Association of Clinicopathological Factors with Radiation Induced Oral Mucositis in Patients with Head and Neck Carcinoma

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Abstract

Objective To evaluate the association of clinicopathological factors with radiation induced oral mucositis in patients with head and neck carcinoma.

Methods This cross-sectional study was carried out at Department of Radiotherapy Neurospine and Cancer Institute and Ziauddin University, Karachi. Inclusion criteria was patients with confirmed non-metastatic carcinoma histologically, age range of > 20 and 70 years, and patients requiring radical radiotherapy showing visible oral and oropharyngeal mucosa in the field of radiation (55 to 66 Gray). The exclusion criteria was a history of more than one tumour recurrence, prior history of radiation to the head and neck region, atypical liver and renal function" unusual haematological status and other deliberated medical condition. The patient was examined under aseptic conditions using sterilized examination instruments. The clinical grading of oral mucositis was done using WHO criteria by the end of 2-3 weeks of radiation treatment. Data was analyzed by means of SPSS version 23.0

Results: Overall 30 patients were included. The mean age was 43 years $\pm$ 5.62 (25-70 years) and 76.7% were males. Approximately 70% cases belong to middle-class families with 90% having no previous family history. Histological grade 2 and grade 3 mucositis were mostly reported. Tobacco and betel nut chewing was the most common habit. Right sided buccul mucosa was the most common affected site. It has been observed that TNM staging and histological grading have shown statistical significance in cases of oral mucositis.

Conclusion This study concludes that oral mucositis is significantly associated with TNM staging and histological grading of tumours. Male gender, elderly age, middle to low socioeconomic status, tobacco and betel nut chewing, right-sided buccal mucosa and stage II TNM staging were the most frequent factors.Grade 2 and grade 3 oral mucositis were the most frequent clinicopathological factors associated with the radiation therapy of head and neck cancer.

Keywords: Radiation, carcinoma, squamous cell, Head neck, mucositis,

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Introduction

The 6th most prevalent cancer in the world is head and neck squamous cell carcinoma (HNSCC), which is the collection of similar neoplasms that occur in the oral cavity, oropharynx, hypopharynx, and larynx. Approximately 650000 new instances of head and neck cancer have been reported[1].

Across the globe, 14.1 million cancers are diagnosed. Of the 3 million cases, are of lip and oral cancers, whereas particularly in Asia, the incidence rate is 48%, in which 5.2% of males and 2.5% of females are included. Head and neck cancers are mostly derived from the mucosal epithelium in the oral cavity, larynx, and pharynx and are known altogether as head and neck squamous cell carcinoma. Squamous cell carcinoma of the head and neck is, and frequently fatal[2].

The exact cause of the increased frequency of young-onset HNSCC is unknown. Although many

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etiological factors have been identified that might participate a significant function in the pathogenesis of the disease, they may include genetical correlation, human papilloma virus(HPV), betel nut and areca nut chewing, use of tobacco and related products, chronic irritations, inflammations,etc. Although the existence of premalignant lesions and conditions may increase the chance of developing oral cancer. Human papilloma virus(HPV) was detected by sequencing DNA from infected tumours, and the majority had a mutational profile compatible with cigarette consumption. According to studies, a portion of the HNSCC in the young populace appear to be caused by an increase in HPV infection, particularly in males (smokers and non-smokers). Other risk factors in young patients with HNSCC include persistent irritation in the oral cavity,systemic disorders, and immunosuppression[3]. Young-onset HNSCC in young patients may have different hallmarks than in older patients due to these unique risk factors. The use of betel quids containing areca nut and lime has long been linked to an elevated risk of mouth cancer in the Indian subcontinent, some parts of Southeast Asia, and Taiwan[4]. Snuff dipping was discovered to be the most common predisposing practice, particularly among female patients (84.61%)[5].

In recent years, surgery and radiotherapy have been the two baseline treatment options for most early-stage HNSCC patients. Although surgery is the main treatment of choice, in respect of anatomical vital structures in the vicinity of the surgical site, radiotherapy is considered the next option. If detected early enough, HNSCC of the oral cavity can be well controlled with surgery or Radiation therapy can be the curative or pa-lliative treatment for nearly 75% of all head and neck cancers, alone or as a part of the multi modulatory approach. Radiation therapy is given in divided doses of multiple fractions, i.e., either conventional fractionation or altered fractionation. Altered fractionation is mostly used due to its fewer toxic effects. Two types of altered fractionation are the hyper fraction and the accelerated fractionation. Radiation therapy, being an alternate treatment modality, has some harmful sequelae also. During treatment, the short term and immediate side effects include severe xerostomia, oral mucositis, ulceration, acute candidiasis, and skin erythema. Long-term side effects of radiation therapy include xerostomia, mucosal and skin atrophy, radiation caries, osteoradionecrosis, tissue scarring and fibrosis, and various organ-related side effects[7].

Radiation-induced oral mucositis (RIOM) is one of the most common side effects in head and neck cancer patients receiving radiotherapy. Oral mucositis is an inflammation related disorder of the oral mucosa produced by radiation-induced damage to the cells of the basal layer of the oral epithelium rather than the surface cells. The incidence rate of RIOM is up to approximately 79.8% in head and neck irradiated cancer patients, and altered fraction radiation therapy is found to have RIOM up to 100%. RIOM has five biological stages during the course of its patho physiogenesis, which include initiation, then primary damage response, which leads to signal amplification, followed by ulceration, and healing in the end[8]. Hyperkeratosis of the oral mucosa accompanied by erythema and pain are among the first clinical signs of RIOM, usually after 10–20Gy of dose, followed by a mild focal area of desquamation and then diffuse mucosal ulceration when the dose reaches up to 30Gy. The high level of RIOM in head and neck carcinoma irradiated patients signifies the importance of its early diagnosis as the symptoms of RIOM include severe pain, dysphagia, speech restrictions, malnutrition and an overall decrease in the quality of life. Understanding the molecular specifics of RIOM would potentially allow for the finding of new prognostic biomarkers and the early diagnosis of patients likely to develop early RIOM as well as promote close tracking and characterization of the side effects[9].

Squamous cell carcinoma of the mouth is the most common cancer in our society. It can be due to the easy and cheap availability of tobacco and its related products, lack of awareness, dependency and addiction, low socioeconomic status,

etc. In a study published in 2020, conducted in Karachi, the data on malignancy reported that oral malignancy constitutes about 57.5% of soft tissue pathologies in Karachi[10]. There is no precise data regarding OM-associated proteins in Pakistan, and international data does not apply to our population because cancer patients differ in terms of culture, genetics, and response to treatment. Therefore, this study aimed to evaluate the association of clinicopathological factors with radiation-induced oral mucositis in patients with head and neck carcinoma.

Methods

This cross-sectional research was conducted at the Radiotherapy department of Neurospine and Cancer Institute, and Ziauddin University, Karachi. The duration of the study was six months from October 2021 to March 2022. The inclusion criteria were patients with confirmed non-metastatic carcinoma histologically, an age range of > 20 and 70 years, and patients requiring radical radiotherapy showing visible oral and oropharyngeal mucosa in the field of radiation (55 to 66 Gray). The exclusion criteria were: history of more than one tumour recurrence, prior history of radiation to the head and neck region, atypical liver and renal function, unusual haematological status, other deliberated medical conditions such as diabetes mellitus or connective vascular disorders, poor oral hygiene, regular smokers or snuff drinkers patients with missing radiotherapy sessions,etc.

After ethical review permission and informed consent, patients fulfilling the inclusion criteria were recruited through non-probability conservative sampling. Confidentiality and anonymity of patients were maintained throughout the research. A sample size of 30 patients was calculated using open epi software. The confidence interval was 95% and the margin of error was 5% and the anticipated frequency of 4.7% with grade 4 mucositis[11].

After taking informed verbal consent the patient was examined under aseptic conditions using sterilized examination instruments by the researcher on each visit. The basic demographics were collected using a predesigned proforma. Basic demographic information includes age, gender, habits, socioeconomic status, and family history of oral cancer, TNM staging, histological grade and site of tumour. The clinical grading of oral mucositis was done using WHO criteria by the end of 2-3 weeks of radiation treatment.

SPSS version 23.00 was used to enter and evaluate the data. For quantitative data age, mean and standard deviation (SD) were determined, as well as qualitative variables like gender, habits, socioeconomic level, family history of oral cancer, TNM staging, histological grade, and tumour site were evaluated as frequency and percentage. Spearmen's correlation test was used to assess the association of several clinicopathological parameters with the grade of oral mucositis. The value of $p \leq 0.05$ was regarded as significant.

Results

There were 30 patients in total. Table 1 summarizes the important clinicopathological characteristics, such as age, gender, tumour site, clinical staging, histological grading therapies, RT modality family history, socioeconomic level, and behaviours. The average age was 43 years $\pm$ 5.62 with the age range of (25-70 years), and 76.7% of the participants were men. The rightsided buccal mucosa was the most frequent primary tumour site, and 70% of the cases were from middle-class families. 90% have no previous family history. Histological grade 2 accounts for the majority of patients, while grade 2 and grade 3 mucositis was reported by most participants. Table 1 shows details of all the variables. Most patients (46.7%) were diagnosed with a moderately advanced stage of disease i.e.II. Evaluation of etiological factors for the development of oral squamous cell carcinoma revealed. The majority of patients have a habit of chewing tobacco and related products therefore tobacco chewing is considered the most common habit among patients, followed by pan, chalia, and betel nut chewing.

Fig 1 displayed the presence of tumours on different sites. It is observed that the most common site affected is the buccal mucosa, followed by the cheek and tongue. The right side of the oral cavity is more frequently affected than the left side.

Table 2 shows the p-value of different variables. It has been observed that TNM staging and histological grading have shown significance in cases of oral mucositis.

Table 1. Shows frequency distribution of variables

S.no.	Variables		n (%)
1.	Gender	Male	23 (76.7)
		Female	7 (23.3)
2.	Socioeconomic status	Low	9 (30)
		Middle	21 (70)
3.	Family history	Yes	3 (10)
		No	27 (90)
4.	Habits	Yes	18 (60)
		No	12 (40)
5.	TNM staging	Stage 1	7 (23.3)
		Stage 2	14 (46.7)
		Stage 3	8 (26.7)
		Stage 4	1 (3.3)
6.	Histological grading	Grade 0	7 (23.3)
		Grade 1	4 (13.3)
		Grade 2	12 (40)
		Grade 3	6 (20)
		Grade 4	1 (3.3)
7.	Grade of oral	Grade 0	6 (20)
		Grade 1	4 (13.3)
		Grade 2	12 (40)
		Grade 3	7 (23.3)
		Grade 4	1 (3.3)

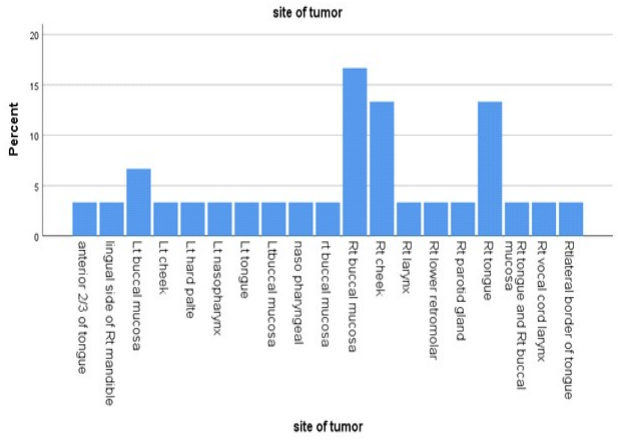

Fig 1. Showing sites of tumors affected by HNSCC

Table 2. Showing p-value of different variables with different variables.

S.no.	variables	Grade of Oral Mucositis
1	Age	0.275
2	Gender	0.318
3	Habits	0.068
4	Socioeconomic status	0.259
5	Family history	0.533
6	Site of tumor	0.529
7	TNM staging	0.046*
8	Histological grading	0.000*

Discussion

Oral cancer has been constantly rising in our society as a result of the increased usage of pan, chalia, and gutka. These products are readily available in our society and a large population use these products on a regular long-term basis. Much research on the involvement of aetiology in oral cancer and other premalignant disorders and their association with oral mucositis has been reported [11].

The patient-related findings in this study are consistent with those in the literature, with the highest prevalence of HNSCC reported in middle-aged men with advanced squamous cell carcinomas around the buccal mucosa and tongue. In this study, the mean age was calculated at 43 years $\pm$ 5.62 years. It could be due to genetic factors and long-term tobacco use, a decrease in immunity, along with comorbidities associated with advanced age, may contribute to the inclusion of adults in our study population.It is in contrast with the study conducted in Lahore in 2018 which reported a more advanced mean age of patients suffering from oral cancer, i.e., 58.33 $\pm$ 20.54[12].

In the study population, males were the most common victims. This could be due to more involvement in addiction and the use of pan, chalia, and tobacco products by them. Long working hours may drive males to chew consistently, and chalia and gutka are the suitable options to fulfil this task. This is also consistent with the study conducted in Pakistan and published in 2006[13].

The relative distribution of key risk variables is largely responsible for variations in cancer incidence by subsite, Head and Neck Cancer. In this study, the majority of patients have the habit of tobacco chewing, followed by areca nut chewing. This is comparable to a study published in 2019 that indicated that addicted patients of both genders have greater rates of oral cancer than non-addicted patients, which could be due to direct contact with betel nuts and tobacco products, which can enhance carcinogenic effects in the mouth cavity. It's possible that the high frequency of oral malignancies in non-addicted patients is due to familial history, HPV infections, or both along with poor oral hygiene[14].

Socioeconomic status has a significant role in people's lives. In our study, the majority of patients belonged to a middleclass, while other studies have reported more incidence of oral cancer in the low-income group. The probable reason is that nicotine in tobacco decreases appetite, resulting in more addiction and patients being more prone to oral cancer[15].

The research on whether family history is a risk factor for mouth cancer is divided. Except for a few Cowden Syndrome cases, there were no hereditary cancer syndromes that demonstrated oral malignancies, according to some experts. Others have proposed that the FHC be classified as an oral cancer risk factor. Increased risks linked with polymorphic genes implicated in alcohol and tobacco metabolism; and increased risks related with genes implicated in DNA repair and genetic stability. Although a family history of oral cancer is not common in our study population, 3 patients have a positive family history, and it seems that family history has very little role in our study population[16].

The TNM classification is a worldwide standard staging approach for determining the extent of cancer and plays a key role in predicting patient outcomes[17].The TNM system's major goal is to produce an anatomically based classification that accurately depicts cancer prognosis. It not only stages the disease but also contributes to therapy selection and outcome prediction, study design, and cancer control actions. The majority of patients with head and neck cancer were diagnosed in the fourth stage, demonstrating a lack of understanding[19].

Broders was the first to develop a histopathological classification for squamous cell carcinoma of the lip, and it was based on distinctions in tumour differentiation. Histological

confirmation was obtained in 96.3% of cases, with 44.5 in grade II or I and remaining in stages III or IV.

Chewers of tobacco had a 3.43% chance of acquiring oral cavity, tongue, and lip cancer. According to Siddiqi and colleagues, the tongue is the most common site of OSCC in Western countries due to extensive smoking and alcohol consumption[22]. One probable explanation is that when smoking, the cigarette makes direct contact with the tongue while the remaining components are inhaled, however chewing gum lingers in the mouth for a longer time. Betel quid was the most often used substance in this study's descriptive analysis, followed by gutka; nevertheless, in univariate and multivariate analyses, gutka users appeared to have the highest chance of developing buccal mucosa cancer. The gutka is put between the teeth rationally, held against the buccal mucosa for a longer amount of time, and lightly chewed and sucked now and then[23].

In the Pakistani population, chewable and non-chewable tobacco, areca nut, betel leaf, poor dental hygiene, oncogenic viral infections, and genetic predispositions are all substantial risk factors. In vitro and in vivo, the chemical content of most of these chewing compounds have been found to have high cytotoxic and genotoxic effects. Long-term exposure to these compounds creates mechanical friction in the buccal mucosa, which can develop into premalignant lesions or invasive malignancies[24].

The pathophysiology of OM is complicated and includes multiple signalling pathways. The nuclear factor kappa beta (NFB) signalling pathway is one of the known signalling mechanisms linked to OM. When activated, this pathway causes tissue damage and the creation of OM lesions by increasing the expression of the pro-inflammatory cytokine TNF [25].

The study's main strengths were the precise clinical inclusion and exclusion criteria, which resulted in a relatively homogeneous group of people. Despite this, the study has several flaws, i including a single-institution design and tumour burden disparities. The study's weaknesses are exacerbated by its cross-sectional methodology and limited sample size. These drawbacks emphasise the necessity for a larger, independent cohort as well as long-term prospective research. So, it is recommended that further studies must be conducted along with a citizen awareness programme for the prevention of squamous cell carcinoma. Screening camps should be planned throughout the country for the early detection of head and neck cancer. Cancer registries should also be made to evaluate the burden of disease.

Conclusion

This study concludes that oral mucositis is significantly associated with TNM staging and histological grading of tumors. Male gender, elderly age, middle to low socioeconomic status, tobacco and betel nut chewing, right sided buccal mucosa and stage II TNM staging are the most frequent risk factors.Oral mucositis of grades 2 and 3 was the most common clinicopathological risk linked to the radiation therapy of head and neck cancer. Although the previous family history is not significantly associated with oral mucositis in our study population.

Conflict of Interests

Authors have no conflict of interests and received no grant/funding from any organization.

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