Regulated Kinase (ERK1/2), were shown to be significantly stronger in OSCCs than in normal mucosa.[22] Both over-expression of activated ERK1/2 and positive expression of the cell proliferation-related index Ki-67 in OSCCs were significantly associated with a moderately or poorly differentiated grade; cyclin D1 immunostaining showed a statistically significant association with both lymph node metastasis and a tumour thickness >5 mm; over-expression of activated ERK1/2 was positively correlated with cyclin D1 protein expression and Ki-67. The results suggest that over-expression of activated ERK1/2 and cyclin D1 protein are involved in oral carcinogenesis, and that activation of ERK1/2 might be related to cell cycle regulation and proliferation in OSCC.[22]

In human carcinoma, genomic mutations and abnormal epigenetic methylation can significantly contribute to gene silencing and carcinogenesis.[23] Methylation is particularly seen in the CpG islands of the regulatory gene promoter regions, but there are considerable differences in the incidence of methylation in the tumour suppressor genes, so that aberrant methylation of p16 (INK4a) is relatively frequently observed in tumours, but methylation of p27(Kip1) is rare, and the methylation of E-cadherin occurs at an intermediate incidence rate. This also suggests that loss of p16 expression is a true oncogenic event, while loss of p27 expression could be more a consequence of carcinogenesis.[23]

Polypeptide growth factors play key roles in the processes of cell migration and invasion and one study showed that transforming growth factor beta (TGFβ) and epidermal growth factor (EGF) differentially affect gene expression in primary and metastatic SCC cells, and likely contribute to the invasive properties of metastatic cells through regulation of both common and specific mediators for each growth factor.[24]

Matrix metalloproteinases (MMPs) are proteinases which with their tissue inhibitors (TIMPs) may play a role in OSCC. MMPs and TIMPs play an important role in several stages of cancer initiation and development. Single nucleotide polymorphisms identified in the promoters of *MMP2* ($-1306C \rightarrow T$) and *TIMP2* ($-418G \rightarrow C$) abolish the Sp1-binding site and thus may down-regulate expression of the genes. These polymorphisms may contribute to the susceptibility and aggressiveness of OSCC: subjects with the *MMP2* CC genotype had significantly increased risk for developing SCC compared with those with the variant genotype ($-1306CT$ or TT). For *TIMP2*, a moderately increased risk of SCC was also associated with the variant allele

(−418GC or CC), compared with the GG common allele. Furthermore, the polymorphisms in both genes showed some additive effect and the highest risk for cancer was observed in those with *MMP2* CC genotype and *TIMP2* variant GC or CC genotype. These findings suggest that the genetic polymorphisms in the promoters of *MMP2* and *TIMP2* may be associated with the development and aggressiveness of SCC.[25] A single nucleotide polymorphism in the MMP-1 promoter −1607 bp appears to be associated with OSCC susceptibility in a Chinese population.[26] Using RT-PCR, expression of MMP-28 was significantly higher in OSCCs than in premalignant lesions and mRNA and protein of MMP-28 were preferentially concentrated in OSCC specimens than in neighbouring tissues. Transfection of OSCC and oesophageal carcinoma cell lines with MMP-28 antisense oligodeoxynucleotide resulted in the reduced secretion of MMP-28 protein and reduced ability of colony formation in soft agar without affecting cell growth. These findings support a role for MMP-28 in the anchorage-independent growth of both OSCC and oesophageal carcinomas.[27]

The plasminogen activator inhibitor-1 allele 4G, by resulting in higher plasminogen activator inhibitor-1 (PAI-1) expression, appears to be a major contributing factor in early stages of OSCC.[28] Possibly, increased PAI-1 promotes initial development of OSCC through regulating cell detachment and delays further tumour progression by inhibiting vascularization.

Gelsolin has important cellular functions, including cell motility, proliferation and apoptosis. A biphasic profile in gelsolin expression was observed during the progression of oral carcinogenesis; normal oral mucosa has high gelsolin expression, whereas only 8% of oral precancerous lesions had positive gelsolin expression. A significant increased positive staining was found in primary (37%) and metastatic (32%) OSCC lesions. Tumours with high gelsolin expression were associated with greater tumour size, invasive growth, younger age and a poor clinical outcome in metastatic disease.[29]

A subset of CD3 lymphocytes described as γ/δ-T-cells, a cell type with potential relevance in non-MHC restricted anti-tumour immune responses, are increased in patients with SCC but there is no correlation between the proportion of γ/δ-T-cells and tumour stage. However, a significantly higher proportion of γ/δ-T-cells is found in patients with recurrent or metachronous second primary and the treatment modality significantly influences the proportion of γ/δ-T-cells.[30]

Diagnosis

The prognostic value of histopathological features related to the primary tumour and the cervical lymph nodes has been reviewed.[31] Emphasis was given to practical aspects of the histopathological assessment, potential inaccuracies, the importance of the partnership between surgeon and pathologist, the need for standardisation throughout the histopathological assessment, and the value of accurate documentation of findings. Markers such as those of cell proliferation (Ki-67 antigen) and apoptosis (Bax, Bcl-2) may also play a role in diagnosis. Apoptotic Bcl-2 expression decreases significantly in dysplastic and early invasive lesions and consequently increases almost to normal tissue level in consequent stages. Ki-67 expression increases sharply in initial stages of OSCC, but significantly decreases in later stages.[32] Reduced E-cadherin expression in OSCC appears to be associated with a more aggressive tumour behaviour and worse prognosis.[33] The expression of laminin $\gamma 2$ chain in OSCC in disseminating and infiltrating cancer cells might indicate a highly malignant state.[34] Decreased tumour cell transmembrane proteoglycan syndecan-1 levels in OSCC may also indicate poor prognosis, but stromal syndecan-1 positivity is a significant risk factor for recurrence.[35]

To assess the different genetic aberrations between the invasive tumour front (ITF), centre/superficiality and the stroma adjacent to OSCC, loss of heterozygosity (LOH) and microsatellite instability (MI) at chromosome 9p21 and 17p13 have been studied by combining laser capture microdissection (LCM) and PCR.[36] Cells at the ITF, centre/superficiality and stroma showed a high frequency of LOH and MI on chromosomes 17p13 (TP53) and 9p21 (RPS6). Comparison of the patterns of allelic loss and MI encountered at the ITF, centre/superficial and stromal cells revealed no concordance. The frequency of RPS6 and TP53 aberrations at the epithelial compartment (both ITF and centre) was statistically higher than the stroma. Furthermore, for the epithelial compartment, the aberrations proportions of TP53 rose from 60.0% to 64.7% between the centre/superficial part and ITF. Also the rate of RPS6 increased from 29.4% to 58.8% between the centre/superficial parts and ITF. The overall frequency of the two markers was statistically higher at the ITF than the centre/superficial part ($p < 0.05$). The study thus revealed that intratumour genetic heterogeneity exists in the different histological areas of OSCCs and some particular tumour cell genotypes have correlation with histological patterns.[36]

Tumour characteristics until recently have only been assessed by histological examination of biopsies or invasive imaging techniques. Recently, there has been increasing interest optical spectroscopy systems to provide tissue diagnosis in real-time, non-invasively and *in situ*.[37] Optical systems rely on the fact that the optical spectrum derived from a tissue will contain information about the histological and biochemical make-up of that tissue. The technique has not only been shown to have a role in the detection of dysplasia and malignancy but also in performing guided biopsies, monitoring of haemoglobin tissue perfusion in free-flaps and therapeutic drug levels during chemo- and photodynamic therapy. The assessment of surgical margins and a role in sentinel node biopsy are also interesting developments. The recent introduction of orthogonal polarization spectral (OPS) imaging for *in vivo* visualization of human microcirculation facilitates high resolution images of the oral mucosa. OSCC are characterized by chaotic and dilated vessels accompanied by numerous areas of haemorrhage and this may possibly play a future role in both the detection of early oral mucosal vascular aberrations and the effect of anti-tumour agents.[38]

Screening

Nine databases were searched for studies reporting a range of measures on the effectiveness of screening for oral can-

cer and precancer in primary care.[39] Only one study, from the Indian sub-continent, reported a randomised controlled trial: interim results showed 14.9% of intervention subjects died after 3 years compared with 56.3% of non-intervention controls. The review overall produced no evidence in favour of, or against, the potential benefits associated with an oral cancer screening programme. It was concluded that there are insufficient available data to make an unequivocal determination as to the effectiveness of oral cancer screening programmes at the present time. Primary care dentists and physicians may however, represent relevant groups for encouraging increased opportunistic screening efforts among their patients.[39] Spanish dentists gave a higher priority for a consultation to patients with tongue ulceration over those who requested prosthetic treatment[40] and a recent US study linking files from the Surveillance, Epidemiology, and End Results Program 1991—2000 for patients with cancers of the oral cavity and pharynx with their files from the Center for Medicare and Medicaid Services Program[41] showed that continuity of care displayed a statistically significant independent association and dose—response pattern with stage at diagnosis when the provider was an internist but not a general or family physician. An independent statistically significant association between continuity of care with an internist and stage at diagnosis was found for oral cavity tumours, but not for pharyngeal tumours.

The identification of serum biomarkers as a means of the early diagnosis and finding possible therapeutic targets in cancers is of increasing interest. Squamous cell carcinoma antigen 1 was up-regulated in tongue cancer patients by RT-PCR and Western-blotting.[12] These results indicate that squamous cell carcinoma antigen 1 may be of potential as a biomarker of tongue cancer.

Treatment and management

The overall 5-year survival rate from OSCC in one recent Taiwanese study was 63.24%. Multivariate analysis revealed that those without religious belief tended to have higher probability of death than those who had religious belief ($p < 0.001$). In addition, those who were single, widow/widower or divorced/separated had a poorer prognosis than those who were married. Apart from clinical features, socio-demographic factors significantly influenced the survival of oral cancer patients.[42] Being $\leqslant$40 years of age at the onset of disease is a significant adverse factor for tongue cancer.[43]

Assessment

Haemoglobin level between surgery and postoperative radiotherapy is an important prognostic factor for both locoregional control and overall survival among patients with SCC treated with surgery and radiotherapy.[44]

Imaging modalities used to evaluate the oral cavity include plain radiography (panoramic radiography and intraoral radiography), nuclear medicine scintigraphy, ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). A review describes these imaging techniques and their utility, primarily CT and MRI.[45] A Dutch observational cohort study prospectively compared the yield of whole body fluorine deoxyglucose positron emission tomography (^{18}FDG-PET) and chest computerized tomography (CT) to detect distant metastases and synchronous primary tumours.[46] Four of 34 consecutive patients with SCC in the head and neck were diagnosed with distant metastases or second primary tumours: CT as well as 18FDG-PET identified one patient with lung metastases and another with primary lung cancer, and 18FDG-PET detected second primary tumours in two further patients (hepatocellular carcinoma and abdominal adenocarcinoma). However, the increased uptake sites at 18FDG-PET in lung, liver and pelvis in five other patients were not confirmed by other imaging modalities. [18F]FDG-PET is also useful for recurrence detection in patients with OSCC, as a negative PET scan predicts a favourable outcome and survival: overall survival in one US study was 71% in the PET negative group and 35% in the PET positive group ($p < 0.01$).[47]

Surgery

The charts of 700 patients who underwent a mandibular resection (commando or composite resection) for an oral and/or oropharyngeal cancer between 1980 and 2002 were reviewed and, of 332 who had been operated without lower lip splitting, the unsplitting of the lip never complicated resection and reconstruction. Furthermore the procedure was time-sparing, and the cosmetic results were better than those obtained by traditional technique and the authors concluded, therefore, that lip-splitting in transmandibular resection for oral and oropharyngeal tumours is not necessary.[48]

In treating early buccal OSCC cT1N0, it has been suggested that elective neck dissection is indicated only when tumour depth $\geqslant$6 mm.[49]

Selective neck dissection is a modification of the more comprehensive modified radical or radical neck dissection that is designed to remove only those nodal levels considered to be at risk for harbouring nodal metastases. The role of selective neck dissection continues to evolve: while initially designed as a staging and diagnostic procedure for patients without clinical evidence of nodal disease, a growing body of literature suggests that selective neck dissection has a therapeutic role in patients with clinical and histologic evidence of nodal metastases. The rationale behind selective neck dissection, its application in the clinically negative but histologically node-positive neck and the extended application of selective neck dissection in patients with clinical evidence of nodal disease are discussed.[50] A recent review also considers the issues of selection of patients for treatment of the neck, choice of modality and extent of therapy, treatment of the contralateral neck, management of recurrence and influence of the site and status of the primary tumour.[51] A prospective study of 73 previous untreated consecutive patients with clinically N0 laryngeal SCC from 1997 to 2002 was undertaken to determine whether level IV lymph nodes can be saved in elective lateral neck dissection performed as a treatment for the N0 neck.[52] The results demonstrated the rare incidence of level IV occult lymph node metastasis, as well as infrequent nodal recurrence after elective neck dissection in the treatment

of clinically N0 laryngeal SCC. Therefore, dissection of level IV lymph node pads, especially in the ipsilateral neck of early T staged tumours or the contralateral neck, may be unnecessary for the treatment of laryngeal SCC patients with a clinically N0 neck.[52] A retrospective analysis of 80 patients treated for T1/T2 N0 tongue OSCC showed the elective neck dissection resulted in improved regional control.[53] The results of salvage treatment were poor. The risk for occult cervical metastasis was high in patients with early tongue tumours and only carefully selected patients should thus be left without prophylactic neck treatment.[53] Selective neck dissection (I—III) for oral cancers offers similar regional control rates with less morbidity as compared with modified radical neck dissection. Charts of 414 patients with OSCC, who underwent selective neck dissection (I—III) during 1994—2001, were analysed retrospectively. Isolated neck failure was observed in 4.8% of patients at 2 years and in 5.8% at 5 years. Eighty three percent of the neck metastases were in the ipsilateral neck and only 16% of these were at levels IV or V. In all, 30% of all regional failures were outside the field of dissection.[54] The data from one study suggest that in cN0 oropharyngeal cancer patients, level IIb lymph nodes may be preserved in ipsilateral and contralateral neck dissection.[55] However, caution is advised when preserving contralateral level IIb nodes in ipsilateral cN+ cases.

A study from the Netherlands has suggested that routine follow-up to detect local recurrence or second primary tumour has almost no value after 5 years and indeed, seems of limited value after 3 years.[56]

Radiotherapy

The Ku protein is essential for the repair of a majority of DNA double-strand breaks in mammalian cells. Overexpression of Ku80 plays an important role in the repair of DNA damage induced by radiation and it may provide an effective predictive assay of radiosensitivity in head and neck cancers.[57]

Blocking angiogenesis may enhance radiation therapy. In a study examining the effects of an angiogenesis inhibitor TNP-470 on human OSCC cell lines, with combining radiation therapy in the nude mouse, TNP-470 significantly enhanced the effect of radiation on the cells with high neovascularization.[58] These findings indicated that individual evaluation of each tumour neovascularization potential will be important before deciding anti-angiogenesis treatment.

Chemotherapy

Chemotherapy commonly induces oral mucositis and a range of other adverse effects. However, encouraging results have recently been reported in patients (pts) with locally advanced unresectable squamous cell carcinoma of the head and neck (SCCHN) when induction chemotherapy (IC) is used and followed by radiotherapy (RT) and one study of an aggressive regimen consisting of docetaxel (TXT), cisplatin (CDDP) and 5-fluorouracil (5-FU) showed improved local control.[59] Oxaliplatin combined with folinic acid (FA) and 5-FU used to treat patients with recurrent SCCHN in advanced stage of disease showed an overall positive of 60.6% with 21.2% complete responders and 39.4% partial responders.[60]

In one study of 74 patients with Stage III and IV biopsy proven SCC of oropharynx, hypopharynx and larynx treated with surgical salvage and late chemo-intensification treatment regimen of 5-FU and cisplatin with conventionally fractionated radiotherapy (70 Gy/7 weeks), locoregional control rate at 3 years was 80.8%. Three year locoregional relapse-free survival (LRFS), overall survival (OS) and disease-free survival (DFS) were 63.1%, 66.7% and 44.4%, respectively.[61] Orotate phosphoribosyl transferase expression may be a prognostic factor of 5-FU efficacy in patients with OSCC.[62]

Immunotherapy

Combined chemo-radio-immunotherapy, especially intra-arterial infusion, may have a therapeutic effect in tongue carcinoma regardless of the tumour stage.[63]

To identify molecular targets for immunotherapy of HNSCC patients, the gene expression profile in matched tumour and normal fibroblast cell lines were determined using microarray technique followed by real-time RT-PCR, leading to the identification of 7 genes which were over-expressed at least 10-fold in tumours over any of the normal tissues and are potential targets for immunotherapy.[64]

B7 co-stimulatory molecules (B7-H1, B7-DC) are expressed in OSCC lines, and their expression was further upregulated by interferon (IFN)-γ stimulation. Successful inhibition of tumour growth by blockade of the B7-H1 pathway may implicate a new approach for immunotherapy of OSCC.[65] At least *in vitro*, interferon α2b (IFNα2b) may be effective as a tool for adjuvant therapy along with conventional therapies to overcome the immunosuppression in OSCC patients.[66] Interleukin 4 (IL-4) induced apoptosis *in vitro* in SCC cells, and 15-lipoxygenase-1 15-LO-1, induced by IL-4, may mediate this apoptotic pathway.[67]

Photodynamic therapy

In a hamster cheek pouch model, photodynamic therapy (PDT) using chlorin p6 (CP6) given either intraperitoneally (IP) or applied topically was measured by optical fibre-based fluorescence spectroscopy.[68] PDT was performed by superficial illumination of tumour with 660 nm (±25 nm) light at a fluence rate of 100 J/cm^2 and tumour response was analyzed histologically. CP6 accumulation was higher in tumours as compared to adjoining tissue and normal mucosa at 4—6 h after its IP administration. For relatively large tumours (size >8 mm), topical application was observed to be more effective than IP. The level of CP6 in tumour, surrounding tissue, normal mucosa and skin was seen to decrease rapidly within 24 h after its administration and was undetectable at longer time (>72 h) intervals. PDT of small tumours at 4 h after IP injection of CP6 resulted in complete tumour necrosis. Whereas, PDT of large tumours receiving CP6 topically caused necrosis in 300—800 μm superficial region of the tumour.

Mono-L-aspartyl chlorin e6 (NPe6) is an effective photosensitizer with a major absorption band at 664 nm that does not cause the adverse effect of prolonged photosensitiza-

tion of normal skin. Used with a diode laser for treatment of tongue cancer in the nude mouse, almost all tumours developed necrosis, while viable-like neoplastic cells remained mainly in the peripheral region of the tumours in some cases.[69] The mean depth of necrosis below the surface was 2.1 mm. The mean tumour thickness below the surface was 2.3 mm. Tumour thickness coincided with the depth of necrosis. NPe6-induced PDT exhibited tumour selectivity and can effectively cause necrosis of tongue cancers.[69] Fractionated light exposure with a 24-h interval appears to be the appropriate fractionation interval between photodynamic therapies (PDTs) for enhanced anti-tumour effects on human OSCC.[70]

Quality of life issues

Recent UK government recommendations state that high quality information must be provided for cancer patients. In one recent study, patients were generally satisfied with information, however key areas of improvement, such as the provision of information about support groups, where to go for financial advice and the long-term affects of treatment on ability to work, physical functioning and quality of life (QoL) were identified. Satisfaction with information before treatment was predictive of depression and Mental Component Summary scores (HR-QoL) 6–8 months after the end of treatment.[71] Anxiety, pain, swallowing difficulties, chewing difficulties, and depressed mood are common problems post-operatively[72] but there are also more specific problems such as xerostomia and candidosis.

Articulatory proficiency of /*r*/ and /*s*/ sounds and speech intelligibility deteriorated significantly. Voice quality and resonance remained essentially normal. Intraoral sensation decreased postoperatively but was not related to speech outcome. Sensate flaps did not prove to be superior in relation to speech tasks. A multidisciplinary approach is advocated in assessment of speech outcome after cancer surgery. Speech therapy is strongly recommended, even in the absence of a gross articulatory handicap.[73]

Facial disfigurement and functional inabilities can lead patients to restrict food intake. Tumour size and loss of tongue mobility, controlled by the higher odds of females and patients living in crowded households, are the most important clinical predictors of food restriction.[74]After cancer therapy, swallowing was impaired objectively and subjectively.[75] Rates for nonsilent and silent aspiration increased during the follow-up. One year after surgery, 86% of the patients ate regular masticated or soft food.[75]

The obstructive sleep apnoea-hypopnoea syndrome – a sleep-related breathing disorder characterised by repetitive pharyngeal collapse – has been reported in 12% of patients treated for head and neck cancer.[76]

Radiation-induced xerostomia results in significant oral microbial changes, which include a marked increase in the number of cariogenic organisms, notably *Streptococcus mutans* and lactobacillus species. Xerostomia creates or promotes the rapid onset and progression of dental caries but fluoride can reduce caries activity.[77] Topically applied fluorides have been successfully used but, because intensive daily self-application is required, compliance is an issue. An intraoral fluoride-releasing system (IFRS) containing a sodium fluoride core is a newly developed, sustained-release, passive drug delivery system that does not require patient involvement except for periodic replacement, thus reducing the effect of patient compliance.[78]

Some 30% of cancer patients receiving specialist palliative care had combined clinical and microbiological evidence of oral candidosis.[79] Oral candidosis was associated with a poor performance status, the presence of xerostomia, and the presence of dentures; but was not associated with the use of oral/parenteral antibiotics, or oral/parenteral corticosteroids. *Candida albicans* was the predominant organism isolated, but non-C. albicans species were the predominant organism in 25% cases, and a contributing organism in a further 19%. Yeasts resistant to azole antifungal drugs are increasingly isolated from the mouths of cancer patients. Tea tree oil (*Melaleuca alternifolia*) is an agent possessing antimicrobial properties that may prove useful in the prevention and management of these infections since all isolates from patients with advanced cancer were susceptible, including 41 that were known to be resistant to both fluconazole and itraconazole.[80]

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