Original Article

Conventional chemoradiation versus accelerated chemoradiation: A prospective study in oropharyngeal cancer

ABSTRACT

Background: Squamous-cell carcinoma of the head and neck is predominantly a loco regional disease, and the primary treatment methods are surgery and radiotherapy. For patients with locally-regionally advanced oropharyngeal cancer, concurrent chemoradiotherapy is the standard treatment.

Material and Method: The aim and objectives of study were a) to compare locoregional response in two arms, b) to compare acute and chronic treatment-related toxicities in the two arms, and c) to compare the quality of life. The study was conducted between August 2014 and April 2016, with 86 patients of histologically proven squamous-cell carcinoma of oropharynx. This is a prospective trial to assess the suitability of five versus six weekly radiotherapy fractions, along with concurrent cisplatin, given to the same total dose, in all stages of oropharyngeal cancer patients.

Result: Patients were randomized into two arms: conventional arm (Arm A), which received 5 fractions per week RT -70GY/7 weeks/35#, and accelerated arm (Arm B), which received 6 fractions per week RT -70GY/6 weeks/35. Locoregional squamous-cell carcinoma improved significantly in the accelerated fractionation group compared with that in the conventional RT group.

Conclusion: Accelerated RT enhances improvement of locoregional control in the squamous-cell carcinoma of head and neck region, with reduction in overall treatment time and concurrent chemotherapy. Locoregional control of carcinoma improved significantly in the accelerated fractionation group compared with that in the conventional RT group.

Keywords: Accelerated chemoradiation, cisplatin, conventional chemoradiation, locoregional, oropharangeal carcinoma

INTRODUCTION

Oral and oropharyngeal cancer, grouped together, is the sixth most common cancer in the world. The annual estimated incidence is around 275,000 for oral and 130,300 for pharyngeal cancers, excluding the nasopharynx. Two-thirds of these cases occur in developing countries. Squamous-cell carcinoma of the head and neck is predominantly a locoregional disease, and the primary treatment methods are surgery and radiotherapy. But surgery has its drawbacks and increased morbidity for the patient. Comparisons of outcomes with radiotherapy with or without neck dissection or surgery with or without adjuvant radiotherapy resulted in similar outcomes with higher complication rates with surgery.[1]

For early-stage oropharyngeal cancers, the use of radiation therapy as a single modality is associated with good outcomes and functional preservation.[2] Randomized

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Received: 06 January 2024, **Revised:** 06 April 2024,
Accepted: 09 April 2024, **Published:** 16 November 2024

Access this article online	
Website: www.njms.in	Quick Response Code
DOI: 10.4103/njms.njms_4_24	

How to cite this article: Singh S, Singh G. Conventional chemoradiation versus accelerated chemoradiation: A prospective study in oropharyngeal cancer. Natl J Maxillofac Surg 2024;15:397-402.

data[3,4] and meta-analysis[5,6] support an overall survival benefit with the use of accelerated fractionation or hyperfractionated radiotherapy. Therefore, for patients treated with radiotherapy, strong consideration should be given to altered fractionation of some sort.

For patients with locally-regionally advanced oropharyngeal cancer, concurrent chemoradiotherapy is the standard treatment. Resection is not recommended given the surgical morbidities. The results of the meta-analysis of chemotherapy in head and neck cancer (MACH-NC), which demonstrated a 6.2% absolute improvement in overall survival at 5 years from the use of concurrent chemoradiotherapy, compared to radiotherapy alone. This benefit was also observed in the oropharyngeal cancer subgroup.[7]

Furthermore, in a substantial number of clinical reports, reduction in the total treatment time has improved tumor control.[3,8,9] A shorter treatment time can be accomplished by applying a higher dose per fraction, but this change will disproportionately increase the rate of late complications. Accelerated treatment is therefore only possible if the weekly number of fractions is increased without increasing the dose per fraction. This of overall treatment time should limit the extent of accelerated repopulation, and therefore, one may expect an increase in the probability of tumor control for the given total dose.[10] shortening

We conducted this prospective trial to assess the suitability of five versus six weekly radiotherapy fractions, along with concurrent cisplatin, given to the same total dose, in all stages of oropharyngeal cancer patients. The aim and objectives of study were a) to compare locoregional response in two arms, b) to compare acute and chronic treatment related toxicities in the two arms, and c) to compare the quality of life.

MATERIALS AND METHODS

Protocol design and patients' eligibility: The case material for the study was selected from the cross section of patients registered at the J. K. Cancer Institute; histologically proven squamous-cell carcinoma patients by way of biopsy were included. Criteria for eligibility were age <70 years, Karnofsky Performance Status score >70, stage T1-T4, N0-N3, M0, invasive squamous-cell carcinoma of the oropharynx, no previous treatment for the malignancy, and normal hematological, renal, and hepatic function status. The study was conducted between August 2014 and April 2016; 86 patients of histologically proven squamous-cell carcinoma of oropharynx were registered, out of which 05 patients defaulted from treatment. Patients with all stages were included. Before treatment, a complete history was recorded, and thorough physical examination including local examination of disease, neck examination, indirect laryngoscopy, direct laryngoscopy, cytology, and biopsy was done. Ethical committee approval was taken by the institute (IEC, Ref No.- KSSSCISOP 03/V1, Date- 06/01/2024). Baseline investigations like complete blood count and blood biochemistry were done. All patients underwent dental checkup before RT. Radiographic examination included X-ray chest and contrast-enhanced computed tomography (CECT) face and neck. The patients were staged as per American joint committee on cancer (AJCC) staging manual 2002.

Patients were randomized into two arms: conventional arm (Arm A), who received 5 fractions per week RT -70GY/7 weeks/35# (Monday–Friday; one fraction/day) along with concurrent cisplatin 100mg/m2 i.v. on days 1, 22, and 43, and accelerated arm (Arm B), who received 6 fractions per week RT -70GY/6 weeks/35# (Monday–Saturday; one fraction/day) along with concurrent cisplatin 100 mg/m2 i.v. on days 1, 22, and 43.

Treatment details

Patients were treated with external beam RT given with Co-60/LINAC beam using bilateral parallel opposed fields and three fields. Thermoplastic cast was used for immobilization in all the patients. Initially, the radiation portals encompassed primary disease and involved lymph nodes and microscopic disease around primary and in clinically uninvolved lymph nodes. In most of the cases, whole neck along with primary disease was included in the initial radiation portals. After 46 Gy/23#, the posterior neck field was reduced to spare spinal cord. After 46 Gy, the field was reduced to include involved primary sites with primary echelon and involved lymph nodes.

Assessment

Assessment for toxicity was done at every week during treatment, and at the end of treatment, toxicity was assessed according to the Radiation Therapy Oncology Group toxicity criteria. The scores were based on the patient's subjective symptoms, objective examination findings, and treatment of the symptoms. At the completion of treatment, toxicity status and locoregional disease status of all patients were recorded. The tumor response was recorded and distributed according to response evaluation criteria in solid tumors (RECIST 1.1 criteria) after 6 weeks of radiation, that is, on second follow-up.

Follow-up

The first follow-up was done at 02 weeks (1st follow-up) and 06 weeks (2nd follow-up) post-radiation treatment.

The subsequent follow-up was 01 monthly for the 1st year, followed by 03 monthly for 2nd year. Side effects of treatment that occurred within 90 days of the start of RT were considered acute effects, and those occurring or persisting more than 90 days after the start of RT were considered late effects. Patients who had a recurrence or persistent disease were considered for salvage surgery if feasible. Palliative chemotherapy was administered in patients in whom surgery was not feasible.

RESULTS

Patient characteristics

Most of the patients in this study were males, that is, 78 (96.29%). The median age of presentation was 58.1 years, ranging from 25 to 70 years. Among all sites, the base of tongue was the most common primary site (46.91%), followed by Tonsillar fossa (29.62%) and soft palate (19.75%). Most of the patients were of the locally advanced stage with stage IV being the most common (66.66%). Patients were well balanced between the two groups in terms of T and N stage as shown in [Table 1].

Out of 81 cases, 75 patients (92.59%) were addicted to tobacco in various forms like chewing, beedi smoking (most common), and cigarette smoking. In ARM A, 37 patients (92.5%) were addicted to tobacco and 03 patients were addicted to Gutka or Masala, while in ARM B, 39 patients (95.12%) were addicted to tobacco and 02 patients were addicted to Gutka or Masala.

Locoregional control and survival

At second follow-up, that is, after 6 weeks of completion of treatment, 22 patients (55%) in Arm A and 27 patients (67.5%) in Arm B had complete response. At a median follow-up of 09 months, CR was seen in 24 patients (52.7%) in ARM A and 28 patients (44.4%) in ARM B. At a median follow-up of 09 months, disease-free survival was 58% in ARM B as compared to 45% in ARM A [Table 2]. Thus, there was a better locoregional and nodal control with accelerated fractionation (ARM B) among patients as shown above.

Pattern of failure

When the pattern of failure was assessed by the site of the primary tumor and regional lymph nodes, nodal failure was similar in both the arms. Local failure was lesser in ARM B as compared to conventional one, though it was not statistically significant ($P = 0.51$), as shown in [Table 3].

TOXICITIES

Toxicity encountered during the course of treatment

All patients were given radiation along with concurrent Cisplatin 100 mg/m^2 3-weekly on days (D) D1, D22, and D43 in both ARM A and ARM B. The skin reactions were observed and graded according to RTOG criteria, and symptomatic treatment was given during and after treatment. Out of the total 81 patients included in the study, 22 patients (27.16%) showed Grade I skin reactions due to radiotherapy by the end of treatment, Grade II skin reactions were seen in 33 patients (40.74%), Grade III skin reactions were seen in 18 patients (22.22%), and Grade IV skin reactions were seen in 08 patients (9.87%) in both the ARMs. The skin reactions were recorded weekly and interpreted, and symptomatic treatment was given. All above reactions were noted on the end day of radiation treatment. Comparing the development of grade II and III skin reaction, reactions were slightly higher in ARM B than in ARM A. The difference between the two arms regarding toxicities was insignificant (P-value = 0.38).

Mucosal reaction due to radiotherapy was also graded according to RTOG criteria. In ARM A and ARM B, Grade I was observed in none of the patients, that is, 0 (0%).

Table 1: Two groups in terms of T and N stage

Patient Characteristics	Number (%)	
	Arm A (5#/week)	Arm B (6#/week)
Sex		
Male	39 (97.5)	40 (97.6)
Female	02 (2.5)	01 (2.4)
Primary site		
Base of tongue	18 (45)	20 (48.78)
Tonsillar Fossa	11 (27.5)	13 (31.70)
Soft palate	08 (20)	08 (19.51)
Valleculla	01 (2.5)	-
Post. pharyngeal wall	02 (5)	-
Composite stage		
I	01 (2.5)	01 (2.4)
II	03 (7.5)	03 (7.3)
III	10 (25)	09 (21.9)
IV	26 (65)	28 (68.29)

Table 2: Type of response

	Type Of response		*P*
Response	ARM A (%)	ARM B (%)	
CR	22 (55)	27 (65.85)	0.31
PR	15 (37.5)	12 (29.26)	
SD	02 (5)	01 (2.4)	
PD	01 (2.5)	01 (2.4)	

Table 3: Site of Failure

Site of failure	ARM A	ARM B	*P*
Local	6	5	0.51
Nodal	5	4	
Local + Nodal	7	5	
Total	18	14	

However, 21 (52.5%) in ARM A and 15 (36.5%) patients in ARM B developed Grade II mucosal reactions, which was comparable. 15 patients (37.5%) from ARM A and 20 (48.78%) from ARM B developed Grade III mucosal reactions, which was again comparable. However, Grade IV mucosal reactions were comparable in both arms, that is, 04 patients (10%) in ARM A and 06 (14.63%) in ARM B. However, all the toxicities were managed by routine medications, with acute skin and mucosal toxicity [Tables 4 and 5 respectively]. Other acute toxicities are as follows [Table 6].

Late toxicities

We have observed late skin toxicities in the form of depigmentation, subcutaneous edema, and subcutaneous fibrosis. Subcutaneous fibrosis was present in 12 patients (29.2%) in ARM B and 7 patients (17.5%) in conventional RT arm, ARM A. This difference was statistically not significant ($P = 0.32$). There was no significant difference in late salivary toxicities between the accelerated and conventional RT arms.

Other complications

All patients in both the ARMs received cisplatin 100 mg/m2 on days 1, 22, and 43. Majority of patients in both ARMs complained of nausea and vomiting post chemotherapy, which continued for 3–4 days after administration of chemotherapy. Cisplatin-induced constipation was also observed in some patients.

Table 4: Acute skin reactions

ARM	No. of patients with acute skin reactions grade (%)			
	Grade I	Grade II	Grade III	Grade IV
ARM A	14 (35)	16 (40)	07 (17.5)	03 (7.5)
ARM B	08 (19.5)	17 (41.46)	11 (26.82)	05 (12.19)
P	0.23	0.93	0.41	0.52

Table 5: Acute mucosal reactions

ARM	No. of Patients of acute mucosal reactions grade (%)			
	Grade I	Grade II	Grade III	Grade IV
ARM A	0	21 (52.5)	15 (37.5)	04 (10)
ARM B	0	15 (36.5)	20 (48.78)	06 (14.63)
P		0.37	0.51	0.57

Table 6: Toxicity

Toxicity	Grade	ARM A (%)	ARM B (%)	*P*
Salivary gland	0	0	0	
	I	19 (47.5)	13 (31.7)	0.33
	II	21 (52.5)	27 (65.85)	0.53
Dysphagia	I	10 (25)	8 (19.51)	0.63
	II	13 (32.5)	12 (29.26)	0.81
	III	17 (42.5)	21 (51.21)	0.63

Type of intervention

Ryles tube feeding was required for patients during the course of treatment due to dysphagia/nutritional support/radiotherapy reactions. In a total of 81 patients, 39 patients required Ryles tube feeding. In ARM A, 12 patients (30%) required Ryles tube feeding, and in ARM B, 27 (65.8%) required Ryles tube ($P = 0.05$) In ARM A, 2 patients (5%) and in ARM B 01 (2.4%) patients required tracheostomy. Treatment break was given in 6 (15%) of patients in ARM A and 8 (19.5%) patients in ARM B though it was not statistically significant (*P*-value = >0.05).

Quality of life was assessed in every patient in both ARMs. UW-QOL Questionnaire (University of Washington -Quality of Life) was used in local Hindi Language and was filled up before starting radiation and after completion of radiation on 6th week. Results were equal in both the ARMs; there was no difference in quality of life in both ARM A and ARM B.

DISCUSSION

Concurrent chemoradiation is a standard of care for locally advanced head and neck cancer.[11,12] Several meta-analyses have demonstrated survival benefits using CCRT compared with radiotherapy alone.[11,13,14] However, accelerated RT improves locoregional control in squamous-cell carcinoma of head and neck, shown in different prospective randomized studies.[15] Accelerated regimens have been shown to increase treatment associated acute morbidity, which in severe cases might lead to an increase in late radiation effects. This study was planned with the objective that reducing overall treatment time and adding concurrent cisplatin would negate the effect of accelerated repopulation and would result in better locoregional control. As with reduction in overall treatment time and concurrent chemotherapy, it is expected that patients will have more acute toxicity and therefore to find out whether the patients will tolerate the new accelerated schedule and will they be able to finish the treatment as planned.

In aspect of locoregional response to RT in our study, we observed better local control at both primary and nodal sites in accelerated RT arm as compared to conventional RT arm. At second follow-up, that is, after 6 weeks of completion of treatment, 22 patients (55%) in conventional arm and 27 patients (67.5%) in accelerated arm had complete response. At a median follow-up of 9 months, CR was seen in 24 patients (52.7%) in the conventional arm and 28 patients (44.4%) in the accelerated arm. Though the difference in locoregional control was not statistically significant, this study clearly indicates a trend toward improved outcome.

In Danish Head and Neck Cancer Study Group (DAHANCA) study,[16] locoregional tumor control improved significantly in the accelerated fractionation group compared with that in the conventional RT group (70% vs 60% 5 years actuarial rate, $P = 0.0005$). There was 10% statistically significant improvement in locoregional disease control in accelerated arm. In International Atomic Energy Agency (IAEA)-ACC study by Overgaard *et al*.,[17] the 5-year actuarial locoregional control was 42% in the accelerated versus 30% in the conventional group ($P = 0.004$). In our study, the statistical significance could not have reached because of the smaller sample size and shorter follow-up. But our study is certainly in accordance with DAHANCA trial and IAEA-ACC study.

At a median follow-up of 9 months, disease-free survival was 58% in the accelerated arm as compared to 45% in the conventional arm; thus, disease-free survival was higher in the accelerated radiation arm as compared to conventional one ($P = 0.13$), but there was no difference in the overall survival. Almost all treatment failures were due to insufficient locoregional tumor control.

Acute complications were considerably more severe in the accelerated RT arm than those of conventional fractionation arm. Grade 3 mucositis was significantly higher in the accelerated arm as compared to conventional arm (48.78% vs 37.5%; $P = 0.51$). Moreover, the mucositis persisted longer in the accelerated fractionation arm, but all healed 3–4 months within the start of treatment. Similarly, Grade 3 and 4 skin toxicities were seen in a higher number of patients in the accelerated RT arm (39.02%) as compared to conventional arm (25%). Acute radiation morbidities were significantly higher with accelerated treatment in the 50–70 years of age group because they formed the major bulk of our patients, which was reflected in this study. Most of the patients older than 65 years in accelerated fractionation suffered from Grade 3 acute radiation toxicities but of statistical significance because of small numbers.

All toxicities were effectively managed and did not lead to more increased frequency of nasogastric tube feeding or treatment interruptions in the accelerated RT arm patients. Regarding late toxicities, it was observed that radiation induced late morbidity in the form of xerostomia and subcutaneous fibrosis of neck and subcutaneous edema, which did not differ significantly in both groups. The six fractions per week schedule, in a 1-week reduction in treatment time relative to conventional treatment, seems to give an improved tumor control and avoidance of excess late morbidity as compared to conventional arm.

The conventional schedule has been evolved in Western countries based on their working convenience as they work 5 days a week. It is also clear from the trials on accelerated RT delivering seven fractions per week that 7 days treatment results into unacceptable early and late toxicities.[18] Trialsin, where the acceleration has been more aggressive, has resulted in unacceptable late morbidity if the total dose was not reduced.[19] Hence, further acceleration of treatment can also not be recommended. With concurrent chemoradiation compared to accelerated RT, accelerated radiation offers a better compliance and toxicity profile already proved in prospective randomized trials.[20]

The higher incidence of acute toxicities could result in inadvertent treatment delays and prolonged overall radiation therapy treatment time. This could severely influence the outcome of RT. Overall treatment time has been observed to be one of the prime independent prognostic factors for RT response, and hence, any therapeutic advantage that could be expected from chemoradiotherapy could be nullified with the prolongation of overall treatment time. Such problems are more evident in patients who are nutritionally deprived and with poor general conditions, as would be commonly seen in developing countries like ours. Thus, six fractions per week can be used as a new and acceptable schedule in developing countries like ours. Moreover, shortening of overall treatment time will increase the turnover on treatment machine which will help to treat a higher number of patients and will reduce the waiting list on machines.

Limitations

As chemotherapy is very likely superior to adjuvant accelerated radiation, only patients who are unable to tolerate concurrent CRT are possible candidates. Further they would need to be at very high risk of local failure and additionally be able to comply with the accompanied aggravated acute toxicities.

CONCLUSION

Accelerated RT enhances improvement of locoregional control in histologically confirmed squamous-cell carcinoma of head and neck region. As with reduction in overall treatment time and concurrent chemotherapy, it is expected that patients will have more acute toxicity and therefore to find out whether the patients will tolerate the new accelerated schedule and will they be able to finish the treatment as planned. Locoregional squamous-cell carcinoma improved significantly in the accelerated fractionation group compared with that in the conventional RT group.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Parsons JT, Mendenhall WM, Stringer SP, Amdur RJ, Hinerman RW, Villaret DB, *et al*. Squamous cell carcinoma of the oropharynx: Surgery, radiation therapy, or both. Cancer 2002;94:2967-80.
2. Eisbruch A, Harris J, Garden AS, Chao CK, Straube W, Harari PM, *et al*. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). Int J Radiat Oncol Biol Phys 2010;76:1333-8.
3. Fu KK, Pajak TF, Trotti A, Jones CU, Spencer SA, Phillips TL, *et al*. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: First report of RTOG 9003. Int J Radiat Oncol Biol Phys 2000;48:7-16.
4. Horiot JC, Le Fur R, N'Guyen T, Chenal C, Schraub S, Alfonsi S, *et al*. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: Final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiother Oncol 1992;25:231-41.
5. Budach W, Hehr T, Budach V, Belka C, Dietz K. A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. BMC Cancer 2006;6:28.
6. Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J. Hyper fractionated or accelerated radiotherapy in head and neck cancer: A meta-analysis. Lancet 2006;368:843-54.
7. Pignon JP, le Maître A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4-14.
8. Nguyen LN, Ang KK. Radiotherapy for cancer of the head and neck: Altered fractionation regimens. Lancet Oncol 2002;3:693-701.
9. Bernier J, Bentzen SM. Altered fractionation and combinedradio-chemotherapy approaches: Pioneering new opportunities in head and neck oncology. Eur J Cancer 2003;39:560-71.
10. Hansen O, Overgaard J, Hansen HS, Overgaard M, Höyer M, Jörgensen KE, *et al*. Importance of overall treatment time for the outcome of radiotherapy of advanced head and neck carcinoma: Dependency on tumor differentiation. Radiother Oncol 1997;43:47-51.
11. Pignon JP, le Maître A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Meta analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4-14.
12. Salama JK, Seiwert TY, Vokes EE. Chemoradiotherapy for locally advanced head and neck cancer. J Clin Oncol 2007;25:4118-26.
13. Bowman GP, Hodson DI, Mackenzie RJ, Bestic N, Zuraw L. Cancer care ontario practice guideline initiative head and neck cancer disease site group. Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer: A systematic review of the published literature with subgroup analysis. Head Neck 2001;23:579-89.
14. Budach W, Hehr T, Budach V, Belka C, Dietz K. A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. BMC Cancer 2006;6:28.
15. Horiot JC, Bontemps P, van den Bogaert W, Le Fur R, van den Weijngaert D, Bolla M, *et al*. Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: Results of the EORTC 22851 randomized trial. Radiother Oncol 1997;44:111-21.
16. Overgaard J, Hansen HS, Specht L, Overgaard M, Grau C, Andersen E, *et al*. Five compared with six fractions per week of conventional radiotherapy of squamous cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet 2003;362:933-40.
17. Overgaard J, Mohanti BK, Begum N, Ali R, Agarwal JP, Kuddu M, *et al*. Five versus six fractions of radiotherapy per week for squamous cell carcinoma of the head and neck (IAEA-ACC study): A randomised, multicentre trial. Lancet Oncol 2010;11:553-60.
18. Skladowski K, Maciejewski B, Golen M, Pilecki B, Przeorek W, Tarnawski R. Randomized clinical trial on 7-day-continuousaccelerated irradiation (CAIR) of head and neck cancer – Report on 3 year tumour control and normal tissue toxicity. Radiother Oncol 2000;55:101-10.
19. Jackson SM, Weir LM, Hay JH, Tsang VH, Durham JS. A randomised trial of accelerated versus conventional radiotherapy in head and neck cancer. Radiother Oncol 1997;43:39-46.
20. Rishi A, Ghoshal S, Verma R, Oinam AS, Patil VM, Mohinder R, *et al*. Comparison of concomitant boost radiotherapy against concurrent chemoradiation in locally advanced oropharyngeal cancers: A phase III randomised trial. Radiother Oncol 2013;107:317-24.