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Neoadjuvant chemotherapy followed by surgery in very locally advanced technically unresectable oral cavity cancers

V.M. Patil [a], K. Prabhash [a,*], V. Noronha [a], A. Joshi [a], V. Muddu [a], S. Dhumal [a], S. Arya [b], S. Juvekar [b], P. Chaturvedi [d], D. Chaukar [d], P. Pai [d], S. Kane [e], A. Patil [e], J.P. Agarwal [c], S. Ghosh-Lashkar [c], A. Dcruz [d]

[a] Department of Medical Oncology, Tata Memorial Hospital, Mumbai 400012, India
[b] Department of Radio Diagnosis, Tata Memorial Hospital, Mumbai, India
[c] Department of Radiation Oncology, Tata Memorial Hospital, Mumbai, India
[d] Department of Head and Neck Surgery, Tata Memorial Hospital, Mumbai, India
[e] Department of Pathology, Tata Memorial Hospital, Mumbai, India

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SUMMARY

Background: The median survival of technically unresectable oral-cavity cancers (T4a and T4b) with non surgical therapy is 2–12 months. We hypothesized that neoadjuvant chemotherapy (NACT) could reduce the tumour size and result in successful resection and ultimately improved outcomes. We present a retrospective analysis of consecutive patients who received NACT at our centre between January 2008 and August 2012.

Patients and methods: All patients with technically unresectable oral cancers were assessed in a multidisciplinary clinic and received 2 cycles of NACT. After 2 cycles, patients were reassessed and planned for either surgery with subsequent CTRT or nonsurgical therapy including CT-RT, RT or palliation. SPSS version 16 was used for analysis of locoregional control and overall survival (OS). Univariate and multivariate analysis was done for factors affecting the OS.

Results: 721 patients with stage IV oral-cavity cancer received NACT. 310 patients (43%) had sufficient reduction in tumour size and underwent surgical resection. Of the remaining patients, 167 received chemoradiation, 3 radical radiation and 241 palliative treatment alone The locoregional control rate at 24 months was 20.6% for the overall cohort, 32% in patients undergoing surgery and 15% in patients undergoing non surgical treatment ($p = 0.0001$). The median estimated OS in patients undergoing surgery was 19.6 months (95% CI, 9.59–25.21 months) and 8.16 months (95%, CI 7.57–8.76) in patients treated with non surgical treatment ($p = 0.0001$).

Conclusion: In our analysis, NACT led to successful resection and improved overall survival in a significant proportion of technically unresectable oral-cancer patients.

Introduction

The oral cavity constitutes a major proportion of cancers (30%) in India [1–3]. The standard treatment for oral cavity malignancies is radical resection whenever feasible and radical chemoradiation when the tumour is deemed unresectable [4]. Unfortunately, 85% patients present late with locally advanced tumours [2]. The prognosis of such unresectable stage IVA or IVB tumours treated with a non surgical approach is poor with median survival ranging from 2 to 12 months [5–10]. Theoretically, the prognosis might be improved if these patients could undergo a complete resection. One study by Liao et al. reported a 5 year survival of 45% in T4b stage oral cancers after surgery [11]. Thus, the feasibility of resection becomes an important prognostic marker in oral cavity cancers.

Resectability in oral cancers is decided primarily by the involvement of anatomical landmarks on clinical examination and on imaging [12]. Extension of the tumour to the base of the skull, prevertebral muscles and encasement or invasion of the carotid artery are absolute contraindications to surgery [12,13]. However, involvement of other anatomical landmarks as detailed by Patil et al. can limit the extent of surgery and make it difficult to achieve clear margins [13]. Such tumours may be labelled technically unresectable. Logically in such patients, reduction in size by the use of

* Corresponding author. Tel.: +91 022 24177214 (O), mobile: +91 9224182898; fax: +91 022 24171734.
E-mail address: kumarprabhashtmh@gmail.com (K. Prabhash).

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neoadjuvant chemotherapy might result in successful surgical resection (R0). At our centre, based on the decision in a multidisciplinary clinic, technically unresectable tumours are routinely treated with neoadjuvant chemotherapy with the aim of performing surgery at a later date. This is an evolving strategy in oral cavity cancers and has not been extensively reported so far. We have previously reported the preliminary experience with induction chemotherapy in a selected population of technically unresectable tumours at our centre [13]. In the present study, we have expanded on our previous experience with induction chemotherapy and report the long term outcomes of consecutively treated patients over 4 years. We have also made an attempt to identify the important prognostic factors affecting the outcome in these patients.

Patients & methods

We present a retrospective analysis of all consecutive patients with oral cavity cancer who received NACT at our centre between January 2008 and August 2012. The data was retrieved from a prospectively maintained database, electronic medical records and the case files of the patients.

The management of all patients was decided in the multidisciplinary head & neck clinic at our centre. Locally advanced oral cavity cancers with features discussed below are considered technically unresectable and selected for NACT

1. Buccal mucosa primary, with diffuse margins and peritumoral edema going up to or above the level of zygomatic arch and without any satellite nodules.
2. Tongue primary {anterior 2/3rds} with the tumour extending up to or below the level of the hyoid bone.
3. Extension of tumour of anterior two third of oral tongue to the vallecula.
4. Extension of tumour into the high infratemporal fossa, as defined by the extension of tumour above an axial plane passing at the level of the sigmoid notch.
5. Extensive skin infiltration impacting the achievement of negative margins.

Patients with frank skull base invasion, prevertebral fascia involvement, carotid encasement were considered inoperable and were excluded.

The chemotherapy protocols have been published previously. The regimens had 2 or 3 drugs and consisted of combinations of a taxane (paclitaxel or docetaxel) and a platinum (cisplatin or carboplatin) with or without 5-fluorouracil [13–17]. The choice of regimens was decided on the patients' performance status, creatinine clearance as calculated by the Cockroft–Gault formula, financial constraints and patient preference [13]. After 2 cycles of chemotherapy, the patients were re-evaluated in the multidisciplinary clinic. Response was assessed clinically by the surgeons and radiologically according to the RECIST 1.1 criteria.

The patients, whose tumours had sufficiently regressed, as assessed by the operating surgeon, were considered resectable. This assessment was done by the same group of surgeons who had initially assessed the patients. These patients underwent surgery followed by adjuvant therapy. The surgical resections planned were according to the post chemotherapy volume. The remaining patients underwent radical chemoradiation, radical radiation, palliative chemotherapy or best supportive care according to their performance status, disease status and informed choice. All patients were followed up till progression and/or death.

SPSS version 16 was used for statistical analysis. Descriptive statistics were applied for the patient profile, response rates & local control. The comparison of response rate with the different regimens was done with Chi-square test. Overall survival {OS} was calculated from the date of the first cycle of chemotherapy to the date of death (or last contact). Kaplan Meier analysis was done for estimating of OS. Univariate analysis and multivariate analysis was done by log rank test and Cox regression analysis respectively to identify factors predicting for OS.

Results

Baseline parameters

There were 721 patients with technically unresectable tumours who received NACT and were included in the analysis. The baseline parameters are shown in Table 1. The most common primary site was the Buccal mucosa in 500 patients (69.3%).

Tumour staging details & reason for NACT

All patients had TNM stage IV disease. The tumour T stage was T4a in 528 patients (73.2%) and T4b in 193 patients (26.8%). The N stage were N0 in 39 patients (5.4%), N1 in 27 patients (3.8%), N2a in 101 patients (14.0%), N2b in 305 (42.3%), N2c in 200 patients (27.7%) and N3 in 49 patients (6.8%). The reasons for NACT are shown in Table 2.

Chemotherapy details

Three-drug regimen was administered in 74 patients (10.2%) while the remaining 647 (89.8%) received 2 drug regimen. The 2-drug regimen included a combination of docetaxel with cisplatin in 245 (34.0%), docetaxel with carboplatin in 38 (5.3%), paclitaxel with cisplatin in 314 (43.6%) and a combination of paclitaxel with carboplatin in 51 (7.1%). The 2-drug regimen was selected over 3 drug regimen due to logistics in 485 patients (75%) and co morbidities in 162 patients (25%). The logistic issues included finances, unwillingness for prolonged admissions and inability to follow-up in outpatient department till the next cycle. The median number of cycles delivered was 2 (1–4). At least two cycles were completed by 607 patients (84.2%).

The reasons for taking one cycle only were logistical issues in 83 patients (80.6%), toxicity in 5 patients (4.1%) and progression of disease in 26 patients (15.3%). Forty-eight (7.91%) of patients completing at least 2 cycles required dose reduction.

Response rate

Response rate was evaluable in 618 patients. The overall response rate was 25.1%. The response rate with the 3 drug regimen, and the 2 drug regimen with docetaxel and with paclitaxel were 50%, 30.4% and 17.2% respectively. The response rate were significantly better with 3 drug regimen ($p = 0.004$) and in the 2 drug regimen, significantly better with docetaxel containing regimen ($p = 0.025$). However on binomial logistic regression analysis among the tested variables of age, regimen (3 drugs versus 2 drugs), taxane used (paclitaxel versus docetaxel) and T stage (T4a versus T4b), the only factor which predicted for resectability was the use of 3 drug regimen (Supplementary Table).

Factors predicting for surgical resection

In 3 drug regimen (49 patients) 66.21% achieved resectability as opposed to 40.34% in 2 drug regimen. ($p = 0.011$). No other factor among the tested factors- type of taxane in 2 drug regimen, age, indication of NACT and T-stage were found to be associated with prediction of surgery.

Table 1
Baseline demographic features.

Variable	*N = 721*
Median age	45 years (22–78 years)
Male	615 (85.3%)
Co morbidities[a] (*n* = 528)	Diabetes: 118 (22.3%) Hypertension: 100 (18.9%) Ischemic heart disease: 70 (13.3%) All three: 47 (8.9%)
Habits[b]	Betel nut use/chewable tobacco: 587 (81.5%) Tobacco users (Bidi users): 498 (69.1%) Smokers (cigarette smokers): 388 (53.8%) Alcohol: 270 (37.5%) No addictions: 19 (2.65%)
Body mass index	Median BMI: 21.45 kg/m^2 (12.85–34.13 kg/m^2) Underweight (below 18.5 kg/m^2): 175 (24.3%)
Serum haemoglobin	Median haemoglobin: 12.8 g/dl (5.2–19.9 g/dl)
Serum albumin	Median albumin: 4.1 mg/dl (2.3–5.2 mg/dl)
Serum Creatinine clearance	Median Serum Creatinine clearance: 73.9 ml/min (31–150 ml/min)
ECOG Performance status	PS 0 or 1: 671 (93%) PS 2: 19 (2.7%) PS not recorded: 31 (4.3%)
Tumour subsite	Buccal Mucosa: 500 (69.3%) Anterior 2/3 of tongue: 157 (21.8%) Floor of mouth: 29 (4.0%) Alveolus: 28 (3.9%) Hard palate: 7 (0.8%)

[a] Data was present in 528 patients only.
[b] Patients may have more than one addiction.

Table 2
Reasons for considering these patients technically unresectable.

Indication	*N = 721* (%)
Peritumoural edema or tumour extending up to zygoma	484 (67.1%)
Peritumoural edema or tumour extending up to hyoid bone	91 (12.6%)
Extension of tumour into the vallecula	48 (6.7%)
Extension of tumour into high ITF	43 (6.0%)
Extensive skin infiltration	55 (7.6%)

Post chemotherapy treatment

A total of 310 patients (42.99%) had sufficient reduction in tumour size and underwent surgical resection. Out of 310 surgeries 294 surgeries were done at our centre. Data is available on histopathology of 294 patients only. In all patients we had R0 resection (100%) Patients with response to chemotherapy were more likely to undergo surgery ($p = 0.0032$). Interestingly, 30.2% of patient with stable disease also underwent surgical resection.

Table 3 enumerates the pathological findings after surgery. Adjuvant therapy with chemoradiation was recommended to all patients who underwent surgical resection. However, only 195 patients (66.3%) actually received adjuvant CT-RT. The adjuvant CTRT consisted of 66 Gy of radiation delivered in 2 Gy fractions along with weekly cisplatin chemotherapy (30 mg/m^2) delivered weekly. Adjuvant CTRT was completed by 90% of patients. Median number of weekly cisplatin cycles received was 5 cycles. The remaining patients did not receive any adjuvant treatment.

Table 3
Pathological details of surgical specimen *N = 294* of surgery done at our centre.

Character	Details *N = 294*
Margin status	>5 mm: 269 (97.04%) <5 mm: 25 (2.96%)
Histopathological type	Squamous cell carcinoma: 294(100%)
pT	No tumour seen at primary: 9 (3.06%) Median decrement in T size: 50% (10–100%)
LN positivity	144 (49.0%)
Median number LN positive	2 (1–19)
Perinodal extension	99 (33.7%)
Lymph vascular emboli	3 (1.0%)
Perineural invasion	20 (6.8%)

Among the patients who were deemed unresectable post induction chemotherapy, one hundred and sixty-seven patients were treated with chemoradiation, 3 patients had radiation alone and the remaining patients received palliative treatment. The radical chemoradiation protocol was 70 Gy in 2 Gy fractions with weekly cisplatin. The palliative radiation treatment offered was either 40 Gy in 16 fractions or 30 Gy in 10 fractions.

Locoregional control at 2 years

The median follow-up for whole of this cohort was 28 months. At a follow-up period of August 2013, 537 patients had progressed (74.5%). 517 patients (96.1%) had loco-regional progression and symptomatic isolated distant metastases were seen in 20 patients (3.7%). The overall local regional control rate at 24 months was 20.6%. However when the different approaches were compared, the locoregional control rate was higher (32%), in patients undergoing surgery followed by adjuvant treatment as opposed to only 15.01% in patients undergoing non surgical treatment ($p = 0.0001$).

Overall survival

The median estimated overall survival for the whole cohort was 10.8 months (95% CI 9.84–11.75 months). The median estimated overall survival in cohort who underwent resection was 19.6 months (95% CI, 9.59–25.21 months) while it was 8.16 months (95%, CI 7.57–8.76) in patients treated with non surgical treatment ($p = 0.0001$) (Fig. 1) The 2 year OS was 47% for patients undergoing surgical resection and 20% for those patients undergoing non surgical treatment. In Cox regression analysis for survival, the tested factors were age, sex, ECOG PS, T stage, regimen, taxane used and the local treatment done (surgical versus non surgical). The factors associated with better survival were ECOG PS 0-1, T stage – T4a and surgical treatment (Table 4).

Overall survival in post surgical resection cohort

Among the patients who underwent resection, adverse pathological factors like presence of nodal disease, perinodal extension, perineural invasion and close margin (less than 5 mm) did not impact the OS. The only factor that improved OS was administration of adjuvant treatment (Supplementary appendix).

The estimated median OS has not been reached in patients receiving adjuvant therapy compared to 16.63 months in patients without any treatment (95% CI 5.6–27.65 months) ($p = 0.006$) (Fig. 2).

Discussion

Compared to western countries, the oral cavity constitutes a major proportion of head and neck cancers in India and southeast Asia [3,18–20]. Patients often present with loco regionally advanced disease (stage IV a or IV b). The prognosis of these tumours treated with radical radiation or chemoradiation alone is far from satisfactory [7,21,22]. The reported local control after use of radical chemoradiation or radical radiation in T3–T4 cohort varies from 16% to 30% in a previous report from our centre [6]. Surgery when feasible in these oral cancer patients is associated

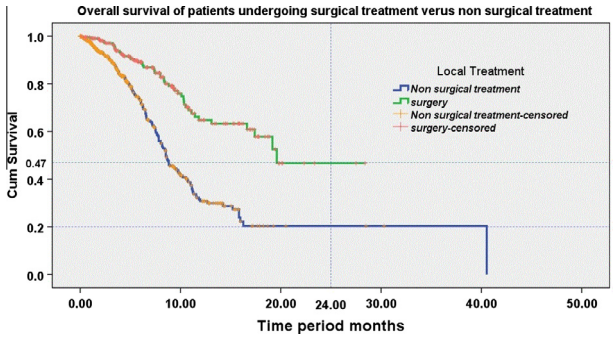

Fig. 1. Kaplan Meier Graph of estimated overall survival of patients who underwent surgical resection post neoadjuvant chemotherapy as opposed to those who were treated with non surgical treatment modality.

Table 4
Factors affecting overall survival on Cox regression analysis.

Variables	Type of variable	*P* value	Hazard ratio
Age	Continuous	0.74	–
Sex	Binomial (male/female)	0.32	–
ECOG PS	Binomial (0–1/2)	0.01	0.36
T stage	Binomial (T4a/T4b)	0.01	0.57
Regimen	Binomial (3 drug regimen/2 drug regimen)	0.51	–
Taxane in chemotherapy protocol	Binomial (docetaxel/paclitaxel)	0.96	–
Local treatment received	Binomial (surgical/non surgical)	0.00	0.57

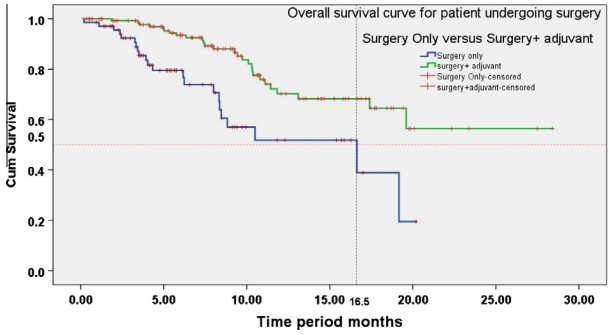

Fig. 2. Kaplan Meier Graph of estimated overall survival of patients who underwent surgical resection post neoadjuvant chemotherapy and received adjuvant treatment as opposed to those who underwent surgical resection post neoadjuvant chemotherapy and did not received adjuvant.

with better results even in advanced stages [11,12]. Theoretically, neoadjuvant therapy could represent an attractive option to decrease the size of tumours and enable successful surgery. Unfortunately, the trials of NACT in head and neck cancers have been contentious and generally did not yield the anticipated results [14,15,23,24]. However, a closer look at the trials shows that the patients included are very heterogeneous in terms of tumour site and presentation. The proportion of oral cavity cancers in the major trials conducted primarily in Europe and North America is around 14–18%. Further, only one trial, the TAX 323 trial by Vermorken et al., exclusively included patients with unresectable disease [14]. In most other studies, with the exception of Paccagnella et al., unresectable diseases are in a distinct minority [23]. Thus, there is little literature available for advanced oral cavity cancers which are predominant in South East Asia [3,18,20]. To the best of our knowledge, the present study is the first to look at this specific population of patients. Our strategy of defining specific technically unresectable subset and giving induction chemotherapy followed by surgery is a novel approach not reported previously.

The issue of unresectability is a major cause of debate. As discussed previously, technical unresectability is a complex interplay between disease status, anatomical site of involvement, surgical skills, quality of life issues and ability to achieve negative surgical margins [12]. The debate is significantly influenced by subjective criteria and therefore subject to individual variation. A closer look at TAX 323 or Paradigm studies clearly shows that in literature stage III and stage IV A tumours have been considered as unresectable. However, the objective criteria for unresectability have not been clearly stated [14,23,24]. At our centre, we have evolved certain criteria based on anatomical landmarks for identifying patients with unresectable tumours where negative margins would be unlikely to be achieved with surgery. These criteria were selected in an interdisciplinary clinic including surgical oncologists, radiologists, radiation oncologists and medical oncologists. The anatomical landmarks were identified based on previous experience with locally advanced & very locally advanced oral tumours. In our previous experience 80% of our margin positive rate was seen in T4 tumours and in literature surgery in T4 oral cancers has been associated with margin positive rate of 55% [25,26]. We stressed on positive resection margins since previous studies have shown them to be associated with a decrease in survival rate by 8–31% and a two-fold increase in local recurrences in oral cavity cancers [25–27]. In conclusion, we specifically excluded patients with features like encasement of the carotid artery or involvement of the prevertebral fascia who would not be suitable for surgery even after good response to chemotherapy. Conversely, patients with features detailed in the methods section could be considered for NACT and surgery, even if unresectable upfront.

The protocol of NACT was based on published literature documenting the efficacy of both 3 drug & 2 drug regimens of taxane & platinum with or without 5 FU [13–17]. The major hurdle to using a 3-drug regimen in our centre is the need for inpatient admission for continuous 5 FU infusion. The 2-drug protocol of a taxane and platinum could be administered on a day care basis. In the final analysis, 40.34% patients receiving the doublet regimen achieved the aim of resectability, thereby confirming the efficacy of these regimens. Though this combination has been used in the past in locally advanced head & neck cancers, it has not been systematically reported in oral cancers [17].

The response rates in our study appear to be lower than reported in other studies [28,29]. This is expected since the patients in our study had advanced stage of disease and involvement of oral cavity, both factors traditionally associated with poor response [13,16]. As seen by Lictria et al., response rates decrease with increasing stage in oral cancers [29]. Thus, our response rates may not be so low.

The intriguing part of our study relates to the response assessment. We used clinical and radiological response to decide respectability. We also categorised the response according to the RECIST criteria. On reviewing the data, we found that nearly 30% of patients with stable disease according to RECIST could undergo successful resection. After review of the scans, it was seen that several patients had a decrement more than 10% which was sufficient for surgery. We have previously reported on the discrepancy between radiological response and pathological response [30]. We had selected patients who had pathological complete response or near complete pathological response in head and neck cancers post induction chemotherapy and retrospectively reviewed the radiological response according to RECIST. Interestingly, there was no correlation between the pathological response and radiological response. We hypothesized that the primary reason for the observed discrepancy could be the complex shapes of Head

and neck cancers. Responses according to RECIST criteria require a predefined decrement in axial diameters which may be nonsignificant even if there is a clinically significant decrement in the area occupied by the tumour in the axial image and a decrement in the volume of the tumour [30]. This reaffirms our belief that the decision to operate should be made on both clinical and radiological grounds.

A significant proportion (44.70% patients) could undergo surgery in our study. All of these patients had R0 resection and on pathological examination the median decrement in size of the tumour was 50% (10–100%). This in contrast with literature associated high rates of margin positivity in T4 tumours where NACT was not used [26]. Pathological complete response was seen in 3.06% (9 patients).

In our study, surgical resection had a positive impact both on local control & survival .The median OS for patients with surgical treatment & adjuvant treatment was 19.6 months, while it was lower for patients undergoing radical chemoradiation (11 months) ($p = 0.0001$). In patients undergoing surgery the factor which affected the survival was postoperative adjuvant treatment. This was in concordance with the EORTC postoperative adjuvant chemoradiation trial, operable Stage IV oral cancers benefited from adjuvant chemoradiation [31,32].

Majority of the recurrences were loco-regional in our study. The incidence of distant metastasis were low as in those patients who recurred locally and were not found to be fit for further treatment were not investigated for distant metastasis. The incidence of sole symptomatic distant metastasis was below 5% again implying the importance of local control in this disease. This also lends credence to the importance of surgery in the treatment.

The major drawbacks of this study are the retrospective nature of data collection, absence of a parallel cohort of patients receiving chemoradiation alone, variable nature of NACT received and variable nature of adjuvant treatment received post surgical resection. In conclusion, we reiterate that every attempt should be made to surgically resect patients with locally advanced oral cavity tumours as this improves outcomes. An aggressive approach of neoadjuvant chemotherapy followed by post surgical chemoradiation appears to provide the best outcomes in a cohort of patients with defined technically unresectable patients.

Conflict of interest

None declared.

Appendix A. Supplementary material

Supplementary material associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.oraloncology.2014.07.015.

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