REVIEW ARTICLE

Current aspects and future strategies in oral cancer research: A review

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Abstract

The prevalence of oral cancer is exponentially increasing and it has become one of the common causes for mortality and morbidity. Oral cancer is a multifactorial disease, but tobacco is regarded as the most important attribute for its development. It can be preventable by the intervention of risk factors. Its early detection can minimize its detrimental effects and can improve the quality of life of the patient. The aim of this review article is to identify the current aspects in oral cancer diagnosis and management and to highlight the future prospects in this field.

Introduction

Oral cancer is a serious and rapidly growing life threatening issue in many parts of the world. Oral and oropharyngeal cancer grouped together, forms the sixth most common cancer in the world.[1] It constitutes approximately 5% of all cancers globally, with 60,000 new cases of oral cancer is reported every year in India.[2] Of the 0.3 million annual cancer related deaths in India, nearly 33% arise from tobacco-related cancers.[1] Oral cancer is associated with mutations in genes that regulate cell growth and apoptosis leading to uncontrolled proliferation of tumor cells, which occur due to the exposure to tobacco, alcohol, betel quid, etc.[1] Recently, alarming changes noticed in the presentation of oral cancer in younger age group i.e. those 40 years or younger with a significant percentage of them having no habits is both enigmatic and disconcerting. Having cancer is in itself tragic, having it at a younger age is cataclysmic.[1] Despite best treatment a person affected by oral cancer may remain socially and functionally handicapped substantial rise in mortality rates among the young individuals have provoked the researchers from various countries to undergo a comprehensive research in oral cancer. The etiology of oral cancer is multifactorial.[3,4] Though tobacco and tobacco products accounts for three-fourths for the development of oral cancer but several other etiological factors are also involved in the development of oral cancer.[1,3,4] Some of the suggested etiological agents of oral cancer are tobacco and its related products, alcohol, human papilloma virus (HPV) type 16, 18 infections, chronic irritation, acinitic radiation, various forms of drug abuse etc.[1,5] Prognosis of oral cancer is very discouraging because it is generally diagnosed at a very advanced stage. However, if oral cancer is detected at an early stage it not only has a good prognosis but can increase the survival rate and can improve the quality of life of the patient also.[1]

Discussion

Early detection of oral cancer is a continuing goal. Thorough head and neck as well as intra oral examination is a prerequisite for that.

Acidophilic metachromatic toluidine blue dye stains acidic tissue components, thereby staining DNA and RNA and renders effective visualization of high risk areas especially with rapid cell proliferation of oral squamous cell carcinoma (OSCC).[6]

Vizilite uses hand-held, disposable chemiluminescent light stick which emitting light at 430, 540 and 580 nm wavelengths, thereby enhancing the visual discrimination

between normal mucosa and oral premalignant lesions. Normal epithelium absorbs light and appear dark, while dysplastic or hyperkeratinized lesions appears white. This variation in color is due to altered epithelial thickness, or the greater density of nuclear content and mitochondrial matrix reflecting light in the dysplastic tissues.[7]

Oral brush biopsy employs the principle of exfoliative cytology to provide a cytological assessment of cellular and dysplastic changes. It provides a complete transepithelial sample, which is fixed on a glass slide, stained with a modified papanicolaou stain and scrutinized microscopically via a computer-based imaging system. Advances in cytomorphometric methods mingled with genetic and proteomic profiling can provide a valuable tool for in depth screening of oral cancer in the future.[8,9]

VEL scope is a hand-held device based on the principle of chemiluminescence and auto fluorescence, which was approved by Federation Dentaire Association for direct visualization of the oral cavity. It is relatively quick and allows complete viewing of the oral cavity in 2 min.[10]

Saliva is widely known as mirror of the body, depicting the entire spectrum of normal and disease states and therefore meets the demands for a non-invasive easily accessible diagnostic tool. Due to inadequate knowledge of disease markers and presence of very minute concentration of these markers in saliva, the diagnostic potential of saliva has not been fully explored. Nevertheless, in the present scenario, extremely sensitive and high-throughput assays such as mass spectrometry, DNA microarray and nanotechnology based sensors are available which can measure protein and RNA markers at low concentrations in saliva, thus amplifying the utility of saliva as a diagnostic medium.[11]

Molecular methods to detect oral cancer involve the use of DNA ploidy, quantification of nuclear DNA content. DNA content of nucleus depends on the number of chromosomes. In oral epithelial dysplasia and malignancy there exists aneuploidy or polyploidy. Therefore the quantitative analysis of DNA content depicts the total chromosomal content, which is performed by a flow cytometer.[12,13]

Tumor markers serve as a valuable aid in detection of oral cancer. Tumor suppressor genes, angiogenic markers, cellular proliferation markers and cell adhesion molecules are some of the potential tools, which help in determining the prognosis of patients with OSCC. Various studies have shown that altered cytokeratin expression has been implicated with the progression of OSCC.[14]

Heat shock protein (HSP) expression has a significant role in the diagnosis of oral cancer. HSP expression helps to predict the abnormal changes, which occurs during the process of carcinogenesis. There is correlation between HSP expression and degree of differentiation in oral malignancies. However, HSP expression is not very useful in diagnostic immunopathology, since it is expressed by a large number of malignant cells and tissues.[15]

Polymerase chain reaction (PCR) is a molecular biology based tool, which can be utilized for detecting oral malignancies. PCR facilitates detailed study of oral malignancy and provides a clear perceptive of the pathogenesis of neoplasia. PCR can be used to identify oncogenes, tumor suppressor genes thereby serving as an important diagnostic tool.[16] Although PCR technique has increased the range and sensitivity of diagnostic procedures yet it poses with a major drawback, as contamination and amplification artifacts may give rise to confusion and can lead to misinterpretation of the final result.[16]

Auto fluorescence spectroscopy is a propitious tool for the detection of oral cancer. It consists of a small optical fiber producing different excitation wavelengths and a spectrograph, which receives and analyzes it with the help of software, the spectra of reflected fluorescence from the tissue. It can be useful in guiding the clinician in identifying the optimal location for biopsy.[17]

Fluorescence photography is a simple, non-invasive and easily reproducible method of detection of oral cancer. Fluorescence positivity shows enlargement and progression of the disease.[18]

Microfluidics engineering has devised a chip on which assessment of various body fluids like blood, cerebrospinal fluid, urine, and saliva can be done in a microscale. However, the device is still under trial and further research needs to be done to assess the outcome of this particular device.[19]

As the technology advances, we can see a metamorphosis from histopathology to genetics in the diagnosis of oral cancer. There are evidences in literature that next generation sequencing has been used to detect HPV sequences, identifying subtypes and calculating viral load in HPV induced verrucous carcinoma cases.[20] The genetic methods for the diagnosis of oral cancer is still under trial and further studies are required to determine their advantages and disadvantages.

Various diagnostic aids for oral cancer are summarized in Table 1.

The prime objective of oral cancer management is to prevent mortality and to improve the quality of life of the patient. The choice of treatment depends upon the site and size of the primary lesion, cell type and degree of differentiation, presence or absence of lymph node metastases, assessment of potential complications of each therapy. Surgery is the most commonly accepted in the treatment of oral cancer, followed by radiotherapy. Chemotherapy is an adjunct to the principal curative modalities of surgery and radiation.

Surgery and Neck Dissection

Surgery is the most common treatment modality for oral cancer. The intention of surgery is to completely remove cancerous tissue, leaving behind histologically normal tissue. Larger tumors often require an approach from outside the oral cavity and the removal of both soft tissue and bone. More advanced oral cancers may involve the lymph nodes. Positive lymph node involvement might necessitate a radical neck dissection. Elective neck dissections are undertaken when the lymph nodes are negative in order to prevent the risk of metastasis. The level of neck dissection depends on the number, size, and site of the lymph nodes involved. The efforts to minimize extensive surgery have resulted in the invention of newer advanced surgical techniques,

Table 1: Various diagnostic aids for oral cancer

Clinical methods	Vital staining-toluidine blue
	Vizilite
Exfoliative cytology	Rapid PAP staining
	Oral brush biopsy
Histopathology	Routine hematoxylin and eosin staining
Saliva based diagnostic tools	Salivary proteinomics
	Salivary transcriptome
	Salivary micro RNA
Light based diagnostic tools	Auto fluorescence
	Chemiluminescence
	Tissue fluorescence spectroscopy
Molecular methods	DNA ploidy and quantification of nuclear DNA content
	Tumor markers and biomarkers
	PGR based diagnostic aids
Genetic methods	Next generation sequencing
	DNA microarray

PGR: Progesterone receptor, PAP: Papanicolaou

which decreased the morbidity and provided an overall benefit to rehabilitate of the patient.[21,22]

Different forms of surgery for the cure of oral cancer

Fluorescence visualization (FV) guided surgery

Auto fluorescence enhances the visualization and helps to depict the lateral spread of the cancer. Direct FV, has made it possible to detect severe dysplasia at the time of surgery, when the tissue appears clinically normal.[22]

Sentinel node mapping

It is a minimally invasive technique and can be employed for the detection of micro metastatic lymph nodes without even the evidence of lymph node metastasis after routine clinical examinations in early OSCC. It directs the surgeons to identify "skip" metastases and unforeseeable lymphatic drainage patterns.[23]

Laser microsurgery

Since its inception in 1960's laser microsurgery has been widely used for the treatment of oral and laryngeal diseases and has shown several advantages over the conventional resection procedures. Laser treatment is more conservative, minimizing the chance of infection, heals faster, bleeding, swelling, and scarring is less when compared with conventional surgery. However, the procedure is technique sensitive and the outcome completely depends on the skills of the surgeon performing it.[22]

Reconstructive surgery

Following resection reconstructive surgery has a vital role, especially when there is loss of structures in the oral cavity which are involved in function or esthetics. Different techniques that may be employed for the reconstructive surgery in the oral cavity are split thickness skin graft, radial forearm free flap, fibula free flap that can be used for reconstruction of composite defects of the maxilla and mandible.[21,22]

Transoral robotic surgery (TORS)

TORS provides a magnified, three-dimensional (3D) view of the cancerous region and the surrounding normal tissue through an endoscope, thereby avoiding the extensive cervical incisions, which is often mandated for open surgeries.[24]

Cyber knife robotic radiosurgery system

It is a breakthrough technology, which is a non-invasive alternative to surgery for the treatment of oral cancer. It delivers beams of high dose radiation with extreme accuracy to the tumors, which are inoperable. However, it is technique sensitive and the success of the treatment depends on the knowledge, skills and the experience of the surgeon.[24]

Osseointegrated implant surgery

Rehabilitation using oosseointegrated implants gives the ability to provide secured prostheses thereby enhancing cosmetic and functional results. Implants has the added advantage that it can be placed in irradiated bone also.[21,22]

Radiotherapy

Radiotherapy involves the use of ionizing radiation to treat cancer. Ionizing radiation may be administered as an external radiation beam targeting the tumor (external beam radiotherapy), or by directly implanting radioactive sources within the tumor (brachytherapy). External beam radiotherapy is usually delivered in fractionated doses, which means that the total dose is delivered over time in smaller doses or fractions. Conventional fractionation schedules deliver treatment in single daily fractions of 1.8-2 Gy, 5 days/week, resulting in dose accumulation of approximately 10 Gy/week. Nearly 50% cancer patients take the delivery of radiotherapy which contributes toward 40% of curative treatment for cancer. New developments in radiation oncology have helped to improve outlook for patients and find more effective treatment with less side-effects.[25]

Different forms of radiotherapy for the cure of oral cancer

Particle radiation therapy

It is one of the traditional method of delivering therapeutic radiation which includes both proton and neutron therapy. Proton rays having the advantage of being able to conform to the shape of the tumor.[25,26]

Stereotactic radiotherapy

It involves the use of single high dose radiation directed directly to the tumor mass. The technique is explicit and painless. An example of this technique is the gamma knife.[26]

Intra operative electron radiation therapy (IOERT)
IOERT excludes the delivery of radiation to normal tissues and the critical structures in and around the target, therefore called as precision radiotherapy as the clinician sights the tumor directly.[26]

Image guided radiotherapy (IGRT)
IGRT can be a useful tool to identify and rectify the geographic skip that might occur in the delivery of treatment.[25,26]

3D conformal radiation therapy
With the invention of 3D conformal radiation therapy, which involves the compilation of reconstructed matched computed tomograms and magnetic resonance images during treatment plan, thereby reducing the risk of geographic skip and the direction of the beam can be limited to the tumor size and shape by the use of custom-made compact block.[26]

Intensity-modulated radiotherapy (IMRT)
IMRT delivers appropriate dose of radiation precisely to the tumor cells, leaving behind the neighboring healthy tissue. This is widely known as tomotherapy. IMRT is delivered by the use of linear accelerators with static or multi-leaf collimator or volumetric arc modulated therapy.[25]

Radioimmunotherapy
It is a form of radiation therapy which uses cytotoxic radionuclides such as iodine-131, yttrium 90 to deliver toxins directly on to the cancerous mass This system of radiation delivery is also known as targeted radiotherapy.[25,26]

Chemotherapy

With the invention of new drugs, chemotherapy has taken a vital role in the treatment of oral cancer. Synergism of chemotherapy and radiotherapy is one of the accepted methods for the treatment of advanced oral and oropharyngeal cancers. The motive behind the use of chemotherapy is to destroy dividing cancer cells thereby restricting invasion and metastasis. There are three different modes of chemotherapy: Induction chemotherapy which is given before surgery, concurrent chemoradiotherapy which is in conjunction with radiation treatment and adjuvant chemotherapy, which is given after surgery. Chemotherapeutic agents can be classified into: Antimetabolites (methotrexate and 5-fluorouracil), platinum compounds (cisplatin and carboplatin) and taxanes (docetaxel). Platinum containing agents are regarded as the major drugs forming the foundation of most chemotherapy schedules.[27,28]

Forms of chemotherapy that are used for the treatment of oral cancer

Targeted therapy
The prime agent is cetuximab, a monoclonal antibody used with the intention to target the epidermal growth factor receptor (EGFR), which is over expressed in epithelial cancers such as OSCC. Cetuximab has the potential to inhibit EGFR.[28]

Other Recent Developments in Oral Cancer Management

Gene therapy

Gene therapy involves the use of DNA as an agent to treat disease. It aims to introduce a functional gene directly into the cells of a patient to reverse an inborn error of metabolism and to modify or repair an acquired genetic abnormality. Presently, most of the gene therapy studies are aimed at cancer and hereditary diseases which are linked to genetic defects. In the future, it can be a precursor to a definitive form of treatment for oral cancer and precancerous lesions, which can be more effective in comparison to that of the current therapies, by minimizing the mortality and morbidity associated with these lesions.[29]

Nutraceuticals

Comprehensive research has provided evidence that cancer can be managed using plant-derived dietary compounds, nutraceuticals is an optimistic approach. They have the potential to treat various cancers due to their chemical diversity, multi-targeting action and safety profile. The anti-tumor effects of curcumin, is already established. Green tea polyphenols can be utilized as therapeutic agents for oral cancer in combination with standard therapy. Resveratrol produced by a variety of plants, such as grapes and mulberries. It has many favorable properties, which has been utilized in treating many diseases including cancer.[30]

Various treatment modalities for oral cancer are briefed in Table 2.

Table 2: Various treatment modalities for oral cancer

Treatment modality	Different forms
Surgery	Fluorescence visualization guided surgery
	Sentinel node mapping
	Laser microsurgery
	Reconstructive surgery
	TORS
	Cyber knife robotic radiosurgery system
	Osseointegrated implant surgery
Radiotherapy	Particle radiation therapy
	Stereotactic radiotherapy
	IOERT
	IGRT
	3D conformal radiation therapy
	IMRT
	Radioimmuuotherapy
Chemotherapy	Targeted therapy
Other recent developments in the treatment of oral cancer	Gene therapy
	Nutraceuticals

TORS: Transoral robotic surgery, IGRT: Image guided radiotherapy, 3D: Three-dimensional, IMRT: Intensity-modulated radiotherapy, IOERT: Intra operative electron radiation therapy

Research Models

Research by the use of *in vitro* and *in vivo* experimental models can enhance the understanding of disease progression and the therapeutic response. Only a limited number of cell lines are available for the culture of oral potentially malignant disorders. Direct culture of dysplastic cells can lead to misleading results due to smaller size of dysplastic samples and the contamination from oral microflora. *In vitro* immortalization of normal and dysplastic cells and carcinogen application can be used to model multistep carcinogenesis. Though *in vitro* models are highly valuable for genetic studies but *in vivo* experimental models that can be generated by exposing the experimental animals to different carcinogens are more effective in simulating the malignant transformation and tumor behavior. All stages of OSCC can be mimicked by using *in vivo* models, which can help in the development of new biomarkers and innovative chemotherapeutic approach.

In vivo models can be used to evaluate and compare the efficacy of different chemotherapeutic agents. Recently it has been found that selective cyclooxygenase (COX)-2 inhibitors delays tumor onset, slows down tumor growth and increases the survival in hamsters. But COX-2 inhibitors are yet to get success in clinical trials.[31]

Conclusion

Oral cancer continues to be a deadly disease for more than 50% of the cases diagnosed every year. This is due to the fact that most of these cases are diagnosed when they have already progressed to the advanced stage. Various studies have revealed that there is a lack of awareness about oral cancer, its signs and symptoms among the general population across the globe. Educating the general population about oral cancer is a must to combat mortality and morbidity arising out of it. It is necessary to have an understanding about the risk factors, how to eliminate them and what needs to be done when one has already got a premalignant lesion, and these missions can only be accomplished through public awareness programs.

Research needs to be done on the natural history, clinical course of the disease, particularly on those precancerous lesions which turn cancerous over time. Invention of new tumor markers with high sensitivity and specificity can lead to early detection of oral cancer and can minimize the damage. Continued research needs to be done to improve the diagnostic and treatment modalities for oral and oropharyngeal cancers, which can not only reduce the mortality but also enhance the quality of life of the patients.[1,31]

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