

“Comparative Study of Response of Induction Chemotherapy between Locally Advanced Tongue and Gingivobuccal SCC”

A proposal for the thesis work of

Dr. Prashant Kumar Sinha

In partial fulfilment of the criteria for the degree of
Doctorate of National Board (DrNB), Surgical Oncology
under National Board of Examinations

Guide

Prof. (Dr.) Saradindu Ghosh

Consultant, Surgical Oncology

Saroj Gupta Cancer Centre and Research Institute

Mahatma Gandhi Road, Thakurpukur, Kolkata – 700063

AIM OF THE STUDY

To study response to induction chemotherapy in locally advanced tongue and gingivobuccal squamous cell cancer.

OBJECTIVES OF THE STUDY

1. To study clinical and demographic profile of patients with locally advanced tongue and gingivobuccal squamous cell cancer.
2. To study how many patients become candidates for further surgical therapy after induction chemotherapy.
3. To study the patterns of recurrence following multimodality therapy

INCLUSION CRITERIA

1. Previously untreated Histologically proven locally advanced tongue and gingivobuccal squamous cell carcinoma.
2. Age 20 to 70 years.
3. Patient must be willing for all three treatment modalities i.e. surgery, chemotherapy and radiotherapy.
4. ECOG performance status must be less than or equal to 2.

EXCLUSION CRITERIA

1. Previous or current malignancies at other sites, or treatment for them in form of CT/RT
2. Patients with histology other than Squamous Cell Carcinoma

3. Other serious illnesses or medical conditions requiring hospitalization during the year preceding study entry.
4. Immunosuppression and collagen vascular diseases.
5. Pregnancy.
6. Past history of RT to neck
7. patients not fit for chemotherapy.

INTRODUCTION

As per the Globocan 2022 data, Oral cancer is the most common cancer among Indian males, fourth most common cancer in female and second most common among both sexes with a prevalence of 11.4 per 100,000 population.¹

Squamous cell carcinoma of oral cavity is an aggressive cancer, reported to have worse survival and higher recurrence rate. The development of oral SCC is the result of the interaction of both environmental factors and genetic inheritance, and is therefore, multifactorial. Smoking and alcohol abuse are major risk factors for the development of this disease.² Human papilloma virus (HPV) is also considered risk factor in about 25% of the disease. At the same time, not all smokers and alcohol users develop oral SCC, suggesting that individual variation in genetic susceptibility plays a critical role.³ The 5-year life expectancy is about 50% when there are lymph 10 node metastases.⁴

Close proximity of these tumors to the mandible and skin makes the latter susceptible to early tumor invasion.

The use of surgery, radiation, and/or chemotherapy depends on tumor resectability and location, as well as whether an organ preservation approach is feasible⁵. The main treatment option for primary as well as recurrent disease is surgical therapy.⁶ Although obtaining negative surgical margins is the primary goal of surgery, achieving this may be difficult in some cases because of infiltration of vital structures such as the carotid artery or the prevertebral fasciae.⁷ Therefore primary radio-chemotherapy is an alternative for patients in such advanced oral carcinomas.

In general, there are 3 main approaches to the initial treatment of locally advanced disease: (1) Concurrent platinum-based chemoradiation (definitive CT/RT), with surgery reserved for residual disease; (2) Surgery with neck dissection and reconstruction, followed by adjuvant radiation or chemoradiation, depending on the presence of adverse risk factors; or (3) Induction chemotherapy followed by definitive chemoradiation and/or surgery.⁸

Traditional therapy for these patients has consisted of surgical resection, reconstruction and postoperative radiation. Although this approach is often effective in loco regional control of disease, there can be devastating effects on personal appearance and critical function, such as speech and swallowing. In patients treated with surgical resection and postoperative radiation, long term survival rates are generally low ranging from 30% to 40%. Despite the diversity of these patients, loco-regional recurrence patterns are more often than distant metastasis.

To improve local resectability, to increase locoregional control, to decrease distant micro-metastasis and to maintain critical functions, the induction chemotherapy has been investigated. Frequently Cisplatin and 5 Fluorouracil, along with taxanes & mitomycin have been used in induction chemotherapy. Induction chemotherapy is highly active in this setting, inducing partial remission in 60% to 90% of previously untreated patients. However randomized trials have failed to demonstrate a clear impact on local tumour control or overall survival. The induction treatment format also provides a useful instrument to evaluate a novel drug regimen. The use of chemotherapy provides the potential for better regional & distant tumour control.

REVIEW OF LITERATURE

As per the current American Joint Committee on Cancer (AJCC) staging system, locally advanced T4a OSCCs are considered as resectable tumors.⁹

However, in routine clinical practice, certain T4a OSCCs are not technically resectable at baseline, due to extensive loco-regional disease extent which does not come under the definition of T4b, for example, presence of skin induration/edema up to the zygomatic arch and/or involvement of the pterygoid muscles. For the purpose of achieving a negative pathological margin, extensive surgical procedures are required in these tumors, which are associated with

unacceptable amount of cosmetic deformity and functional morbidity.¹⁰

As a consequence, locally advanced T4a OSCCs with these above mentioned features, are still considered technically unresectable, despite recent advances in surgical and reconstructive techniques. As of current practice, these technically unresectable oral cavity tumors are treated with definitive chemoradiation at most centers. However, the results of this nonsurgical local treatment modality in locally advanced OSCCs are disappointing with a reported 1-year disease-free survival ranging from 10% to 40%, in various studies.¹¹⁻¹⁷

Two large landmark studies, the TAX323 and TAX 324, had highlighted the role of induction chemotherapy (IC), in unresectable and locally advanced head and neck cancers.¹⁸⁻¹⁹ The use of true-positive fraction (TPF) (docetaxel, cisplatin, and 5-fluorouracil) regimen in these trials led to an overall response rate (ORR) of about 68%. However, these two landmark studies were not exclusively designed for OSCC and <15% of the included patients had oral cavity cancers. In a phase III randomized controlled trial, Licitra et al. showed that the use of IC in resectable OSCCs was associated with 33% clinical complete response (CR) and 82% ORR.²⁰

According to Rudresha et al. the assessment of response to IC, stable disease was documented in 49 patients (61.3%), followed by a partial response (PR) in 17 patients (21.3%) and disease progression in 14 patients (17.4%). None of our patients achieved a CR after IC. 19

patients (including the 17 partial responders) achieved resectability after IC. On univariate analysis, achievement of PR was found to be a significant factor for achievement of resectability ($P = 0.000$). The rate of febrile neutropenia was 18.8% ($n = 15$) with IC. The rate of other Grade 3-4 toxicities were as follows: haematological toxicity– 21.3% ($n = 17$); mucositis–2.5% ($n = 2$), and diarrhoea– 2.5% ($n = 2$). Two of our patients required 25% dose reduction in the next cycle, due to severe mucositis and diarrhoea.²¹

MATERIALS AND METHODS

STUDY SITE

This prospective study will be conducted in the Surgical Oncology Department, Saroj Gupta Cancer Centre and Research Institute, Thakurpukur.

STUDY POPULATION

Patients presenting in Surgical Oncology OPD of SGCCRI, Kolkata with histologically confirmed oral SCC and deemed operable by Multidisciplinary Team will be included in the study.

STUDY DESIGN

Prospective observational study

STUDY DURATION

One year

SAMPLE SIZE

Sample size justification by applying Danial sample size formula :n =

$$Z^2 * P (1 - P) / d^2$$

where,

Z: Statistic for a level of confidence (For the level of confidence 95%, which is conventional, Z is 1.96

P: Expected prevalence

d = Precision (0.03 to produce good precision and smaller error of estimate)

Prevalence of Oral cavity cancer in India is 0.0114 (Globocan 2022 data)

So,

$$n = 1.96 * 1.96 * 0.0114 (1-0.0114) / 0.03 * 0.03$$

$$= 1.96 * 1.96 * 0.02177 * 0.9886 / 0.0009 = \mathbf{48.10}$$

METHODOLOGY

Data collection

The relevant data are collected as per predefined proforma for each patient.

Study technique