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Identification of clinical and pathological parameters to predict the efficacy of neoadjuvant chemotherapy in locally advanced oropharynx cancer - a prospective study

Abstract

The aim of the study is to evaluate the efficacy of Taxane based neoadjuvant chemotherapy in terms of tumor response and its effect on different morphological subtypes of oropharyngeal cancer followed by concurrent chemoradiotherapy in Indian scenario. Patients with locally advanced newly diagnosed, histological proven squamous cell carcinoma of the oropharynx were treated with neoadjuvant chemotherapy followed by concomitant chemoradiotherapy. These patients received treatment by 2D planning (Cobalt 60) method (two lateral opposed field and anterior neck) with shrinking field technique, total dose (60-70Gy) over 6-7weeks interval by conventional fractionation along with concomitant chemotherapy Inj.cisplatin 30mg/m^{2}weekly. The primary end point was loco-regional response.The overall clinical RR after completion of 3 cycles of NACT was better than 2 cycles of NACT. Hence, it may be concluded that 3 cycles of NACT are better than 2 cycles but looking at OS and DFS 2 cycles appears to be better than 3 cycles with DFS and OS of 14.2months and 18.4months respectively, which is 8months and 16.2months with 3 cycles. As per stage, after 3 cycles of NACT the overall clinical RR in stage IV was (30.4%) and in stage III (21.7%) which is more than after 2 cycles, which again is an indicator of greater efficacy of 3 cycles then 2 cycles, but with limitations of smaller sample size and follow up duration.

Keywords: NACT, oropharynx cancer

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Abbreviations: NACT, neoadjuvant chemotherapy; CR, complete response; PR, partial response; PD, progressive disease; NR, no response; ANOVA, analysis of variance

Introduction

In India, head and neck cancer account for 30%-40% cancers at all sites, out of which 9.4% being the oral cavity and pharynx and is the sixth common cause of death in males and seventh in the females.[1] Almost all of these malignancies originating from the mucosa of epithelium are the squamous cell carcinoma.[2] In India, most prevalent sites are oropharynx and oral cavity followed by larynx and hypopharynx respectively.[3] Carcinoma oropharynx forms the largest group and comprises less than 0.5% of all cancers in men.[4,5] The most common primary site involved is base of tongue and tonsil.[4–7] According to NCRP, ICMR, Hospital Based Cancer Registry 2004-2006, Bangalore the number of oropharyngeal cancer is 184 per year (6.36%) while Population based cancer registry, Chennai, Adyar,is 5.4%.[8] Incidence increases with age (i.e. 4th and 5th decades of life) and male to female ratio is 4:1.[9–11] The commonest known etiological factor is tobacco abuse and smoking in approximately 90% of diagnosed cases.[3,12] Majority of these patients (70-80%) are diagnosed as locally advanced disease (stage III/IV) with lymph node involvement in 30-50% at presentation,[13] so treated with combined modality approach (neoadjuvant chemotherapy, concomitant chemoradiotherapy).[14,15]

The use of neoadjuvant chemotherapy is based on significant tumor destruction and thus rapid shrinkage of the primary and nodal tumor. Neoadjuvant chemotherapy followed by RT or chemoradiotherapy offers the added advantage of organ preservation in optimum cases.[16] Based on these backgrounds, this study was planned to evaluate the efficacy of Taxane based neoadjuvant chemotherapy in terms of tumor response along with its effect on different morphological subtypes of oropharynx cancer in Indian scenario. This study will also look into the efficacy of sequential use of taxane based NACT followed by concurrent chemoradiotherapy.

The present investigation deals with the following objectives:

i. To evaluate the compliance and loco-regional response of NACT (TPF) in Indian context.

ii. To assess the toxicity and disease free survival treated with NACT followed by concomitant chemoradiotherapy.

Methods and materials

After the Ethics Committee approval, this prospective study (forty six patients) was conducted in the department of Radiation Oncology, Mahavir Cancer Institute and Research Centre, Patna, Bihar, India from April 2010 to September 2010 and follow up till September 2011. Patients with locally advanced newly diagnosed, histological proven squamous cell carcinoma of the oropharynx,[17] age between 25 - 75years with normal range of biochemical tests and having KPS 60-100%[18] were analyzed. These patients received multimodality treatment neoadjuvant chemotherapy (NACT) followed by CT+RT.[19–23] These

patients received treatment by 2D planning (Cobalt 60) method (two lateral opposed field and anterior neck) with shrinking field technique, total radiation dose in the range of 60-70Gy over 6-7weeks@ 2Gy per fractions interval by conventional fractionation schedule along with concomitant chemotherapy Inj. Cisplatin 30mg/m^{2}weekly. As neoadjuvant chemotherapy TPF regime with Inj.cisplatin (50mg/m^2), Inj5Flourouracil (750mg/m^2) and Inj. Docetaxel (75mg/m^2) in 2-3 cycles for 3 days were given with proper premedication, adequate hydration and forced dieresis. Patients were reassess after 2 cycles of NACT followed by concomitant chemoradiotherapy.[24,25]

Tumor response to NACT was assessed clinically twoweeks after the completion of NACT by Hopkin's Laryngoscope and CT scan (as pretreatment planning for CT-RT). Response analysis was again done clinically fourweeks after completion of chemoradiotherapy, and if there was any progressive disease, patients were removed from study protocol. Response was evaluated according to RECIST criteria and documented at both, primary tumor and nodal site.[26] Clinical response was graded as complete response (CR), partial response (PR), progressive disease (PD) and no response (NR) as mentioned. Acute toxicity assessment was done as per NCI, CTCv2. 0criteria for toxicity including radiation therapy and chemotherapy.[27,28] Late toxicity was evaluated at 3-6, 12 and 18-24months intervals as per RTOG/EORTC late radiation morbidity scoring scheme.[27]

Statistics

Data was collected and were expressed as percentage, mean and standard deviation. Independent t- test, Pearson- coefficient of correlation and one way analysis of variance (ANOVA) tests were used.

Results

A total of 46 cases of oropharyngeal cancer were included between April 2010 to September 2010.

Patient's and tumor profile

Nearly 86.9% patients were in 4th-7th decades of life with M: F ratio -3.6:1. Out of these, 78.26% smoked beedi/cigarette, 30.44% chewed tobacco and 13.04% were non-smokers. As per morphology mixed type were seen in 62.2% and histopathological pattern of MDSCC in 73.91% cases. Commonest subsites was BOT and tonsil each (39.2%). Majority of these patients had stage IV (73.91%) disease with T3 tumor in 60.87% and T4 in 39.13%. Nodal involvement was seen in 73.9% cases (Table 1).

Table 1 Patients and tumor factors

S.no	Characteristics		Number	Percent (%)
1.	Sex	Male	36	78.26
		Female	10	21.74
2.	Age(yrs)	40 – 70 yrs	40	86.9
		70 -80	4	8.7
3.	KPS (%)	80 -90	26	56.5
		90 – 100	16	34.8
4.	Habits	Smoking	18	39.1
		Tobacco	2	4.35
		Alcohol	2	4.35
		Smoking+Tobacco+Alcohol	18	39.1
		Nil	6	13.0
5.	Tumour Morphology	Ulcerative	2	4.35
		Proliferative	12	26.09
		Infiltrative	2	4.35
		Mixed	30	65.22
6.	Tumour Histopathology	WDSCC	4	8.7
		MDSCC	34	73.9
		PDSCC	8	17.4
7.	Tumour Subsites	BOT	18	39.2
		Tonsil	18	39.2
		Soft Palate	6	13.0
		Oropharyngeal wall	4	8.6
8.	Tumour Stage	Stage III	28	60.8
		Stage IV	18	39.2
9.	Nodal wise	N0	12	26.09
		N1	6	13.0
		N2	28	60.8

Treatment profile

All 46 patients took first cycle of NACT, out of which 18 patients (39.1%) had taken 2 cycles of NACT and 28 patients (60.9%) had 3cycles of NACT. Six patients developed progressive disease with unrelated cause, so these six patients were removed from the protocol and finally 40 patients were available for final analysis.

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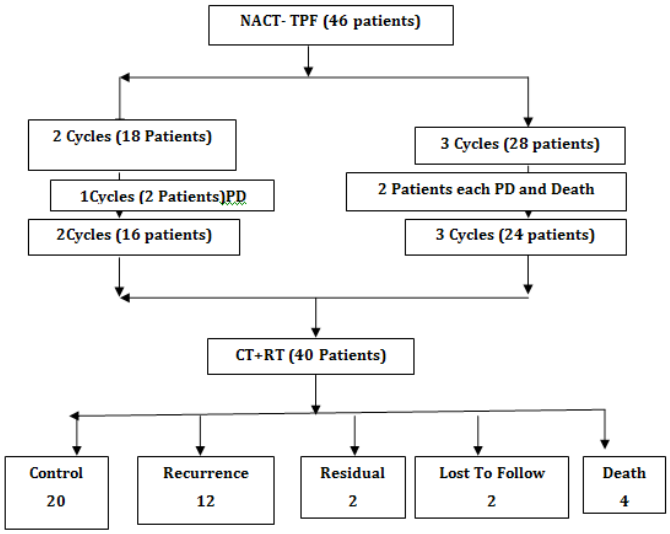
Flow chart



Response assessment

The overall clinical RR after completion of 2 cycles of NACT was 34.8% but with 3 cycles NACT 54.7%, similarly at the end of treatment protocol, the RR with 2 cycles was 40% as compared to 3 cycles was 60% (Table 2 & Table 3).

Response in different tumor morphology after NACT

It was observed that proliferative and mixed morphology tumors respond better to chemotherapy as compared to infiltrative and ulcerative type (Table 4).

Comparison of mean overall survival with respect to various factors

Among various factors studied which affects the response of chemotherapy and radiotherapy includes age, sex, tumour stage, nodal involvement, histology and grade. We had analyzed these factors and found a trend towards better survival with lower T stage (p=0.2), proliferative morphology (p=0.1) and good KPS status (p=0.1) will respond better as compared to other prognostic variables (Table 5).

Acute and late reaction

Treatment related adverse events were seen in all patients. Acute and late reactions were noticed in almost all patients. Non-hematologic Gr. III/IV toxicities were (43.5%).In our study Gr. III/IV neutropenia was seen in 21.4 % of the cases on TPF regime.

Status at last follows up

Total of 40 patients treated with NACT followed by CT-RT, the disease was controlled in50.0%, recurrence in 30.0% of which one nodal, one local and four loco regional recurrences, residual disease in 5.0% and death occurred in 10.0% cases. Out of 40 patients, treated with 2 cycles NACT followed by CT-RT the disease was controlled in 30.0%, recurrence in 5.0% and death occurred in 5.0% patients, but treated with 3 cycles NACT the disease was controlled in 20.0%, recurrence in 25.0%, residual disease in 5.0% and death occurred in 5.0% patients respectively.

Disease free duration and overall survival as per cycle

It was observed that the mean value +SD of DFS of patients with 2 cycles of NACT followed by CT-RT was 14.12+5.61 and in 3 cycles of NACT followed by CT-RT was 8.0+4.306 respectively. The mean value +SD of OSS of patients with 2 cycles of NACT followed by CT-RT was 18.38+5.805 and in 3 cycles of NACT followed by CT-RT was 16.25+4.245 respectively (Figure 1).

Table 2 Clinical response rate after 2 and 3 cycles of NACT

Response	2cycles of NACT	3cycles of NACT
Overall clinical RR	34.8%	54.7%
	At completion of protocol after 2 cycles of NACT	**At completion of protocol after 3 cycles of NACT**
Overall clinical RR	40%	60%

Table 3 Stage wise response after completion of protocol with 2cycles of NACT

Stage	Primary			Nodal		
	CR*(%)	PR*(%)	Total response (%)	CR*(%)	PR*(%)	Total response (%)
III	0 (0.0)	2 (5.0)	2 (5.0)	2 (5.0)	0 (0.0)	2 (5.0)
IV	14 (35.0)	0 (0.0)	14 (35.0)	12 (30.0)	2 (5.0)	14 (35.0)

After completion of protocol with 3 cycles of NACT

Stage	Primary			Nodal		
	CR*(%)	PR*(%)	Total response(%)	CR*(%)	PR*(%)	Total response (%)
III	10 (25.0)	0 (0.0)	10 (25.0)	10 (25.0)	0 (0.0)	10 (25.0)
IV	10 (25.0)	4 (10.0)	14 (25.0)	8 (20.0)	6 (5.0)	14 (20.0)

CR*, complete response; PR*, partial response

**Figures in parenthesis shows percentage

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Table 4 Response in different tumor morphology after NACT

Morphology	CR* (%)	PR* (%)	PD* (%)	Total (%)
Ulcerative	0 (0.0)	2 (4.3)	0 (0.0)	2 (4.3)
Proliferative	10 (21.7)	2 (4.3)	0 (0.0)	12 (26.1)
Infiltrative	2 (4.3)	0 (0.0)	0 (0.0)	2 (4.3)
Mixed	22 (47.8)	2 (4.3)	6 (13.1)	30 (65.2)

Table 5 Comparison of mean overall survival with respect to various factors

Variables	Groups	Mean±S.E	Std. dev.
Sex	Male	17.00 ± 5.123	
	Female	17.67	4.163
Tumour	T3	18.08	4.271
	T4	15.29	5.794
Node	N0	19.00	1.604
	NI	15.67	2.309
	N2A	17.33	7.371
	N2B	14.80	5.891
	N2C	18.33	4.01
Stage	Stage III	18.00	1.265
	Stage IV	16.71	5.823
Morphology	1,2,3	15.00	4.342
	4	18.50	4.902
Kps	2	15.75	4.413
	3	19.12	5.167
Cycle	2 Cycles	18.38	5.805
	3 Cycles	16.25	4.245
Dose	5000-6000cGy	15.00	2.828
	6000-7000cGy	17.33	5.076

*'t' test,** One way analysis of variance

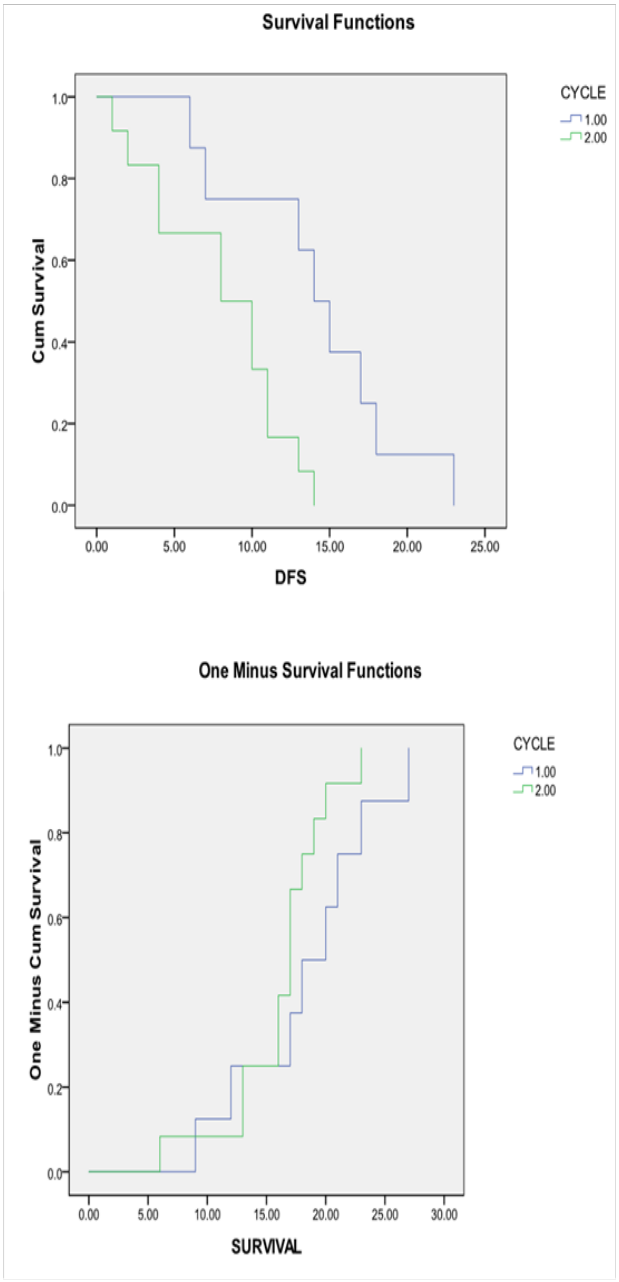

Figure 1 One minus survival functions.

Discussion

The present study aims at prospectively exploring the potential of taxane based sequential NACT followed by chemoradiotherapy for the treatment of loco regionally advanced oropharyngeal cancer. As per the 17th annual Report of Hospital Cancer Registry, NCRP, TMH-year 2007,[7] Mumbai, 4.1% patients presented with locally advanced oropharyngeal cancer at the time of diagnosis of which BOT(1.9%), Tonsil (1.1%) and others (0.8%) with maximum number of patients having 50years of age with male-female ratio 4.1:1. In our study the mean age of presentation was 50.78years (range: 37-70years) and male-female sex ratio was 3:2.[9,10,24,25] Majority of these patients were of stage IV (73.91%) has been reported.[24,25] This study excluded the

patients with KPS ≤70 as the treatment protocol was considered to be intensive for patients having lower KPS.

The most common histopathological pattern in our study was MDSCC (73.91%), this parallels the results of[26] who also reported 91% of grades I (WDSCC) and II (MDSCC). In present study mixed type of morphology was seen in 65.22%, proliferative growth in 26.09%and ulcerative type/infiltrative type in 4.35%.

Commonest primary subsites in our study was BOT and tonsil (39.2%) each.[29] Also by Manocha S et al.[30] who showed BOT (26%), tonsil (19%) and soft palate (3%) respectively. Nodal involvement was seen in 73.9% cases who presented to us, out of which 13.05% were of N1 stage while N2 stage comprised 60.87%.[3,24,25,29]

The treatment of choice in locally advanced oropharyngeal cancer is combined modality treatment which consists of surgery followed by radiotherapy or chemoradiotherapy.[31–34] We had planned the protocol with taxane based 3 drugs resegime (TPF) as NACT that three drugs regimen (TPF) is better than two drugs (PF) for survival , local control and organ preservation,[24,25] as there is no published Indian experience of its use in Ca oropharynx. Adding neoadjuvant chemotherapy before concomitant chemotherapy could decrease the Distant metastasis but had no statistical significant effect on locoregional recurrence.[35,36] All 46 patients took first cycle of NACT, out of which 18(39.1%) had taken 2 cycles of NACT and 28(60.9%) had 3cycles of NACT. Two patients developed progressive disease after first cycle, 2nd cycle and 3rd cycle respectively, so these six patients were removed from the protocol and finally 40 patients were available for final analysis.

Chemoradiotherapy is the standard modality of treatment for head and neck cancers but protocols are highly toxic especially concomitant chemoradiation, which requires adequate nutritional support without which there may be substantial morbidity and even mortality. This is especially true for developing countries like ours as has been highlighted by Kumar S et al.[38] It may also lead to dropouts of patients in between the treatment and hence, poorer compliance. In our study, 75% required nasogastric tube insertion and 35% intravenous supplementation during treatment.

The overall clinical RR after completion of 2 cycles of NACT was 34.8% but with 3 cycles of NACT it was 54.7%, similarly at the end of treatment protocol, the response in group of patients receiving 2 cycles was 40% as compared to 3 cycles where it was 60%. Hence, it may be concluded that 3 cycles of NACT are better than 2 cycles but looking at OS and DFS 2 cycles appears to be better than 3cycles with DFS and OS of 14.2months and 18.4months respectively, which is 8months and16.2months with 3cycles. Although this difference in observation of response and survival may also be due to small number of patients and lesser follow up time as none of the results are not significant statistically.

As per stage, after 2 cycles of NACT the overall clinical RR in stage III 4.3% and in stage IV was 30.4% and while after 3 cycles of NACT in stage III, the overall clinical RR was 21.7% and in stage IV it was 30.4% which again is an indicator of greater efficacy of 3 cycles then 2 cycles, again with given the limitations of smaller sample size and follow up duration. We can also conclude that if there is no difference in survival between 2 or 3 cycles of NACT as a part of sequential chemoradiotherapy and if there is good clinical response with 2 cycles itself (i.e. >PR), there seems to be no benefit of giving additional 3rd cycle and patients can be started on definitive local therapy without further delay.

We had planned to study the effect of different tumor morphologies on the responses of neo-adjuvant chemotherapy. It was observed that proliferative and mixed morphology tumors respond better to chemotherapy as compared to infiltrative and ulcerative type. Among various factors studied which affects the response of chemotherapy and radiotherapy (age, sex, tumor stage, nodal involvement, histology and grade). We had analyzed these factors and found a trend towards better survival with lower T stage (p=0.2), proliferative morphology (p=.1) and good KPS status (p=0.1).

Treatment related adverse events were seen in all patients Non-hematologic Gr.III/IV toxicities were (43.5%), similar as reported.[25] No differences in non-haematologic toxic effects between the two arms, but in haematologic toxic effects, the grade 3-4 febrile neutropenia (RR=11.41, 95% CI 2.71-48.03, P=0.0009) and leukopenia (RR=1.46, 95% CI 1.01-2.10, P=0.04) differed.[37] In our study Gr.III /IV neutropenia was seen in 21.4% of the cases on TPF regime,[24,26] but there was no interruption of RT because of hematologic toxicity.[35,36] These severe toxic effects were major risk factors for infection-related morbidity and mortality and also a significant dose-limiting toxicity in cancer treatment, which might impact the success of treatment, particularly when treatment intent was either curative or to prolong survival.

Looking at the results of this study, which are at par with randomized trials based upon similar protocols, it can be concluded that treatment with 2 cycles of TPF followed by CT-RT is safe, effective and well tolerated in Indian scenario also without affecting the compliance to loco-regional treatment i.e. concomitant chemoradiation, although the long term survivals and toxicities remains to be seen.

Conclusion

Taxane based neoadjuvant chemotherapy is well tolerated is safe and does not affect the compliance of definitive treatment. The important factors affecting the response are morphology stage and KPS. 2 cycles of NACT are sufficient before concomitant chemoradiotherapy.

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None.

Conflict of interest

Author declares that there is no conflict of interest.

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