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Does haematological parameters can be used as an indicator for long term prognosis following treatment for Oral Squamous Cell Carcinoma - A review

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ABSTRACT

Oral cancer includes a group of neoplasms affecting any region of the oral cavity, pharyngeal regions and salivary glands.This term is used interchangeably with oral squamous cell carcinoma which represents the most frequent of all oral neoplasms.Despite the advances of therapeutic approaches, percentages of morbidity and mortality of OSCC have not improved significantly during the last 30 years.Database search was done in Pubmed,Cochrane library.Grey literature was also included.Search terms such as oral squamous cell carcinoma, neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio and platelet-lymphocyte ratio and prognosis were used.The aim of this review was to investigate whether haematological parameters can be used as an indicator for long term prognosis following treatment for oral squamous cell carcinoma.

Keywords: *Oral squamous cell carcinoma, Neutrophil-lymphocyte ratio, Lymphocyte-monocyte ratio and Platelet-lymphocyte ratio, Prognosis*

INTRODUCTION

Oral cancer includes a group of neoplasms affecting any region of the oral cavity, pharyngeal regions and salivary glands[1].This term is used interchangeably with oral squamous cell carcinoma (OSCC) which represents the most frequent of all oral neoplasms[2]. It is estimated that 90% of all oral neoplasms are OSCC.OSCC is a malignant neoplasm of stratified squamous epithelium[3].Despite the advances of therapeutic approaches, percentages of morbidity and mortality of OSCC have not improved significantly during the last 30 years[4].Cancer therapy are associated with morbidities that may negatively affect the quality of life:-from the time of diagnosis, during cancer therapy, in the immediate period after the cancer treatment, and continue throughout the life of the patient[5].The older literature often combines oral squamous cell carcinoma and oropharyngeal cancer making the evaluation of epidemiology, pathogenesis, and outcomes difficult to assess as it is now recognized that OSCC and OPC must be evaluated individually[6].

The oral cavity includes the lips, the labial and buccal mucosa, the anterior two-thirds of the tongue, the retromolar pad, the floor of the mouth, the gingiva, and the hard palate. The oropharynx includes the palatine and lingual tonsils, the posterior one-third (base) of the tongue, the soft palate, and the posterior pharyngeal wall[7].Percentages of morbidity and mortality in males are 6.6/100,000 and 3.1/100,000 respectively, while in females percentages are 2.9/100,000 and 1.4/100,000 respectively[8]. The incidence of OSCC is increasing among young individuals aged 18 to 44 years, particularly among men. The percentage of 5-year survival for patients with OSCC varies from 40-50%[9]. Regardless of the easy access of oral cavity for clinical examination,OSCC is usually diagnosed in advanced stages[10].According to World Health Organization,squamous cell carcinoma of oral cavity in males in developing countries is the sixth commonest cancer after lung, prostrate, colorectal, stomach and bladder cancer, while in females it is the tenth commonest site of cancer after breast, colorectal, lung, stomach, uterus, cervix, ovary, bladder and liver[11].Recent studies confirm that oral cancer are seen in many areas of India.Tobacco and alcohol are the two most important known risk factors for the development of oral cancer[12].Other factors in OSCC include dietary factors, immunodeficiency and viral infections like HPV 16/18.Although OSCC has a lower incidence than other malignant tumors, it is known to produce high mortality and serious disturbances or discomfort in the patient[13].The objective of this review was to investigate whether haematological parameters can be used as an indicator for long term prognosis following treatment for oral squamous cell carcinoma.Our team has extensive knowledge and research experience that has translate into high quality publications.[14–27]

Etiology of oral squamous cell carcinoma

Early detection of cancer is a key factor for good prognosis and increased patient survival rate. Even though the oral cavity can be easily examined and assessed by direct visual examination, most OSCC cases are not identified early[28].Mostly patients do not seek dental care on a regular basis because oral cancers in the early stages are asymptomatic. In order to diagnose early and increase the prognosis of cancers, patient awareness about regularly visiting dentists and the importance of maintaining good oral hygiene is to be done[29]. There are many potentially malignant disorders in the oral cavity that have the predisposition to transform into OSCC.The most common type of oral cancer is epidermoid carcinoma[30] which originates in abnormal mucosa as either leukoplakia, erythroplakia or speckled leukoplakia[31].OSCC most commonly begins in a leukoplakia which can be smooth or rough, flat or elevated, ulcerated.Leukoplakia is manifested histologically by a thickening of the mucosa[32].When the thickened surface layer contains cells with retained nuclei it is termed hyperparakeratosis; if the thickened surface layer cells do not contain nuclei it is termed hyperorthokeratosis[33,34].Many leukoplakia lesions result from combinations of the various thickenings, for example -hyperparakeratosis with acanthosis.These hyperplastic lesions of oral mucosa such as hyperparakeratosis, hyperorthokeratosis, acanthosis or combinations have a benign course[35].The stage following hyperplasia in the pathogenesis of oral cancer is dysplasia.[36]. It is not proved that the removal of the cause of dysplasia in the oral cavity will result in resolution of the disease therefore dysplastic areas are considered irreversible precancerous lesions.Carcinoma in situ, cancer confined to the surface epithelium, shows all the histological criteria of carcinoma.However this process has not spread beyond the boundaries of the surface epithelium.Therefore, invasion and metastasis are not present in carcinoma in situ[37] .Metastases which generally occur via the lymphatics of the neck are presented as fixed, indurated, matted swellings of the neck. These neck metastases show increase in size, produce fistulation and cause discomfort to the patient.Some precancerous conditions that can progress to OSCC are :- Erythroplakia,Leukoplakia , particularly erythroleukoplakia (nodular or verrucous) and proliferative verrucous leukoplakia , actinic

cheilitis , lichen planus (mainly the erosive and atrophic type) , sideropenic dysphagia (Plummer-Vinson syndrome) ,submucous fibrosis,dyskeratosis congenita , discoid lupus erythematosus[38].

Various etiological factors of OSCC have been reported in the literature. The most common are cigarette smoking,tobacco and alcohol[39].There are two forms of smoking -smoke and smokeless.

a.Smoked tobacco

Bidi is the most popular form of tobacco in India.Bidi produces a smaller volume of smoke than cigarette,as they contain a small amount of coarsely ground tobacco compared to 1 gram of finely cut tobacco in cigarettes.Reverse smoking is a type of smoking where tobacco is smoked with the lighted end inside the mouth.Air is supplied to the burning zone through the unlightened end of the cigarette and smoke is expelled through the cigarette or through the mouth[40].

The various smoking habits seen in India are the following:-

Bidi:- About 0.2-0.3 grams of sun dried tobacco flakes are hand rolled in a rectangular piece of tembhurni (Diospyros ebenum) or tendu (Diospyros melanoxylon) leaf and tied with a thread.

Chillum:- It is a straight measuring about 10-14cm long conical clay pipe used for smoking tobacco .The chillum is held vertically and to prevent tobacco from entering the mouth , a pebble or a stopper is introduced into the chillum .It is filled with coarsely cut tobacco pieces and a glowing charcoal is kept on top of the tobacco[41].

Chutta:-It is a cylindrical coarsely prepared cheroot.Cured tobacco is wrapped in a dried tobacco leaf.Cigars are made of air cured ,fermented tobacco usually in modern factories .Cheroors are small cigars made of heavily bodied tobacco.These forms usually does not have a wrapper[42].

Cigarettes:-About 1 gram of tobacco cured in the sun or artificial heat is covered with paper.The tobacco is generally treated with a variety of sugars,flavoring and aromatic ingredients.They are estimated to contain 1-1.4 mg nicotine and 19-27 mg of tar.Only 51% are filter tipped and filter length averages of 12mm.The filters of Indian cigarettes comparatively trap less nicotine[43].

Dhumti:-These are conical cheroots.Rolled leaf tobacco is used inside a leaf of jackfruit tree.Sometimes dried leaf of the banana plant is used.This form of tobacco is sometimes used for reverse smoking among women[44].

Hookah:-It is also called water pipe or hubble-bubble.It is used in places with strong Mughal cultural influence.Hookah is purely a indian origin which corresponds with the introduction of tobacco in India.The tobacco smoke is drawn through the water in the base of the hookah which cools and filters the smoke.

Hookli:-It is a clay pipe of short stem varying from 7-10 cm with a mouthpiece and a bowl.

b.Smokeless tobacco

Paan chewing is the most common habit of smokeless tobacco usage in India.It is alkaline in nature.It causes chronic alteration to the oral mucosa in habitual paan chewers because of the pH alteration ,due to slaked lime usage many times a day.The buccal mucosa loses its smoothness and the rough areas retain the quid for sometime which gradually shows discolouration[45].

The various forms of smokeless tobacco used in India are:-

Khaini:-It is powdered sun dried tobacco ,slaked lime (calcium hydroxide)-paste mixture occasionally used with arecanut.It is simply placed in the mouth or chewed.The ingredients are vigorously mixed with the thumb to make mixture alkaline and placed inside the mouth.

Mainpuri tobacco:-Ingredients used in this are tobacco,slaked lime,finely cut arecanut,camphor and cloves.

Mawa:-it is a preparation containing thin shavings of arecanut with the addition of some tobacco and slaked lime.It is usually wrapped in cellophane paper and tied in the shape of a small

ball.Before consumption , the packet is rubbed vigorously to mix the contents and mixture is chewed until it becomes softer.

Mishri/Masheri:-It is prepared by roasting tobacco on a hot metal plate until it is uniformly black and then powdered.It is used along with or without catechu.Catechu is a residual extract obtained by soaking the wood of the tree Acacia catechu or Acacia suma in boiling water.

Paan:-It refers to the betel leaf and often as quid.The quid(also called as beeda ,tambula)contains arecanut (which may be used raw ,baked or boiled),lime obtained from limestone or seashells and according to local customs may also include aniseed,catechu ,cardamom,cinnamon,coconut,cloves,sugar and tobacco wrapped in betel leaf[46].

Snuff:-contains finely powdered air-cured and fine-cured tobacco leaves.It may be dry or moist ,used plain or with other ingredients and used orally or nasally.Bajjar is a dry snuff used by women in Gujarat.It is carried in a metal container.A twig is dipped into it and applied over the tooth and gingiva.

Zarda:-Tobacco leaf is boiled in water along with lime and spices until evaporation.The residual tobacco is then dried and coloured with dyes.It is chewed.

Gutka:-It is a preparation of crushed betel nut,tobacco and sweet or savoury flavourings.

Pan masala:-It is a mixture of betel leaf with lime,areca nut ,clove ,cardamom,mint,tobacco in the form of granules[47].

Gudakhu:-Is a paste of powdered tobacco,molasses (brown sugar).It is predominantly used by women in Bihar[8].

The constituents usually present in tobacco include nicotine,tar,carbon monoxide,nitrogen oxides,hydrogen cyanide;metals like nickel,arsenic,cadmium,chromium and lead;radioactive compounds like polonium-210 ,potassium-40,radium-226,radium-228 and thorium -228[39].

Alcohol:-The carcinogens that are present in the alcohol have been implicated in development of oral cancer. Consumption of alcohol and tobacco found to act synergistically and pave the way in development of oral cancer. In few studies alcohol itself is found to be an independent risk factor in development of oral epithelial dysplasia and oral cancer.Alcohol leads to increase permeability of oral mucosa, causing alteration in morphology, characterized by epithelial atrophy, leading to easier penetration of carcinogen in the oral mucosa[48,49].

Viral infections:-Viruses have been found to play a role in development of oral squamous cell carcinoma. Viral genes are proto-oncogenes, they become oncogene once they get inserted into hosts DNA leading to malignant transformation[50]. Viral infections of latent or chronic nature are mainly responsible for inducing malignant transformation by disrupting host cell cycle, which in turn affects cell growth and proliferation[51]. The viruses that are mostly involved in OSCC are human herpes virus Epstein– Barr virus (EBV), Human papillomavirus (HPV) and Herpes simplex virus[52].However the role of Epstein Barr virus and Herpes simplex virus is still unclear.Human papilloma viruses are the most common virus that play role in development of oral squamous cell carcinoma. HPV type 16 and 18 are found to be the major cause in development of OSCC[49].

C.Other risk factors

In population based studies ,some authors proposed that there may be gene alterations implicated in the development and progression of oral squamous cell carcinomas and the stages of carcinogenesis [53].Genetic changes commonly observed in oral squamous cell carcinoma include loss of heterozygosity at the site of known or suspected tumour suppressor gene.Other factors like poor oral hygiene, sharp or fractures cusp, ill-fitting dentures are also seen in the development of OSCC with presence of other risk factors[54].Consumption of fruits and vegetables is associated with reduced risk for oral cancer due to the antioxidant vitamins C and E and flavonoids[2].Occupational risks like individuals who are exposed to sunlight, ultraviolet rays are prone for carcinoma in the lips.Even though several risk factors play a role

in the development of OSCC, the most common and established factor is tobacco[1].

Molecular Pathogenesis of OSCC

Several studies have been proposed to the significance of heredity in oral carcinogenesis. Several genes are implicated in genetic predisposition of oral cancer[55]. Gene polymorphisms participating in the metabolism of xenobiotic factors, such as cytochrome P450 1A1 (CYPIA 1) and glutathione S-transferase Mu 1 (GSTM1) are related to the increase in the carriers.OSCC arises as a consequence of multiple molecular events that develop from the combined effects of an individual's genetic predisposition and exposure to environmental carcinogens, such as, tobacco, alcohol, chemical carcinogens, ultraviolet or ionizing radiation and micro-organisms[56]. Chronic exposure to carcinogens may damage individual genes as well as larger portions of the genetic material[57] such as chromosomes. Genetic damages may activate mutations or amplification of oncogenes that promote cell survival and proliferation. Mutations include DNA general hypomethylation, hypermethylation or hypomethylation of certain genes such as cyclin D, and alterations of chromatin[58]. Genetic damages may also inactivate tumor suppressor genes involved in the inhibition of cell proliferation.All these events lead to cell dysregulation to the extent that growth becomes autonomous and invasive mechanisms develop[59].As OSCC grows and invades, new blood vessel formation occurs. This angiogenesis is an essential part of tumor formation[60]. According to field cancerization theory, since the oral epithelium is exposed to carcinogenic factors, the entire area is at increased risk for the development of malignant lesions from the accumulation of genetic alterations of oncogenes and tumor suppressor genes[61]. OSCC presents different clinical aspects which are related with the location of the tumor, evolution time, precancerous lesions and risk factors. The most frequent clinical aspects are: tumor, ulcer, vegetans, verrucous and mixed forms such as ulcerous-vegetans or verrucose- ulcers[62]. Leukoplakia, erythroplakia or erythroleukoplakia are the most frequent clinical aspects that are present in superficially eroded areas. The lesions are asymptomatic initially,which are small in size that show changes on the surface and do not respond to local treatments[63]. The lesion progresses and develops as an exophytic, irregular lobulated lesion or an irregular growth pattern characterized by a depressed ulcer with grayish-white edges, elevated, everted and indurated borders and an infiltrated base[64]. In most cases, lesions are asymptomatic,pain occurs only when muscles or nerves are invaded at advanced stages of the disease[65]. Tongue carcinoma represents 30-40% of OSCCs, the lateral tongue being the most frequent site (80%), followed by ventral and dorsum. Lateral borders of the tongue and ventral surface OSCCs are usually presented by traumatic lesions caused by sharp cusps or sharp edged teeth, by badly positioned teeth or by maladjusted dentures that chronically rub the mucosal areas[66]. Ulcerated forms are the most frequently seen followed by exophytic tumors, which generally produce pain irradiating to the ear. In the ventral area, ulcer-vegetant or mixed forms predominate.OSCC located in the anterior half of the tongue usually lead to lymphadenopathy in the suprahyoid region while those located in the posterior half lead to submaxillary, carotid and retropharyngeal nodes[67].It is not painful at early stage although the tongue’s mobility can eventually be impaired. It advances from the surface to the depths of the tissues, invading the floor of the mouth muscles, the submental, submaxillary and cervical nodes. Most buccal mucosa SCC is characterized by developing on previous lesions[33].According to OSCCs, invasive lesions would lead their spreading through the lymph nodes. Mobile, painless nodes where size increases and gets fixed to surrounding tissue in the advanced stages are those that are clinically suggestive of malignancy[68].

A.Markers in Oral Squamous cell carcinoma

Despite improved therapeutic modalities, the survival of patients with oral cancer has remained unchanged over the last three decades. The fate of the patient depends decisively on the conventional prognostic factors used in clinical

practice[63]. In many cases, these factors remain inadequate and are unable to discriminate against tumors of the same clinical stage that may have distinct clinical outcomes and respond differently to the same treatment. Therefore, it is important to look for biologic prognostic indicators that might be incorporated to predict prognosis of treatment outcome[69] .

B.Biomarkers

The molecular biology of head and neck squamous cell carcinoma suggests that specific pathways are relevant to the development and progression of this disease. Over the last decade, scientific research related to these events has been performed to investigate biological, diagnostic, and prognostic parameters[70].These include growth factors and their receptors, signal transducers, transcription factors, cell cycle regulators, proliferative and apoptotic proteins, cyclooxygenase 2, nuclear factor kappa B, hypoxia-related proteins, and angiogenesis. In head and neck cancer, except for epidermal growth factor receptor (EGFR)[71], there are few studies that have correlated the protein expression of signal transducer and activator of transcription 3 with clinicopathologic parameters[72].Furthermore, in OSCC, most of the studies pertain to components associated with the well-defined cell cycle regulatory pathways.Most of these published studies have used single markers,whereas a minority of studies have used small groups of prognostic indicators [47]. Through the analysis of few molecular indicators , the relationship and complex interplay between these molecular carcinogenic cascades cannot be ascertained.It is clinically important to simultaneously analyze molecular alterations to find out the most important ones that may help to accurately reflect the biological aggressiveness of disease and predict prognosis and also providing more precise information about treatment response[73].Molecular biomarkers may highlight biological differences between cancers and help to prognose patient outcome.More than one hundred molecular biomarkers (identified by immunohistochemistry) were introduced as prognosticators for OSCC. Five biomarkers including p53, Ki-67, p16, VEGFs and cyclin D1 were most often reported.The evaluation of molecular biomarkers in different subsites of the oral cavity is common in literature[74]. However, variations in the immunohistochemical staining results reflect variations in proteomic and genomic properties of OSCC between different oral sites. For example, various immunohistological biomarkers analysed in tongue and buccal mucosa oral squamous cell carcinoma samples did not associate with survival in oral tongue squamous cell carcinoma, whereas some of them were prognostic in buccal carcinoma [75].Almost all of the most reported biomarkers ,except vascular endothelial growth factors, which contribute to tumour angiogenesis reflect important growth-related properties of the cancer cells[76]. However, non-neoplastic cells of the tumour stroma, including fibroblasts, endothelial cells and inflammatory cells, seem also to have a critical role in cancer progression[77]. Accordingly, biomarkers of the stromal microenvironment might even have a greater impact on prognosis than biomarkers related to tumour cells [77]. However, biomarkers related to tumour microenvironment such as Activin A [78]are not yet widely studied in oral tongue squamous cell carcinoma. The only tumour microenvironment biomarker that was reported repeatedly in oral tongue is the cancer-associated fibroblast identified by a α-smooth muscle actin antibody.About 86% of the studies claimed to have found at least one biomarker to have prognostic value. Relationships between biomarkers and clinicopathologic manifestations, other than survival, have been reported in many studies[79].

C.Genetic markers

Oral squamous cell carcinoma like other malignancies arises from the accumulation of a number of discrete genetic events that lead to invasive cancer. These changes occur in genes that encode for proteins, which control the cell cycle, cell survival, cell migration and angiogenesis. Cytogenetic analysis has shown a series of alterations in OSCC, most frequently in chromosome 9, chromosome 17 gene as well as 3P, 13q21 and 18q21[80]. The proteomic

analysis of OSCC specimens revealed correlation of thirteen RNAs with their encoded proteins implying transcription control with survival rate. Among these, reduction of Desmoplakin, Plakophilin 1 and Tripartite motif-containing protein are directly related to poorer disease specific survival.Several cytogenetic and molecular studies have investigated the occurrence of genetic alterations in head and neck squamous cell carcinoma, demonstrating that oncogene activation and tumor suppressor gene inactivation are involved in the development of the disease. Genetic alterations, mainly gene amplification, mutation and overexpression, leading to oncogene activation have been observed in OSCC[81].Amplification and overexpression of the oncogenes myc and epidermal growth factor receptor have been observed in head and neck squamous cell carcinoma and are correlated with a poor prognosis. Overexpression of myc leads to malignant transformation[82]. Although no association has been found between the c-myc amplification and sex, gender, tumor size, clinical stage or differentiation, studies showed that patients with tumors with high levels of c-myc showed shortened overall survival. The EGFR gene is frequently amplified and overexpressed in cell lines and primary head and neck tumors. In a recent study of head and neck squamous cell carcinoma, overexpression of cyclin D1 has been correlated with lymph node metastases and advanced clinical stage. In addition, cyclin D1 immunoreactivity is more frequent in tumors of patients with shortened disease-free interval and overall survival [83].Genetic alterations involving the tumor suppressor genes p16 and TP53 are frequently observed in head and neck tumors. Inactivation of these genes appears to be involved in the early stages of the disease. However, the diagnostic and prognostic value of these genes remains unclear at present[84].

D.Haematological markers

Prognostic biomarkers are important for treatment because they provide essential information about the patient's overall outcome[85]. However, molecular biomarkers that need tissue specimens for analysis impose a burden on patients as it requires an invasive approach for sample collection[86].The analysis time for tissue biomarkers is also long. Therefore, there is an urgent need for convenient and non-invasive prognostic biomarkers for oral cancer.It is well known that cancer has a close relationship with inflammation[87]. Inflammatory responses cause tumor progression such as initiation, progression, and metastasis[88]. The peripheral blood cell counts of the lymphocytes, monocytes, neutrophils, and platelets are reported to be associated with prognosis in several cancers[89]. These values can be activated by oxidative stress, chemokines, and cytokines during cancer initiation and progression[90]. One report suggested that leukocytes work differently in patients with cancer and those without. The neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) are important hematological biomarkers and have been reported to be significant prognostic markers of several cancers(lung carcinomas and tongue carcinomas).

Neutrophil-lymphocyte ratio

The association between NLR and prognostic factors have been reported in various cancers. The peripheral NLR was calculated as the ratio of the absolute peripheral neutrophil count to absolute lymphocyte count[91].The measurement of NLR is very accessible and affordable because blood sampling is used. NLR could be used as a simple indicator of systemic inflammatory responses in cancer patients. Neutrophils secrete matrix metalloproteinase 9 to promote carcinogenesis and tumor cell proliferation into the cancer microenvironment[92]. In contrast, lymphocytes suppress tumor progression and are associated with an increased survival in various cancers. In the Takumi et al study , high NLR was associated with poor disease specific survival and Overall survival[93].In Japan, Nakashima et al. and Sano et al. reported that the cutoff values were two times higher than the standard cut off values.In his study, NLR was a prognostic indicator of OS and independent of known risk factors (age, sex,

smoking, or alcohol drinking)[63,69], tumor behavior characteristics (tumor size, tumor site, histological grade, and TNM staging) and utilization of adjuvant treatment (chemotherapy or radiotherapy).They found that tumor size and TNM staging were associated with Overall survival and relapse free survival, and lymph node metastasis was associated with relapse free survival .The association between NLR and clinicopathological factors such as lymph node metastasis, T stage, differentiation, and perineural invasion was reported also reported in Tsai et al study.In his study there were differences in the presence of pathological multiple lymph node metastases in the patients with high NLR like in several reports[94]. Therefore, NLR may be useful in predicting multiple lymph node metastases.

Lymphocyte-monocyte ratio

The total and differential white blood cell (WBC) count has been historically used as a marker of infection and inflammation[94].The peripheral LMR was calculated as the ratio of the absolute peripheral lymphocyte count to absolute peripheral count of monocyte.It has become an important prognostic measurement of outcomes in cancer treatment[83]. Many studies have shown association between pretreatment peripheral inflammatory cells and prognosis in different kinds of cancers[91].As part of the functional relevance, inflammatory responses lead to chronic oxidative stress and generate oxygen free radicals, which have been shown to stimulate cancer initiation, promotion, and progression[95].The association between LMR and prognostic factors were reported in head and neck cancers. Ong et al. reported that low pretreatment LMR indicated poor survival in patients with early tongue cancer. In Takumi Hasewaga study ,low LMR was associated with poor disease specific survival and Overall survival. A low LMR may mean a relative decrease in lymphocytes and increase in monocytes. The decreasing lymphocytes may be related to high NLR or high PLR(Platelet - Lymphocyte ratio).Tsai et al. reported that a higher pretreatment count of circulating monocytes was independently associated with poor prognosis in patients with oral cancer[9,30]. Chronic inflammation including cancer increases the monocyte count by the secretion of various cytokines such as TNF-α, IL-1, and IL-6[96]. Generally, the monocytes differentiate into macrophages[9]. Pollard et al. reported that an increased number of tumor-associated macrophages was associated with poor prognosis in cancers .Their results showed that factors such as absence of nodal involvement and early stage were associated with favorable prognosis for oral cavity cancer patients[97]. They found that an elevated neutrophil lymphocyte ratio and monocyte count were significantly associated with poorer overall survival and were independent of other variables to predict the prognosis for oral cavity cancer patients. However, these studies relied on a relatively smaller sample and the cut-off value for monocyte count was based on a median value of circulating monocyte count. There is evidence that in advanced cancers,the host systemic immune response is an important independent predictor of outcome, and that pretreatment measurements of the systemic inflammatory immune response can be used to independently predict cancer survival[97]. Sasaki and colleagues studied the pre-operative absolute monocyte count in patients who had liver resection due to hepatocellular carcinoma, as well as in patients who underwent hepatic surgery due to colorectal metastasis and found that pretreatment absolute monocyte count was an independent prognostic indicator of tumor recurrence and survival in patients with hepatocellular carcinoma. Similarly, absolute monocyte count has been reported to be independent prognostic indicator for breast cancer, gastric cancer, Hodgkin's lymphoma, Colorectal cancer, and Ovarian cancer.The exact underlying mechanism explaining the association between the elevated number of monocytes and unfavorable cancer prognosis is unclear but there is a possible mechanism saying that monocytes secrete various proinflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-10, and TNF-α have been associated with shorter survival and worse prognosis in malignancies[98]. Moreover, monocytes upon stimulation are known to release monocyte chemo-attractant protein-1 and

mediate tumor-associated macrophage infiltration in solid tumors, which could produce a variety of chemokines such as TGF-α, TNF-α, IL-1, and IL-6 to promote tumorigenesis, angiogenesis, and distant metastasis of malignant tumors[99]. Further, studies have linked monocytes with an increased number of bone marrow-derived myelomonocytic cells[100]. These cells infiltrate the tumor and differentiate into tumor-associated macrophages, which in turn release many angiogenic factors and have been shown to be associated with poor prognosis in cancers[101].

Platelet lymphocyte ratio

Traditionally, the clinical management including the treatment strategy and the prognosis of cancer has been based on the TNM staging system.It has been debated that prognostic markers considering patient characteristics and host-related conditions, such as Glasgow Prognostic Score (combination of C-reactive protein and albumin), may be superior to TNM staging system considering tumor behavior only. NLR and PLR, the ratio between specific circulating cell counts from a routine blood test before surgery has constituted an inexpensive and widely available indicator.The relationship between PLR and poor prognosis is controversial. Several investigators suggested that a high PLR indicated poor prognosis in patients with head and neck squamous cell carcinoma. In Takumi at al study, a high PLR was associated with poor DSS. In contrast, Yu et al. indicated that preoperative PLR was not associated with survival or relapse in oral, pharyngeal, and lip cancer [102]. The exact mechanism of the association between a high PLR and poor prognosis is not clear.Platelets can promote tumor progression by increasing angiogenesis through secretion of vascular endothelial growth factor, and invasion, and metastasis through epithelial-mesenchymal transition[103].These results suggest that the host immune-inflammatory status represented by preoperative NLR value determines the prognosis of patients with cancer[32]. Although a high PLR was positively correlated with larger tumor size, later clinical stage, more male and more smoking and/or alcohol drinking as well, there were no significant differences of OS and RFS between high and low PLR groups. Rassouli et al. in his study of 273 patients showed that both a high NLR and a high PLR are associated with higher mortality rate in head and neck squamous cell carcinoma[104]. They also found that high NLR, but not PLR is associated with higher rates of recurrence.Rachidi et al. in his study of 543 patients showed that an increased NLR was associated with less survival time. Chen et al. suggested that PLR, but not NLR as an independent indicator in predicting survival in patients with OSCC[105].Oz turk's study showed that NLR and PLR were not associated to predict OS and RFS in early stage tongue SCC but were associated with local recurrence in early stage tongue SCC . [47]

Prognosis

Unfortunately, the 5-year survival rate has not changed during the last half of the century, still being around 50–55% in spite of the advances in diagnosis and treatment[106]. Early diagnosis is a foremost step for reducing cancer mortality, since the identification of smaller lesions allows less aggressive and debilitating treatments. However, almost half of intraoral cancers have late diagnosis (stages III or IV)[107]. Survival rates were related to age, gender, location, stage, risk factors and treatment; 74% of the patients were male with a median age of 60 years. The lowest survival rate was found between 61 and 70 years of age. After five years of OSCC diagnosis, the general survival rate reached 35-40 %[108]. The most frequent cancer location was in the tongue (26%), followed by gum (23%) and floor of the mouth (11%).When surgery was the only treatment indicated, patient survival rate was 55%. When radiotherapy complemented surgery, the rate decreased to 33%, which is in good agreement with the literature[109]. As far as risk factors are concerned, it is seen that the majority of the patients were smokers and heavy drinkers; higher mortality rates were found especially in male patients having these habits compared to those with only one or none of them[49]. However, previous studies show that younger people have a considerably better five-year

survival. Age is therefore a determining factor to good outcomes for OSCC patients [68].

Recurrence

Factors that influence the recurrence of OSCC have been extensively seen in recent years. Ebrahimi et al.have reported that T stage and N stage were important factors affecting regional recurrence in OSCC[30]. Camisasca et al. have analyzed patient clinicopathologic data, including tumor sites, clinical and pathologic stage, histological grade, invasion mode, and perineural invasion. They have concluded that tongue cancer and poor differentiation contributed to OSCC recurrence after surgery[110].Vázquez-Mahía et al. have reported that the recurrence rate was 44.9% in 118 patients with OSCC in his study[111]. Statistical analysis in his study showed that comorbidities, degree of tumor differentiation, and tumor stage were important prognostic factors for recurrence. However, for patients at T3-T4 stages and with poorly differentiated tumors, primary tumor resection margin should be expanded, generally 2 cm or more from the tumor, to ensure surgical safety[112]. Flap repair should also be performed. The results in their study showed that the application of flap repair significantly reduced local tumor recurrence. Vicente et al. have followed up 98 patients with OSCC[113]. In addition to that, neck lymph nodes should be carefully cleaned while resecting the primary tumor. They found that the regional recurrence rate was significantly lower in patients who underwent selective neck lymph node dissection than in those who underwent primary tumor resection only[114]. Thus, neck lymph node dissection is an important prognostic factor for the recurrence of OSCC. Preoperative neoadjuvant chemotherapy and postoperative adjuvant chemotherapy or radiotherapy can also reduce recurrence and improve prognosis[32]. All patients in this study underwent 1-2 cycles of preoperative neoadjuvant chemotherapy, and patients in advanced stages were treated with 4 cycles of adjuvant chemotherapy or radiotherapy after surgery[115]. The recurrence rate was 32.7%, and the 5-year survival rate was 54.5%. Cooper et al. have also reported that postoperative radiotherapy and chemotherapy can improve disease-free survival and improve local and regional control rate in patients with head and neck squamous cell carcinoma.OSCC has a bad prognosis and survival time is short in spite of the technological[112] advances applied to treatments. Most patients, disregarding the initial symptoms, report at advanced OSCC stages. OSCC is related to preventable risk factors.Intensive public promotion and educational campaigns are essential to increase patient awareness[114]. Dental professionals play an important role both in primary prevention of oral cancer by inducing healthy lifestyles and in secondary prevention by detecting oral cancer or its precursor lesions at early stages.

CONCLUSION

Inflammatory process plays a major role in the initiation genesis progression of oral cancer.High levels of inflammatory response would have a poor prognosis on cancer outcomes.Prognostic indicators should be able to predict the disease outcome following treatment in patients with oral squamous cell carcinoma.Hematological inflammatory indicators like Neutrophil-Lymphocyte ratio,Lymphocyte -monocyte ratio, Platelet -Lymphocyte ratio could be used both pre-treatment and at regular intervals post treatment to evaluate and assess the long time prognosis.

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