Review Article

Clinicopathological Prognostic Implicators of Oral Squamous Cell Carcinoma: Need to Understand and Revise

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Abstract

In spite of the vast amount of research and the advances, oral squamous cell carcinoma implies quite significant mortality and morbidity rates. This has motivated the search of factors with prognostic relevance. A web based search was initiated for all published articles by using Medline/PubMed, Google Scholar with key words such as prognosis, survival rate, risk factors associated with oral squamous cell carcinoma, prognosis of oral squamous cell carcinoma. The search was restricted to articles published in English language with no restriction to date of publication. This review was focused on clinical, pathological and molecular factors associated with survival and prognosis of oral squamous cell carcinoma patients. Most articles had described one or two parameters related to prognosis. Considering the biological behavior and nature of cancer, all the parameters were interrelated and so could not predict the prognosis independently. Consideration of all the parameters was required to assess the prognosis. We hypothesize the use of combination of clinical and pathological indicators together to assess the prognosis. The care givers can assess the prognosis in a more better and definitive way by using prognosis assessment sheet.

Key words: Oncogenes, oncoviruses, oral squamous cell carcinoma, prognosis in oral cancer, tumer node metastasis staging

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Introduction

Prognosis, a Greek word derived from the term ″gignosko″ meaning ''to know.'' It is defined as ″the prediction of probable cause, duration and outcome of disease based on general knowledge of the pathogenesis of the disease and the presence of risk factors for the disease″.[1] It is the prediction of the course or outcome of a disease and is often confused with risk. Generally, it deals with likelihood that an individual will develop a disease in a specified period.

Cancer patients and their loved ones face too many unknowns. Understanding cancer and what is to be expected can help patients in many ways, like helping in planning treatment, thinking about lifestyle changes, making decisions about their quality of life and also management of finances. Morse *et al*., had stated that ''most important was to see what the patient wants to know and then find out what the patient actually took away from the communication.''[2] The study showed that younger oncologists were more likely to talk to patients about a terminal prognosis and 5 year survival rate.[2]

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Oral squamous cell carcinoma (OSCC) is a multifactorial disease. It has a remarkable incidence worldwide and has fairly burdensome prognosis, encouraging further research on factors that may modify disease outcome.[3] Though some of the factors proved to be causative agents like tobacco, alcohol and human papilloma virus, the prognosis of disease is also determined by many other factors. These factors range from simple demographic factors to molecular markers, encompassing the clinical and histopathological factors. Chen *et al*., suggested that predictive factors in oral and pharyngeal carcinoma survival are: Ethnic

groups, period of diagnosis, gender, diagnostic age, anatomic site, type, and therapy.[3] It has been observed in literature that many authors have tried to show the correlation of some independent factors or group of factors with prognosis of patients with OSCC. But none of the factor can alone influence the prognosis of individual with OSCC. While determining the prognosis of individual with OSCC all the factors like demographic, general physical factors, clinical factors, histological factors, and molecular factors should be taken in to consideration.

5 year survival rate

"Survival rates have shown the percentage of people who live for a particular length of time after learning that they have cancer."[3] It included people at different stages like people who were free of disease, or who had few or no signs or symptoms of cancer, or people were receiving treatment for cancer.

This statistics applied to group of people and could not be used to predict what would happen to a particular person. No two people are exactly alike, and treatment and responses to treatment also vary greatly. Oral cancer survival rates have been increased approximately 15 percent within the time frame of 1960s until 2004.[3] Overall, 60% of people with oral cancer survive for 5 years.[4] Camisasca *et al.*, reported that the 5 year survival rate was 92% in OSCC patients without recurrence and 30% in patients with recurrence.[5] Very recently Wang *et al.*, have showed that 5 year survival rate is 31.8% in OSCC patients with recurrence and 79.9% without recurrence.[6]

Categories of prognostic factors

Clinical implicators of OSCC [Table 1]

Demographic factors

Age

Patient's age was a commonly considered co-variable and was known to influence the outcome of treatment. Increase in incidence of tongue cancer in young adults as compared to older adults of more than 40 years of age was found. Schantz *et al.*, had stated that genetic susceptibility to environmental carcinogens may influence the risk for OSCC in young adults.[7] While the correlation of prognosis with age seemed controversial, many others were able to demonstrate, a far worse prognosis in older individuals. It is generally held view that OSCC in young people are less aggressive and have a good prognosis [Table 1].

Gender

Gender did not seem to be a significant determinant of survival for patient with OSCC. Neither for men nor women exhibited any significant clinical differences in outcome. The survival analysis confirmed that gender did not affect survival.[8]Although some authors have reported lower survival rates in females [Table 1], it was attributed to delayed seeking of medical care and lower acceptance of treatment.[7]

Race

African Americans were almost twice as likely to present with terminal stage as compared to their white counterpart.[9] Swerdlow *et al.*, in 1995 had shown that mortality rates for the oral cancer in Indian migrants residing in England and Wales were higher as compared to those born in England.[10] In United States the increasing trend of oral cancer among older black men and among young white men (aged 30-34 years) and women (aged 25-29 years) merits careful observation.[11]

Ethnicity was also hinted to strongly influence prevalence and death rates owing to social cultural practice, where they represent risk factors. Indians had poor outcome as compared to westerns, because of the lack of awareness which made them to approach very late for treatment.

Habits

Most authors have reported higher mortality in smokers and alcohol drinkers. Betel quid chewing had also been specifically correlated with poorer prognosis.[7] The effect of alcohol was tested by using Michigan Alcoholism Screening Test (MAST) given by Deleyiannis *et al*. It is three tire alcohol severity staging system for assessing prognosis of head and neck cancer.[12] According to this system patients with present drinking habit and having history of alcohol related systemic health problems were more likely to die as compared to non alcoholics and abstinent (less than one drink per week) alcoholics without a history of any alcohol related systemic health problems[12] [Table 1].

Any smoking during 6 weeks course of radiotherapy decreased the complete response from 74 to 45%. In such patients 2 year survival decreased from 66 to 39%, and the survival time from 30 to 16 months.[12] Cessation of smoking habit had a significant relation with survival. Risk reduction is 40% for those who quit habit less than 12 weeks prior to diagnosis and 70% for those who quit habit 1 year prior to diagnosis.

Day *et al.*, showed the influence of frequency and duration of smoking and alcohol consumption. The risk for second primary tumor showed an increase by five times for those who smoke 40 cigarettes per day for more than 29 years whereas 15 or more drinks of beer per week, showed increase in the risk by 3.5 times compared to light drinkers (4 drinks per week).[12]

Table 1: Clinical parameters in prognosis assessment sheet

Sr. No	Factors related	Parameters		Indicated score		Applied score
I	Demographic parameters	Age	Below 40 years = 1	Above 40 years = 2		
		Gender	Male = 1	Female = 2		
		Race	White = 1	Negroid = 2	Mongoloid (southeast Asians) = 3	
		Tobacco	No tobacco consumption = 0	History of tobacco consumption = 1	Presently consuming tobacco = 3	
		alcohol habits	No alcohol consumption = 0	Abstinent/Light drinkers = 2	Heavy drinker = 3	
		Diet	Fruits and vegetables = 1	Meat, roosted, fried or broiled meat = 2		
II	Patients general medical condition	Comorbid illness	Low- No systemic illness = 1	Moderate - poorly controlled hypertension, old stroke, and history of an alcoholic seizure. = 2	Severe - CCF or MI within the last 6 months, recent stroke = 3	
		Nutritional status	Well nourished = 1	Malnourished = 2	Tumor Chahexia = 3	
		Anemia Hemoglobin level	Male ≥ 14.5 = 1 Female≥ 13	Male < 14.5 = 2 Female < 13		
III	Miscellaneous factors	Sociodemographic parameter	Married and religious = 1	Non married, Widowed, divorced, single non religious = 2		
		Treatment	Combination therapy = 1	Radiation therapy alone = 2	Surgical therapy alone = 3	
					Total applied score	

CCF – Congestive cardiac failure, MI – Myocardial infarction

Factors related to the patient's general medical condition

Comorbidity

Presence of other diseases, illnesses, or conditions not directly related to the index cancer is comorbidity. Multiple instruments have been utilized to characterize comorbidity. According to Piccirillo *et al.*, 24% of patients with head and neck cancer had moderate or severe comorbidity. Moderate comorbidity included poorly controlled hypertension, old stroke, and history of an alcoholic seizure. Severe comorbidity includes congestive heart failure or myocardial infarction within the last 6 months, recent stroke, and severely decompensated alcoholism.[13]

Nutrition and oral cancer

The Greek physician Hippocrates, regarded as the father of modern medicine, said, "Let food be your medicine and medicine be not your food." Almost 2500 years later, this is an advice still worth following. Malnutrition is common in patients with head and neck cancer and attributable to a number of causes including poor dietary habits, excessive alcohol consumption, local tumor effects, and tumor-induced chachexia.[14]

Epidemiological literature on the relationship between nutrition and human cancer indicated that certain food items such as butter, eggs, red meat and most notably processed meat containing nitrosamines that posed an increased risk. High consumption of fruits and vegetables was implicated to have a protective effect against development of oral cancer. High meat intake is accounted for 49% of oral and pharyngeal cancers, low vegetable intake for 65% and low fruit intake for 54%. Prolonged consumption of foods rich in nitrites and nitrosamines such as preserved meats and fish increased a lifetime risk for the development of oral cancer. Consumption of fried or broiled foods and employment of microwave cooking increased the risks of oral cancer owing to the formation of heterocyclic amines.[15]

Fruits and vegetables contain Vitamin C, carotene and other carotenoids which act as efficient antioxidants, prevent damage to chromosomes, enzymes, and cell membranes caused by the peroxidation of free radicals.[14] The strongest protective effects were reported from citrus fruits and in vegetables those available as in raw form, such as fresh tomatoes, green peppers, carrots and thus pointed to a mechanical cleansing effect of raw fruits and vegetables on the oral cavity.[14]

Anemia and oral cancer

Anemia would also influence tissue oxygenation and thus worsened local control and survival in patients who received radiotherapy as a component of their treatment. Multivariate analysis revealed that hemoglobin was the only significant predictor of local control and survival. Hemoglobin level of 14.5 in men and 13 in women was associated with improved locoregional and survival control.[15]

Pathological prognostic implicators of OSCC:

Factors related to primary tumor

Tumor dimension

Tumor size and extensions determine clinical and pathological T stage of Tumor (T) Node (N) Metastasis (M) (TNM) staging of head and neck tumor. Clinically, tumor dimension is the maximum surface diameter of mucosal neoplasm. Pathologically, it is the maximal cross-sectional diameter of a resected specimen. Moore *et al.*, stated that 84% of patients with tumor diameter less than 2 cm survived a disease free period of 3 years as compared to 52% of patients with a tumor larger than 2 cm in diameter.[16]

Tumor thickness

Tumor thickness is a more consistent predictor of nodal metastasis than surface diameter. Tumor thickness and risk for nodal metastasis were confirmed for several sites of head and neck.[17] Wolggar *et al.*, showed mean tumor thickness with a positive nodal metastasis was 19 mm. In the group in which tumor depth exceeded 5 mm, the metastatic rate was 64.7%.[18] In contrast, when the depth of invasion was less than 5 mm, the incidence of cervical metastasis was only 5.9%.[18] It was suggested that there is a discerning point at 5 mm of tumor depth at which cervical metastasis was probable. This statement can also be supported by the fact that in deeper connective tissue the presence of lymphatic channels acts as road entry for cervical metastasis [Table 2].

Tumor thickness is measured with ocular micrometer. The measurements were recorded from the top of granular layer of overlying epithelium to the deepest invasive tumor cells. Traditional categories were when tumor thickness was 0 to 0.76 mm; it was considered as superficial, whereas when it is 0.76 to 1.50 mm tumor thickness it was considered as intermediate depth, and finally the deep lesion was those when tumor thickness is greater than 1.50 mm. Five year disease free survival was 98% for histologically superficial lesions, 44-63% for deep lesions group.[19]

Total tumor volume

Total tumor volume (TTV) is measured by computed tomography (CT) scan, which can act as a prognostic indicator. TTV of less than 6 cm^3 had better local control over tumor progression. Calculation of TTV by using diagnostic imaging techniques can supplement traditional clinical staging for prognostic information [Table 2].[7]

Margin status

The margin refers to how close the cancer cells are to the edge of the normal tissue surrounding the tumor. The presence of residual carcinoma at the margins of surgical resection is an important risk factor for local recurrence in OSCC. Positive margins indicated microscopically aggressive tumor biology.

Margins were described in the following three ways

Positive margins: Invasive tumor within 5 mm of final surgical margin. Cancer cells were involving the outer edge of tissue. Carcinoma *in situ* involved final surgical margin. Dysplasia involved final surgical margin.

Negative margins: No cancer cells were seen at the outer edge. The standard negative measurement in most hospitals is 2 mm of normal tissue beyond the edge of the tumor.

Close margins: Cancer cells were very nearby but did not involve the outer edge of tissue. Between positive and negative margins.[7]

Local recurrence rate, ranged from 64 to 84% for positive margins. The presence of positive margins predicted poor overall survival for oral cancer. Intraoperative use of frozen sections for determining margin status reduced the local recurrence. Patients with clear margins had a survival rate of 69% at 5 years compared to 58% with close and 38% with involved margins.

Margins of tumor could also be categorized as follows

Clinical margins: the margins of tumor on clinical examination that is on observation and palpation. It was always included during the surgical removal of tumor tissue.

Surgical margins

The status of the surgical margin was an important predictor of outcome. The surgical margin, in contrast to the other prognostic indicators is under the direct control of the surgeon. Close surgical margins were considered as positive margins. High correlation existed between histological indicators of aggressive disease and close or involved surgical margins. These results implied that close surgical margins in OSCC could be regarded as an indicator of aggressive disease.

Histological margins: When outer edge or tumor front area, on microscopic examination showed positivity for tumorcells then it was considered as histological margins are positive. Intraoperative use of frozen sections for determining margin status also reduced the local recurrence.

Molecular margins: With advanced technology like the use of molecular markers to predict the positivity of tumor front or outer edges of the excised tissue. It has actually proved to be an ideal method to determine the adequacy or extent of tumor tissue removal. Various molecular markers could also be utilized for this purpose.

Anatomic location

The anatomic location of the lesion could also be considered as a prognostic indicator, since the tumors behave differently depending on anatomic location [Table 2].

In TNM staging, early stage clinical cases occurred mostly in patients with lower lip lesions, most of the tongue lesion cases were an advanced stage. Most of the

Table 2: Pathological parameters in prognosis assessment sheet

Sr. No	Factors related	Parameters	Indicated score			Applied score
I	Primary tumor	Tumor dimension	Less than 2 cm = 1	More than 2 cm = 2		
		Tumor thickness	Less than 5 mm = 1	More than 5 mm = 2		
		Total tumor volume	Less than 6 cm3 = 1	More than 6 cm3 = 2		
		Margin status	Negative = 1	Close = 2	Positive = 3	
		Tumor site	Lip, Buccal mucosa = 1	Floor of mouth, Tongue, Soft palate, retromolar area, alveolus = 2		
II	Histopathology	Malignancy grading	Malignancy point score is 6-10 = 1	Malignancy point score is more than 10 = 2		
		Pattern of invasion	Pushing well defined, solid groups or cords of cells = 1	Small clusters of cells, scattered, dispersed = 2		
		Perineural invasion	Absent = 1	Present = 2		
		Perivascular invasion	Absent = 1	Present = 2		
III	Cervical lymph nodes metastasis	Number of metastatic lymph node	1 lymph node positive = 1	2 lymph node positive = 2	More than 2 lymph node positive = 3	
		Extracapsular extension	No ECE = 1	Microscopic ECE = 2	Macroscopic ECE = 3	
		Node location	Only Sentinel (Level I, II, III) lymph nodes = 1	Outside sentinel (lower neck) lymphnodes involvement = 2		
		Node size	Less than 2 cm = 1	More than 2 cm = 2		
IV	Molecular factors	p53	Mutation Negative = 1	Mutation positive = 2		
		Angiogenesis related factors	MVD normal = 1	MVD elevated = 2		
		Cyclin d1	Negative in primary tumor = 1	Positive in primary tumor = 2		
		EGFR and TGF	Negative in primary tumor = 1	Positive in primary tumor = 2		
		Human Papilloma virus (HPV)	Presence of HPV in primary tumor = 1	Absence of HPV in primary tumor = 2		
					Total applied score	

ECE – extracapsular extension, EGFR- epidermal growth factor receptor, MVD- Microvessel density, HPV- human papilloma virus,

floor of the mouth and soft palate cases were classified as T4. Findings suggested that tongue, soft palate and floor of the mouth presented with the worst prognosis for OSCC.[20] Costa *et al.*, had found that lower lip tumors often had a better prognosis when compared to other oral locations. Squamous cell carcinoma of the tongue and floor of the mouth generally have poor prognosis due to the frequent presence of cervical metastases, inaccessibility, and late reporting by patients.[21]

Factors related to histopathology

Malignancy grading system

Pathologists have since long recognized the potential significance of cellular pathology. In 1920 Broder's grading system came into existence which is a simple scheme for assessing prognosis.[22] According to this system poorly differentiated OSCC meant one with poor prognosis. This system was criticized for its subjectivity and failure to predict survival in a multivariate modeling. Many grading systems were proposed in order to standardize the grading system and prognostic factors. Consideration was given to tumor host relationship also. In 1987, Anneroth *et al.* proposed a new malignancy grading system.[22] Recent study by Akhter *et al*., proved that Anneroth's classification system wasconsidered to be standard diagnostic and predictive factor for lymph node metastasis.[23]

A 5 year survival rate in patient with total malignancy score of 6 to 10 was 57%. When the score was more than 10, the 5 year survival rate was only 19%. Many studies had attempted to find out which histological parameter contributed most strongly in determining the prognosis and they showed that the pattern of invasion was an independent predictor for prognosis. Tumor cells invading in the form of small clusters or groups or in a dispersed pattern was associated with poor prognosis. In addition to pattern of invasion, lymphoplasmacytic infiltration also had a prognostic implication. The presence of intratumoral and peritumoral infiltration decreased the chances of cervical lymph node metastasis.[22] Recent studies have used Bryne's grading system for prediction of prognosis. In this system vascular invasion parameter had also been added, which was strongly associated with distant spread of tumor and caused specific survival.[24]

Perineural Invasion

Infiltration of perineural spaces occurs in upto 52% of OSCC. Mediated through nerve cell adhesion molecule (NCAM), on the surface of cancer cells which engage in homophilic binding with NCAM receptors (expressed by neural and perineural tissue).[25] The presence of perineural invasion (PI) in primary tumor is a predictor for cervical metastasis, locoregional recurrence. Centripetal and centrifugal propagation of tumor cells along perineural spaces and away from primary tumor is responsible for local recurrence.[26] Most tumors allow 2 centimeter (cm) of dissemination of tumor cells along perineural space, so malignant cells that evade surgical excision and radiotherapy, results in local recurrence. The relationship between PI and prognosis is independent of nerve diameter, so in all cases of OSCC, the pathological specimen should be examined for PI even in nerves less than 1 mm in diameter.

Vascular invasion

It is defined as, "the presence of neoplastic cells within an endothelial cell lined channel." It occurs in more than 50% of head and neck squamous cell carcinomas (HNSCCs). It correlates with the presence of concomitant cervical metastases and showed an increased risk of distant metastatic disease.[24] The skin of face and scalp is most commonly affected by metastases, suggesting that blood vessels and patterns of innervations may influence the spread of metastases.[27]

Factors related to cervical lymph nodes

Number of positive lymph nodes

Lymph nodes histologically positive for OSCC provide one of the simplest and perhaps the most important markers in head and neck cancer. Lymph node number exhibited a strong dose-response correlation with distant metastasis and survival.[28] It also indicated the risk for regional recurrence and distant metastasis. The relative importance of extracapsular extension (ECE) *versus* the number of positive nodes remains somewhat controversial. Moe *et al.*, found that ECE, not the number of positive nodes, was an independent predictor of poor survival.[28]

Extracapsular extension

Extracapsular extension (ECE) occurs in approximately 60% of patients with positive cervical nodes and is of paramount importance in predicting patient outcomes. A recent study reported a strong association between the presence of ECE and clinical N stage, in TNM staging.[28]

Level of ECE

The extent of ECE can be stratified into the following three levels based on the morphology of the involved cervical lymph nodes: (a) Macroscopic extracapsular spread with the involvement of adjacent anatomic structures such as the internal jugular vein or skeletal muscle; (b) Macroscopic extracapsular spread confined to the perinodal fibroadipose tissue; and (c) Microscopic extracapsular spread.

Regardless of its relationship with local recurrence, ECE is a significant determinant of prognosis due to its

association with an increased risk of recurrence in the neck and distant metastasis. The presence of gross or macroscopic ECE tripled the risk of neck recurrence. Patients with gross ECE were 1.5 times more likely to develop regional recurrence as compared to patients with microscopic ECE. Recent studies on 83 neck dissections for ECE and survival were assessed. When ECE was present, cause specific survival rate (3 years) was 32% whereas 5 year survival rate was 24%. Thus, ECE is strong predictor for estimation of survival.[28]

Nodal Location

Mamelle *et al.*, defined sentinel lymph node as ''those nodal groups that provide the primary lymphatic drainage for particular site within head and neck.''[28] Sentinel nodes for oral cavity tumors are level I, II, III. When the presence of nodal metastasis was outside the sentinel lymph node there was decrease in the 5 year survival rate by 50%. The presence of lower neck lymph node indicated chances of distant metastasis increasing by 33%.[28]

Nodal Size

The diameter of largest metastatic cervical lymph node correlates with N stage of TNM stage for OSCC. Carter *et al.*, had indicated that when node size was greater than 2 cm in diameter, there was an increased risk for regional recurrence.[28]

Molecular prognostic factors

There are vast array of molecular factors studied in head and neck cancer. Proto-oncogene is a gene which is transformed into an oncogene when its protein product becomes unresponsive to the normal regulatory processes that control cell division. Tumor suppressor genes (antioncogenes) inhibit cellular proliferation.

p^{53}

p^{53} is a transcription factor with tumor suppressor function that negatively regulates the cell cycle and serves to protect the integrity of the genome. Resides on chromosome 17p1. p^{53} mediates Gap 1 (Gl) arrest during cell cycle. p^{53} induction also results in apoptosis. Therefore, p^{53} protects the cell from propagating mutations to subsequent generations and is considered the ''guardian of the genome.'' In multivariate analysis, patients with p^{53} mutations were 2.4 times more likely to develop loco-regional recurrence conferred by the presence of positive cervical lymph nodes.[29]

Angiogenesis related factor

The sprouting of new blood vessels from a pre-existing endothelium enables the growth of tumors beyond microscopic size. Many growth factors and cytokines have been shown to promote angiogenesis. Vascular endothelial growth factor (VEGF) family plays a pivotal role in angiogenesis and VEGFC for lymphangiogenesis.

Elevated tumour microvessel density (MVD) correlates with the risk for concomitant cervical lymph node metastasis in oral cavity and nasopharyngeal carcinoma. Increased level of MVD correlates with increased locoregional recurrence.[29]Angiogenic activity can be assessed by IHC proteins such as factor VIII, CD31, CD34, and CD105, where CD is cluster of differentiation. Studies stated expression of CD105 (endoglin), which is a marker of neovascularization, was strongly correlated with poor disease free and overall survival, suggesting that the proliferating endothelial component was the primary determinant of tumor behavior.

Cyclin D 1

Cyclin D1, also known as PRADl, is a proto-oncogene located on chromosome llq13 that serves as the rate limiting controller of G1-phase progression through the cell cycle. Over expression of cyclin D1 shortens the G1 interval and reduces the dependence of the cell on mitogens for proliferations. When there is clinically negative cervical lymph node and if primary tumor is showing positivity for cyclin D1 than there is four-fold risk of histologically positive lymph node on neck dissections. Observations suggested that deregulation of cyclin D1 increased the overall aggressiveness of certain cancers by desensitizing cellular proliferations to inhibitory signals.[29]

Epidermal growth factor receptor and transforming growth factor alpha

The receptor tyrosine kinase epidermal growth factor receptor (EGFR) and its ligand transforming growth factor alpha (TGFRα) are frequently overexpressed in HNSCC. EGFR expression may also modulate tumor radio resistance. In agreement with laboratory data, clinical studies had established a correlation of EGFR overexpression with poor prognosis and radio resistance.[29]

Loss of heterozygosity

A malignant pathway toward malignancy is the loss of function of both alleles of tumor suppressor gene. Studies had demonstrated that loss of heterozygosity (LOH) at different loci were likely markers for prognosis in HNSCC. LOH at 3p region in early stage of OSCC was significantly correlated with reduced disease free and overall survival (LOH positive patient survival was 42 months).

Cytokeratin 8/18

The expression of cytokeratin (CK) 8/18 in SCC's of the oral cavity is an independent prognostic marker and indicates a decreased overall and progression free survival.[30]

Human papilloma virus

Males detected with human papilloma virus (HPV) had better overall and disease specific prognosis than males with HPV-negative tumors, but this was not observed among females. The common HPV strain associated with OSCC is HPV 16 type (63.5%) followed by HPV 18 type (30.8%) with less common being HPV 6 and 11. The presence of HPV was significantly correlated with a better survival in patients with OSCC.[31] This better survival was attributed to the fact that tumor cells infected by HPV were more radiosensitive as compared to HPV negative tumor cells.

Miscellaneous factors

Socio-demographic factors

Multivariate analysis revealed that those without religious belief tended to have higher probability of death than those who had religious belief [relative risk (RR): 2.057, $P < 0.001$]. Those who were single, widow/widower or divorced/separated had a poorer prognosis than those who were married (RR: 1.528, $P = 0.008$).[32] Therefore, care providers should take socio-demographic issues into consideration aside from ordinary clinical health care.

Treatment and oral cancer prognosis

In the early reported cancer patients, the 5 year cumulative survival rate for the patients undergoing surgery is 92%, radiation therapy is 69%, and combination therapy is 71%. This prognosis alters if patient is reported in advanced stage. The 5 year cumulative survival rate then for the surgery group is 74%, for radiation therapy is 37% and for combination therapy is 51%.[33]

Prognosis assessment sheet

Since prognosis of OSCC is multifactorial aspect and cannot depend upon single or independent factor. Even TNM staging system, which is purely clinical staging system, cannot predict the prognosis accurately. Authors had designed this prognosis assessment sheet, as a tool for proper assessment of prognosis. In this sheet all the parameters were considered which could influence the outcome of disease either directly or indirectly. In this sheet the applied score for a particular parameter was derived by using indicated score and thus total applied score was calculated. As the total applied score increases, the prognosis of individual decreases. So prognosis is inversely proportional to total applied score. When the combined score of clinical and pathological factors increases more than 54 than prognosis will be worst as even molecular prognostic indicators should be positive to cross the applied score beyond 54.

Summary

In demographic view prognosis of OSCC was found to be poor for females, patients above 40 years of age, Southeast Asian origin, with tobacco and alcohol consumption, people with diet of mostly non-vegetarian. Patients with the presence of or history of any systemic illness would have poor prognosis. Combination therapy of radiotherapy and surgical therapy provided better prognosis. Patients with tumor at floor of mouth, soft palate and posterior tongue and when tumor diameter was more than 2 cm, thickness of tumor more than 5 mm and total tumor volume more than 6 cm^3 would have poor outcome. Histologically, patients with poor grade tumor with most of margins were positive and involvement of more than two cervical groups of lymph nodes with extracapsular invasion would have poor survival rate. Molecular markers could also adjunct the assessment of prognosis.

Conclusion

Understanding the vast array of factors that contribute to the prognosis of patients with HNSCC, an accurate assessment of patient risk can be made there by promoting the development of optimal treatment strategies. In addition, novel targeted therapies are emerging, which enabled clinicians to mitigate the risk have associated with adverse molecular factors. Prognosis assessment sheet is a new kind of hypothesis which needs to be testified by conducting multicentre case control longitudinal studies at a large sample scale.

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