Original Article

Surgical Outcomes Post Neoadjuvant Chemotherapy in Stage IV cancers of Oral Cavity

Tarun Kumar, Kiran Kothari, Mahesh H. Patel, K. Ravi, Vijay Yadav

Gujarat Cancer Research Institute, Ahmedabad, India

Abstract

Aim: To know the effect of neoadjuvant chemotherapy on surgical outcomes (R1 resections, post–operative complications, recurrence and follow up) in Stage IV borderline operable cancers of oral cavity.

Materials & Methods: Patients in group A (n=45) were those who were referred for neoadjuvant chemotherapy (NACT) with an intention to operate at a later date. These were compared with 45 patients of group B who were operated upfront. All 90 patients have stage IV squamous cell carcinoma of oral cavity. Details of patients were studied retrospectively from hospital records of surgical, medical, radiotherapy and pathology departments. All patients referred for NACT were wet lesions with perilesional edema and diffuse margins of lesions where the demarcation from normal tissue was not clear. Treatment response was assessed clinically and radiologically. Any reduction in tumor size on CT scan, MRI or clinically was considered response to chemotherapy.

Various chemotherapy regimens were given in different patients – TPF (Taxol– Docetaxel or Paclitaxel, Cisplatin, 5 Fluoro Uracil), PMF (Cisplatin, Mitomycin C, 5 Fluoro Uracil), Cisplatin + Methotrexate and Cisplatin with 5 Fluoro Uracil.

Inoperability was defined as involvement of the upper infratemporal fossa where R0 resection was difficult. Patients were followed up monthly after completion of treatment for one year and three monthly thereafter. Survival was calculated from the day of surgery to the death of the patient or last patient contact. The time of recurrence was also calculated from the day of surgery. Statistical methods used in the study were simple frequencies and proportion. Test of significance was Z test. $Z \geq 2$ was considered significant. Kaplan Meir survival analysis was used through SPSS software for disease free survival

Results: Total 39 patients were operated in group A as remaining six progressed to inoperability while on chemotherapy. There were 3 R1 resections in group A and 9 R1 resections in group B (Z= 1.67). Eleven and three postoperative complications in group A and B respectively (Z= 2.67). There were nine and 16 recurrences so far in group A & B respectively (Z=1.27). DFS at one year was 90% and 55% respectively (p= 0.017).

Conclusion: Though the study shows a trend in favor of NACT when R1 resections, recurrences and survival at one year are considered but this was at the cost of those six patients who progressed on NACT and could have been operated initially. Such patients were present in each and every subset of chemotherapy used.

Keywords: neoadjuvant chemotherapy, pre–operative chemotherapy, Stage IV oral cancer.

Introduction

Three doctors sit thoughtfully around a table, the surgeon instantly recognizable in green, the radiotherapist and medical oncologist indicated more subtly by film badge or stethoscope. “Advanced Head and Neck Cancer...Diagnosed” states the caption. “Decision... Sequential Multimodality Treatment.” Overpage, this advertisement for induction chemotherapy claims that “Blexoxane induction regimens have demonstrated significant efficacy.”

Supported by five references, all of them to uncontrolled trials, there follow the claims: (1) “High response rate, complete remissions and significant tumor reduction” (true); (2) Long disease free survival following induction chemotherapy and definitive surgery with or without

Corresponding Author: Tarun Kumar, Resident, Department of Surgical Oncology, Gujarat Cancer and Research Institute, New Civil Hospital Campus, Asarva, Ahmedabad – 380016, India.
Email: batra_tarun@hotmail.com

Figure 1. Showing the kind of lesions referred for chemotherapy.

irradiation" (true that those respond to chemotherapy live longer than those who do not), and so on.

This advertisement is clearly effective; otherwise, it would not continue to appear in the leading cancer journals. But it is misleading. Where are the references to the randomized controlled trials that have failed to show long term benefit of chemotherapy, including those where the chemotherapy regimens contain bleomycin? [1]

This was the scenario way back in 1986. Gone are the days of Bleomycin in head and neck oncology however the controversy still prevails.

Materials & Methods

This is a retrospective study of 90 patients of stage IV (T4, N2b) oral cancers. Patients in group A (n=45) were those who were referred for neoadjuvant chemotherapy (NACT) with an intention to treat at a later date from February 2011 to September 2012. Group B also had 45 patients who were operated upfront from April 2009–September 2012.

All patients referred for NACT were borderline operable wet lesions with perilesional edema and diffuse margins where the demarcation from normal tissue was not clear (Figure 1). No patient had satellite lesion at the time of surgery.

The following chemotherapy regimens were used. (Table 1)

Response evaluation was done after every cycle i.e. after 21 days. Most of the patients were given 2–3 cycles of chemotherapy. Treatment response was assessed clinically and radiologically however pre and post chemotherapy scans (CT/ MRI) were not available for all the patients and final response assessment and decision to operate was left to the surgeon. Any reduction in size

TPF (Taxanes + Cisplatin + 5 Fluorouracil) - 15 patients Docetaxel: 75mg/m^2 OR Paclitaxel: 175mg/m^2 + Cisplatin:100mg/m^2 + 5 Fluorouracil:1000mg/m^2 for three days as continuous infusion Cycle to be repeated every 21 days G-CSF: 300mcg/day for seven days. Starting from 24-72 hours.
PMF (Cisplatin + Mitomycin C + 5 Fluorouracil) - 14 patients Cisplatin:100mg/m^2 + Mitomycin C: 10mg/m^2 + 5 Fluorouracil:1000mg/m^2 for three days as continuous infusion Cycle to be repeated every 21 days
P+F (Cisplatin + 5 Fluorouracil) - 7 patients Cisplatin:100mg/m^2 + 5 Fluorouracil:1000mg/m^2 for three days as continuous infusion Cycle to be repeated every 21 days
Cisplatin + Methotrexate - 9 patients Cisplatin:100mg/m^2 + Methotrexate: 50mg/m^2 Cycle to be repeated every 21 days

Table 1. Various Chemotherapy Regimens Used

on CT scans, MRI or clinically was considered response to chemotherapy. Inoperability was defined as involvement of upper infra temporal fossa above the sigmoid notch. All tongue cancers were operated with adequate margins.

Surgeries performed were wide excision of the tumor (1–1.5 cm margin) with modified neck dissection with flap reconstruction.

Apart from the epidemiological details two groups were studied on the response to chemotherapy, postoperative complications, R1 resections, recurrence and patient survival.

All the patients were staged according to the 7th edition AJCC cancer staging manual. [2] Statistical methods used in the study were simple frequencies and proportion. Test of significance was Z test. $Z \geq 2$ was

Parameter	Group A	Group B	*p*
Age in years	46.36	48.8	-
M:F	36:9 (5:1)	30:15 (2:1)	-
Bone Involvement	22 (48%)*	31 (68.8%)*	0.8
Skin Involvement	31(68.8%)*	13 (28.8%)*	0.06

Table 2. Comparison various parameters of the two groups.

considered significant. Kaplan Meir survival analysis was used through SPSS software for disease free survival.

Concurrent CT+RT were given to all the patients with adverse prognostic factors such as perineural invasion, lymphatic invasion, and extracapsular spread and R1 resection. Rest of the patients were referred for radiotherapy.

Patients were followed monthly for 1 year and 3 monthly thereafter. Survival was calculated from the day of surgery to the death of the patient or last patient contact. The time of recurrence was also calculated from the day of surgery.

Observation

- Out of 90 patients, 66 (73%) were males and 24 (27%) were females. In group A 36 (80%) were males and 9 (20%) females whereas in group B there were 30 (67%) and 15 (33%) males and females respectively.
- Mean age of the patient was 46.36 years. 48.8 for group A and 46.11 in group B respectively.
- All the patients in the study were stage IV tumor.
- In group A, 19 patients had only skin involvement, 10 patients had only bone involvement and 12 patients had both skin and bone involvement.
- In group B, five patients had only skin involvement, 23 had only bone involvement and 8 had both skin and bone involvement. One patient of carcinoma buccal mucosa was stage IV by virtue of N2b nodes.
- Out of 90 patients 31 (35%) have well differentiated (WD) tumors, 55 (61%) have moderately differentiated (MD) tumors and 04 (4%) had poorly differentiated (PD) tumors.
- In group A, 31 patients have stage IVa and 14 patients have IVb disease, where as in group B, 44 have IVa disease and only one patient had stage IVb disease.
- Amongst the patients who received NACT no response was seen in 10 patients, positive response was seen in 26 patients and progression of disease was seen in 09 patients. This data can be further segregated according to the primary tumor site. (Table 5)
- On final histopathology there was no complete response or stage progression however 8 patients were down staged from IVb to IVa on final histology. One patient had Stage II on final histology in group A.

The following site distribution was seen: (Table 3)

Site	Group A	Group B
Buccal Mucosa (BM)	26	11
Retromolar trigone (RMT)	04	02
Central Arch	02	07
Gingivo buccal Sulcus (GBS)	01	03
Angle of mouth (AOM)	01	-
Floor of Mouth (FOM)	01	-
Tongue	04	10
Alveolus	05	12
Lip	01	-
Total	**45**	**45**

Table 3. Site of primary tumor

Tumor	Group A	Group B
WD	18	13
MD	24	31
PD	03	01

Table 4. Differentiation of the tumor

The following table shows response for various chemotherapy regimens

- Out of nine patients who progressed on chemotherapy, six were not operated due to doubtful R0 resection in surgery. Therefore, total

Progression	
BM	08
AOM	01
Total	**09**

No Response	
Tongue	01
RMT	02
BM	07
Total	**10**

Good Response	
BM	11
CA	02
GBS	01
RMT	02
Tongue	03
Alveolus	05
FOM	01
LIP	01
Total	**26**

Table 5. Differential tumor response according to the site of tumor

	TPF (15 patients)	PMF (14 patients)	P+F (07 patients)	Cisplatin + Methotrexate (09 patients)
Good response	08 (53.3%)	08 (57.1%)	05 (71.1%)	05 (55.5%)
No response	03 (20%)	04 (28.5%)	01 (14.2%)	02 (22.2%)
Progression	04 (26.6%)	03 (21.4%)	01 (14.2%)	01 (11.11%)
Postoperative complications	09 (60%)	04 (28.5%)	01 (14.2%)	02 (22.2%)
Recurrences	04 (26.6%)	01 (7.1%)	02 (14.2%)	02 (22.2%)

Table 6. Response to Chemotherapy

39 patients were operated in group A. 15 patients have adverse prognostic factors in group A. There were 03 R1 resections out of 39 operated patients in group A. 11 patients have postoperative complications in the form of skin flap necrosis, orocutaneous fistula and wound infection.

- There were 9 recurrences, seven locoregional one systemic and one had both systemic and locoregional. Out of these 9 patients 5 have adverse prognostic factors. There were no defaulter of adjuvant treatment
- 11 patients were referred for adjuvant concurrent chemoradiation and 28 patients for adjuvant radiotherapy. 6 patients were referred for palliative care that was not operated. All these patients died within 6 months of diagnosis.
- Mean follow up was approximately 52 weeks (4.2–68.5 weeks)
- In group B all 45 were operated, 8 patients have adverse factors, 9 patients have R1 resection. Postoperative complications were seen in 3 patients. Twenty–seven patients were referred for adjuvant radiotherapy and 11 patients for adjuvant chemo radiotherapy. There were seven adjuvant defaulters in group B.
- 16 (14 locoregional & 2 systemic) out of 45 have recurrences. Five patients out of these have adverse factors and three were adjuvant defaulters. One patient had adverse factors and had not taken adjuvant treatment.
- Mean follow up 56.53 weeks (2–195 weeks).
- Disease free survival at one year was 90% for patients in group A, whereas in group B 55% of patients were alive and disease free at one year.

	Group A	Group B
Total Operated	39	45
Adverse Factors	15	08
R1 Resection	03	09
Complications	11	03
Recurrence	09	16
Adjuvant CT+RT	11	11
Adjuvant RT	28	27

Table 7. Comparison between two groups

Discussion

It was not possible to relate all the data to treatment in meaningful manner because various chemotherapy regimens were used and various sites in oral cavity known to respond differently creating numerous groups resulting in too few patients for reliable analysis. Apart from this there are many other biases in the study. Patients referred for NACT have larger more advanced lesions with skin involvement which is individual factor for bad prognosis.[3]

There were no set objective criteria for response evaluation and response was evaluated subjectively by the surgeon. Time frame of the two groups is not similar and group B patients are considered from 2009 onwards whereas group A patients from 2011 onwards.

In an Italian prospective study by Licitra et al [4] which concluded that NACT significantly reduced the number of patients who needed to undergo mandibulectomy or radiation therapy without any improvement in overall survival. In our study all the patients have stage IV cancers which were anyway going to be referred for

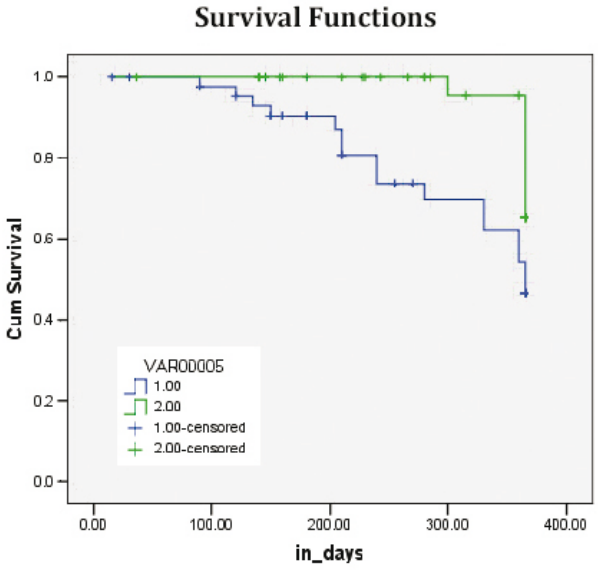

Figure 2. Kaplan Meir chart for survival

Licitra et al				Our Study		
	NACT	Upfront Surgery			NACT	Upfront Surgery
R1 resections	4.08%	12.3%		R1 resections	7.6%	20%
Recurrences	29.1%	31.5%		Recurrences	23%	35.5%
Postoperative Complications	44.9%	51.6%		Postoperative Complications	28.2%	6.7%
DFS at five years	57%	46%		DFS at one year	90%	55%

Table 8. Comparison of our study vs Licitra et al

adjuvant radiotherapy or chemo radiotherapy. And also no marginal mandibulectomies were done as all the cases were advanced.

There was a similarity with decreased number of R1 resections. Licitra et al showed 4.08% R1 resections in NACT arm and 12.3% in upfront surgery arm. As compared to this study, we have 7.6% R1 resection in group A and 20% in group B. However, this finding in either study is not statistically significant.

They also reported insignificant difference in the recurrences, 29.1% in chemotherapy arm and 31.5% in upfront surgery arm. In our study there were 23% recurrences in chemotherapy arm and 35.5% in surgery arm. This is in contrast to another Japanese study by Okura et al [5] who reported that induction chemotherapy was associated with significant increase in locoregional failure in carcinoma oral cavity. However out of 33 patients who received induction chemotherapy only 9 were stage IV patients.

28.2% had postoperative complications in the form of skin flap necrosis, orocutaneous fistula and wound infection in group A. In group B only 6.67% of the patients had postoperative complications. This issue has not been discussed extensively in western papers [5, 6, 7] however Licitra et al showed no difference in postoperative complications in the two groups. Increase in postoperative complications in our study did delay the adjuvant treatment of the patient however this did not precipitate in increased recurrence in the same patient group.

In another study by Kohno et al [8] showed that NACT has maximum advantage for non–locally advanced T1–T3 disease. However, the study was limited by less number of patients (n=13).

Conclusion

The gist of the study can be summarized in the following points:

- Total 39 patients were operated in group A as remaining six progressed to inoperability while on chemotherapy.
- There were 3 R1 resections in group A and 9 R1 resections in group B (Z= 1.67).
- Eleven and three postoperative complications in group A and B respectively (Z= 2.67).
- There were nine and 16 recurrences so far in group A & B respectively (Z=1.27).
- Though the study shows a trend in favor of NACT when R1 resections, recurrences and survival at one year are considered but this was at the cost of those six patients who progressed on NACT and could have been operated initially. Such patients were present in each and every subset of chemotherapy used.

References

1. Tannock IF, Browman G.:Lack of evidence for a role of chemotherapy in the routine management of locally advanced head and neck cancer J Clin Oncol 1986;4:1121–6.
2. AJCC Cancer Staging Manual. 7th edition. 2010.
3. Fang FM, Leung SW, Huang CC et al. Combined–modality therapy for squamous carcinoma of the buccal mucosa: treatment results and prognostic factors. Head Neck 1997;19:506–12.
4. Licitra L, Grandi C, Guzzo M et al. Primary chemotherapy in resectable oral cavity squamous cell cancer: a randomized controlled trial. J Clin Oncol. 2003;21:327–33.

5. Okura M, Hiranuma T, Adachi T et al Induction chemotherapy is associated with an increase in the incidence of locoregional recurrence in patients with carcinoma of the oral cavity: results from a single institution. Cancer.1998;82:804–15.

6. El–Sayed S, Nelson N. Adjuvant and adjunctive chemotherapy in the management of squamous cell carcinoma of the head and neck region. A meta–analysis of prospective and randomized trials. J Clin Oncol.1996;14:838–47.

7. Zorat PL, Paccagnella A, Cavaniglia G et al. Randomized phase III trial of neoadjuvant chemotherapy in head and neck cancer: 10–year follow–up. J Natl Cancer Inst. 2004 ;96:1714–7.

8. Kohno N, Ikari T, Kawaida M.Survival results of neoadjuvant chemotherapy for advanced squamous cell carcinoma of the head and neck. Jpn J Clin Oncol. 2000 ;30:253–8.