Research Protocol

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Dentistry Section

Disease-free Overall Survival in Patients Operated for Poorly Differentiated Squamous Cell Carcinoma: A Research Protocol for a Retrospective Cohort Study

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ABSTRACT

Introduction: Oral cavity cancer is the leading cause of cancer-related death. Squamous Cell Carcinoma (SCC) is the most common malignant tumour of the oral cavity. The degree of differentiation of Oral Squamous Cell Carcinoma (OSCC) has been related to several clinical features and outcomes, including prognosis. In OSCC with inferior tumour histological classifications, there is a substantial correlation between the likelihood of developing recurrence and distant metastasis after therapy and Extracapsular Spread (ECS) and perineural invasion of the main tumour.

Need of the study: Studying the Disease-Free Overall Survival (DFOS) postsurgery will help analyse and improve the efficacy of surgical intervention in controlling the disease and improving treatment strategies leading to better prognosis postsurgery in Poorly Differentiated Squamous Cell Carcinoma (PDSCC).

Aim: To analyse the effects of surgical intervention (with or without adjuvant radiation or chemotherapy) in poorly differentiated OSCC patients by studying and analysing the DFOS postsurgery.

Materials and Methods: An retrospective cohort study will be conducted in the Department of Oral and Maxillofacial Surgery at Sharad Pawar Dental College and Hospital, Wardha, Maharashtra, India from December 2024 to December 2025. The study will include 45 subjects who underwent surgical removal of lesions between January 2016 and January 2019 at Siddharth Gupta Memorial Cancer Hospital, AVBRH, Sawangi Wardha, Maharashtra, India. Medical records will be reviewed, and telephonic interviews will be conducted. Patients who have not had any follow-up appointments after five years will be contacted to confirm their survival. Subsequently, further clinical and radiological tests will determine the DFOS rate and the variables impacting long-term survival. The Kaplan Meiyer test will be applied to assess the long-term survival rate and factors that influence DFOS. Pearson/Spearman correlation test will be applied to assess the correlation between TNM staging and overall survival rate and a p-value of <0.05 will be considered statistically significant.

Keywords: Disease-free survival, Head and neck tumours, Metastasis, Oral cancer

INTRODUCTION

Longer life expectancies and an ageing population are contributing to an increase in the number of cancer cases. Half of all tumours arise in the head and neck region, which makes up 5% of all tumour cases [1]. A domestic study carried out in Korea suggests that 1.6% of all cancer patients annually are affected by cancer in the oral and maxillofacial region [2]. The OSCC accounts for 300,000 of the around 615,000 occurrences of oral cancer that have been documented since the 2000s [1]. Oral cavity cancer is the leading cause of cancer-related death, and its fatality rate has noticeably increased in the last few years. Oral cavity cancer primarily affects men between the ages of 30-60 years who are exposed to many risk factors, such as chewing betel quid, smoking cigarettes, and drinking alcohol. More than 90% of oral cavity cancers are SCC [3]. Oral cancer is the sixth most prevalent type of cancer worldwide, with approximately one-third of cases occurring in India, which ranks second in terms of case count, with 52,000 deaths and 77,000 new cases. Given that oral cancer is among the most common cancers in India, community health should place a high priority on addressing its rising prevalence [4].

Approximately, 70% of instances of oral cancer in India are estimated to be in advanced stages, making it a far greater cause for concern [5]. Kerala has the lowest epidemiologically reported incidence of oral cancer in India, whereas West Bengal has the highest. The age group of 60 years and above is found to have the highest incidence of oral cancer in Maharashtra's western districts. This age group is followed by those between 40 and 59 years old, with a male-to-female ratio of 2:1. The age group of people older than 30 years of age presented the greatest number of instances [6]. The most frequent malignant tumour of the oral cavity, SCC, varies in occurrence throughout the world. The prevalence of SCC varies globally, and this diversity has been related to different sociocultural traits, significant regional variations in risk factors, variations in data collection, and the degree of health service development in different populations [7].

Based on the degree of keratinisation and differentiation of the tumour cell, tumours are classified into one of two categories under Broder's classification (1920):

Grade-I: Well-differentiated tumours, in which 75-100% of the cells are differentiated.

Grade-II: Tumours with moderate differentiation, 50-75% of the cells differentiated.

Grade-III: Tumours with poor differentiation, 25-50% of the cells differentiated.

Grade-IV: Anaplastic tumours: 0-25% of cells is differentiated [8].

Many clinical characteristics and outcomes of OSCC have been linked to the degree of differentiation. The prognosis is affected by the tumour's histological differentiation. In the case of OSCC, poorer tumour histological classifications are substantially linked to ECS, perineural invasion of the initial tumour, and the likelihood of recurrence and distant metastases following treatment. Furthermore,

the clinical results of patients with PDSCC are inferior to those of people with tumours that are well or moderately differentiated [3]. Poorly differentiated tumour cells are primarily young cells with more mitotic figures, fewer interstitial bridges, and fewer or no keratinising beads. In contrast, well-differentiated tumour cells resemble normal squamous cells. The survival period and recurrence rate of poorly differentiated cancers are shorter than those of well- and moderately differentiated tumours [9]. The poorly differentiated lesions are highly anaplastic and tend to have more incidence of nodal metastasis than the well-differentiated growths [10].

This phenomenon can be explained by poorly differentiated tumours having a larger risk of distant metastases, a lower rate of net control, and a higher rate of pathologically positive nodes as compared to both well and moderately differentiated tumours. Despite this data, aggressive surgery- with or without adjuvant therapy- remains the primary and only treatment option for patients with oral cavity SCC who do not have distant metastases. This is true regardless of the existence of certain risk factors or varying levels of differentiation [3].

REVIEW OF LITERATURE

To evaluate the effectiveness of procedures and develop more targeted treatment strategies for improving Disease-Free Survival (DFS) for patients with PDSCC, a combination of medical treatment, lifestyle changes, and regular monitoring is necessary. Regular screenings and prompt treatment of any suspicious lesions are crucial. Hence, the present study will be carried out to analyse the survival and recurrence rate of subjects with PDSCC treated by primary surgical resection.

In a study conducted by Geum DH et al., 37 patients with oral cancer were monitored for over five years. The study revealed that 40.5% of the patients experienced recurrences, leading to a 5-year survival rate of 46.7%. The classification of clinical and pathological TNM stage, local recurrence, and metastasis of cervical lymph nodes after surgery were identified as the three most significant characteristics impacting survival [11].

Kang CJ et al., performed a retrospective study on 102 patients with PDSCC in 2011 to ascertain predictive markers for clinical outcomes and to pinpoint specific prognostic groupings that potentially influence therapeutic decisions. The study revealed that a subpopulation of patients with poor clinical outcomes had atleast four pathologically positive lymph nodes and a pathological tumour depth of less than 11 mm in cases of PDSCC. Individuals who possess both risk factors are good candidates for the creation of innovative treatment strategies [12]. Additionally, a retrospective study of all patients treated for OSCC at Kidwai Memorial Institute of Oncology between January 2009 and January 2012 was carried out by Suresh GM et al., in 2019. It included data from 147 OSCC patients. According to the study's findings, patients under 65 years of age, female patients, alveolus and tongue lesions, as well as early T Stage, N0, and negative margin, significantly improve the overall survival and DFS of patients with oral cancer [10].

The present study aims to analyse the probable effects of surgical intervention (with or without adjuvant radiation or chemotherapy) in poorly differentiated OSCC patients by studying and analysing the DFOS postsurgery.

Primary objective:

- To review the outcomes and recurrence rates of patients with PDSCC treated by primary surgical resection, with or without adjuvant radiation or chemotherapy.

Secondary objectives:

- To evaluate whether surgical salvage has impacted survival and identify factors that affect loco-regional control.
- To correlate TNM staging with overall survival.

MATERIALS AND METHODS

A retrospective cohort study will be conducted at the Department of Oral and Maxillofacial Surgery in Sharad Pawar Dental College and Hospital from December 2024 to December 2025. The study will include 45 patients affected by PDSCC who were treated surgically with or without adjuvant radiotherapy or chemotherapy at Siddharth Gupta Memorial Cancer Hospital, AVBRH, Sawangi Wardha, Maharashtra, India between January 2016 and January 2019. Before collecting any information, the patients will be informed and their informed consent will be obtained. Ethical clearance has been obtained from the IEC, and the registered IEC number is DMIHER(DU)/IEC/2024/232.

Inclusion criteria:

- Patients confirmed to have OSCC through biopsy.
- Patients with a tumour of histologic differentiation as PDSCC.
- Patients with no history of malignant tumours affecting other body parts.
- Patients operated by the primary radical surgery undergoing any type of neck dissection either with or without adjuvant radiotherapy or chemotherapy.
- Patients undergoing neoadjuvant chemotherapy followed by surgery would be included in the study.

Exclusion criteria:

- Patients with synchronous primary tumours.
- Patients with a previous history of other malignancies.
- Patients with higher levels of histopathologic differentiation.
- Patients not undergoing neck dissection and surgery and patients having radiotherapy/chemotherapy as a primary intervention.
- Patients not complying with the study protocol, or lost to follow-up due to change of phone number/loss of data will be excluded from the study.

Sample size calculation:

Cochran formula for sample size estimation:

$$n=\frac{Z^2\ P\ (1-P)}{d^2}$$

If your population is more than 10,000

Where,

Z: statistic for a level of confidence. (For the level of confidence of 95%, which is conventional, Z value is 1.96)

P: expected prevalence or proportion (P is considered 0.5)

d: precision. (d is considered 0.05 to produce good precision and smaller error of estimate)

Z=1.96

P=Proportion of poorly differentiated cases

=13.3%=0.133 [11]

d=Desired error of margin=10%=0.10

$$n=\frac{1.962\ *0.133*(1-0.133)}{0.10*0.10}$$

=44.29

=45 participants needed in the study

The study will involve reviewing the medical records of patients and conducting interviews, either over the phone or in person. After five years, patients who do not have follow-up appointments will be contacted to confirm their survival and schedule a follow-up appointment. Once their survival has been confirmed, further clinical and radiological testing will be conducted to determine the long-term survival rate and factors that influence DFOS. The analysis will also focus on the impact of poor differentiation and TNM staging on the overall survival rate of patients without illness.

The parameters that will be studied are overall survival and DFS of the patients operated for PDSCC with or without adjuvant chemotherapy or radiotherapy.

Outcomes

- **Overall Survival (OS):** The time from treatment to death from any cause.
- **Disease-Free Survival (DFS):** The time from treatment to the recurrence of cancer.
- **Locoregional Control (LRC):** Time from treatment to the recurrence of cancer in the local or regional area.

STATISTICAL ANALYSIS

The data obtained will be entered into an Excel sheet and Statistical Package for Social Sciences (SPSS) Software version 29 will be utilised for Statistical Analysis. The Kaplan Meiyer test will be applied to assess the long-term survival rate and factors that influence DFOS. Pearson/Spearman correlation test will be applied to assess the correlation between TNM staging and overall survival rate. A p-value of <0.05 will be considered as statistically significant.

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