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Analysis of a treatment strategy for advanced stage OSCC patients. A 100 day multimodal approach

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ABSTRACT

Aim The present study aimed to evaluate the feasibility and efficacy of neoadjuvant chemoradiotherapy (NACRT) followed by definitive surgery and free fibular transfer in advanced stage oral squamous cell carcinoma patients.

Methods Patients diagnosed with resectable oral squamous cell carcinoma, Stage IVa were enrolled for the study. The patients underwent a planned protocol of neoadjuvant radiotherapy and concurrent chemotherapy, insertions of dental implants in fibula followed by curative and reconstructive surgery. Objective response rate, overall survival, disease free survival and patient quality of life assessments were carried out.

Results A total of eight patients with Stage IVa oral squamous cell carcinoma were enrolled for the study and treated according to the planned protocol. All patients completed neoadjuvant chemoradiotherapy and surgery; 6 (75%) patients achieved complete response while 2 exhibited partial response (downstaging) on post surgical pathological analysis. After a median follow-up time of 24.6 months and maximal follow up of 34 months, the overall survival was 75% and disease free survival was 87%. Two patients suffered from trismus and are currently undergoing oral physiotherapy. Six patients had orocutaneous fistula which healed. One had extrusion of fibular graft and two patients died.

Conclusion The present study elucidates a treatment strategy for patients with locally advanced squamous cell carcinoma validated for better functional and aesthetic outcome with improved quality of life. Further evaluation is required in a bigger cohort size.

INTRODUCTION

Oral cancer accounts for more than 400,000 new cases of cancer worldwide, with oral squamous cell carcinoma being the most common tumor type (1). In India, cancer of oral cavity, is the most common cancer in males with more than 110,000 new reports every year (2). Most tumors are regionally advanced and the patients are treated with radical resection, reconstruction, radiation and/or chemotherapy (3). OSCC includes a group of patients with differences in the extent and localization of disease. In patients with early and limited disease, either surgery or radiotherapy is considered as a course of treatment, with no or very less ambiguity. In case of advanced disease, the opinions and treatment considerations are variable and often include multimodality approach including radiotherapy, chemotherapy and surgery. Radiotherapy is generally given adjuvant to surgery to achieve an enhanced locoregional control or to the cases where surgery is unsuitable (4). Primary surgery is the recommended option for stage IVa OSCC by NCCN guidelines with an option of clinical trial (5).

Studies have suggested survival benefits of pre-operative chemotherapy with radiotherapy (6,7), but these studies have included Stage III and Stage IV patients, with different node diseases, possibly leading to different clinical outcomes. Data from non-randomized studies have also shown increased overall survival and decreased probability of local recurrence when preoperative concurrent chemo radiotherapy is administered (8)

Bone involvement in stage IV patients with resectable disease, not only impacts the prognosis and survival but also quality of life for those who survive. Resecting the

tumor in a neoadjuvant CRT patient allows preserving more healthy tissue (mucosal) while achieving clear margins. Additionally, prosthodontic implantation is important for rehabilitation and regaining oral functions in head and neck cancer patients. Reconstruction with bone grafts can lead to a good recovery of the patient's facial shape, mouth and jaw function (9,10). Most of the patients receive radiotherapy to primary area of surgery and neck after resection and reconstruction, which can lead to restrained wound healing, osteonecrosis, trismus, and xerostomia. Patients receiving a high dose radiation post-surgery generally exhibit a poor response to prosthetic rehabilitation (11,12).
With this premise the present study was carried out to validate a study protocol involving NACRT followed by definitive and reconstructive surgery.

MATERIALS AND METHODS

Patients

Previously untreated and histopathologically confirmed OSCC stage IVa patients were enrolled into the study from March 15, 2016 to December, 2017. Eligible patients required to be within the age range of 18-70 years with a life expectancy of > 6 months. Pretreatment analysis included liver function test, renal function test, cardiac health analysis, X-ray, computed tomography (CT), magnetic resonance imaging (MRI) and dental evaluation. Patients with concomitant malignancy, heart disease or other severe disease were not included in the study. The study protocol was reviewed and approved by the institutional review board at the participating centres. All patients provided written informed consent before entering the study.

Treatment regimen

Treatment for the study was planned in three steps. All the patients were treated by this protocol.

- Step 1a. Neoadjuvant treatment of radiotherapy to the primary disease and draining lymph nodes with total dose of 45 to 50 Gy was given along with concurrent weekly Cisplatin 100 mg/m^2 for 5 cycles.
- Step 1b. CT scan of head and fibula on the same side of the lesion (for mandibular lesions) and opposite side (for maxillary lesions) was done. Preoperative virtual planning was carried out and the CT data was converted into 3D printed models. The reconstruction template was created using coronal, sagittal as well as axial planes to ensure optimal contour. Pre-operative impressions were made, bite was registered with addition silicone putt and dental prosthesis was made. The segment of the mandible/maxilla to be resected was marked on the model and was resected. The defect in the jaw bones was reconstructed with segment/segments of fibula with appropriate wedge osteotomy to get an optimal contour for the reconstructed part and fixed in position with plates and screw. The dental prosthesis was attached in position of occlusion and the sites for osseointegrated implants were marked.
  Bone cutting guides were made according to the planned osteotomies of the fibula (Fig. 1).
- Step 2. During second week of chemoradiotherapy, surgery for insertion of implants into the predetermined sites of fibula was done. Implants were covered with split skin graft and covered with dual mesh with non-adherent surface on the skin grafted side.
- Step 3. Definitive surgery was planned 6 weeks after completion of chemoradiotherapy and reconstruction was done by free fibular segment with primary dental prosthesis after checking the occlusion of oral bite. Segmental mandibulectomy or partial/total maxillectomy with supraomohyoid neck dissection was performed. Bone cuts were carried

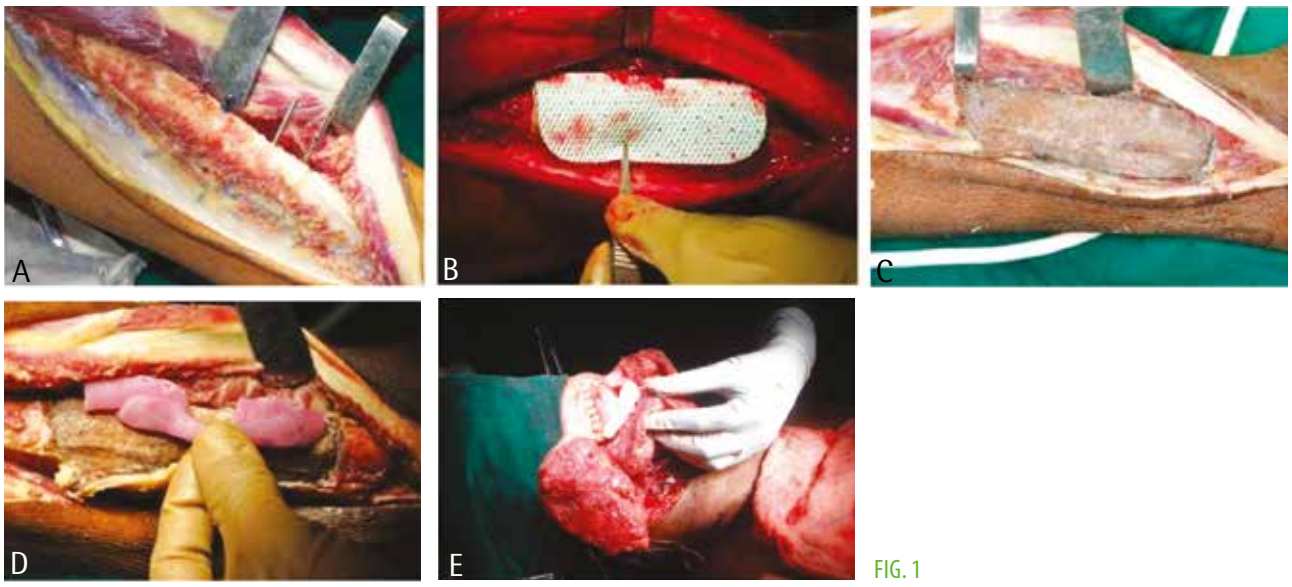

FIG. 1

Case	Gender	Age	Site	Node status	RT (Gy)	CT (Cisplatin- mg)	Post- surgery PR	Follow up (months)	Status	ORN	Trismus	Recurrence
BK	M	55	Mandible	N0	45	200	Complete Response	34	Alive	No	No	No
HN	M	38	Mandible	N2	45	160	Complete Response	34	Alive	No	No	No
SK	M	58	Mandible	N0	45	200	Partial Response	34	Alive	No	Yes	No
IS	M	38	Mandible	N0	45	200	Complete Response	31	Alive	No	Yes	No
GR	M	42	Mandible	N2	45	200	Complete Response	30	Alive	No	Yes	No
RB	M	56	Mandible	N0	50	200	Complete Response	0.5	Dead	No	No	No
NK	M	36	Maxilla	N0	50	200	Partial Response	32	Alive	No	No	No
KC	M	42	Maxilla	N0	50	200	Complete Response	11	Dead	No	No	Yes

TABLE 1 Clinical characteristics, treatment data and outcome of the patients Abbreviations: RT- Radiotherapy, CT- Chemotherapy, ORn- Osteoradionecrosis.

out according to cutting guides. Excision of diseased segment was performed exactly as per the plan and the temporary dental prosthesis were fixed on to the osseointegrated implants. Fibular segment was transplanted and fixed.

Treatment evaluation and follow up

Assessment of tumor resection was carried out by pathological examination of resected tissue to deduce complete and partial response. Complete response was defined as no invasive and no *in situ* residuals present in the surgical specimen and partial response was defined as at least 30% reduction in the size of the lesion in the surgical specimen (13).

The patients were under regular follow-up every 3 months over a period of one year and 6 monthly periods in the following years. At each follow-up, patients were clinically evaluated for evidence of locoregional tumor recurrence, speech, aesthetic results and masticatory functions. Outcome indexes included objective response rate, overall survival (OS) and disease free survival (DFS). Implant failure, defined as removal due to marginal bone loss, infection, failure to establish or maintain osseointegration was also evaluated. Physiological parameters like trismus, osteonecrosis and xerostomia were also assessed. Quality of life was assessed at 1 year using the University of Washington Quality of Life Questionnaire (UW- QOL v.4). The UWQOL forms were given to the patients to fill during the time they came for follow-up. The domains are scored on a scale varying from 0 (worst) to 100 (best). The scores were calculated according to the standard scoring system for individual domains mentioned in UWQOL guidelines. The validated UWQOL questionnaire available in vernacular language (Marathi) was used (14).

RESULTS

Eight patients qualifying the eligibility criteria were included in the study. N stage and tumor location are mentioned in Table 1. All the patients were male and had a mean age of 46 (range; 36-55 years). All the patients completed treatment protocol which lasted for about 100 days; 7 out of 8 patients came back with orocutaneous fistula which healed with treatment in all cases.

The overall clinical response rate for the primary tumor was 100%; 75% of patients had complete response and 25% had partial response on histopathology. Histopathology response rate was adjudged based on tumor regression rate. No disease progression was observed in any of the patients. One patient died in post-operative period. The patient had secondary haemorrhage on 18th day due to erosion of implant plate into the neck vessels. He also had dehiscence of the wound and partial loss of flap. He died due to uncontrolled haemorrhage. The median follow-up time of the patients was 24.6 (0.5-32) months. Among the 8 patients, one was initially lost to follow up but came back after 8 months with a recurrence. For various reasons, the patient did not undergo complete treatment and died. At a follow up of 32 months, the OS and DFS of patients were 75% and 87% respectively.

Functional and aesthetic results		N = 6
Swallowing		6
Chewing	Ability to chew soft food	2
	Ability to chew hard food	3
	Only semi liquid diet	1
Mouth opening	1-2 cm	1
	More than 2 cm but restricted to 3 cm	1
	Normal mouth opening	4

TABLE 2 Subjective outcomes at 2 years post treatment.

In 7 patients, 6 prosthetic rehabilitations were performed on implants. Three patients experienced difficulties in adapting to the dentures and refused usage. Median healing period was 8 months. At 1 year follow up, three patients who underwent successful prosthetic placement had acceptable outcomes. Membrane construction using skin graft may have facilitated self-maintenance of implants which led to faster healing. One patient experienced graft loss post infection and declined further oral rehabilitation. Osteonecrosis was not observed in any of the patients. Out of eight patients followed up for 2 years, six patients are alive and free of disease at follow up of 32 months. Oral function and denture satisfaction were high in 62% patients and did not change over time.

Swallowing, chewing and mouth opening results per patient are summarized in Table 2. Two patients had trismus and underwent oral physiotherapy. Patient-reported QoL assessment at 1 year is presented in Table 3. Five patients (83%) chose swallowing ability as the most preferred domain, followed by 4 patients (67%) choosing chewing and 3 patients (67%) choosing speech as second and third preference respectively. Shoulder stood as the least preferred domain, probably because supraomohyoid neck dissection was performed causing no discomfort to shoulder region. 100% of patients scored about the same or somewhat better or much better health related quality of life compared to a month before they had cancer.

Interestingly, the most common complaint of oral cancer patients receiving radiotherapy, i.e. saliva, recorded a good score in our assessment. None of our patients experienced xerostomia, probably the reason behind the good scores in QoL domains of speech, taste and saliva.

DISCUSSION

Neoadjuvant chemotherapy and radiotherapy or concomitant chemo-radiotherapy followed by surgery has been shown to improve survival in advanced oral cancer. Many studies over years have confirmed advantages of preoperative radiotherapy along with chemotherapy in terms of overall survival (6,7,8), with some reports of higher toxicity induced by chemotherapy (15,16). MACH-NC analysis has shown the benefit of adding chemotherapy to treatment regimen in various tumour locations of head and neck squamous cell carcinomas (17), though use of neoadjuvant chemotherapy is still debated upon (18). A study also demonstrated use of NACRT in surgically less favourable cases to obtain clear margins. (19) Low-dose cisplatin monotherapy has also been shown to be reliable therapy regimen for locally advanced OSCC (N0) (20). Other than oral cancer, preoperative chemoradiotherapy has shown to increase the overall survival and decrease the incidence of local recurrence in different types of

UoW-QoL Scores	UW-QOL scores 0	25	30	50	70	75	100	Mean (SE of mean)	Rank
Pain	0	0		0		2	5	92.86±12.20	=4
Appearance				1		6		71.43±9.45	=4
Activity						4	3	85.71±13.36	=5
Recreation						6	1	78.57±9.45	8
Swallowing					4		3	82.86±16.04	1
Chewing	1			6				42.86±18.9	2
Speech					5		2	78.571±14.64	3
Shoulder							7	100±0	9
Taste					4		3	82.86±16.04	=5
Saliva					6		1	74.29±11.34	=4
Mood				2		4	1	71.43±17.25	6
Anxiety					3		4	87.14±16.04	7

TABLE 3 UW-QOL scores of patients 1 year post treatment (NA- Not applicable).

cancers (20, 21, 22). NACRT is becoming the choice of treatment for different types of cancers even where only radiotherapy was indicated earlier (23).

Disease stage and consideration of treatment keeping in mind the functional preservation should ideally guide the choice between surgery and CRT for patients with resectable disease. More well-designed studies are required to further assess the feasibility and efficacy of NACRT for locoregional and node positive oral cancers and its long term effects.

For oral squamous cell carcinoma, adjuvant radiotherapy is indicated for primary stage T1/ T2, N stage (N0) in treatment guidelines. T3/T4, N (0-3) is treated either by surgery followed by concurrent chemoradiotherapy or clinical trials to improve survival (5). Involvement of cervical lymph nodes is one of the important factors in selecting patients for surgery, more importantly for late stage disease. A potentially resectable patient with multiple lymph node involvement will benefit with an adjuvant treatment prior to surgery. Also, since radiotherapy is more effective in a well oxygenated tissue, it becomes all the more important to give preoperative radiotherapy (24). Post radiotherapy, a waiting period before surgery not only gives the tumor adequate time to regress but also enables patients to improve and obtain adequate nutritional support (25). Apart from disease free survival, success of implants remains one of the biggest challenges in Stage III/IV OSCC.

Prefabricated fibular flap technique for reconstruction of mandible and maxillary defects known as 'Rohner's technique' requires planning and prefabrication of fibular segment with dental implants six weeks before definitive surgery (26). This technique ensures that the flaps will allow for prosthetically correct implant placement, but, due to mandatory delay of 6 weeks required for osseointegration of dental implants in fibula, this technique cannot be used with primary ablative surgery in oral cancer. With this technique, we adapted a new concept of preoperative concurrent chemoradiotherapy followed by reconstruction of mandibular/maxillary segment with prefabricated microvascular fibular graft with osseointegrated implants. With these techniques we could successfully improve the post-operative oral rehabilitation with proper dental occlusion and minimal side effects of radiotherapy.

An important aspect of preoperative radiation and chemotherapy was that fibula was not exposed to radiation and hence osseointegration was not affected. Split thickness skin grafting helps form gingiva and maintaining biological width hence significantly reducing chances of peri-implantitis and implant failure (27). All patients had bone involving lesions and would have been candidates for post-operative adjuvant radiotherapy, which combined with inevitable post-operative fibrosis leads to many disabling complications. Combination of grafted bone with radiotherapy is considered a negative prognostic factor of implant survival. Various studies have shown a significant difference in implant survival between non-irradiated and irradiated patients with a higher implant survival in the non-irradiated bone (9,10). Osseointegration of implants can weaken or be damaged by radiation therapy. Incidentally, studies have also indicated a higher success rate of mandibular implants as compared to maxillary implants (28,29). One of our patients who died during post-operative period had a large dissection of middle third free fibular flap which required four osteotomies. Few osteotomies were less than 2 cm in size, which jeopardized the supply to the segment and causing partial loss of flap and further complications. Through our experience we learnt that the location is indeed important and can affect success of the procedure although, further evaluation is warranted to ascertain this and enable better management of such patients.

Our study protocol of pre-operative neoadjuvant chemo-radiotherapy was effective as a treatment modality, which is borne by the fact that six out of eight patients had no residual neoplastic tissue in the histopathologic examination of resected specimens. Such complete response to neoadjuvant therapy is a known surrogate marker of long term survival (30). Our short term follow up shows that six patients are healthy and free of disease at 32 months post procedure. Higher probability of long term survival is indicated as there was pathological complete response in 6 out of 8 patients. The improved survival of patients obtaining pCR could be due to the beneficial effect of chemoradiotherapy. A randomized control study can elucidate this causal relation, which we plan to undertake in a bigger patient cohort. Oral rehabilitation was also moderately successful with four out of six patients achieving final prosthetic placement with proper dental occlusion. The procedure looks promising as it provides both the treatment of malignancy affecting mandible and maxilla and also a complete rehabilitation improving the quality of life.

CONCLUSIONS

Osseointegrated fibular implant reconstruction after preoperative chemoradiotherapy in oral cancer is a promising technique in operable/locally aggressive oral cancer with bony involvement. Concomitant chemoradiotherapy can be used with organ-preserving intent, resulting in improved cosmesis and function compared with surgical resection with or without adjuvant treatment. Chemotherapy can act as a radiosensitizer, improving the probability of local control and, in some cases, survival, by aiding the destruction of radioresistant clones. NACRT might be an effective choice for patients with locally resectable OSCC stage

IVa, to improve treatment effects, long term survival and quality of life, though further validation by a bigger cohort size study is necessary.

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Conflict of interest

All authors declare no conflict of interest.

Ethical Committee approval

The study was approved by the Poona Medical Research Foundation's Institutional Ethics Committee. All patients provided written informed consent to participate. This trial is listed in the Clinicaltrials.gov.in (NCT03923998)

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