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A written consent was obtained from each patient before recruitment in the study.

The study was approved by the local ethics committee of the department of clinical oncology and nuclear medicine, Cairo University (Ref: a12016).

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Comparison between hypo-fractionated dose-escalated volumetric modulated arc therapy and conventional concurrent chemo-radiation in locally advanced head and neck cancer: a pilot study

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Abstract

Objective: In the treatment of locally advanced head and neck cancer (LA-HNC), both dose escalation and hypo-fractionation can improve tumour control rates with uncertain role of addition of concurrent chemotherapy. We aimed at developing a new radiotherapy protocol for patients not eligible to receive the standard concurrent chemo-radiation therapy (CCRT) with little toxicity profile.

Methods: A total of 63 LA-HNC patients were randomised to receive either: 70 Gy in 35 fx in 7 weeks concurrently with cisplatin 100 mg/m2 every 3 weeks for 3 doses (Arm A) or 74 Gy in 33 fx in 6·5 weeks (Arm B). Volumetric modulated arc therapy plans were created for both treatment arms. We compared the local control (LC), progression-free survival (PFS), overall survival (OS) and acute and late toxicity between the two arms.

Results: A total of 33 patients were in Arm A versus 30 patients in Arm B with median follow-up 24·2 months. No significant differences in LC, PFS and OS between the two arms. Complete remission occurred in 54·5 and 63·3% of patients in Arms A and B, respectively. All toxicities were significantly less in Arm B than Arm A.

Conclusion: Slightly dose-escalated hypo-fractionated regimen is safe and feasible and has comparable efficacy and less acute and late side effects than conventional dose CCRT with avoidance of chemotherapy-related toxicities in LA-HNC patients.

Introduction

Concurrent chemo-radiation therapy (CCRT) is considered the standard treatment of locally advanced head and neck cancers (LA-HNC).[1] A conclusion of the meta-analysis of chemotherapy in head and neck cancer (MACH-NC) is that adding chemotherapy to radiotherapy results in a 5-year absolute survival benefit around 8% for oral cavity and oropharyngeal cancers and around 5% for laryngeal and hypo-pharyngeal cancers.[2] However, many studies concluded that the combination of chemotherapy with radiotherapy improves the results with the cost of increased toxicity.[3]

In many randomised trials, accelerated radiotherapy without concomitant chemotherapy has been proved to be an effective regimen for patients with head and neck squamous cell carcinoma (HNSCC). For accelerated regimens without dose reduction, the MARCH meta-analysis showed a significant absolute reduction in locoregional relapse of slightly above 7% translating into a small (2%) but significant benefit in overall survival (OS). The benefit in locoregional control was in favour of altered fractionation versus conventional radiotherapy (6·4% at 5 years; $p < 0{\cdot}0001$).[4]

Intensity-modulated radiation therapy (IMRT) is used for the treatment of head and neck (H&N) patients with complex-shaped planning target volumes (PTV), especially as the concave targets are close to a large number of organs-at-risk (OAR).[5]

Graded dose levels to tumour targets and for subclinical tumour spread, lymph node-bearing areas with sparing normal tissues to the greatest extent, can be done using 'simultaneous integrated boost' (SIB). The SIB-IMRT strategy is also an easier, more efficient and perhaps a less error-prone way of planning and delivering IMRT.[6]

Many studies comparing volumetric modulated arc therapy (VMAT) to IMRT in H&N radiotherapy showed that VMAT has comparable dose distribution with less number of monitor units and less treatment time.[7,8]

Although the efficacy of adding chemotherapy concomitantly with radiotherapy has been proven in many studies, the additive value of concurrent chemotherapy on local/regional control and survival rates for LA-HNC patients treated with IMRT is largely unknown.[9]

A retrospective study prescribing 70 Gy/33 fr for T1 & T2 lesions and 74 Gy/33 fr for T3 & T4 lesions in 333 patients with locally advanced nasopharyngeal cancer (LA-NPC) did not demonstrate any significant differences in LC, OS, DFS and distant metastasis-free survival (DMFS) between patients treated with IMRT-SIB with or without concurrent chemotherapy.[10] Another study done in early and moderately advanced SCC of H&N concluded that dose escalation SIB-IMRT protocol using 69, 72 and 75 Gy/30 fr was safe and effective as a sole treatment without chemotherapy. The 2-year LC was 82% for the three groups. The 2-year OS was 89% for dose levels I and II and 95% for dose level III.[11]

In this work, we hypothesised that the added benefit of chemotherapy to radiotherapy may be compensated by increasing the biological effective dose through using the dose-escalated hypo-fractionated regimen omitting chemotherapy. To the best of our knowledge, no randomised trials were done to compare the dose-escalated hypo-fractionated regimen without chemotherapy with the conventional CCRT regimen.

The aim of this study is to compare the slightly dose-escalated accelerated hypo-fractionated VMAT regimen omitting chemotherapy in radical treatment of LA-HNC to the standard CCRT regimen in terms of **local control (LC), progression-free survival (PFS), OS** and also acute and late toxicities.

Materials and Methods

This is a pilot study that was carried out during the period from January 2016 to September 2018. Sixty-three patients with histopathologically confirmed locally advanced HNSCC (T3-T4 &/or N1-3) (stage IIB, III and stage IV-A), according to TNM staging (7th edition),[12] who met the inclusion criteria for definitive radiation treatment were recruited and were randomised to both treatment arms.

Radiotherapy technique

Patients were immobilised in the supine position with thermoplastic head, neck and shoulder masks. Computed tomography (CT) scan was done for each patient from skull vertex to the middle of the chest, with 2·5 mm slice thickness with intravenous (IV) contrast. CT scan images were transferred to the treatment planning system.

Definition of the target volumes was done according to the International Commission on Radiation Units (ICRU) report 50 and the supplement ICRU 62 and 83 guidelines.[13] The primary tumour and clinically involved lymph nodes were delineated as gross target volume (GTV). Image fusion with magnetic resonance imaging (MRI) and/or positron emission tomography-computed tomography (PET-CT) was done if available. Clinical target volume (CTV) primary is created around GTV with a 5-mm margin to account for possible microscopic spread. PTV is created around CTV with a 5-mm margin to account for setup errors. The cervical lymph node stations were delineated based on the published DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG and TROG consensus guidelines.[14]

The following OARs were delineated: brain stem, temporal lobes, optic chiasma, bilateral optic nerves, bilateral cochleas, bilateral globes, bilateral lenses, bilateral parotids, uninvolved oral cavity, mandible and temporomandibular joint, brachial plexus, larynx excluding laryngeal cancers, thyroid gland, spinal cord and pituitary gland.

Rapid arc plans were produced for all patients, at least two arcs plans were created for better dose homogeneity and risk organs sparing. Eclipse treatment planning system was used (from Varian Medical System Inc., UK) version 11.0 with anisotropic analytical algorithm (AAA) and Acuros XB (AXB) algorithms.

The patients were randomised to either:

Arm A: Thirty-three patients were treated by 6MV photons Varian linear accelerator (Inc.3100 Hansen Way, Palo Alto, CA, USA), 5 fr/week, with a total treatment time of 7 weeks (47 days). The prescribed dose was 70 Gy in 35 fr at 2 Gy/fr to the PTV of the GTV primary or lymph nodes, 60 Gy to the PTV of the CTV high risk, and 54 Gy to the PTV of the CTV low risk volumes. The chemotherapy was cisplatin 100 mg/m^2 every 3 weeks for three doses during the radiation course (Conventional CCRT-VMAT protocol) or

Arm B: Thirty patients were treated by 6MV photons Varian linear accelerator, 5 fr/week, with a total treatment time of 6·5 weeks (45 days). The prescribed dose to PTV of the primary or nodal GTV was 74 Gy in 33 fr at 2·24 Gy/fr, 60 Gy to the PTV of the CTV high-risk and 54 Gy to the PTV of the CTV low-risk volumes (VMAT—SIB alone protocol).

Plan quality was analysed using dose–volume histogram (DVH) data. The treatment goal was to deliver 95% of the prescribed dose to ≥ 95% of each PTV.

Accepting the plan risk organs in both arms according to:

Arm A: QUANTEC model risk organs dose constraints and

Arm B: calculated EQD2 in comparison to 2·24 Gy according to α/β ratio.

Both are demonstrated in Table 1.

Patients were treated on 'UNIQUE' Varian machine.

Acute toxicities were scored according to common terminology criteria for adverse events (CTCAE, version 4.03) from the start of radiation therapy until 3 months of follow-up.[15] Late toxicities were scored thereafter until the end of follow-up.

The response evaluation criteria in solid tumours (RECIST 1.1) were used to score tumour response at the end of the second-month post-radiotherapy, by regional MRI with contrast.[16]

Statistical methods

Data were coded and entered using Statistical Package for the Social Sciences (SPSS) version 25. Data were summarised using mean, standard deviation, median, minimum and maximum quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. The non-parametric Kruskal–Wallis and Mann–Whitney tests were used to compare between quantitative variables. For comparison of serial measurements within each patient, the non-parametric Friedman test and Wilcoxon signed rank test were used. Chi square ($\chi 2$) test was done to compare categorical data. When the expected frequency is less than 5, exact test was performed instead. For survival curves Kaplan–Meier method was used and compared using the log-rank test. Independent prognostic factors were estimated by the Cox proportional hazards in univariate and multivariate regression models. Statistically significant p-values were considered as less than 0·05.

Results

Sixty-three patients were included in the study (33 patients were in Arm A and 30 patients were recruited in Arm B). Median follow-up period was 24·2 months (ranging from 13·4 to 31·2 months).

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Table 1. Organs at risk dose constraints in both arms

	α/β	Arm A (70 Gy/35 fr)	Arm B (74 Gy/33 fr)	End point
Brain stem	3	Mean < 54 Gy	Mean < 51·52	<5% permanent damage
		Dmax < 60 Gy	Dmax: < 57·25	
Brain	3	Dmax < 60 Gy	Dmax < 57·25	<3% necrosis
Optic chiasma	3	Dmax < 55 Gy	Dmax < 52·4	<3% optic neuropathy
Optic nerve	3	Dmax < 54 Gy	Dmax < 51·52	<5% permanent damage
Spinal cord	<3·3	Dmax < 50 Gy	Dmax < 47·6	0·2% myelopathy
Brachial plexus	<5·3	V60 < 100%	V57·25 < 100%	5% clinical plexopathy
		V62 < 33%	V59·05 < 33%	
Mandible/ temporomandibular joint	<3·5	Dmax < 70	Dmax < 66	5% osteoradionecrosis
		V60 < 66%	V57·25 < 66%	
		V65 < 33%	V61·9 < 33	
Eye	3	Mean < 45	Mean < 42·38	
Retina	3	Dmax < 50	Dmax < 47·6	<1% blindness
Lens	1·8	V18 < 100%	V16·98 < 100%	50% cataractogenesis
Cochlea	3	Mean <= 45	Mean <= 42·83	<15% hearing loss
Oral cavity	10	Mean < 45	Mean < 42·38	
One parotid	3	Mean < 20	Mean < 18·87	<20% salivary function <25% baseline
Both parotids	3	Mean < 25	Mean < 23·58	<20% salivary function <25% baseline
Larynx	3·8	Mean < 44Gy	Mean < 42·31	<20% oedema
		Mean < 50	Mean < 48·08	<30% aspiration
		Dmax < 66	Dmax < 63·46	<20% vocal dysfunction
		V50 < 27%	V48·08 < 27%	
Thyroid	3	V45 < 100%	V42·38 < 100%	8% clinical hypo-thyroid
		V60 < 100%	V57·27 < 100%	13% clinical hypo-thyroid
		V70 < 100%	V66 < 100%	35% clinical hypo-thyroid

Median age of all patients was 58 year old with range (19–70). Most of the patients were males representing (43 patients: 68%). Thirty (47·6%) patients were non-smokers and 42 (66·7%) patients were performance status (PS) 0/1.

Patients' and tumours' characteristics were well balanced between the two groups of patients (Table 2).

Response assessment

Thirty-seven patients (58·7%) of the whole cohort had complete remission (CR): 18 (54·5%) patients in Arm A and 19 (63·3%) patients in Arm B. Response across the two groups was not statistically significant ($p = 0·328$).

Twelve patients (19%) had recurrences, six patients in each arm ($p = 0·854$). In Arm A, four patients had locoregional recurrences in Arm A and two patients had distant recurrences while in Arm B, there were five patients with locoregional recurrences and one patient with distant recurrence. Twenty patients died during the follow-up period (Table 3).

Assessment of toxicities

There was statistical significance in all symptoms experienced including anaemia, neutropenia, elevated kidney function tests (KFT), nausea and vomiting in favour of Arm B ($p < 0·001$). There was no statistical significance between the two groups in grade 3/4 toxicities; however, neutropenia presentation had a trend towards significance ($p = 0·054$).

Mucositis, oral pain, voice alteration, fatigue, acute dysphagia and late dry mouth were all statistically significant in favour of Arm B ($p < 0·05$). Grade 3/4, fatigue, acute dysphagia and late dry mouth were statistically significant in favour of group B ($p < 0·05$). Mucositis G3/4 was present in 38 patients (38%) (Table 4).

Forty-seven (74·6%) patients developed G3/4 toxicities with borderline statistical significance among the two groups ($p = 0·05$). Regarding non-haematological toxicity, results were not statistically significant among the two groups despite there being more patients in Arm A (26 patients) versus 19 patients in Arm B, respectively.

Survival analyses

Progression-free survival

The mean PFS for the whole group of patients was 20·6 months (95% CI: 18·8–23). The median PFS was not reached at the time of data collection. The mean PFS for group A was 20·52 months

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Table 2. Patients' characteristics

Variable	Arm A ($n = 33$)	Arm B ($n = 30$)	p-value
Age (years)			
-mean ± SD	56·5 ± 11·5	53·57 ± 16·1	0·620
-median	60	57	
-range	28–70	19–70	
Sex:			
-males	25 (75·8%)	18 (60%)	0·180
-females	8 (24·2%)	12 (40%)	
Performance status			
-0	3 (9%)	2 (6·1%)	
-1	30 (91%)	31 (93·9%)	0·088
Weight pre-RTH (kg)			
-mean ± SD	75·36 ± 15·36	73·17 ± 14·48	0·606
-median	74	74·50	
-range	47–112	49–109	
Surface area (m2)			
-mean ± SD	1·83 ± 0·2	1·78 ± 0·2	0·340
-median	1·87	1·80	
-range	1·56–2	1–2	
BMI			
-mean ± SD	26·29 ± 4·92	26·91 ± 5·92	0·901
-median	26·60	25·80	
-range	18–34·4	18·3–41	
Smoking history			
-yes	19 (57·6%)	14 (46·7%)	
-no	14 (42·4%)	16 (53·3%)	0·454
Charlson comorbidity index (CCI)-mean ± SD	0·88 ± 1·14	0·6 ± 1·1	
-median	1	0	0·156
-range	0–5	0–4	
Trismus			
-yes	5 (15·2%)	8 (26·7%)	0·259
-no	28 (84·8%)	22 (73·3%)	
Cranial nerve affection			
-yes	1 (3%)	1 (3·3%)	0·730
-no	32 (97·0%)	29 (96·7%)	
Hb level pre-TTT			
-mean ± SD	12·61 ± 1·86	12·81 ± 1·48	0·544
Albumin level pre-TTT			
-mean ± SD	3·68 ± 0·48	3·68 ± 0·34	0·776

(95% CI: 17·29–23·75) with median PFS was 19·5 months and for group B, the mean was 19·91 months (95% CI: 16·53–23·29). The median PFS was not reached. The difference between the two groups was not statistically significant ($p = 0·929$) (Figure 1).

Table 3. Response details

Variable	Arm A ($n = 33$)	Arm B ($n = 30$)	p-value
Response details			
-CR	18 (54·5%)	19 (63·3%)	
-PR	13 (39·4%)	9 (30%)	
-SD	0 (0%)	1 (3·3%)	0·328
-DP	0 (0%)	1 (3·3%)	
-No assessment	2 (6·1%)	0 (0%)	
Response			
-LC (CR)	18 (54·5%)	19 (63·3%)	0·674
-locoregional failure	13 (39·4%)	11 (36·7%)	
Recurrences			
-yes	6 (18·2%)	6 (20%)	0·854
-no	27 (81·8%)	24 (80%)	
Recurrences			
-locoregional	4 (12·1%)	5 (16·7%)	0·787
-distant	2 (6·1%)	1 (3·3%)	
-non	27 (81·8%)	24 (80%)	
Died			
-yes	9 (27·3%)	11 (36·7%)	
-lost FU	2 (6·1%)	0 (0%)	0·522
-no	22 (66·7%)	19 (63·3%)	

Overall survival

The mean OS for the whole group of patients was 24·9 months (95% CI: 22·7–27·1).The median OS was not reached. The mean OS for group A was 25·8 months (95% CI: 23–28·6) and for group B was 23·02 months (95% CI: 19·9–26·1). The median OS was not reached in either group. There was no statistically significant difference between the two treatment arms ($p = 0·374$) (Figure 2).

Discussion

CCRT is known to be superior to radiotherapy alone in the treatment of LA-HNSCC. However, the resultant acute toxicity and long-term morbidity can reduce the compliance to therapy, quality of life and life expectancy. And hence, altered fractionation was offered as an alternative treatment option.[17]

Many centres use the relatively simple 6 fr/wk regimen or mild hypo-fractionation as (2·12 Gy/fr) as the standard radiotherapy for patients with LA-HNSCC.[18]

The addition of concurrent chemotherapy to altered fractionation radiotherapy may increase the acute mucosal dose. Altered fractionation radiotherapy did not offer any advantage regarding the LC, PFS and OS, when concurrent chemotherapy was added compared to the conventional fractionation group in the updated MARCH meta-analysis in 2018. So, adding chemotherapy to altered fractionation was not advised.

Both cisplatin 100 mg/m^2 given during D1, 21 and D42 and weekly cisplatin 40 mg/m^2 can be given with conventionally fractionated irradiation as the standard of care for patients with advanced HNC.[19–21]

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Table 4. Assessment of acute and late radiotherapy toxicity

	Any grade	Grade ¾	Any grade			Grade¾		
	Total ($n = 63$)		Arm A($n = 33$)	Arm B($n = 30$)	*P*-value	Arm A ($n = 33$)	Arm B($n = 30$)	*p*-value
Variable	*n* (%)		*n* (%)			*n* (%)		
Mucositis	63	38	31 (93·9%)	25 (83·3%)	0·02	23 (69·7%)	15 (50%)	0·110
Oral pain	63	23	30 (90·9%)	24 (80%)	0·01	12 (36·4%)	11 (36·7%)	0·980
Laryngitis	49	4	26 (78·8%)	23 (76·7%)	0·51	2 (6·1%)	2 (6·7%)	1
Voice alteration	51	3	29 (87·9%)	22 (73·3%)	0·023	1 (3%)	2 (6·7%)	0·601
Fatigue	51	7	33 (100%)	18 (60%)	<0·001	7 (21·2%)	0 (0%)	0·011
Tinnitus	32	5	18 (54·5%)	18 (60%)	0·051	4 (12·1%)	1 (3·3%)	0·357
Dysgeusia	44	0	22 (50%)	22 (50%)	0·144	0 (0%)	0 (0%)	–
Acute dysphagia	62	28	32 (97%)	30 (100%)	0·02	20 (60·6%)	8 (26·7%)	0·007
Acute xerostomia	63	19	28 (84·8%)	26 (86·6%)	0·62	8 (26·6%)	11 (36·7%)	0·283
Dermatitis	63	29	33 (100%)	30 (100%)	0·371	18 (54·5%)	11 (36·7%)	0155
Plexopathy	28	0	15 (45·5%)	13 (43·3%)	0·869	0 (0%)	0 (0%)	–
Late dry mouth	59	20	31 (94%)	28 (93·3%)	0·006	16 (48·5%)	4 (13·3%)	0·003
Late dysphagia	33	5	15 (45·5%)	18 (60%)	0·571	3 (9·1%)	2 (6·7%)	1

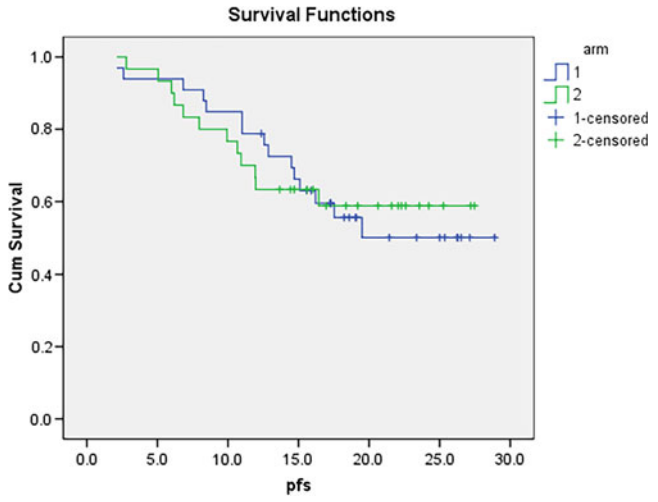

Figure 1. Kaplan–Meier survival curve showing PFS across the two arms (Arm A = 1 and Arm B = 2).

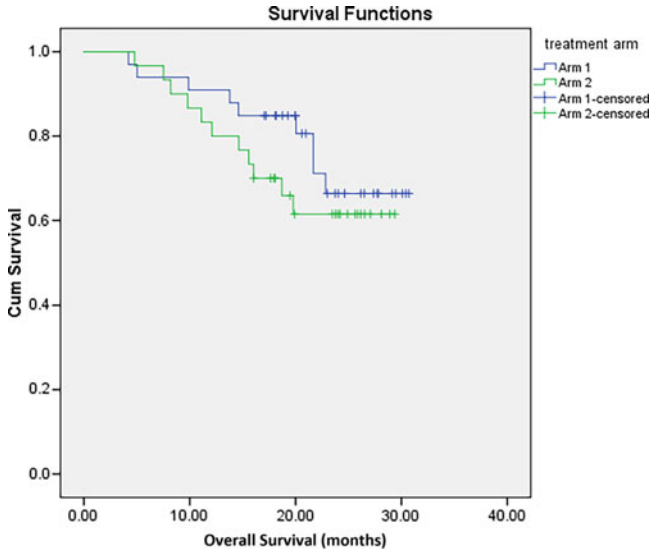

Figure 2. Kaplan–Meier survival curve showing OS across the two arms (Arm A = 1 and Arm B = 2).

The survival benefit of concurrent chemotherapy in older patients (>65 year old) was not proved,[22] due to the risk of bone marrow suppression, increased infections/pneumonia and nutritional problems.

However, with IMRT technique, significant disease locoregional control and better OARs sparing were achieved, and the role of CCRT was reconsidered.[23]

There were concerns about the use of hypo-fractionated regimens due to the higher risk of late toxicity. However, the use of IMRT, with a careful patient selection, hypo-fractionation may prove to be safe and effective regimen.[24]

Radiobiological view

We prescribed the same dose as in Yi et al.; the study used 74 Gy/33 fr for T3/T4 H&N tumours.[10] The prescribed doses to the GTV were 74 Gy with 2·24 Gy/fr given in 5 fr/week for locally advanced primary and nodal lesions. Their equivalent biological dose was 75·5 Gy if given in 2 Gy/fr according to the linear quadratic model, which is about 7·85% increase of total dose when comparing it to 70 Gy/35 fr at 2 Gy/fr.

There is a steep dose–response relationship in HNC for locoregional control and thus improved survival. An increase of 1·7% of locoregional control per 1% change in total dose, considering an α/β is 10 Gy for H&N tumours.[25] And hence, the LC rate of our patients would be 13·6% higher than those patients who received 70 Gy at 2 Gy/fr in the non-IMRT era, if we refer to dose–response curve for HNC.[26] Also this investigational dose escalation was higher than the average gain of 3·6 fr of 2 Gy for the effect of

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concurrent chemotherapy in H&N radiotherapy as concluded by Kasibhatla et al.[27]

In our schedule, acute BED was 55·49 Gy10 (EQD2 = 46·24 Gy) which lays in the 'grey zone' 59–61 Gy10 wide (EQD2 = 49–52·5 Gy10) for tolerable acute mucosal reactions proposed by Fowler et al., to guide further treatment regimens in H&N radiotherapy and to compare acute responses in chemo-radiotherapy.[28] The conventional arm acute mucosal BED was 47·02 Gy10 (EQD2 = 39·2 Gy10). It was less than the investigational arm; however, addition of concurrent chemotherapy to the conventional fractionation added more acute mucosal reactions proved that the average gain of chemotherapy addition concurrently to radiotherapy was 3·6 fr of 2 Gy/fr with no verified method to calculate it in clinical practice.[29]

When comparing late tissues BEDs, despite the relatively high late tissue BED3/2·24 (129·2 Gy3) in the dose-escalated hypo-fractionated arm, concurrent chemotherapy used in the conventional arm with late BED3/2 (116·7Gy3) would add to the late effect which could not be accurately calculated.

Response and survival analysis

Our results did not demonstrate any significant differences in LC, PFS and OS between patients treated with either treatment regimens at a median follow-up period 24·2 months.

In our study, LC (CR patients) for the whole group of patients was 58·7%, representing 54·5 and 63·3% in the CCRT and dose-escalated arm, respectively. There was no significant difference ($p = 0·674$) in the LC between both groups. The overall response rate (CR, PR and SD) was 93·9% in concurrent conventional arm versus 96·7% in dose-escalated accelerated arm. Our investigational arm has comparable results to Bahl et al. who recorded CR in 68% of patients treated with VMAT concurrent with chemotherapy 66–70 Gy/33–35 fr, and their median disease-free survival was 16 months.[30]

The median PFS was 19·5 months in the CCRT arm; however, the median PFS was not reached in the dose-escalated arm. The median OS was not reached in either arm. This necessitates further long-term follow-up.

The 2-year PFS and OS were 50 and 66·4% in CCRT arm versus 58·8 and 61·5% for the dose-escalated hypo-fractionated arm. Our results were higher than results of RTOG 9003 using different dose schedules including accelerated concomitant boost as 72 Gy/42 fxs/6 weeks. RTOG 9003 study concluded that 2-year DFS and OS in the concomitant boost were 39 and 51%, respectively. This is mainly due to the dose escalation leading to this improvement in the outcomes.[31]

RTOG 0225 study evaluated IMRT (70 Gy/33 fr) concurrent with chemotherapy in the treatment of 68 patients with stage I–IVB nasopharyngeal cancer, the estimated 2-year PFS rate was 72·7% and the OS rate was 80·2%.[32] These rates were higher than our results, most probably due to inclusion of all stages of NPC patients only, as a group of patients were in lower stages. RTOG 99–14 used CCRT concomitant boost radiotherapy (72 Gy/42 fxs/6 weeks) and concluded that 2-year OS and PFS were 71 and 53·5%, respectively. They had 18% of patients developed distant metastasis.[33] The difference compared to our study may be due to different prognostic patients as age, comorbidity, anemia and hypo-albuminemia, in addition to short follow-up period.

Toxicity assessment

All chemotherapy-related toxicities, (anaemia, neutropenia, nausea and vomiting) were evident in most of CCRT arm patients and some developed elevated KFT grade I. However, a small number of patients in the dose-escalated arm had anaemia pre-treatment and one patient had nausea during radiotherapy administration ($p < 0·001$).

The acute adverse effects during radiotherapy were mostly statistically significant in favour of the dose-escalated arm including mucositis, oral pain, voice alteration, fatigue and acute dysphagia. It was noticeable that higher grades of fatigue ($p = 0·011$) and acute dysphagia ($p = 0·007$) were found in the CCRT.

Late effects were higher in the CCRT arm versus the dose-escalated arm. The significant one was late xerostomia in which less number were in the dose-escalated arm ($p = 0·006$) even with higher grades ($p = 0·003$) with noticeable early recovery of xerostomia in the dose-escalated arm.

The relatively small number of patients is the main limitation of our study. However, the study has concluded that omitting of chemotherapy during radical radiotherapy to LA-HNC can be possible using slightly dose-escalated accelerated hypo-fractionated regimen with comparable efficacy and less toxicity in comparison to the standard conventional CCRT. This regimen can be beneficial to patients who cannot receive cisplatin. Also, this study opens the window to evaluate this regimen in further prospective randomised trials to confirm that benefit on larger number of patients.

Conclusion

Slightly dose-escalated accelerated hypo-fractionated VMAT regimen omitting chemotherapy presented here used in LA-HNC is safe and feasible with moderate acute toxicities and late side effects and resulted in comparable outcomes to CCRT arm. Larger randomised trials with longer follow-up period are needed for further evaluation of the outcomes.

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Clinical trial information. This study was registered in clinicaltrials.gov data base with NCT number: **NCT03699969.**

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