

**Research Article****Feasibility and Efficacy of Neoadjuvant Chemoradiation in Lower Gingivobuccal Complex Cancers Involving Mandible**

Authors

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Lower gingivobuccal complex cancers is the most common oral cavity cancers which has an increasing trend in India due to tobacco and alcohol intake.

**Aim of the Study:** Assessment of feasibility and efficacy of Neoadjuvant chemoradiation in locally advanced gingivobuccal complex cancers involving mandible in achieving better clinical response and its impact on survival.

**Methods and Materials****Inclusion Criteria**

Biopsy proven locally advanced gingivobuccal complex cancer patients with radiological confirmation of involvement of mandible and are fit for chemotherapy and surgery.

**Exclusion Criteria**

- 1) Early stage Head and Neck cancer patients.
- 2) Patients unfit for surgery and chemotherapy

Patient with locally advanced lower gingivobuccal complex cancers were taken for analysis after all investigation done. Patient with disease considered as not resectable due to extensive soft tissue involvement were considered for neoadjuvant chemoradiation followed by which reassessment for surgery done. Patient will be given chemotherapy and radiotherapy for total dose of 50Gy using either conventional or conformal techniques. Patients will be reviewed at 50Gy for assessment for feasibility of surgery. Surgery considered if patient had resectable soft tissue component.

**Results:** Out of 34 patients considered for Neoadjuvant chemoradiation 7 patients undergone surgery with no evidence of locoregional and distant metastases.

**Conclusion:** Though we dont have clearcut indications for Neoadjuvant chemoradiotherapy it can be considered in selected subset of patients with extensive soft tissue disease for feasibility of surgery which has impact on locoregional and distant control and functional outcome .Larger studies should be done to assess the credibility of this study.

**Keywords:** Neoadjuvant chemoradiation, Gingivobuccal complex cancers, locally advanced un resectable cancers, extensive soft tissue component disease.

## Introduction

Lower Gingivobuccal complex involves buccal mucosa, gingivobuccal sulcus and lower gingivum. It constitutes most of the oral cavity cancers in India due to high tobacco and alcohol intake. Though it is a major health problem it can be preventable and if detectable earlier has good survival on par with locally advanced disease which has poor outcome. Extensive soft tissue involvement makes difficulty in feasibility of surgery since it leads to extensive resection and difficult in achieving adequate margins. Larger or more deeply invading tumors of soft tissue are more likely to invade mandible and show more aggressive (invasive) form of tumor spread reducing the option of more conservative resection<sup>(3)</sup>. There is no category I evidence for neoadjuvant chemoradiation<sup>(1,2,4-7)</sup> in operable cancers. This approach may be considered in borderline operable tumors to enhance resectability.

## Aim of the Study

Assessment of feasibility and efficacy of Neoadjuvant chemoradiation in locally advanced gingivobuccal complex cancers involving mandible in achieving better clinical response and its impact on survival.

## Materials and Methods

### Inclusion Criteria

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neoadjuvant chemoradiation followed by which reassessment for surgery done.

Patient will be given chemotherapy mostly cisplatin is given and if considered not fit for cisplatin then carboplatin given. Patient will be given radiotherapy for total dose of 50Gy using either conventional or conformal techniques. Patients will be reviewed at 50Gy for assessment for feasibility of surgery. Surgery considered if patient had resectable soft tissue component.

## Results

Total number of patients in lower gingivobuccal complex were 432 as on table 1.

Extensive soft tissue involvement makes difficulty in feasibility of surgery since it leads to extensive resection and difficult in achieving adequate margins as on table 2. Larger or more deeply invading tumors of soft tissue are more likely to invade mandible and show more aggressive (invasive) form of tumor spread reducing the option of more conservative resection.

Patients were planned for chemotherapy which includes either 3 wky CDDP+ BLM or 3Wkly CDDP alone or wky CDDP or Carboplatin. Chemotherapy in patients planned for neoadjuvant chemotherapy along with radiotherapy as on table 4.

Around 50% of the patients were planned for 3 wky cisplatin along with bleomycin of which only six of the 16 pts complete entire cycle. Six pts were considered for 3 wky CDDP of which all patients complete entire regimen. Eleven patients were considered for wky CDDP of which six patients complete entire regimen remaining were incomplete. Only one patient planned for carboplatin wky schedule for which he completed 4 cycles. Evidence of mucositis and neutropenia more in patients receiving 3 Wkly CDDP+BLM when compared to other cycles as on table 5.

EBRT to patients receiving NACT+RT were given either Cobalt beam therapy for about 19 pts and conformal therapy in 12 pts and IMRT in 3 patients. Patients were given radiotherapy to

primary and ipsilateral whole neck. Evaluated for response at the end of 50Gy table 6.

Out of 33 patients having response for radiotherapy 7 patients undergone surgery after neoadjuvant chemotherapy in view of soft tissue resectability while the remaining patients were under follow up as on table 7.

Patient completing NACT+RT followed by surgery and those who were not considered for surgery for whom concurrent chemoradiation given were kept under follow up and evaluated for evidence of locoregional progression recurrence and distant metastases.

### **Disease Progression**

Out of 34 pts 7 undergone surgery while the remaining were kept under follow up after completion of concurrent chemoradiation. On follow up 19/27 patients developed progressive disease and on supportive care in less than two years. Locoregional recurrence and progression is found in more than 50% of the patients in less than 2 yrs. In patients where surgery done no patient developed recurrence at the surgery site.

### **Discussion**

Neoadjuvant chemoradiation plays an important role in downsizing the tumor thereby improves resectability of the tumor with adequate margins which helps in obtaining adequate oromandibular function and cosmesis. R0 resection plays an important role in obtaining good locoregional control thereby improving disease free and overall survival of the patient.

Neoadjuvant chemoradiotherapy plays an important role in having good regional and distant control since there is reduction in time lapse between the initial primary management and distant control.

With this sort of management where initial primary management is delayed to obtain adequate surgical resection which makes the lesion amenable for surgery. Locoregional failure is most common cause of failure in advanced lower

Gingivobuccal complex cancers and when adequate curative management is given with distant control by means of chemotherapy it helps in improving not only the locoregional control but also causes reduction in distant metastasis.

There is no Level I evidence for this type of management in advanced lower Gingivobuccal complex cancers but trials shows improvement in locoregional control which is common cause of failure. Further with this sort of management curative intent of treatment can be tried since according to guidelines concurrent chemoradiation is standard line of management in advanced Gingivobuccal complex cancers and the intent of treatment is palliative.

Multiple modalities of treatment is considered in patients with advanced lower Gingivobuccal complex cancers which includes induction chemotherapy followed by surgery based on response or neoadjuvant chemo radiotherapy followed by reassessment for surgery. With both of the above regimens curative intent of treatment can be considered. Neoadjuvant chemo radiotherapy is known to have better locoregional control when compared to chemoradiotherapy or radiotherapy alone in view of organ at risk and though adverse effect of radiation is magnified when given along with chemotherapy since chemotherapy acts as a radiosensitizer.

Evidence of recurrence in patients who were undergone surgery both during the initial time of management or after neoadjuvant chemo radiation is very less when compared to that of those who had undergone concurrent chemoradiation. 1/33 patients who had undergone surgery followed by postoperative radiotherapy developed recurrence. Patients were given either 3 wkly CDDP + BLM or 3 Wkly or Wkly CDDP or Carboplatin chemotherapy along with radiotherapy. Evidence of radiation induced mucositis, skin reaction and dyselectrolytemia were found during neoadjuvant chemoradiation.

Evidence of Gr II / Gr III mucositis were found more in patients receiving 3wkly CDDP+BLM when compared to other chemotherapy regimen

more than eighty percent of the patient developed Gr II – III mucositis. Skin reaction is found in more than sixty percent of the patients for which supportive care given. Evidence of radiation induced reactions were found in other chemotherapy regimens as on table 5.

Side effects of radiation is found in more than 50% of patients receiving chemotherapy for which supportive care given. More than 50% of the patients had incomplete chemotherapy schedule due to radiation induced adverse effects.

Evidence of Gr II neutropenia is found in more than 50% of the patients receiving 3 Wkly CDDP + BLM for which supportive care with GCSF given. Incidence of neutropenia is found in patients who had received other forms of chemotherapy regimen also. (table 8)

Patients for whom surgery is not feasible due to extensive soft tissue involvement were considered for concurrent chemo radiation. These patients were considered for concurrent chemo radiotherapy on palliative intent and will be kept under follow up. Out of 34 patients 27 pts were considered for radical chemo radiotherapy due to extensive soft tissue involvement. Of which 19 pts developed progressive disease and the remaining 8 patients were on follow up for further events at the end of 2 yrs. Evidence of locoregional recurrence is more in patients received chemoradiotherapy. On the contrary only seven out of thirty four patients were done surgery and those patients who had undergone surgery curative intent of treatment is tried and achieved. No evidence of locoregional recurrence and distant metastases (table 9)

This shows that loco regional control is achievable in patients who were considered for neoadjuvant chemo radiation in borderline operative/ unresectable tumours where only palliative management is considered as standard management of therapy. With this mode of treatment curative intent of treatment is achieved in locoregionally advanced lower Gingivobuccal cancers.

Patients who had completed entire schedule of therapy were kept under periodical follow up. 27 patients was planned for concurrent chemo radiotherapy on palliative intent in these patients and 19/27 patients developed locoregional progression.

3/27 patients developed distant metastasis with two of the three patients had metastasis in lung and the other one has bone metastasis. These patients were planned for palliative and supportive management.

On assessing the survival status of the patient increased mortality is found in patients who were planned for concurrent chemo radiation. But since the study has short evaluation time it is need to be considered in long term basis to assess the overall survival of the patient. To assess the impact of management on disease free survival and overall survival it should be assessed for a considerable period (table 10).

There is no absolute difference in the overall survival of the patient but this should be analysed after adequate time interval from the initial primary management. Life table analysis shows there is 20% difference in the overall survival between the two methods of management but its significance is questionable. The cause of death in these patients may be due to loco regional progression which affects the intake thereby creating metabolic imbalance which may lead to calamity.

**Table 1:** Stage wise Distribution

STAGE	NO . OF PATIENTS
STAGE I	18
STAGE II	38
STAGE III	129
STAGE IVA	218
STAGE IVB	16

**Table 2:** Soft Tissue Component Status

Soft tissue component	No.of pts	(%)
Extensive	45	55%
Minimal	35	45%

**Table 3:**

PLAN OF MANAGEMENT	No of Patients
NACT+RT – SX	34
SX – PORT	33
CT + RT	9
NART – SX	2
RT	2

**Table 4:** Chemotherapy Regimen Given

CHEMOTHERAPY REGIMEN	NO.OF PATIENTS
3 WKLY CDDP+ BLM	16
3 WKLY	6
WKLY	11
CARBOPLATIN	1
TOTAL	34

**Table 5:** Adverse Reactions due to Chemoradiotherapy

No of Pts	CHEMO	MUCO SITIS	NEUTROPE NIA	DYS ELECT ROLYTEMIA
16	3wkly CDDP+ BLM	13	6	4
6	3 Wkly CDDP	3	2	2
11	Wkly CDDP	4	3	2
1	Carboplatin	-	-	1
		20	11	11

**Table 6:** Response Evaluation at end of Neoadjuvant Treatment

RESPONSE	NO.OF PATIENT	(%)
PARTIAL	33	97%
COMPLETE	-	-
PROGRESSIVE	1	3%
	34	100%

**Table 7:** Status of Surgery

NO.of Patients	PLAN	SURGERY	(%)
27	NACT+RT	NOT DONE	79.4%
7	NACT+RT	DONE	20.6%

**Table 8:** Clinical Status of disease after Initial Treatment

Plan	No.of pts	Prog.disease	Recurrence
NACT+ RT f/b Surgery	7	Nil	Nil
NACT+ RT conv To CT+RT	27	19	Nil

**Table 9:** Locoregional and Distant Control Status

Plan	No of pts	Local progression/ Nodal metastasis	Distant metastasis
NACT+ RT f/b Surgery	79 (20%)	Nil	Nil
NACT+ RT converted to CT+RT	27 (80%)	19(70%)	39(11%)

**Table 10:** Mortality Status

Plan	No. Of pts	Mortality
NACTRT f/b Surgery	7	1
NACTRT conv.to CT+RT	27	8

**Conclusion**

Buccal mucosal cancers represent commonest and relatively more aggressive subsite of oral cavity cancers. The disease has variable spectrum of biological behaviour that has its impact on response to radiation. About 70% of the patients are in a locally advanced status during the time of presentation. More patients are in a relatively younger age and these patients have a relatively different biological disease as compared to the older patients.

The largest data of buccal mucosal cancers are from Indian Subcontinent as the best of our knowledge. But we are following western guidelines that has its own impact in the management and survival of the patient. The treatment options of these patients are surgery followed by postoperative radiotherapy or chemo radiotherapy based on the postoperative histopathological examination.

Patients who were not amenable for surgery were considered for chemo radiation since the data available from the Head and Neck cancer studies shows concurrent chemo radiotherapy is better than radiotherapy alone. Although concurrent chemo radiotherapy has become the standard in loco regionally advanced squamous cell carcinoma of Head and Neck no consensus has

been reached regarding the optimal combination and timing.

There is no Category I evidence for Neoadjuvant chemo radiotherapy in locally advanced tumours. In the absence of randomized adequately powered series the best currently available data is from the case series report till now. Being an aggressive subsite addition of chemo radiation in adjuvant setting has the potential to be beneficial.

This approach can be considered in borderline resectable tumors to enhance resectability. Surgery is considered as curative intent treatment and in cases where neoadjuvant chemo radiotherapy is considered curative intent of management can be tried to achieve.

Neoadjuvant chemo radiotherapy plays an important role in downsizing the tumour that facilitates better resection. By this sort of management cure rates can be maximised while preserving oromandibular function that helps in not only improving the clinical outcome of the disease but also reduces cosmetic disfigurement. Management of dissemination of micrometastasis is started at the initial phase of treatment and hence both loco regional and distant control is tried at the same time.

Loco regional failure is most common cause of recurrence in Head and Neck cancers and when a curative resection done it reduces the incidence of failure both loco regionally and distally. Negative margin status is achieved most of the time where neoadjuvant therapy is considered and this aids in management.

Surgical margin is studied in almost every trial of Head and Neck Cancer and has been uniformly accepted as one of the important prognostic markers worldwide. Neoadjuvant chemo radiation helps in achieving adequate margins since radiation and radio sensitising effect of chemotherapy plays an important role in downsizing tumor

Several areas of clinical and basic research still remains to be conducted before all questions regarding the optimum management of this cancer can be answered. India having the largest patient

population with this cancer needs to conduct well organised randomized trials in addressing key areas of research.

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