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Research Article

ADVANCES AND THE HALLMARKS OF ORAL CANCER

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ABSTRACT

Oral cancer is the sixth most common cancer worldwide with a high prevalence in South Asia. Cancer of oral cavity accounts for almost 3% of cancer cases in the world. The incidence varies widely reflecting geographic differences in exposure to risk factors. Several risk factors for development of oral cancer are now well known including smoking, drinking and consumption of smokeless tobacco products. Genetic predisposition to oral cancer has been found in certain cases but its components are not yet entirely clear. The recent rise in younger age groups and females seen in many countries is of particular concern. Treatment and management of complications, loco regional recurrence and further primary tumors result in high morbidity and mortality especially when the disease is advanced stage at initial diagnosis. Progress in cancer research has provided abundant new knowledge about cellular processes and molecular biology underlying oral carcinogenesis and tumour progression. The natural history of oral cancer seems to gradually evolve through transitional precursor lesions from normal epithelium to a full-blown metastatic phenotype. A number of genomic lesions accompany this transformation and a wealth of related results has appeared in recent literature and is being summarized here. Furthermore, several key genes have been implicated especially well-known tumor suppressors like the cyclin dependent kinase inhibitors, TP53 and oncogenes like the cyclin family, EGFR. Viral infections, particularly with oncogenic HPV subtypes and EBV can have a tumorigenic effect on oral epithelia and their role is discussed along with potential therapeutic interventions. The present review attempts to summarize the current most widely-used research approaches and their application in the prevention, diagnosis, effective treatment, and improved outcome of oral cancer.

INTRODUCTION

Although the incidence of oral cavity cancer is not well documented since it is unfortunately often grouped with oropharyngeal subsites, it is thought to be the 8th most frequent cancer in the world among males and the 14th among females accounting for nearly 3% of all cancer cases.[1] According to the International Classification of Diseases (ICD version 9, categories: 140–146, 149), oral cancer refers to a subgroup of head and neck malignancies that develop at the lips, tongue, salivary glands, gingiva, floor of the mouth, oropharynx, buccal surfaces and other intra-oral locations. Oral cancer is the sixth most common cancer worldwide. Life style, habits, and demographic as well as genetic factors influence geographic variations in incidence of oral cancer.[2] For example; oral cancer is the most common cancer in India and accounts for 35% of all newly diagnosed cancers in men. The etiology of oral cancer is well established in most instances with consumption of tobacco in any form and alcohol being the most common etiologic agents.[3] Squamous cell carcinoma originating in the mucosal linings accounts for more than 90% of oral cavity cancers.[4, 5] Oral cancers is predominantly a disease of older age. More than 92% of oral and pharyngeal cancers occur in individuals older than 40 years, with the average age being 63. Its incidence increases until the age of 70 to 74 and then declines slightly.[6] Once a predominantly male disease, females have experienced a steady rise in the incidence of oral cancer since the increase in female smokers began in the 1950s.[7-10] A Swedish group reported on 132 patients and concluded that females have a greater risk for oral cancer than men given the same quantity of tobacco use.[11] A report by Muscat and co-workers agreed that females are at higher risk than men who report the same number of pack-years of smoking.[12] This increased risk in older women was explored in a separate case-control study of 530 women with oral cancer. The authors suggested the possibility of a hormonal influence related to estrogen deficiency in postmenopausal women, although the data were not conclusive.[13] Pain is a common symptom in oral cancer patients, representing 30–40% of their main complaints. There were 12 different descriptions of pain; pain was related to TNM

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staging in the tongue and the tongue/mouth floor.[14] Although pain is the main symptom, it usually arises only when the lesions have reached a remarkable size and is the time when the patient requests medical assistance. Thus, early carcinomas often go unnoticed because they are asymptomatic.[15] In later and larger lesions, symptoms may vary from mild discomfort to severe pain, especially on the tongue. Other symptoms include ear pain, bleeding, and mobility of teeth, problems in breathing, difficulty in speech, dysphagia and problems using prosthesis, trismus and paraesthesia.[16]

OSCC (oral squamous cell cell carcinoma) may appear in any location although there are certain areas in which it is more commonly found. The most common locations are the tongue and the floor of the mouth.[17-21] In Western countries it occurs in over 50% of cases. Other areas of involvement are the buccal mucosa, retro molar area, gingiva, soft palate and less frequently the back of the tongue and hard palate. The lip is involved more frequently in some geographic areas.[22] Advances in cancer research have provided abundant knowledge about cellular processes and molecular biology in OSCC. Our knowledge of carcinogenesis, identification of biological markers and molecularly targeted therapies is advancing through basic research, translational research, clinical trials, and ultimately analysis of factors specific to the individual and their tumor may result in effective ''personalized medicine''.[23] In the present sections, recent advances and hallmarks of oral cancer and their impact on prevention, diagnosis, effective treatment, and improved prognosis are considered.

Risk factors

Multiple factors have been associated with increased risk for oral cancer. Although the most compelling evidence implicates tobacco and alcohol. Other associated factors including viruses, nutritional deficiencies, previous upper aerodigestive malignancy and immunocompromised status have been proposed. Population based studies confirm the correlation between tobacco use and risk for oral cavity cancer.[24] Tobacco smoking is an independent risk factor with a relative risk of up to eight times that of non-smokers.[25] Oral cancer is twice as likely to develop in women as in men given the same amount of tobacco consumption.[26] It is thought that exposure to carcinogens leads to malignant transformation of cells. Even though smoking cessation is effective in reducing risk, former smokers still have higher risk than never smokers. Individuals who refrain from smoking for 1 to 9 years showed a 30% reduction in risk whereas a 50% reduction in risk was noted for individuals who ceased smoking for more than 9 years.[24]

The deleterious effects of tobacco use and excessive alcohol consumption are well known.[27] There are approximately 1.1 billion smokers worldwide with 80% living in developing countries. The prevalence of OSCC in cigarette smokers is 4–7 times greater than in non-smokers.[28, 29] In Southeast Asia, areca nuts (Areca catechu) inverted smoking and smokeless tobacco (snuff) are additional, important risks.[30,31] Although tobacco and alcohol are independent risk factors, they have a synergistic effect in combination with a clear dose dependent correlation between duration and frequency of exposure and tumor development.[32, 33] Ethanol increases permeability of the mucosa permitting the action of nitrosamines, hydrocarbons and acetaldehyde. Smoking increases the acetaldehyde burden following alcohol consumption and the alcohol consumption enhances the activation of pro-carcinogens by induction of cytochrome P450-2E1-dependent microsomal biotransformation system in the mucosa.[34] Carcinogenic agents may directly cause mutations in the DNA but also suppress the DNA repair enzymes (the critical component against human cancer). Alcohol is recognized as a distinct risk factor for the development of oral cancer especially for consumers of dark liquors. The majority of patients in whom oral cancer develops are consumers of alcohol.[35] Lewin *et al* demonstrated that low to moderate alcohol use does not increase the risk for oral cancer but high intake (>50 g) was an independent risk factor with a relative risk of 5.5. For consumers of very high levels of alcohol, risk for the development of oral cancer may be greater than that for smoking alone.[36]

Multiple viruses have been implicated in the etiology of oral cancer including Epstein-Barr virus, herpes simplex viruses, retroviruses, and human papilloma viruses (HPVs). Human herpesvirus-8 is recognized as the most important pathogen in Kaposi sarcoma; although presence of the virus alone is not sufficient to cause malignancy.[37] Much of the recent research has focused on the link between HPV and upper aerodigestive malignancies. Human papillomavirus (HPV) could also be considered to be related to life style and it is strongly associated with the development of oropharyngeal cancers. Patients with HPV positive tumors have a significantly better prognosis than do those with HPV negative tumors.[38] Although data for the role of HPV in the development of oropharyngeal carcinoma are clear, the role of HPV in oral cavity cancer is not as well defined. Unfortunately, some authors consider cancers arising from the oral cavity and oropharynx together as ''oral cancer''. This is reflected in differences in reported incidence figures. Whereas HPV is very relevant and frequent in oropharynx cancer often treated with (chemo) radiotherapy, it is uncommon and less relevant in oral cancers which are treated surgically.[39, 40] A 2001 study found HPV-16 to be present in oral cancer at a rate five times that in normal mucosa.[41] Over half of oral squamous cell carcinomas have been reported to harbor HPV.[42] However, direct causation has not been established and the methodology of some studies has been questioned.[43, 44] The literature shows a broad range of oral HPV prevalence in oral cavity cancer because of the multiple techniques used for detection of the virus which vary in sensitivity.[45] Detection rates are also higher in samples taken from frozen tissue than from paraffin embedded tissue.[42] These technical factors probably contribute to the wide range of reported prevalence rates which makes causation difficult to establish.

Other factors are found in higher degrees in patients with oral cavity cancer including poor diet, nutrition, poor oral hygiene and ill-fitting oral prostheses. The chronic iron deficiency seen in patients with Plummer-Vinson syndrome has been associated with a higher incidence of oral and hypopharyngeal cancer.[46] A deficiency in vitamins A, C and E has been associated with oral cancer.[47] Oral cancers have also been associated with low intake of fruits, vegetables and a protective role may be afforded by diets high in fruits, vegetables, and fiber.[48, 49] Poor oral hygiene as measured by caries and periodontal disease is noted more frequently in oral cancer

patients.[50] A case-control study based in China found that poor oral hygiene was an independent risk factor for the development of oral cancer after controlling for smoking and alcohol.[51] A Swedish study reported that ill-fitting dentures were an independent risk factor for oral cancer whereas another study from the United States found no correlation.[52] Familial aggregation of oral cancer possibly with an autosomal dominant mode of inheritance was reported in a very small percentage of patients but the responsible genes are unknown.[53] A germ line p16 mutation segregated with cancer predisposition in a single family with increased head and neck cancer risk. Thus it is likely that the mutant p16 (p16R87P) is implicated in head and neck squamous cell carcinoma (HNSCC) tumorigenesis.[54] A most prominent predisposing genetic factor is a mutation in one of the Fanconi anemia genes, which act in a complex DNA repair system involved in homologous recombination.[55] Patients with Fanconi anemia are characterized by congenital malformations, bone marrow failure and cancer predisposition most prominently acute myeloid leukemia and SCCs, particularly in the oral cavity. The increased risk for Fanconi anemia patients to develop HNSCC is 500–1000x and the accumulated life time risk is estimated as >30%.[56,57] Genome-wide association studies have been successful in identifying common genetic variation involved in susceptibility to etiologically complex disease. Recently such a study identifying common genetic variation involved in susceptibility to upper aero-digestive tract (UADT) cancers has been published. The identification of a (genetic) risk profile for individuals to develop HNSCC and OSCC in particular may not only lead to better understanding of OSCC but also to improved counseling and clinical decision making on treatment and follow up.

The genetic evolution of oral cancer

The multi-step model of carcinogenesis is widely accepted and requires the step-wise transition from pre-malignant lesions to the metastatic tumor phenotype.[58] A variety of alterations accumulate to potentiate this transition and gradually increase malignancy.[59] A similar progression has been shown to occur in oral cancer from benign hyperplasia to dysplasia, to carcinoma in situ and advanced cancer with accompanying genomic alterations.[60]Several oral lesions are of particular relevance to oral cancer: oral leukoplakia, oral lichen planus and oral erythroplakia.[61-63] Oral leukoplakia is a clinical diagnosis that describes white patches or plaques that cannot be attributed to any other disease. It is common especially in older men and is associated with a variable risk of underlying epithelial alterations depending on its location. Approximately 10–15% of oral leukoplakias will be diagnosed as mild or moderate dysplasia and another 5% may be diagnosed as severe dysplasia or carcinoma in situ.[64] The long term risk of progression to invasive cancer varies between studies from 4% to 18% and warrants careful clinical management.[65-67] Oral lichen planus is also quite common and is estimated to incur a 1–4% risk of subsequent cancer development.[68, 69] Oral lichen planus is believed to be an autoimmune disease and the mechanism of its malignant conversion is not yet well understood. Oral erythroplakia is rare but has a very high risk of progression (14–50%) and is frequently diagnosed histologically as carcinoma in situ or severe epithelial dysplasia. Oral leukoplakia, oral lichen planus and oral erythroplakia can show varying degrees of histological abnormalities from mild dysplasia to carcinoma in situ. A subset of these lesions will progress to oral cancer and warrant early and aggressive treatment while others may progress slowly if at all. This progression has been linked to the presence of genomic instability and the appearance of extensive genomic alterations such as aneuploidy.[70] Indeed, the evaluation of influential genomic alterations may supplant traditional markers that are unable to predict the time course of pre-malignant lesions.

Genetic changes in OSCC

Chromosomal aberrations such as deletions, amplifications, and structural rearrangements are hallmarks of malignancy and are seen in head and neck tumors. There is a relatively common pattern of DNA allelic loss during the progression from premalignant to malignant phenotype such as acquisition of specific chromosomal losses at chromosome arms 3p, 9p, 17p and mutations in TP53 (Tables 1).[71]

Table 1 Common chromosome regions aberration in head and neck carcinomas

Chromosome	Chromosome region – alteration
1	Loss 1p36.3
2	Loss 2q35, 2q36
3	Loss 3p13–14, 3p21, 3p25; gain 3q25-ter
4	Loss 4q25, 4q31–32
5	Loss 5q21–22; gain 5p
6	Loss 6q13, 6q25
7	Loss 7q31; gain 7p11
8	Loss 8p21, 8p22, 8p23; gain 8q22, 8q23-ter
9	Loss 9p21
10	Loss 10q23, 10q26
11	Loss 11q22.2–22.3; gain 11q13
12	Gain 12p12.2–13
13	Loss 13q14.3
14	Gain 14q31–32.2
15	Gain 15q15
16	Gain 16q23–24
17	Loss 17p13; gain 17q24–24
18	Loss 18q; gain 18p
19	Gain 19q
20	Loss 20p11.2; gain 20q
21	Loss 21q11.1, 21q21, 21q22.2
22	Loss 22q13

In comparative genomic hybridization studies, one of the most promising areas under investigation is a copy number gain on chromosome 3q and a loss of chromosome 3p which are found at high frequency suggesting these regions may harbor oncogenes and tumor suppressor genes important for the initiation or progression of head and neck cancer.[72-80] An early and common genetic event in oral premalignancy with potential value in early diagnosis and tumor surveillance is loss of heterozygosity (LOH) in 9p21 in dysplasia (30%) and OSCC (70–80%).[80] Microsatellite or SNP panels to assess LOH are not yet commercially available but in the future, LOH testing may become routine and improve OSCC survival by early diagnosis and prediction of tumor recurrence. Carcinogen exposure can cause simultaneous genetic defects throughout the upper aero-digestive tract (UADT) epithelium, putting the epithelium at high risk for development of premalignant lesions at different stages of carcinogenesis.[81] The concept of ‘‘field cancerization’’, a characteristic of head and neck cancers, was introduced in 1953 based on the hypothesis that prolonged exposure to carcinogens leads to the independent

transformation of epithelial cells at multiple sites in the adjacent mucosa.[82] The aggregation of genomic alterations during progression is assumed to occur in a wide population of cells, a heterogeneous ''field of genetically altered cells'' that is might give rise to a visible precursor lesion. This theory attempts to explain the high frequency of local recurrences and the emergence of second primary tumors in patients with OSCC. This theory has been confirmed in many retrospective studies using genetic markers. Current data show that approximately 30% of the oral and oropharyngeal cancer cases are surrounded by large fields of cells with cancer associated genetic changes that indicate a clonal relation to the invasive carcinoma.[83] These fields frequently remain behind when the tumor is excised causing secondary tumors that are clinically assigned as local recurrences and second primary tumors depending on the distance and time related to the index tumor.[84-87] What the clinical relevance of these observations is needs to be determined but identification of such fields eventually may have implications for adjuvant treatment and intensity of follow-up. Metastasis is a complex process requiring tumor cells to progress through multiple stages, governed by successive changes in expression of certain genes or alterations of gene structures and encoded products. It begins with cell disassociation within the primary tumor and in OSCC generally results in metastasis within regional (cervical) lymph nodes.[88, 89] Identification of biological parameters associated with regional metastasis may provide additional information on the metastatic behavior of tumors and may be helpful in clinical decision making on the treatment of the neck.[90] For the much debated issue of treatment of the clinically N0 neck, implementation of these signatures in the clinic could impact decision making.[91] This will be relevant in T1 and T2 oral cancer in particular since in larger tumors the neck will usually have to be entered for vascular anastomosis of free flap reconstructions. Moreover, depth of invasion may also influence the prior chance on nodal metastasis and could also be taken in consideration. Anyway, these signatures should first be validated in multicenter settings and other procedures like sentinel node mapping will need to be considered in a decision model for implementation. Sentinel lymph node procedures in particular are becoming increasingly relevant and due to recent developments like the use of RT-PCR for detection of tumor cells, the procedure becomes more reliable and more convenient.[92] The combination of the use of imaging, sentinel node procedures and biological information may provide complementary information to obtain the most accurate information on the nodal status of patients. Development of distant metastasis after initial treatment of OSCC is not considered a common event but it is associated with fatal outcome.[93] Markers for distant metastasis may act as prognostic indicators and may play a role in patient counseling and clinical decision making as well.

Tumor suppressor genes

Another important area involves tumor suppressor genes that prevent cells from acquiring malignant characteristics and usually act in regulating discrete checkpoints during cell cycle progression, monitoring DNA replication and mitosis.[94] Inactivation of tumor suppressor genes can occur via epigenetic or genetic mechanisms. The reasons underlying this choice of gene inactivation routes during tumorigenesis have not been clarified. Chemical carcinogens in tobacco smoke may contribute to the genetic mutations in TP53.[95] The inactivation of the TP53 tumor suppressor signaling pathway is seen in most human cancers including OSCC (Table 2).[96]

Table 2 Common gene alterations and potential biomarkers in oral carcinomas.

Markers	Function	Significance/association
TP53 (p53)	Cell-cycle regulation	Decreased overall survival
CDKN2A (p16)	Senescence, cell-cycle progression	Decreased overall survival
CDKN1A (p21)	Cell-cycle regulation	Tumorigenesis
CDKN1B (p27)	Cell-cycle progression	Poor prognosis
MDM2	Cell-cycle regulation	Tumorigenesis
MGMT	Promoter methylation	Decreased overall survival
EGFR	Cell proliferation, growth	Nodal metastases; more rapid clinical course, consideration for targeted therapy
ERBB2	Cell proliferation, growth	More rapid clinical course
RARB	Cell growth and differentiation	Decreased overall survival
MYC	Cell growth, apoptosis	Tumor progression
BCR-ABL1	Cell-cycle regulation and differentiation	Tumor progression
RAS	Signaling, growth	Poor prognosis
CCND1	Cell-cycle regulation	Nodal metastases; more rapid clinical course
STAT-3	Cytokine signaling, cell proliferation	Decreased survival
VEGF	Angiogenesis	Consideration for targeted therapy
EBV	Cell-cycle regulation	Diagnostic/screening
HPV	Cell-cycle regulation, apoptosis	Improved prognosis/local control

The aberrant p53 protein activity may be caused by mutations in the TP53 sequence producing truncated or inactive mutant proteins or by aberrant production of other proteins that regulate p53 activity (such as gene amplification of MDM2 or viral proteins). Recent studies have also suggested that inherited genetic polymorphisms in the p53 pathway influence tumor formation, progression, and/or response to therapy.[96] In the same way, the expression of $p16^{INK4A}$ protein encoded by the CDKN2A suppressor gene is negative or low in up to 83% of OSCCs and up to 60% of pre-malignant lesions. Several studies have shown frequent CDKN2A gene mutations or the frequent loss of gene expression in oral lesions suggesting that it is an early step in oral carcinogenesis.[97]

High throughput genotyping is being utilized in many tumor types to probe known oncogene and tumor suppressor gene mutations across large numbers of human tumor samples. This approach has the ability to accelerate oncogene and tumor suppressor gene identification. Results once obtained offer great potential for identification and targeting of key pathways implicated in tumor progression to guide rational strategies for therapeutic intervention. Work of this nature is underway in head and neck cancer that may identify novel ''drug'' targets.[98]

Update in clinical prevention and diagnosis

Toluidine blue and Lugol's iodine have been used as clinical aids to identify occult mucosal abnormalities and to demarcate the extent of a potentially malignant lesion prior to excision.[99-104] When applied topically or as an oral rinse, toluidine blue binds to DNA and can help identify malignant lesions with reasonable accuracy. Furthermore, false positive stains are too frequent for use as a valid screening tool in primary care settings.[104] In addition, controversy exists regarding the

subjective interpretation of mucosal staining and criteria for positive results.[105, 106] In conclusion, no convincing evidence is available to support the use of these adjunctive techniques. Acetic acid induced whitening of oral mucosa has been proposed to enhance and highlight dysplastic lesions similar to its use on cervical mucosa.[107, 108] ViziLite™ (ViziLite system – Zila Pharmaceuticals, Phoenix, AZ) is one commercially available tool that makes use of 1% acetic acid induced whitening of oral tissues followed by examination under diffuse chemiluminescent blue/ white light (wavelength of 490–510 nm).[109] Acetic acid removes the glycoprotein barrier and slightly desiccates the mucosa, the abnormal cells then absorb and reflect the blue/white light differently to normal cells.[110, 111] Most investigations have evaluated highly subjective parameters such as brightness, sharpness, texture and not surprisingly the findings are inconsistent and contradictory with poor discrimination between keratotic, inflammatory, malignant or potentially malignant white lesions. Recently, visual autofluorescence (autofluorescence spectroscopy) has been tested in the mouth with promising results that it can distinguish normal tissues from tumors. The system consists of a small optical fiber that produces various excitation wavelengths and a spectrograph that receives and records on a computer and analyzes via dedicated software, the spectra of reflected fluorescence from the tissue. This technique has the advantage of eliminating subjective interpretation and can provide diagnosis in real-time, non-invasively and in situ.[111] The method is yet to be refined and currently cannot determine tumor depth or histological grade. Moreover, it is poor at detecting early lesions and demarcating large lesions as the optical fiber can sample only a small mucosal area.

Narrow band imaging (NBI) is an endoscopic technique using narrow-band spectrum optical filters to enhance the visualization of mucosal and submucosal microvascular patterns. The technique is based on the fact that the depth of penetration of light is dependent on its wavelength. The filters used in NBI select blue and green light with wavelengths of 415 and 540 nm respectively corresponding to the peaks of absorption of haemoglobin. These filtered wavelengths penetrate the superficial layers of mucosa thus highlighting the capillary network and at deeper levels enhance submucosal vessels. In this way, superficial mucosal lesions that would be missed by standard white light (WL) endoscopy are better identified in view of their neoangiogenic pattern. Additionally, the best image definition for both conventional WL and NBI endoscopy is achieved using a high definition television (HDTV) camera, which provides 1080 lines of resolution thus allowing a signal definition that is 4.26 times better than standard definition television. The application of this new technology in the diagnostic work up of patients with OSCC (and also with oropharyngeal SCC) was evaluated in a recent study.[112] The sensitivity of this technique in detecting OSCC was 96% with a specificity of 100% and an overall accuracy of 97%. The authors confirm the utility of NBI in pre and intraoperative settings with better definition of superficial extension of the lesion, detection of synchronous tumors and identification of unknown primaries. Moreover, the authors found that HDTV NBI also played a relevant role during follow up with early detection of persistences, recurrences, and metachronous tumors. The specificity obtained by NBI-HDTV underscores the potential of this technology in the diagnosis and follow up of OSCC.

Another recent development in the detection of tumor deposits is the use of near infrared fluorescence imaging. Fluorescent molecules labelled to tumor specific proteins or antibodies or other tumor specific probes could make real time visualization of tumor tissue during surgery possible. The use of this technique could help to obtain adequate surgical margins and could lead to better local control and oncological outcomes without sacrifice of functionally important normal surrounding tissue. The technique can also be used for sentinel node procedures as an alternative for or complementary to radionuclides. The main challenges are to develop specific probes with sufficient tumor to normal tissue ratios and the development of optimal optical devices to visualize the generated signals. The use of saliva and plasma in detection of tumors including distant metastases is being investigated.[113, 114] These sources have been used to identify epigenetic changes of hypermethylation specifically of promoters of tumor suppressor genes p16, MGMT, RARb, E-cadherin, and DAPK. Genomic and proteomic studies of tumor tissues, plasma, and saliva have identified several promising cancer signatures of potential diagnostic value. Saliva has a cluster of protein, secretome which permits the use of tumor markers that circulate in blood. In this way, high levels of ErbB2 (c-erbB-2/HER2) and cancer antigen 15-3 (CA15-3) were found in saliva in women with breast cancer compared with a low quantity in healthy women.[115] Using subtractive proteomics, Hu *et al* revealed several salivary proteins at differential levels between OSCC and matched control subjects. Expectations for future use of saliva like substrate diagnosis are still evolving.

Another important issue is deciding which potentially malignant, intra-epithelial lesions will progress to invasive cancer. The available dysplasia grading systems are incapable of reliably predicting malignant progression and additional molecular information could enhance clinical decisions on treatment and follow up.[116] Ploidy analysis or DNA copy numbers may provide such information.[117-119] The presence or absence of these aberrations in resection margins may be predictive of recurrences.

Advances in treatment modality

The basic prognostic factors in OSCC are encompassed in the TNM classification system: tumor size (T), regional nodal involvement (N) and the presence or absence of distant metastasis (M). Although the system is imperfect partly because tumors with similar morphology and stage may behave differently due to their differing biological characteristics, it is widely used in treatment planning, prognostication, and comparison of outcomes.[120] However, in the future it seems likely that biomarkers will supplement or even replace traditional prognosticators. A variety of molecular tumor markers have been studied in the clinic for their potential to predict disease outcome or response to therapy in OSCC. However, none of these markers appears to provide definitive prognostic or predictive information. Additionally, it is unlikely that any one molecular factor determines the complete behaviour of a tumor and that the complex interaction among oncogenes and tumor suppressor genes cannot be ascertained through the analysis of a few molecular markers. A more

comprehensive screen of the molecular defects in head and neck squamous cell carcinoma obtained through microarray analysis has revealed that the molecular classification of these tumors was a better predictor of disease-free survival than clinical and pathological parameters154, and that specific gene expression signatures were associated with prognosis in OSCC.[121, 122] These findings suggest that microarray technology could provide a novel system of classification of OSCC. It could be used as an auxiliary tool in the classification of specific clinical categories of disease and the improvement of specific treatment modalities and patient outcome.

Most OSCCs exhibit limited responsiveness to chemotherapy involving cytotoxic drugs due to mechanisms that either block intracellular transport of these agents or interfere with their intracellular molecular targets.[123] In OSCC, surgery remains the primary treatment modality of choice except for inoperable cases. A better understanding of the molecular and biological profiles of OSCC and the molecular heterogeneity of the disease could facilitate the development of more efficient targeted therapies. Most traditional anticancer drugs directly interfere with mitosis, DNA synthesis and repair systems. A new class of agents induces tumor growth retardation (cytostasis) and apoptosis by exploiting aberrant tumor stroma (as embrane-bound receptor kinases), protein dynamics, tumor vasculature, microenvironment and cellular signaling mechanisms. Drugs that target these pathways have already entered clinical practice.[124] Nevertheless, since OSCC is predominantly a locoregional problem at least in its early stages, surgery will likely remain as an important initial treatment with therapies like molecular targeting and gene therapy reserved for the adjuvant or palliative setting.

CONCLUSION

The study of oral cancer is particularly challenging. Oral cancer is an important cause of morbidity and mortality, especially in developing countries and its prevalence may rise in the foreseeable future. Advances in diagnosis and treatment have slowly accumulated but a sound understanding of underlying cell biology is likely to enable further much needed progress.

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