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Phase III randomised trial

Comparison of concomitant boost radiotherapy against concurrent chemoradiation in locally advanced oropharyngeal cancers: A phase III randomised trial

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ABSTRACT

Purpose: To test the toxicity and efficacy of concomitant boost radiotherapy alone against concurrent chemoradiation (conventional fractionation) in locally advanced oropharyngeal cancer in our patient population.

Methods and materials: In this open-label, randomised trial, 216 patients with histologically proven Stage III–IVA oropharyngeal cancer were randomly assigned between June 2006 and December 2010 to receive either chemoradiation (CRT) to a dose of 66 Gy in 33 fractions over 6.5 weeks with concurrent cisplatin (100 mg/m^2 on days 1, 22 and 43) or accelerated radiotherapy with concomitant boost (CBRT) to a dose of 67.5 Gy in 40 fractions over 5 weeks. The compliance, toxicity and quality of life were investigated. Disease-free survival (DFS) and overall survival (OS) curves were estimated with the Kaplan–Meier method and compared using log rank test.

Results: The compliance to radiotherapy was superior in concomitant boost with lesser treatment interruptions ($p = 0.004$). Expected acute toxicities were significantly higher in CRT, except for grade 3/4 mucositis which was seen more in CBRT arm (39% and 55% in CRT and CBRT, respectively; $p = 0.02$). Late toxicities like Grade 3 xerostomia were significantly high in CRT arm than CBRT arm (33% versus 18%; $p < 0.0001$). The quality of life was significantly poor in CRT arm at all follow up visits ($p < 0.0001$). The rates of 2 year disease-free survival were similar with 56% in the chemoradiotherapy group and 61% in CBRT group ($p = 0.2$; HR-0.81, 95%CI-0.53–1.2). Subgroup analysis revealed that patients with nodal size >2 cm had significantly better DFS with CRT ($p = 0.05$; HR-1.59, 95%CI-0.93–2.7).

Conclusion: In selected patients of locally advanced oropharyngeal cancer, concomitant boost offers a better compliance, toxicity profile and quality of life with similar disease control, than chemoradiation.

Concurrent chemoradiotherapy (CRT) is a standard organ-preservation approach for patients with locally advanced oropharyngeal cancers (OPC) [1]. Robust and mature data from various randomised studies and meta-analyses have favoured platinum chemoradiation (CRT) typically with cisplatin dosed at 100 mg/m^2 every 3 weeks [2]. However, the toxicity associated with CRT is frequently unsatisfactory [3,4] and is exaggerated in frail patients with poor nutritional reserve, which is a vital problem in developing countries which contribute a major bulk of oropharyngeal cancers. However, a paucity of data exists regarding the outcome of radiotherapy alone in this population; therefore a pragmatic approach is to explore management options to reduce long-term complications of intensive multi-modal therapy without compromising disease control and survival.

Radiobiologically it is hypothesised that altered fractionation is predicted to improve the therapeutic ratio through the differential response between tumours and normal tissues. The two groups of biologically sound fractionation regimen that have been extensively studied are hyperfractionation and accelerated fractionation [5]. Hyperfractionation stemmed from the observation of preferential sparing of late responding tissues relative to epithelial tissues and some tumours as a result of decreasing the size of radiation dose per fraction; and accelerated fractionation regimens emerged through the recognition of the magnitude and hazard of tumour clonogen proliferation during course of radiotherapy [6]. Results of large randomised trials addressing the optimisation of radiation fractionation collectively show that a number of biologically sound

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altered fractionation schedules have a modest improvement in the locoregional control rate and overall survival [5,7,8].

The university of Texas, M.D. Anderson Cancer Centre [9] has introduced the novel concept of accelerated fractionation with concomitant boost radiotherapy (CBRT) to counteract the effect of accelerated repopulation in the latter half (>3 weeks) of radiotherapy schedule. A similar CBRT schedule was introduced into routine practice in our institute more than a decade ago and has shown favourable results [10]. Although accelerated fractionation induces more severe acute mucositis, the general observation is that the late toxicity is not appreciably increased. Hence we decided it would be interesting to compare treatment compliance, toxicity (early and late), overall quality of life and oncological outcome in concomitant boost radiotherapy (CBRT) versus concurrent chemoradiation (CRT).

However, conducting clinical trials of non-inferiority in any disease with very low event rates is challenging [11] and to the best of our knowledge, this is first such study comparing CRT versus CBRT in locally advanced oropharyngeal carcinoma in a randomised setting.

Materials and methods

Study design (Fig. 1)

Patients

Between July 2006 and June 2010, two hundred and sixteen patients of histologically proven stage III–IV-A oropharyngeal carcinoma were randomised using computer-generated procedure to CRT and CBRT arm.

Patients had Karnofsky performance status >70 and adequate haematologic (haemoglobin >10 gm/dl, absolute neutrophil count >1500/μl, platelets >100,000/μl), hepatic and renal function (calculated creatinine clearance >60 mL/min). Exclusion criteria included stage IV-B disease, previous treatment with RT or chemotherapy, any prior or synchronous malignancy, hypersensitivity to platinum agents and serious medical disease or pregnant state. Patients whose lymph nodes were large enough or extending behind the spinal cord, where it would be difficult to spare the cord, were not included in the study. The study was carried out only after the protocol was approved by the institution's ethics review board. The study was registered in the central trial registration of India (registration number-CTRI/2012/01/002369).

Radiation

All patients were simulated on Simulator CT (Phebus Mecaserto, France) after immobilisation with a thermoplastic mould and treated with either Co-60 γ-rays or 6 MV photons. The enlarged lymph nodes were delineated by lead markers externally before simulation. Patients were treated by parallelly opposed lateral portals in both arms without any tissue compensators. Nodes were treated electively in all patients. A parallel anterior lower neck field was used in selected patients. In the CRT arm, 40 Gy/20 fractions/4 weeks was given to the primary and draining lymph nodes (phase I) followed by 20 Gy/10 fractions/2 weeks after sparing the spinal cord (phase II), and final 6 Gy/3 fractions (phase III) was delivered through additionally reduced portals with a margin of 2 cm around the original gross tumour. In CBRT arm, dose of 45 Gy/25 fractions/5 weeks as phase I was given to the primary tumour and the draining lymph nodes. After the completion of 10 fractions, the primary tumour and enlarged lymph nodes with a margin of 1.5–2 cm, were boosted by a smaller field i.e. 'field-within-a field' (concomitant boost) as a second daily fraction, with a minimum inter-fraction interval of 6 h, to dose of 22.5 Gy/15 fractions/3 weeks as phase II to a total dose of 67.5 Gy/40 fractions/5 weeks. Hence, electively irradiated regions received 45 Gy and gross tumour 67.5 Gy over a short time of 5 weeks. The biological equivalent dose (BED) in both arms was calculated with the linear quadratic model using the α/β value of 10 for tumour control probability in squamous cell cancers of the head and neck region and 3 for late reacting normal tissues. The BED for chemoradiation arm was 79.2 Gy_{10} and 110 Gy_3 while that of CBRT was 78.98 Gy_{10} and 105.75 Gy_3 for tumour control and late reacting normal tissue complication, respectively.

Chemotherapy

In the CRT arm, concurrent single agent cisplatin, 100 mg/m^2 intravenously was administered on days 1, 22 and 43 of the radiation schedule after proper hydration. RT was administered within 2 h after the cisplatin administration. A complete haemogram and renal function tests were done before every cycle of cisplatin. Chemotherapy was withheld in cases of any grade 2 or more haematologic or renal toxicity, till the normal values were recovered after specific management.

Acute and late treatment toxicities and follow up

Patients were monitored for mucosal and skin reactions at least weekly during radiotherapy. Patients' weight was also recorded weekly to monitor nutritional status. Prophylactic antimycotics were initiated in all patients during initial week of treatment. The severity of acute toxicities was scored using the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) scale [12].

The first clinical follow up was scheduled at 6 weeks and thereafter every two months for the first year and then quarterly. Up to 24 months, most patients underwent routine CT or MRI of head and neck region at 6 monthly intervals. Chest X-rays were obtained at 6 months intervals. All the patients were clinically examined in a joint tumour board. Local control for the purpose of this analysis was determined by clinical and radiological freedom from tumour above the clavicles. Persistence of disease was considered as local or regional failure from day zero. Fine needle aspiration cytology or a biopsy was carried out to document a recurrence in clinically suspicious cases.

Late toxicities were scored at each follow-up evaluation according to CTCAE scale [12]. Detailed statistical analysis was performed for patients with >12 months of complete toxicity data to study differences in toxicity profile between the two treatment arms.

Assessment of quality of life was done at randomisation, at completion of treatment, 6 weeks and 6 months using University of Washington Quality of life Questionnaire (UW-QOL) version 4.1 which is a pre-validated and accurate, and accepted internationally. The Indian patient population validation of the QOL questionnaire was also done and published in 2007, one year after we embarked on this study [13,14].

Quality control

Two senior radiation oncologists in the department reviewed the radiotherapy records of each randomised patient, including their verification films (phase 1 and 2 portals), total dose and dose per fraction as per the protocol. The documentation of acute and late toxicities was also verified. All the patients on follow up were clinically examined in a joint tumour board for response and toxicity assessment.

Statistical analysis

This trial was an open-label, randomised trial with 1:1 allocation ratio by means of permuted block randomisation method using a computer generated in-house system. Frequency tables with counts and percentages were used to describe pre-treatment and treatment characteristics for each group. The categorical clinical characteristics between the two treatments were compared

using chi-square (χ^2) test. For continuous variables, mean and median values were compared between the groups using the *t*-test.

The 2-year disease free survival was used as primary end point because locoregional as well as distant failures after 2 years was infrequent. Secondary endpoints included acute and late toxicities, tumour response, quality of life and overall survival.

Actuarial disease free survival and overall survival rates were calculated by the Kaplan–Meier method and stratified by stage groups. The comparison between treatment arms were done using log-rank test. Exploratory subgroup analysis was carried out on various prognostic variables. Cox proportional hazard regression was used to estimate the hazard ratios with 95% confidence intervals for disease-free survival for each arm. A *p*-value of <0.05 was taken as significant. Data were analysed using the statistical software SPSS for windows (version 19.0).

Results

Patient cohort and characteristics

Patients were well balanced between the two groups in terms of age, sex, histology, stage distribution (Table 1).

Treatment compliance

The mean tumour dose was 65.3 Gy and 67.1 Gy in chemoradiation and concomitant boost arm, respectively. Patients who were able to complete their treatment within the stipulated time plus a 3 day allowance for logistical problems and public holidays were considered to have completed on time. Approximately 3% of CBRT and 7% of CRT patients completed treatment $\geqslant$1 week treatment break because of non-compliance and acute toxicities. The median length of interruption was 11 days (CRT) and 4 days (CBRT) ($p = 0.004$).

Compliance to chemotherapy was moderate, with 65% patients completing three cycles of cisplatin. All except one patient, received at least two cycles (200 mg/m^2 cumulative dose). Most common reason was inadequate haematologic, renal function and severe asthenia. One patient developed severe (>90% blockade) multiple arterial thrombosis involving descending aorta, common iliac and femoral artery five days after the first cycle chemotherapy requiring vascular bypass graft .

Hospital admission and supportive care was required in 28 CRT patients (28%) of at some point of their treatment, and in two patients of CBRT arm ($p < 0.0001$). Treatment related mortality i.e. death during or within 1 month of treatment, was seen in 8 patients in CRT arm and none in CBRT.

Acute toxicity

The acute toxicity rates confirmed the excellent tolerance of the concomitant boost regimen (Table 2A). Although grade 3 mucositis occurred in 54% of CBRT patients, it did not cause any treatment interruptions. There was significantly higher incidence of severe vomiting, asthenia and weight loss >10% in CRT patients. Predominant chemotherapy induced toxicity were leucopenia, intractable vomiting and deranged renal functions necessitating hospital admission and appropriate management interventions. No grade 4 nephrotoxicity was observed. Treatment related mortality was also higher in chemoradiation arm.

Response to treatment and disease free survival

The response to treatment was assessed at 6 weeks after therapy according to World Health Organization criteria for assessing

Table 1
Profile of patients and radiotherapy details.

Gender	CRT ($n = 106$)		CBRT ($n = 110$)		*p*-Value
	No. of patients	%	No. of patients	%	
Male	101	95	103	94	0.9
Female	5	5	7	6	
Age (years)					–
Mean/median	48.7/49		52.6/52		
Range	32–65		35–68		
T stage					
T1	2	2	2	2	0.09
T2	15	14	26	24	
T3	49	46	51	46	
T4a	40	38	31	28	
T4b	0	0	0	0	
N stage					
N0	16	15	36	33	0.05
N1	60	57	46	42	
N2	30	28	28	26	
N3	0	0	0	0	
TNM Stage					
III	50	47	61	56	0.2
IVA	56	53	49	45	
Overall treatment time					
Mean/median (days)	48 / 47.5		36.4 / 36		
RT equipment					
Co-60	84	79	85	77	
6MV (linac)	22	21	25	23	
Median field size (cm^2) (Avg. width $*$ length)					
Phase I	160 (10 × 16)		160 (10 × 16)		
Phase II	103 (7 × 16) [off cord]		54 (7 × 8) [C. boost]		
Phase III	52 (7 × 8) [boost]		–		

Table 2
Distribution of (A) acute and (B) late toxicities according to CTCAE scale.

Toxicity	Grade	CRT (n = 106)		CBRT (n = 110)		p (χ^2)
		N	Valid%[a]	*N*	Valid%[a]	
A. Acute toxicity						
Mucositis	0	0	0	0	0	0.02
	1	0	0	0	0	
	2	64	62	50	46	
	3	40	38	60	55	
	4	0	0	0	0	
Dermatitis	0	0	0	0	0	0.06
	1	18	17	2	2	
	2	54	52	21	19	
	3	28	27	67	61	
	4	4	4	20	18	
Dysphagia	0	0	0	0	0	0.04
	1	5	5	16	15	
	2	55	53	56	51	
	3	44	42	38	34	
	4	0	0	0	0	
Vomiting	0	19	18	100	91	0.02
	1	40	38	8	7	
	2	38	37	2	2	
	3	7	7	0	0	
Dysguesia	0	0	0	0	0	0.5
	1	0	0	2	2	
	2	104	100	108	98	
Salivary changes	0	0	0	8	8	0.02
	1	80	77	81	78	
	2	24	23	15	14	
Weight loss	0	5	5	18	16	<0.0001
	1	24	23	53	48	
	2	57	55	39	36	
	3	18	17	0	0	
Asthenia	0	5	5	29	26	<0.0001
	1	31	30	56	51	
	2	61	59	25	23	
	3	7	7	0	0	
Pain	0	17	16	25	23	0.09
	1	17	16	32	29	
	2	57	55	40	36	
	3	13	13	13	12	
Haematotoxity	0	53	51			
	1	15	14			
	2	21	20			
	3	9	9			
	4	4	4			
Renal dysfunction	No	60	58			
	Yes	44	42			
B. Late toxicity						
Xerostomia	0	0	0	13	19	0.004
	1	8	13	22	32	
	2	32	53	21	31	
	3	20	34	12	18	
Persistent dysguesia	0	4	7	22	32	0.001
	1	12	20	32	47	
	2	44	73	14	21	
Dysphagia	0	42	70	63	39	0.04
	1	12	20	3	39	
	2	2	33	1	18	
	3	4	7	1	4	
Fistula		0	0	2	2	

[a] Excluding missing values.

response in solid tumours. A summary of response rates is given in Table 3. Overall, the complete remission rate for locoregional disease was comparable (p = 0.3) between the treatment groups.

The disease free survival analysis was done on intention to treat basis. The Kaplan–Meier estimate yielded 2 year disease free survival probabilities of 56% (CRT) and 61% (CBRT) (p = 0.2, hazard ratio (HR)-0.81, 95% confidence interval (CI)-0.53–1.2) (Fig. 2A). The 2-year overall survival was statistically equivalent among both the arms (p = 0.17; HR-0.73, 95%CI-0.34–1.18).

Table 3
Best tumour response at 6 weeks after treatment.

Response group	Chemoradiation arm (n = 106)[a] Number (%)	Concomitant boost arm (n = 110) Number (%)	p Value (χ^2)
Complete response	72 (68)	81 (74)	0.3
Partial response	23 (22)	27 (25)	
Progressive disease	2 (2)	0	
Unevaluable	2 (2)	2 (2)	

χ^2, Chi square test.
[a] Seven patients (7%) in the CRT patients died before the first evaluation.

Attempt for salvage therapy

All recurrences were verified histologically, unless obvious by clinical examination. In patients with residual tumour, disease recurrence, or progression of disease, salvage surgery or palliative treatment was offered, depending on the status of the individual patient, their symptoms and previous treatment. Four patients exhibited clinical evidence of persistent nodal disease with complete remission of local disease 6 weeks after radiotherapy underwent neck dissection. In the analysis of DFS, they were scored as disease free.

Effect of stage on locoregional tumour control

Although the study was not powered adequately for a subgroup analysis, an exploratory subgroup analysis was undertaken to identify criteria for patients who were more likely to benefit from the experimental arm. Univariate analysis was done for disease stage group (III versus IVA) and T and N stages. Patients with stage III disease benefited most with CBRT (HR-0.63, 95%CI-0.31–1.2), though patients with stage IV (HR-1.15, 95%CI-0.65–1.91) fared better with chemoradiation (Fig. 3A and B, electronic supplement). T stage did not affect the treatment outcome. One interesting finding in this study was that patients with nodal size greater that $2 * 2$ cm (unilateral or bilateral), had significantly poor DFS with CBRT as compared to CRT (66% versus 35% CRT versus CBRT, respectively, p = 0.05; HR-1.59, 95%CI-0.93–2.7) thus was the most significant predictor of poor response to CBRT [Fig. 2B].

Thus with these results we can interpret that concomitant boost is an efficient treatment option for locally advanced disease with the maximum nodal size less than $2 * 2$ cm, while chemoradiation should be offered for all other patients with larger nodes.

Late toxicity

Late toxicity data were based on minimum of 6 months of toxicity scoring. The characteristics of these patients were representative of the entire patient cohort. The late toxicity rates are quantified in Table 2B. The most common toxicity was secondary to impairment of salivary function, resulting in grade 3 xerostomia, which was seen significantly higher in CRT arm. Grade 4 skin reaction in the form of fistula was seen in two patients of CBRT group. Osteoradionecrosis, laryngeal necrosis and myelopathy were not observed.

Quality of life

Quality of life (QOL) was assessed using the University of Washington-Quality of Life (UW-QOL) questionnaire. The QOL score post treatment, 6 weeks and at 6 months was compared with the baseline (pre-treatment) QOL score (Table 4 electronic supplement).

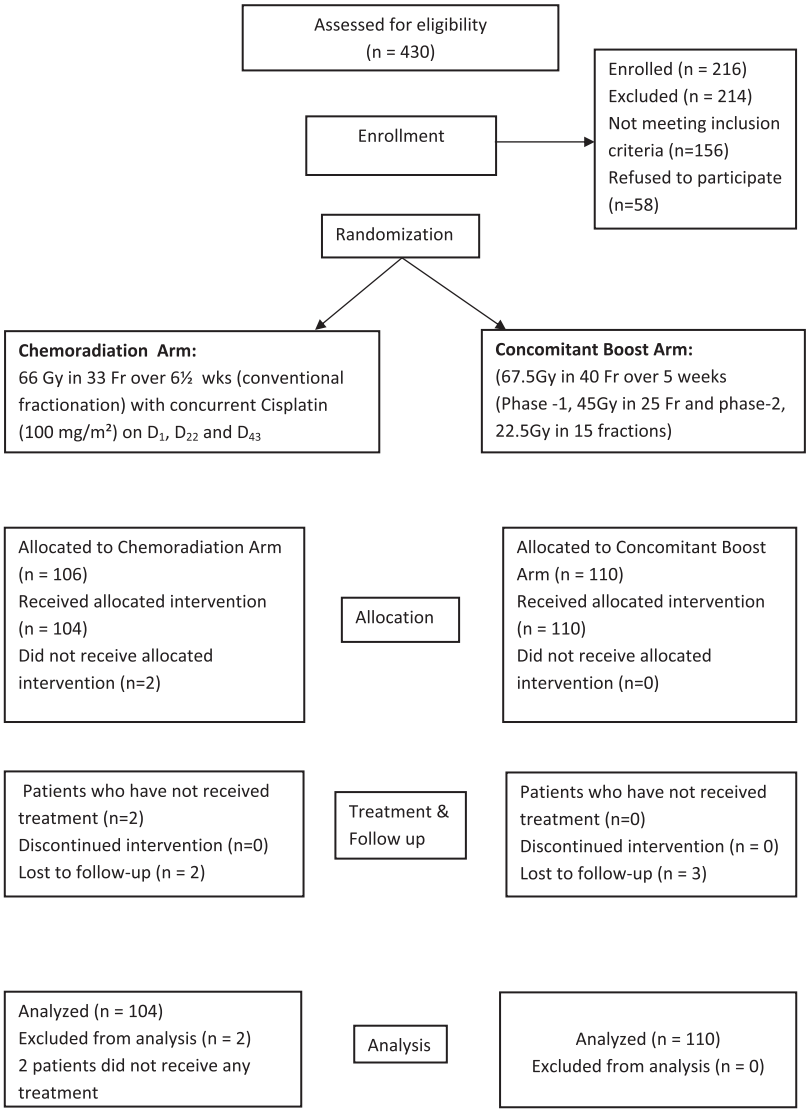


Fig. 1. Study design of the randomised trial.

Thus, any changes in values suggest the change in QOL attributed to the treatment or disease progression. The composite quality of life score decreased after treatment in both arms, attributed by the increased acute toxicities. But this difference in composite QOL score was seen more in CRT arm, signifying patients having significantly poorer QOL immediately after treatment and at 6 weeks post treatment than for the CBRT arm ($p < 0.0001$ & $p < 0.0001$, respectively). At 6 months, the CBRT patients has reached their baseline QOL score as compared to CRT patients who needed more time to repair the damage conceived during the treatment ($p = 0.001$) (Fig. 4 electronic supplement).

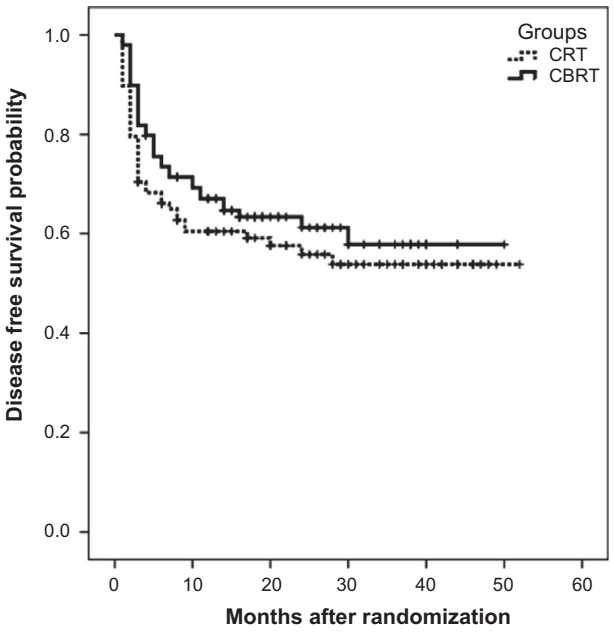
Discussion

To the best of our knowledge, this is the first published randomised controlled study of non-inferiority comparing chemoradiation with concomitant boost radiotherapy looking at acute/late toxicity, health-related quality of life and loco-regional disease control in locally advanced oropharyngeal cancers. Though our results did not indicate any difference in loco-regional control, however, toxicity profile (acute and late) and quality of life were significantly better in concomitant boost arm.

Head and neck squamous cell carcinoma is the sixth most common cancer worldwide. The incidence of head neck cancers varies widely around the world. Oropharyngeal cancer constitutes 3–5% of the malignancies in Europe, while this figure in parts of Southeast Asia and India reaches up to 40–50% [15,16] contributing to a major burden of disease. In contrast to the western population, majority of Indian patients are frail and nutritionally deprived and therefore are more likely to harbour treatment related morbidity and mortality. Although multiple randomised trials [17,18] and meta-analyses [2] have favoured concurrent platinum chemoradiation in treatment of locally advanced head and neck cancers but at the cost of increased toxicity which is over-exemplified in these frail patients, and therefore a significant issue in developing countries [4]. Therefore a pragmatic approach is to evaluate alternative and viable radiation schedules that provide superior response rates and yet maintain favourable toxicity profile.

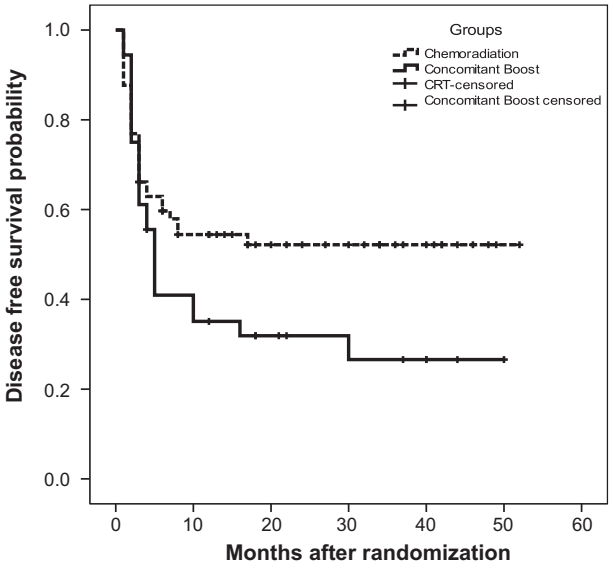
By the time this trial was conceived there was enough evidence to suggest the superiority of concomitant boost (CBRT) over conventional fractionation especially for oropharyngeal cancers [7,10,19,20]. The CBRT was designed to shorten overall length of treatment thereby diminishing the opportunity for accelerated repopulation of clogenic cells during therapy [6]. In oropharynx cancers, a 10 day reduction in overall treatment time to around

(A) Disease free survival by treatment group:



No at risk						
CRT	98	48	35	20	8	1
CBRT	106	58	29	15	5	1

(B) Disease free survival by groups in lymph node size > 2 cm:



No at risk						
CRT	62	26	18	13	5	1
CBRT	35	12	7	5	2	1

Fig. 2. Disease free survival curve (Kaplan–Meier estimate). (A) The Kaplan–Meier curve shows the disease free survival is almost similar between the two treatment arms at 2 years ($p = 0.231$; log rank test). (B) The Kaplan–Meier curve shows that for tumour with lymph node size >2 cm have significant better DFS with CRT as compared to CBRT. ($p = 0.054$) CRT, chemoradiation; CBRT, accelerated fractionation with concomitant boost.

5 weeks is estimated to yield a 10–15% improvement in local control [21]. The accelerated concomitant boost has gained use in many centres because of convenience and radiobiological rationale [10,22,23]. By limiting the volume of tissue exposed to accelerated therapy, a reduction in overall treatment time on the order of 1.5–2 weeks is possible without requiring reduction in the total dose or the introduction of a treatment break. The RTOG 90–03 study had shown an improved disease free survival rates of approximately 8% favouring hyperfractionation and accelerated concomitant boost radiotherapy over standard fractionation with

comparable late toxicity [7]. Because hyperfractionation is more costly and labour intensive, the RTOG has recommended accelerated concomitant boost RT as the new standard in this patient population.

Although the present fractionation schedule was based on that developed at University of Texas M.D. Anderson Cancer Centre, a modified concomitant boost delivery is practised in our centre, in which the 15 daily fractions of 1.5 Gy were given in a progressively accelerated manner starting on day 10 of the basic treatment (1.8 Gy/fraction). The schedule design was based on the notion that the incremental dose required to compensate for tumour proliferation might increase progressively towards the end of treatment [24,25].

In this study we observed significantly poor treatment compliance in chemoradiation group with higher treatment interruption, hospital admissions and mortality, all attributed to the added toxicity due to chemotherapy, leading to poor quality of life and increased treatment cost. The chemotherapy compliance was moderate with 65% patients completing full three cycles of chemotherapy but all patients received at least two cycles of chemotherapy. However, chemotherapy compliance was still superior to some published data of chemotherapy compliance in literature [26]. Compliance to chemotherapy was poorer probably due to relatively poor nutritional reserve and frailty, leading to poor tolerance and increased chemotherapy related morbidity.

Drug toxicities were chiefly haematological, with an incidence of 30% (grade 2/3/4). Severe nephro-toxicities were rare, though altered renal function was seen in 40% of patients. One patient in the CRT arm developed acute thrombosis of descending aorta five days after the first chemotherapy, which is an exceedingly rare but potentially devastating complication of cisplatin, documented in few case series [27].

Not unexpectedly, high rates of grade 3–4 acute mucosal reaction were seen in CBRT arm, however, our results were consistent with the values of 52–94% reported by other investigators [22,25]. In accelerated treatment, decreasing the duration of treatment causes an increase in the rate of dose accumulation; thus acute mucositis is expected to be enhanced. In contrast to our previous observation with the similar RT technique, we observed greater acute mucosal toxicity in this study, probably because in the previous study due to inclusion of other subsites (larynx and hypopharynx), the boost field volume was relatively smaller. Although the mucositis was intense, it did not cause treatment interruption, this was largely because the boost was sequenced during last phase of treatment. Consequential late reaction caused by severe acute mucositis was not seen. These results corroborated with earlier publications by MacKenzie et al. [20] who showed superior outcome with less morbidity by delayed concomitant boost. There were significantly higher incidences of severe vomiting, asthenia, weight loss >10% and grade 3/4 dysphagia in chemoradiation arm.

Treatment related mortality i.e. death during or within 1 months after treatment was seen in 8% of chemoradiation arm in contrast to none in concomitant boost arm. High 30-day mortality with chemoradiation has been reported in other phase II trial conducted at a different academic teaching hospital in India, although different in clinical design, it highlighted the risks of giving intensive schedules without adequate support infrastructure [28].

Treatment response and the 2-year disease free survival were similar between the groups. Exploratory subgroup analysis was undertaken to identify patients who were more likely to benefit from the experimental arm. The efficacy of concomitant boost RT was more pronounced for stage III disease than for stage IV disease where chemoradiation fared better. Thus stage III disease was more likely to benefit with concomitant boost. A further substratification was done to see the difference in response among the two arms based on T (tumour) and N (nodal) stages. This revealed an interesting finding in the study. Though there was no difference among the arms based on T stage, but patients with nodal size greater that $2 * 2$ cm had significantly poor disease free survival with concomitant boost as compared to chemoradiation. This selectively poor control at nodal target with accelerated schedules in not unique and is well corroborated with earlier publications including the MARCH collaborative group meta-analysis, which has shown that the effect of altered fractionation was significantly more pronounced on the primary tumour than on the nodal disease [29]. The probable argument in favour of above mentioned findings is that the stage III disease is more localised with small nodes (N1) and is properly covered with adequate margins in the boost field, delivering tumouricidal dose of 67.5 Gy to gross disease. While the uninvolved neck on the other hand receives 45–50 Gy which is sufficient for sterilizing the subclinical microscopic disease. But with a larger nodal disease there may be chances of geographical miss while planning boost portal. Tumour is adequately irradiated with adequate margins in both the arms, thus not affecting the treatment outcome. Therefore, two major limitations of CBRT technique in oropharyngeal cancers is that it is not suitable for large nodal disease reaching up to posterior triangle of neck, as it would hamper the spinal cord sparing by conventional radiotherapy plus there will be chances of geographical miss. Secondly, in patients with node/s in levels IV/V/VI would increase the size of boost field and thus markedly increase acute toxicity. Though we cannot deduce a firm conclusion, however, this subgroup analysis would help us to select patients appropriately both for clinical practice and as well as in stratifying patients for designing future studies using concomitant boost technique.

Late toxicity is a significant issue when comparing new radiotherapy regimen against the standard in head and neck cancers. As exemplified by the GORTEC and RTOG trial, concurrent chemoradiation is associated with higher late toxicity [4,30]. In our trial, late toxicities in form of grade 2/3 xerostomia, dysphagia and grade 2 dysguesia were observed significantly higher in the chemoradiation arm (86%, 40% and 73%, respectively) as compared to concomitant boost. Therefore, by limiting the volume of tissue exposed to accelerated therapy and because large fraction sizes are avoided and inter-fraction intervals are maintained at more than 6 h, the rate of serious late complication in concomitant boost arm remained acceptable. Thus the results of CBRT have been consistent with radiobiological predictors.

In contrast to most studies, we did not find any advantage of chemoradiation over concomitant boost. A possible explanation could be that due to relatively poor nutritional reserve and frailty of our patients, full scheduled course of three cycles of chemotherapy was received by 65% of patients. Though there are data in literature suggesting that cumulative dose 200 mg/m^2 is sufficient to yield beneficial anti-tumour effect [31], and all our patient received at least 2 cycles i.e. 200 mg/m^2 of cisplatin. Furthermore, CRT was complicated by poor compliance, greater toxicity and poor quality of life. Secondly, low volume/risk disease subgroups, had shown an excellent tumour control with the accelerated regimen, which were at par with the control arm.

Another important advantage of concomitant boost schedule is that it offers optimising the utilisation of available resources by abbreviating the overall treatment time from 7 to 5 weeks which is more so advantageous in settings where either facility are scarce or places where the available facilities are clustered geographically within a few regions [32]. Finally, the observed high 30-day mortality with chemoradiation (8%) within monitored settings makes a much stronger case to concentrate on relatively less intensive yet beneficial and pragmatic altered radiation-only fractionation schedules.

Although we observed benefits with concomitant boost in terms of tumour control and a manageable toxicity profile, the

implementation of altered fractionation schedules as a routine practice is yet to be established. Strict selection of patients and inherent inconvenience due to daily multiple fractions and a greater rate of acute reactions, particularly acute radiation mucositis [7,19,33] and translating the benefits of these fractionation schedules to patients outside a clinical trial are yet to be assessed and addressed. The follow-up of the present study was relatively short and prevents us from commenting on the long term disease free and overall survival. Further follow-up is warranted to highlight the efficacy of this regimen to bring forth the true essence. Another limitation of the study is that this is much selected group, those patients requiring any posterior electron boost or with parapharyngeal extensions which may require complex planning were not included in this study. Finally, HPV status of majority of patients was unknown (who were accrued before 2010), since by the time the trial was started, there was not enough evidence regarding the importance of HPV positivity in these patients. Though most of our patients had tobacco related cancer with >90% had history of smoking or tobacco chewing, this still remains one of the major limitations of this trial, as HPV has proven to have both prognostic as well as predictive roles in oropharyngeal cancers. Nevertheless, taking into consideration the social conditions, the nutritional status of our population and the infrastructure, as highlighted in a few of the recent studies from Asia [34], this study has brought forth the importance of conducting such a trial and has shown that an accelerated regimen is equally effective modality as chemoradiation for locoregionally advanced oropharyngeal cancers in our set-up.

Based on the results obtained, it is plausible that less morbid, "radiation only" concept like accelerated fraction with concomitant boost may be appropriate for low-risk subgroups (stage III/N0/N1) of locally advanced oropharyngeal cancers. However, the efficacy of RT only treatment with concomitant boost technique compared with chemoradiation in these subgroups of patients merits further study in appropriate large scale randomised study.

Conflicts of interest

The authors declare no conflicts of interest in the preparation of the manuscript or during the study. No financial grants were obtained during the study period.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2013.05.016.

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