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Original Article

Acute toxicity of concomitant boost radiation therapy by volumetric-modulated arc therapy in head and neck cancers

Kannan Perisamy[1], Ashutosh Mukherji[1], Saravanan Kandasamy[1], K. Sathyanarayan Reddy[2]

[1]*Department of Radiotherapy, Regional Cancer Centre, JIPMER,* [2]*Department of Oncology, Mahatma Gandhi Medical College and Research Centre, Puducherry, India*

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Abstract

Introduction: Volumetric-modulated arc therapy (VMAT) is an advanced form of intensity-modulated radiation therapy that reduces treatment time without compromising plan quality. This study assessed acute toxicities in patients having carcinomas of oropharynx, larynx and hypopharynx treated with concomitant boost radiation therapy by VMAT.

Materials and methods: In this study, 30 patients of stages II–IVA disease were treated with concomitant boost radiation therapy using VMAT and those with stages III and IV also received concurrent chemotherapy with cisplatin 100 mg/m^2 weekly thrice for two cycles. The total dose was 68·4 Gy/40 fractions/5.5 weeks (1·8 Gy/fraction/day to the large field for 28 fractions +1·5 Gy/fraction/day to boost field for the last 12 days of treatment). Radiation Therapy Oncology Group acute radiation morbidity scoring criteria was used to grade acute effects.

Results: All patients completed scheduled treatment with median duration of 44 days. No grade 4 skin and mucosal toxicities were observed; grade 3 skin and mucosal toxicities seen in six (20%) and eight (26·67%) patients, respectively; grade 3 dysphagia and laryngeal toxicity in eight (26·67%) and three (10%) patients, respectively; two patients had grade 4 laryngeal toxicity. No grade 3 or grade 4 haematological toxicities were seen.

Conclusion: VMAT-based concomitant boost radiation therapy allows for dose escalation with good patient tolerance by limiting acute toxicities.

Keywords: acute chemo-radiation toxicities; altered fractionation; concomitant boost radiation therapy with volumetric arc IMRT; head and neck cancers; volumetric arc therapy in head and cancers

INTRODUCTION

Radiation therapy and surgery have been the main methods of management to achieve disease control in head and neck cancers. These modalities have been used either alone or in combination with or without chemotherapy. Conventional radiation therapy is usually delivered at 1·8–2 Gy/day for 5 days a week over 6–7 weeks. However, the disease control and survival of locally advanced head and neck cancers have remained poor with conventional radiation therapy with <30% of

Correspondence to: Dr Ashutosh Mukherji, Department of Radiotherapy, Regional Cancer Centre, JIPMER, Puducherry 605006, India. Tel: 09 489 146 747. E-mail: drashutoshm@gmail.com

patients being cured of their cancers.[1] Moreover, it was seen that accelerated tumour cell repopulation in malignancies of head and neck during radiation therapy treatment could have been an important cause for the lack of good results with conventional irradiation alone.[2,3] This poor outcome with conventional irradiation has led to the promulgation of studies using altered fractionation regimens to decrease treatment time; use of concurrent chemo-radiation to cause additive tumour cell kill as well as dose escalation by newer techniques such as intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT).

Concomitant boost radiation therapy is a type of altered fractionation (accelerated fractionation) regimen, wherein, the total dose, which is about same as conventional radiation therapy, is achieved by adding a second fraction after an interval of at least 6 hours after the first fraction during the second half of the treatment period. This schedule leads to a reduction in treatment duration by 1 week, thereby overcoming accelerated repopulation during radiation treatment. Studies have demonstrated better loco-regional control with concomitant boost radiation therapy in head and neck cancers; but this technique has been associated in the past with significant acute normal tissue toxicities because the radiation was delivered using two-dimensional (2D) techniques.[4–6] In recent years, techniques such as IMRT have become the standard treatment technique in head and neck cancers due to better sparing of critical normal structures surrounding the target volume.[7–9]

Thus, with the advances in technology and sophistication of radiation techniques, it may be possible to reduce the acute normal tissue effects associated with concomitant boost radiation therapy. In this study, the feasibility of delivering concomitant boost radiation therapy by VMAT, a form of IMRT, has been assessed in squamous cell carcinomas of oropharynx, larynx and hypopharynx, and its resultant acute reactions on normal tissue surrounding the target volume.

MATERIALS AND METHODS

A total of 30 patients with previously untreated biopsy proven squamous cell carcinomas of oropharynx, larynx and hypopharynx with stages II–IVA were selected for this study after obtaining consent from the institute ethics committee (No. IEC/SC/2012/5/216). These patients received irradiation by VMAT technique by an accelerated fractionation using a concomitant boost protocol with a dose of 1·8 Gy/fraction (#)/day, 5 days/week to large field along with 1·5 Gy/#/day to a smaller boost field for the last 12 treatment days to a total dose of 68·4 Gy/40#/5.5 weeks. Concurrent chemotherapy with cisplatin 100 mg/m^2 IV three weekly was administered to stages III and IVA patients during week 1 and week 4 of radiation therapy where indicated. Computed tomography simulation was undertaken after preparing a thermoplastic mask for immobilisation and contrast-enhanced scan of the target region was taken with a slice thickness of 3 mm. The initial phase clinical target volume (CTV) encompassed the gross tumour volume (GTV) with a 10 mm primary tissue margin for subclinical microscopic disease. It also included lymph node regions of the neck that were at risk which, mostly, included bilateral levels IB–V and retropharyngeal regions. The boost volume CTV comprised of the GTV with a 10 mm margin and any involved lymph node level. An isometric margin of 3–5 mm was given to both initial phase CTV and boost volume CTV to create the planning target volumes (PTV). VMAT plans were generated to cover at least 95% of the PTV with 95% of the prescribed dose respecting normal tissue constraints. The maximum dose was kept <110%.

Statistical analysis

Patient characteristics and acute toxicities have been described using frequency tables with counts and percentages. The significance and relationship between the variables have been determined by applying χ^2 test/Fischer exact test. All statistical analyses have been carried out for two-tailed significance at 5% level of significance with p value <0·05 being considered as significant.

RESULTS

Patient characteristics

The patient characteristics are shown in Table 1. Out of 30 patients, 24 patients (80%) were males.

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Table 1. Patient characteristics

Characteristics (n = 30)	Number of patients	% of patients
Sex		
Male	24	80
Female	6	20
Age		
Median	52 years	
Range	36–65 years	
Eastern cooperative oncology group performance status		
1	18	60
2	12	40
Subsites		
Tonsil	8	27
Base of tongue	6	20
Soft palate	2	7
Supraglottis	2	7
Glottis	6	20
Pyriform sinus	4	13
Posterior pharyngeal wall	1	3
Postcricoid	1	3
Duration of radiation therapy		
≤46 days	26	86·67
>46 days	4	13·33
Chemotherapy received		
Yes	25	83·33
No	5	16·67

The median age was 52 years (range 35–65). The site and stage distributions of the tumour are shown in Figures 1 and 2. Oropharyngeal primary was found in 16 patients (53%). Concurrent chemo-radiation was received by 25 patients.

Treatment compliance

All patients completed the scheduled treatment. The median duration of radiation therapy was 44 days (range 40–49). In total, 26 patients completed the radiation therapy in ≤46 days and four patients in 47–49 days. There were no treatment interruptions because of acute toxicities. The treatment breaks were either due to machine breakdown or public holidays.

Status of acute toxicity

The patients who underwent treatment were assessed for acute toxicity using Radiation Therapy Oncology Group (RTOG) criteria.[10] The grade of toxicity was documented weekly, and the single maximum grade of acute toxicity for each of the toxicity parameters that the patient developed was documented. The maximum toxicity per patient and the status of acute toxicity of our patients are shown in Table 2 and Figure 3.

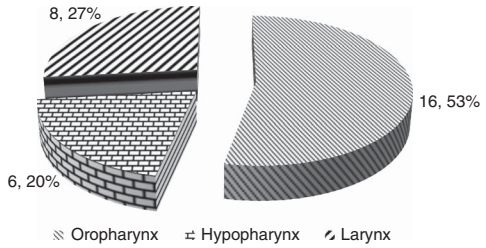

Figure 1. Site wise distribution of cases.

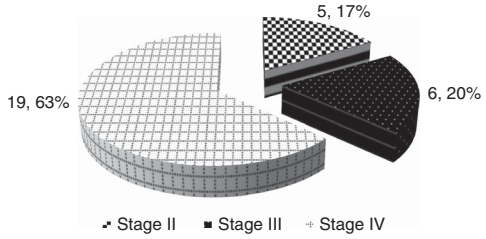

Figure 2. Stage wise distribution of cases.

Skin

All patients developed skin reactions. In total, 24 patients (80%) had grade 1 and grade 2 toxicities. Six patients (20%) had acute grade 3 toxicity. No patients developed grade 4 toxicity. The most common toxicities observed in the skin were hyperpigmentation, dry desquamation and patchy moist desquamation. The six patients who developed grade 3 reaction had confluent moist desquamation and were treated conservatively. These grade 3 skin reactions developed at the end of the treatment.

Oral mucosa

Out of 30 patients, 28 had mucosal toxicity; six (20%) had grade 1; and 14 (46·67%) had grade 2 toxicity. Eight patients (26·67%) had acute grade 3 complication. There was no grade 4 toxicity. The most common toxicity seen in the oral mucosa was patchy mucositis. The eight patients who developed grade 3 toxicity had a confluent mucositis and were treated conservatively.

Pharyngeal toxicity

All patients developed pharyngeal toxicity. Three patients (10%) had acute grade 1 and 19 (63·33%)

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developed acute grade 2 toxicity. Eight patients (26·67%) had grade 3 toxicity. No patients had grade 4 toxicity. The majority of the patients had moderate dysphagia requiring liquid diet. Of the eight patients with grade 3 toxicity, six had a nasogastric feeding tube during treatment.

Laryngeal toxicity

Out of 30 patients, 13 patients (43·33%) developed acute grade 1 and 12 developed (40%) acute grade 2 toxicity. Acute grade 3 toxicity was observed in three patients (10%) and grade 4 toxicity in two patients (6·66%). Grade 4 complication developed at ~2 months after the start of treatment requiring tracheostomy tube. Patients with grade 2 and grade 3 laryngeal toxicities were managed conservatively with steroids.

Haematological toxicity

Out of 30 patients, seven patients had haematological toxicity. Acute grade 1 toxicity was seen in four patients (13·33%) and grade 2 in three patients (10%). No patients developed acute grade 3 and grade 4 complications. Leucopoenia and neutropenia were the commonly observed haematological toxicities and no patients developed thrombocytopenia.

Table 2. Maximum toxicity per patient

Parameters	Status of toxicity	Frequency	%
Maximum toxicity per patient	Grade 1	2	6·67
	Grade 2	12	40
	Grade 3	14	46·67
	Grade 4	2	6·67
	Total	30	100

Distribution of toxicity in relation to stage of tumour

The association between stage of the tumour and toxicity was analysed and tabulated (Table 3). The occurrence of toxicity with respect to the stage of the disease was not statistically significant.

Distribution of toxicity in relation to site of tumour

The association between site of the tumour and toxicity was analysed and tabulated (Table 4). The occurrence of toxicity with respect to the site of the disease was not statistically significant.

DISCUSSION

Concomitant boost radiation therapy is an accelerated fractionation regimen, wherein, the total dose, which is about same as conventional radiation therapy, is achieved by adding a second fraction after an interval of at least 6 hours after the first fraction during the second half of the treatment period. The superiority of concomitant boost radiation therapy over standard fractionation in head and neck cancers had been established by several studies.[4–6] In the RTOG 9003 randomised control study by Fu et al.,[4] four different types of fractionation schedules were used. Patients received either standard fractionation or concomitant boost or hyper-fractionation or split fractionation.

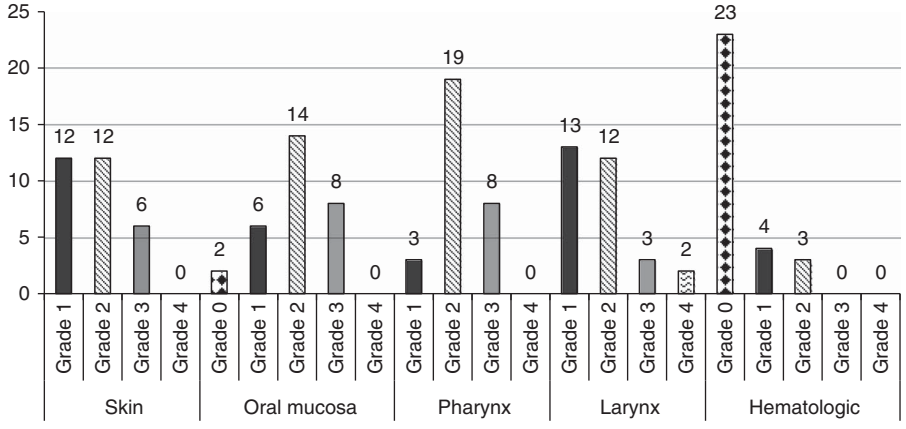

Figure 3. Status of acute toxicity.

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Table 3. Distribution of toxicity in relation to tumour stage

Stages	Grade 2 and less (*N*)	%	Grade 3 and above (*N*)	%	Total	*p* value
II and III	7	23	4	13	11	0·25
IV	7	23	12	40	19	
Total	14	47	16	53	30	

Table 4. Distribution of toxicity in relation to the tumour site

Sites	Grade 2 and less (*N*)	%	Grade 3 and above (*N*)	%	Total	*p* value
Oropharynx	7	23	9	30	16	1
Hypopharynx and larynx	7	23	7	23	14	
Total	14	47	16	53	30	

In the concomitant boost arm, a total dose of 72 Gy was delivered in 42# over a total duration of 6 weeks, in which the boost field received dose at 1·5 Gy/#/day as a second daily treatment for the last 12 treatment days. It was found that the loco-regional control and disease-free survival were significantly improved in patients who received concomitant boost radiotherapy and hyperfractionation. Ghoshal et al.[5] in their study randomised patients of head and neck malignancies to receive either concomitant boost or conventional fractionation. Patients who were treated with conventional fractionation were delivered a total dose 66 Gy in 33# at 2 Gy/#, whereas the concomitant boost arm patients received a total dose of 67·5 Gy in 40#over a total duration of 5 weeks. The loco-regional control and disease-free survival were improved in patients treated with concomitant boost regimen. Similarly, Srivastava et al.[6] also demonstrated that concomitant boost radiation therapy gives much better results in head and neck cancers than conventional radiation alone. This study also revealed that concomitant boost radiation therapy with concurrent chemotherapy produces better outcome than radiation alone. Wolden et al.[11] showed that the tumour control and survival rates were better in nasopharyngeal carcinoma patients treated with concurrent chemoradiation using concomitant boost schedule in comparison with patients managed with radiation therapy alone.

Thus, while concomitant boost regimen produced better outcome than standard fractionation, it was associated with an increase in acute toxicities. Fu et al.[4] treated 296 stages II–IV head and neck cancer patients with concomitant boost radiation therapy and reported acute grade 3 toxicity in 155 patients (58%) and acute grade 4 toxicity in two patients (1%). Ang et al.[14] treated 76 patients with concomitant boost with concurrent cisplatin and reported acute deaths in two patients (3%); one patient died of treatment-induced sepsis and the other due to pneumonia with acute respiratory distress syndrome. Therefore, we can see from these studies that acute normal tissue toxicity is the most important limiting factor in concomitant boost radiation therapy. With the advances in conformal radiation therapy (IMRT), acute normal tissue effects can be effectively reduced without compromising on loco-regional control.[7–9] In head and neck cancer patients, although IMRT has become an accepted mode of conformal treatment technique, studies have proven that VMAT can produce similar plans as IMRT with the added advantage of shorter delivery time.[12,13] However, although there are studies on advantages of head and neck IMRT, there is a paucity of literature on the clinical utility and advantage of VMAT in head and neck cancers. Moreover, there are few studies on concomitant boost radiation therapy with IMRT, and there is a lack of literature on concomitant boost radiation therapy with VMAT. This was the guiding principle behind designing this present study in which concomitant boost radiation therapy was delivered with VMAT technique which delivers radiation by simultaneously changing the gantry position, multileaf collimator position and dose rate, mainly to reduce acute toxicity.

Our study results demonstrated that none of the patients developed grade 5 toxicity (deaths); acute grade 4 toxicity were seen in two patients (6·67%) and grade 3 in 14 patients (46·67%). Ang et al.[14] treated 76 patients with concomitant boost with concurrent cisplatin as in our study, but the radiation was delivered by 2D technique and reported acute deaths in two patients (3%); 19 patients (25%) developed acute grade 4 toxicity, and 49 patients (64%) developed acute grade 3 toxicity. Schoenfeld et al.[15] in their study treated 85 patients with concomitant boost IMRT (72 Gy/42#/6 weeks) and reported grade 5 toxicity in three patients (3%); and all patients who died during treatment (grade 5

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toxicity) had received concurrent chemotherapy. Monroe et al.[16] treated 26 patients with concomitant boost IMRT and found no grade 5 toxicity as in our study, but the combined acute grade 3 and grade 4 complications were slightly higher than our study (62 versus 53·34%). Kubes et al.[17] treated 65 patients of stages II–IV head and neck cancers with concomitant boost using conformal or IMRT technique. A total of 10# of 2 Gy (fractions 1–10) plus 15# of 1·8 Gy (fractions 11–25) were delivered to the initial volume and 15# of 1·8 Gy (22·5 Gy), starting from fraction 11 were delivered to the boost volume. The total dose was 69·5 Gy over 5 weeks. Concurrent chemotherapy was contraindicated in the majority of patients or was refused by the patient. In all, 10% of cases had acute grade 3 skin reaction; 42·6% had acute grade 3 mucositis; 42·3% had acute grade 3 pharyngeal toxicity; and 4% developed acute grade 3 laryngeal toxicity. In our study, 20% of patients had grade 3 skin toxicity, 26·67% developed acute grade 3 mucositis and grade 3 pharyngeal toxicity, and 10% had grade 3 laryngeal toxicity. Thus, the acute grade 3 mucosal and pharyngeal toxicities were lower and acute grade 3 skin and laryngeal toxicities were higher in our study. Though direct comparisons cannot be made because of different protocols and techniques, our study results have shown that the overall acute toxicities of concomitant boost radiation therapy by VMAT were relatively less despite patients having received concurrent chemotherapy (25 out of 30 studied patients) when compared with most other studies of concomitant boost radiation therapy by 2D and IMRT techniques. The summary of literature review and comparison of acute toxicities of concomitant boost radiation therapy is presented in Table 5.

The most important consequence of acute normal tissue toxicities with concomitant boost radiation therapy by 2D technique is the treatment interruption which may impair the loco-regional control. Allal et al.[18] managed 296 patients with concomitant boost radiation therapy and demonstrated that 20 patients (7%) had breaks during treatment and in a study by Ghoshal et al.,[5] of the 145 patients in the concomitant boost arm, two patients had treatment interruptions due to acute toxicities. In a phase 2 trial on concomitant boost radiation therapy by Kumar et al.,[19] 11 out of 95 patients had treatment interruption because of acute toxicity. In our study, all the patients completed the scheduled treatment without treatment interruption related to acute morbiditiy, thus contrasting with other existing literature, but admitting the fact that the sample size was low in our study.

All these findings as well as from other similar studies favour the use of modern conformal techniques in the treatment of head and neck

Table 5. *Literature review of acute toxicities of concomitant boost radiation therapy*

Organ/tissue	Grade	Ang et al.[14] (*N* = 76)	Fu et al.[4] (*N* = 268) (%)	Kubes et al.[17] (*N* = 65)	Present study (*N* = 30)
Skin	3	4	11	9·5[a]	20
	4	1	0		0
	5	0	0		0
Oral mucosa	3	50	46	42·6[a]	27
	4	3	1		0
	5	0	0		0
Pharynx/oesophagus	3	58	29	42·3[a]	27
	4	4	1		0
	5	0	0		0
Larynx	3	Not mentioned	7	4[a]	10
	4		0		6·67
	5		0		0
Maximum toxicity per patient	3	64	58	Not mentioned	46·67
	4	25	1		6·67
	5	3	0		0

Note:
[a]Only grade 3 toxicities mentioned in this study.

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cancers, which improves patients' compliance to treatment by decreasing the acute toxicities. However, the results have to be further confirmed by large randomised studies.

CONCLUSION

Thus, concomitant boost radiation therapy helps in completing the radiation therapy treatment in a shorter duration of 6 weeks and is expected to counter the phenomenon of accelerated tumour cell repopulation. The use of VMAT helps in reducing the dose to organs at risk thereby allowing completion of treatment with less toxicity. Although patients may have some reactions due to radiation therapy and concurrent chemotherapy, the grade of these reactions encountered due to use of VMAT technique was seen to be low which then enables rapid healing of these reactions in the treated patients. However, this has to be further confirmed by large randomised studies comparing different conformal techniques.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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