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Long-Term Outcomes of Reduced High-Risk Clinical Target Volume Margin for Intensity-Modulated Radiotherapy in Locally Advanced Head and Neck Cancers

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Abstract

Background: Long-term outcomes of intensity modulated radiotherapy with reduced high-risk clinical target volume (HRCTV) margin for radical chemoradiation of locally advanced head and neck cancers (LAHNSCC).

Method: The present retrospective study involved 83 LAHNSCC patients treated with chemoradiation. HRCTV was created with uniform margins of 5 mm around the primary tumor- gross tumor volume (GTV), and the nodal tumor GTV, edited at bone and air interface. The first echelon nodal station in N0 neck and that harboring disease in N+ neck was taken as intermediate-risk clinical target volume (IR-CTV). The remaining nodal stations were taken as low-risk CTV. High-, intermediate-, and low-risk regions were prescribed 70, 63, and 56 Gy, respectively, in 35 fractions, five to six fractions per week over six to seven weeks. 63 patients received five fractions and 20 patients received six fractions per week. Acute toxicities were assessed using CTCAE version 4.0 and the survival analysis was performed via Kaplan Meier method.

Results: Acute toxicities were grade 1 dermatitis in 77%, grade 3 mucositis in 35%, and xerostomia was predominantly grade 1 in 68.6%. Moreover, 10% required the placement of nasogastric tube during radiation therapy due to grade 3 dysphagia. Complete clinical and radiological response (CR) of respectively 89.1% and 85.5% was observed in primary and nodal disease at the end of the treatment and 100% and 94% at three months, respectively, after chemo radiation therapy. At a median follow-up of 48.1 months, the five-year overall survival was 63.2%.

Conclusion: Reduced HRCTV margin of 5 mm was found to be efficient and had good compliance with tolerable acute toxicities, reduced overall treatment time, and reasonable long-term outcomes.

Keywords: Head and neck cancer, Radiation therapy, Intensity modulated radiotherapy, Clinical target volume

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Introduction

Radiation therapy (RT) is an important and potentially curative modality for head and neck cancers. For several primary sites within the head and neck, RT yields better functional outcomes than surgery and thus, is often preferred for localized diseases.[1] For loco-regionally advanced lesions, RT is often used in combination with chemotherapy as a definitive organ and function-preserving approach.

Intensity-modulated radiation therapy (IMRT) has been the technique of choice in squamous cell carcinomas of head and neck, owing to its ability to provide high conformity and steep dose gradients to spare normal tissues, such as the parotid gland, spinal cord, auditory apparatus, optic apparatus, mandible, and larynx.[2]

Several guidelines have been proposed in an effort to help standardize the target delineation process.[3-5] These guidelines translate surgically and radiographically defined neck nodal levels for the practicing radiation oncologist. Site-specific treatment recommendations regarding nodal station coverage are thus provided from historical surgical data and from patterns of loco-regional failure.

The definition of clinical target volume (CTV) is believed to be complex concerning head and neck cancer and has several unresolved problems. The amount of expansion for CTV of primary tumor has never been clearly defined[6] until the recent consensus guidelines from Gregoire et al.[7]

Certain investigators have suggested that the GTV be expanded anatomically to create the HRCTV before a planning target volume (PTV) margin is added.[8] However, cooperative groups prefer to specify volumetric expansions of HRCTV based on its ease and reproducibility; for example, RTOG 00-22,[9] the first head-and-neck trial testing IMRT in oropharyngeal cancer, suggests a 10-25-mm margin. In contrast, the RTOG 0615 trial[10] on IMRT for nasopharyngeal cancer suggests a 5-10-mm margin.

The present study was conducted to evaluate the outcomes of patients treated with 5-mm margins through volumetric expansion around the GTV-primary and node.

Materials and Methods

Retrospective analysis of acute toxicity and survival outcomes was carried out for the LAHNSCC patients treated between 2010 and 2015 with reduced HR CTV margins. The scientific review board and ethical committee of Kidwai Memorial Institute of Oncology (KMIO/MEC/009/11, April 2022) approved the study. This retrospective analysis involved 83 patients of head and neck cancer with a median age of 58 years, Eastern Co-operative oncology group (ECOG) performance status of 0-1, locally advanced non-metastatic tumors (stages III and IV) treated with concurrent chemo irradiation, and IMRT and curative intent. Written informed consent was taken from all the patients. The subjects with any prior oncological interventions, uncontrolled diabetes, hypertension, or retroviral (HIV) positive were excluded from the study. Human papilloma virus (HPV) status was not done.

Pretreatment evaluation

All the patients underwent a detailed clinical, endoscopic examination (direct flexible fibre optic endoscopy or direct laryngoscopy). Haematological serum biochemistry evaluation was performed to assess the bone marrow, renal, and hepatic reserve. Imaging was also performed to stage the local and distant metastasis via contrast enhanced computed tomography (CECT) scan or MRI of paranasal sinus, neck, and chest radiograph. Biopsy samples were centrally reviewed, if done outside the host institution. Pre-RT dental evaluation was routinely done. All the patients were staged as per the 2009 TNM/AJCC classification.

Treatment methodology

We immobilized all the cases in the supine position with customised thermoplastic head and neck masks. CECT images indexed every 2.5 mm were obtained, extending from the vertex to 5 cm inferior to the heads of clavicle. Target localization was accomplished using CT simulation and the volumes were defined.

High-risk volume

GTV-primary and node were contoured based on clinical and endoscopic examination and

CECT. CTV1 for primary and node were generated separately with volumetric expansion of GTV by 5 mm edited at bone and air cavity interface.

Intermediate-risk volume

CTV2 was the nodal level which harboured the nodal disease in N+ and for N0 neck, the first echelon nodal level was contoured.

Low-risk volume

CTV3 comprised low-risk nodal levels. PTVs were generated by volumetric expansion of CTV by 5 mm and edited in skin by 2-3 mm, if there were no skin involvements by the node (Figures 1 and 2). The doses prescribed to high-, intermediate-, and low-risk PTVs were 70, 63, and 56 Gy, respectively, in 35 fractions.

We contoured the neck as per consensus guidelines laid by DAHANCA, EORTC, GORTEC, NCIC, and RTOG.[2] All the patients were treated with six MV photons via IMRT-simultaneous integrated boost technique with inverse planning using seven to nine beams. The plans with 100% PTV receiving 95% of dose were preferred, but 95% PTV receiving at least 95% of the dose were also accepted. Parotids on the side of uninvolved neck were restricted to the mean dose of 26Gy and on the involved neck, 50% of the volume receiving 30Gy was acceptable. No attempt was made to spare that parotid where volumes were under-dosed. The spinal cord maximum dose was restricted to 45Gy. No attempt was made to spare the constrictor muscles. Treatment verification was conducted using electronic portal imaging device with MV X-ray images as per institutional protocol.

Out of 83 patients, 63 were treated with five fractions per week for over seven weeks and 20 were treated with six fractions per week for over six weeks. Concurrent weekly Cisplatin 40 mg/m^2 was infused for six weeks. Acute mucosal, skin, and haematological toxicities were examined on a weekly basis and were graded as per CTCAE v4.0 toxicity criteria. We performed a clinical response evaluation at RT conclusion and one month after conclusion. Radiological evaluation with CECT was done after three months and followed up once in three months up to two years.

Table 1. Patients' demographics and disease characteristics

Variable	Results
Age distribution	Range 32-76 years median=58 years
Sex distribution	Male: female= 66:17
Primary site distribution	
Oropharynx	20 (24.1%)
Hypopharynx	36 (43.4%)
Larynx	27 (32.5%)
Stage distribution	
III	14 (16.9%)
IVA	59 (71.1%)
IVB	10 (12%)
The number of cycles of chemotherapy	
<four cycles of Cisplatin or Carboplatin	19 (22.9%)
four cycles of Cisplatin	32 (38.5%)
>four cycles of Cisplatin	32 (38.5%)
Overall treatment time	
	Range 40-70 days Median= 49 days
Type of fractionation	
Conventional/SIB	63 (75.9%)
Hyperfractionated	20 (24.1%)

SIB: Simultaneous integrated boost

It was then performed once in six months. The subjects with complete response at primary and residual nodal disease underwent salvage neck dissection.

The data for analysis was compiled on the SPSS version 21. Descriptive statistics was utilized for demography characteristics. Survival was analyzed via Kaplan Meier analysis.

Results

Tables 1 and 3 represent the stage-wise distribution of the patients. Out of 83 patients, 14 (17%) were stage III and 69 (83%) were stage IV head and neck cancers.

Subsite-wise distribution of oropharynx larynx and hypopharynx were 24.1%, 32.5%, and 43.4%, respectively.

The median overall treatment time was 49 (40-70) days. Among the subjects, 24% received six fractions per week. Weekly Cisplatin (40mg/m2) was given concurrently, 10 patients received Carboplatin (AUC2), and 77% received a minimum of four cycles of Cisplatin.

Table 2. Acute toxicity outcomes during the treatment

Parameter	Grade/ incidence	Multivariate analysis
Dermatitis	1 = 64 (77%)	*P* = 0.96
	2 = 19 (23%)	
Mucositis	1 = 11 (13%)	*P* = 0.33
	2 = 43 (51%)	
	3 = 29 (35%)	
Dysphagia	1 = 43 (51%)	*P* = 0.27
	2 = 33 (39%)	
	3 = 7 (10%)	
Xerostomia	0 = 17 (20.4%)	*P* = 0.8
	1 = 57 (68.6%)	
	2 = 9 (10.84%)	
Leucopenia	1 = 40 (48%)	*P* = 0.06
	2 = 22 (26%)	
	3 = 21 (26%)	
Thrombocytopenia	0 = 11 (13%)	*P* = 0.32
	1 = 52 (66%)	
	2 = 20 (21%)	
Anemia	0 = 75 (90%)	*P* = 0.25
	1 = 6 (7%)	
	2 = 2 (2%)	

Toxicity and treatment outcomes

Grade 3 mucositis was seen in 35% of the participants, grade 3 dysphagia in 10%, radiation dermatitis was predominantly grade 1 (77%), Xerostomia was predominantly grade 1 in 68.6%, and 10% required placement of nasogastric tube. Myelosuppression of grade 3 was seen towards the completion of the treatment in 24% of the cohort, predominantly in the total leukocyte count (Table 2).

Response to treatment

Complete clinical and radiological responses of 89.1% and 85.5% were seen in primary and nodal disease at the end of the treatment and 100% and 94%, respectively, in primary and nodal disease three months after the treatment. Three patients needed neck dissection for residual disease.

Survival analysis

Survival analysis was carried out employing Kaplan Meier method. At a median follow-up of 48.3 months, the five-year OS was 62.3% (Figure 3). Deaths were found to be due to distant metastasis in 4% and due to other medical causes in 8% of the cases. Disease-free survival and loco-regional control rates were not reported since 14 patients were lost for the follow-up or died; their disease status and cause of death were not known.

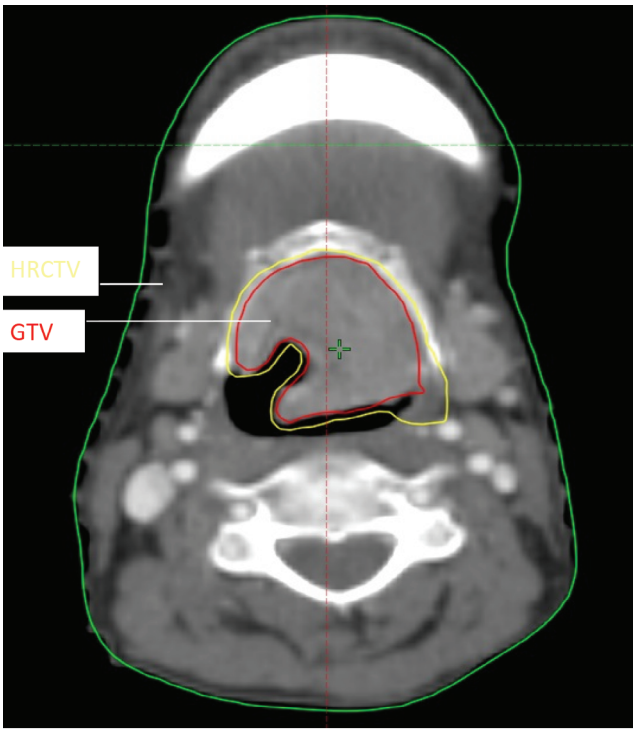

Figure 1. Primary tumor volumes show gross disease (Red) and HRCTV (Yellow).
GTV: Gross tumor volume, HRCT: High-risk clinical target volume

Table 3. Disease and treatment characteristics

Variable	Result				Univariate Analysis (*P*-value)
Response (clinical and radiological)	**CR**		**PR**		
	Primary	**Node**	**Primary**	**Node**	
At the end of the treatment	74 (89.1%)	71(85.54%)	9 (10.84%)	12 (14.4%)	
Three months post-treatment	83 (100%)	78 (93.97%)	0	5 (6%)	
Site of primary	Oropharynx verus Hypopharynx Vs. Larynx				0.8
Stage	III Vs. IVA Vs. IVB				0.9
Type of fractionation	Conventional versus HFRT				0.9
Overall treatment time	</> 49days				0.19
Feeding procedure through nasogastric tube	Yes = 8 (10%)			No = 75 (90%)	0.2
Treatment interruptions (OTT > 49 days)	1-7 days = 23			>7 days = 13	0.8

CR: Complete response; PR: Partial response; HFRT: Hyper-fractionated radiation therapy; OTT: Overall treatment time

Discussion

The present work started when guidelines on the CTV margins for the primary and nodal disease were not present. In previous studies, increased acute toxicity has been reported in patients treated with concomitant radiation and chemotherapy and additional increase in all toxicity end points has been observed in patients treated with accelerated fractionation.[11] IMRT is preferred to reduce the mucosal toxicity to achieve the therapeutic gain.

Radio chemotherapy with reduced HRCTV (5 mm) IMRT was well tolerated in our patients with more than 77% of them receiving at least four cycles of chemotherapy; the maximum mucosal toxicity was grade 3 in 35% and dysphagia was grade 3 in 10% of the patients, which is significantly less compared with those

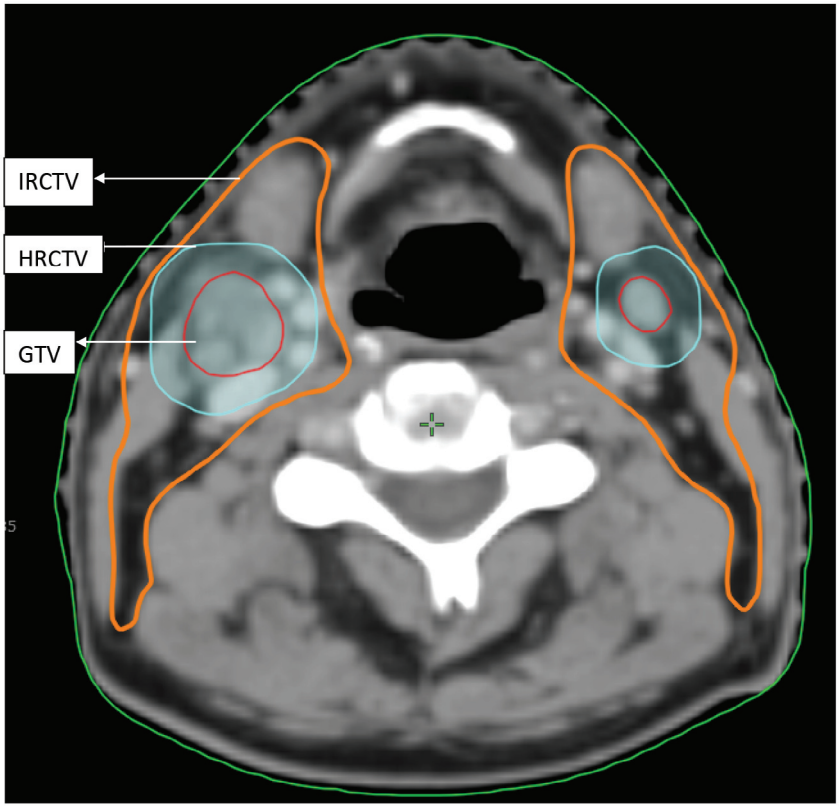

Figure 2. Nodal tumor volumes show gross disease (Red), HRCTV (Blue), and IRCTV (Orange).
GTV: Gross tumor volume, HRCTV: High risk clinical target volume, IRCTV: Intermediate risk clinical target volume

Table 4. Toxicity outcomes of radiation therapy (IMRT) in head and neck cancer

Study IMRT (+/- CT)	Number of patients	Skin toxicity (Gr III+)	Mucositis (Gr III+)	Xerostomia (Gr III+)	Dysphagia (gr III+)
Van Gestel et al.[20]	78	7%	82%	<5%	
Andrew Lauve et al.[21]	20	25%	75%	20%	5%
Tao, Y et al.[22]	94	9%	45%	8%	63%
Chakraborty Santam et al.[23]	20	0%	65%	0%	15%
Our study	83	0%	35%	0%	10%

IMRT: Intensity-modulated radiation therapy

reported in other studies on IMRT in head and neck cancer treated with conventional margins (Table 4).[12-15] This result was owing to reduced mucosal surface getting a high dose of radiation on account of reduced CTV margins.

The median overall treatment time (OTT) was 49 days. Regarding the patients whose OTT was beyond seven weeks, it was either due to machine breakdown, festivals, national holidays, or the patients being non-compliant rather than intentional breaks due to increased toxicity. Hence, reduced margin HRCTV-IMRT is a feasible option in terms of toxicity and compliance to treatment.

A five-year OS rate of 62.3% was noted in our work. The OS rates were not inferior to the studies using higher CTV margins with geometric or anatomic expansion.[16-21] Despite that, the majority of our patients were stage IVA and hypopharyngeal subsite. The study by Caudel et al., compared volumetric expansion of CTV-HD to anatomic component of CTV-HD and found no differences in loco-regional failure ($P = 0.10$).[22] Single institution retrospective data using either anatomic or volumetric expansions of 5-20 mm have reported similar loco-regional control rates. Reduced CTV margin of 5 mm seems to be adequate and may reduce the heterogeneity in contouring, making the comparison of IMRT

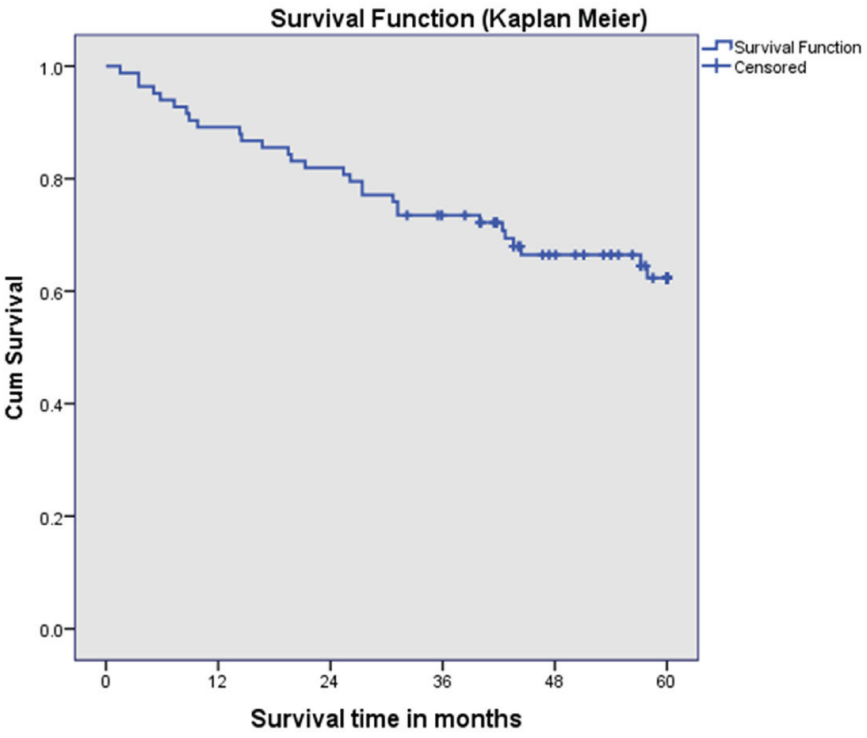

Figure 3. This figure exhibits the OS (Kaplan Meier analysis) of the LAHNSCC patients treated with reduced HRCTV margin.
LAHNSCC: Locally advanced head and neck cancer; Cum: Cumulative; HRCTV: High-risk clinical target volume; OS: Overall survival

results more appropriate in terms of toxicity and survival.

In neck nodal levels contouring, a high level of concordance has been noted among various cooperative groups,[23, 24] whereas there has been no consensus on margin for expansion around the primary and nodal GTV to create HRCTV in head and neck cancer until recently in 2018.[7]

Variation in contouring CTV (range 37-676 cm^3 (average 250 cm^3)) was noted in a study conducted by Hong et al., in which institutes with expertise in IMRT were asked to contour CTV of primary disease and nodal disease.[25] A survey on 14 institutes by Ho et al. has demonstrated that 0.3-1 cm was the minimum margin used for creating CTV around GTV; 2 cm was the maximum CTV employed in two centres and anatomic compartment was used as CTV in four centres.[26]

The study on microscopic extent of disease outside GTV by Campbell et al. in oral tongue has shown that the microscopic extent of the disease outside GTV was within 4.75 mm and 95% was within 3.75 mm from GTV.[27] The 5-mm margin to the primary used in the current research was reasonable.

Smith et al. recommended 1-cm margin for N1 nodes without gross infiltration into musculature, but the nodes were at high risk for extracapsular extension (ECE). Meanwhile, the microscopic disease extent noted was within 5 mm in 96% of nodes with ECE.[28] Ghadjar et al. did a quantitative analysis of ECE in 231 lymph nodes with metastatic disease and showed that the extent of ECE was 5 mm in 97% and 3 mm in 91% of the nodes. However, they recommended 1-cm expansion around nodes with metastatic disease.[29] Since the nodal station harbouring the gross node was considered as intermediate-risk volume, 5-mm expansions around the gross node may be appropriate.

Based on these findings, we employed a 5-mm margin to create HRCTV around primary and nodal GTV, which is also in accordance with the guidelines proposed by Grégoire et al.[29] Nonetheless, we did not utilize the CTV2 for primary on the contrary to their guidelines and the entire nodal station with gross disease was treated as intermediate-risk volume.

Progression-free survival and rates of Locoregional failure were not assessed since most patients were contacted remotely to ascertain survival as they were mostly located outside the province of treatment. Regarding those who died, the cause of death was not known.

This study was the first of its kind reporting the long-term survival outcomes in patients suffering from head and neck cancer with reduced CTV margins.

Conclusion

IMRT with concomitant chemotherapy and reduced CTV margins of 5 mm did have good compliance with the treatment, with tolerable acute toxicities, reduced overall treatment time, and reasonable long-term OS rate compared with studies with larger CTV margins or anatomic expansions. This result was obtained even though the majority of our patients were in stage IVA and from hypopharyngeal subsite.

Conflict of Interest

None declared.

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