Long-term Prospective Comparative Analysis of Ototoxic and Survival Outcomes of Sequential Boost and Simultaneous Integrated Boost of Volumetric Modulated Arc Therapy for Head-Neck Carcinomas

Original Investigation

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Abstract

Objective: To compare the ototoxicity and survival in head and neck carcinoma patients treated with sequential (SEQ) and simultaneous integrated boost (SIB) of volumetric modulated arc therapy (VMAT).

Methods: This long-term prospective study enrolled patients with histologically confirmed head and neck carcinoma, all receiving VMAT treatment. Audiological assessments were done using various tests at baseline, two weeks, treatment completion, six months, and 12 months. The changes in bone conduction pure tone thresholds were correlated with cochlear dose, comparing SEQ and SIB plans. We also investigated other significant late toxicities that led to dysphagia, voice changes, and xerostomia. Survival was assessed with the Kaplan-Meier analysis.

Results: The study included 93 patients (186 ears), 40 receiving radiation alone and 53 undergoing chemoradiation. Baseline hearing levels for the right and left ears were 13.3±2.3 dB and 14.2±1.5 dB. After 12 months of radiation, levels were 18.5±2.4 dB and 19.11±1.9 dB, respectively. No significant changes were observed between SEQ and SIB plans, but high-frequency shifts occurred. The cochlea tolerated up to 28 Gy without hearing loss in the radiation-alone group but showed loss at 9 Gy when combined with cisplatin chemotherapy. The maximum dose (D_{max}) and the mean dose (D_{mean}) of pharyngeal constrictor muscles predicted dysphagia. No significant SEQ vs. SIB differences were found in late toxicity or survival outcomes.

Conclusion: Modern radiotherapy techniques like VMAT adhere to cochlear dose limits. No significant differences were found between SEQ and SIB plans in sensorineural hearing loss, late toxicity, or survival, making both suitable for head and neck carcinoma treatment.

Keywords: Head and neck cancer, volumetric-modulated arc therapy, radiotherapy dose fractionation, ototoxicity, sensorineural hearing loss, survival analysis

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Introduction

According to 2020 data, cancer affects 6.46 million males, with head and neck malignancies ranking highest among men and fourth among women, primarily presenting in locally advanced stages in Asian countries like India (1,2). Radiotherapy (RT) plays a pivotal role in oncology treatment, but its drawback is the potential for acute and chronic organ toxicity (3). Innovations like intensity-modulated RT and volumetric arc therapy aim to mitigate this issue by focusing on the organs at risk (OAR) to spare them while delivering effective therapeutic doses (4).

Recent advancements in RT include novel techniques within volumetric modulated arc therapy (VMAT): Simultaneous integrated boost (SIB) plans and sequential plans (SEQ). SEQ involves administering radiation doses in distinct phases with identical fractions per phase. At the same time, SIB-IMRT (intensity-modulated radiotherapy) increases the dose to boost volume while maintaining a lower dose of the elective volume in the same fraction. SIB can shorten treatment duration and increases prescribed and biological doses. However, limited data exist on the response of normal tissues, tiny organs like the cochlea, to SIB/SEQ techniques (5-7).

This study aims to explore the ototoxic profile of SIB vs. SEQ VMAT plans in head and neck cancer patients undergoing RT. Secondary objectives include comparing the two plans' survival outcomes and other late toxicities. Given the novelty of this research, there is a lack of comprehensive data on the subject, particularly concerning sensorineural hearing loss (SNHL) and its progression post-radiation.

Methods

In this prospective single-arm interventional study, we enrolled 93 individuals diagnosed with head and neck cancer who had no prior history of otological diseases after obtaining their informed consent. The study was conducted at All India Institute of Medical Sciences between January 2019 and December 2021. Ethics and research committee approval was obtained from the institution and the study was conducted within the scope of the specialization thesis of the first author (decision number: AIIMS/IEC/2019/1680, date: 21-01-2019).

All patients in the study received treatment at the Department of Otorhinolaryngology and Radiation Oncology. Exclusion criteria were age over 70 years, a history of or current otological disease, having previously undergone chemoradiation for head and neck conditions, and default on treatment.

The entire patient cohort was then grouped based on the primary disease subsite. The paranasal sinus region, nasopharynx, and parotid glands were classified as high-risk for cochlear irradiation, while all other major sites were classified as low risk.

It is worth noting that even though the cochlea is not intentionally included in the clinical target volumes (CTVs) for high neck and skull base malignancies, it does receive quantifiable dosages from the primary entrance, exit, and scattered beams, as illustrated in the dose-volume histograms.

Radiotherapy

Simulation and Contouring

Patients were simulated using a 16-slice simulator (Optima 580, GE Healthcare, Waukesha, USA). Customized thermoplastic masks were made to immobilize the patients, and helical scans were performed with 1 mm slice thickness with intravenous contrast. Segmentation was undertaken in the Monaco planning system (V5.11.02 CMS Elekta, Sunnyvale, CA).

Segmentation and Treatment Planning

The gross tumor volume (GTV) encompasses all visibly diseased areas identified in the simulation computed tomography (CT) image. To create the high-risk CTV, we expanded the GTV by 5 mm. For the intermediate and low-risk CTVs, we adhered to the guidelines established by the radiation therapy oncology group (RTOG) (8).

It is important to note that the cochlea is particularly vulnerable when the retropharyngeal and retrostyloid nodes are subjected to radiation. For delineating cervical nodes, we followed the Trans-Tasman Radiation Oncology Group consensus guidelines (8). To establish the planning target volume (PTV), we applied a 3 mm margin around the CTV per institutional protocols. VMAT plans with a 6 mega volt beam were generated. Two arcs (in clockwise and anti-clockwise directions) were utilized in the plans with an increment angle of 20 degrees. A maximum of 180 control points with a segmental width of 1 cm were used for the plan optimization. Monte Carlo [(MC) v1.6)] algorithm was utilized using the cost functions of the contoured structures with a 3 mm grid size and 2% calculation uncertainty based on the performance of the VERSA HD linear accelerator (Elekta, UK). In the SEQ type of VMAT, the PTV receives a dose of 2 gray (Gy) per fraction during each phase. The accumulated prescribed doses for PTV-high, PTV-intermediate, and PTV-low in the SEQ approach are 66-70 Gy, 60 Gy, and 54-50 Gy, respectively. On the other hand, in the SIB type of VMAT, the prescribed dose to PTV-high, intermediate, and low are 66 Gy, 60 Gy, and 54 Gy all delivered in 30 fractions, respectively. It translates to a fractional dose of 2.2 Gy to PTV-high, 2 Gy to PT-intermediate, and 1.8 Gy to PT-low. Constraints were standardized according to the RTOG 0225 protocol.

The treatment was undertaken with image guidance on the first three consecutive days. If and if the shifts were within the limits of the PTV, an average shift was calculated and used for the rest of the treatments. After that, we used weekly cone beam computed tomography to confirm the accurate delivery of treatment.

Cochlear Contouring and Dosimetry

The cochlea possesses a conical structure with both an apex and a base and is positioned within the depths of the temporal bone, specifically within the otic capsule. The base of the cochlea is situated ventrally to the internal acoustic canal, while the apex is oriented in a ventrolateral and inferior direction towards the internal carotid artery. For this study, we followed the guidelines established by Sun et al. (9) to contour the cochlea. In our practical approach, we utilized a 1 mm CT slice with a bone window setting, adjusting the bone level to 1600 and the window width to 450 to accurately delineate the cochlea.

Patients were grouped as right/left/midline according to the primary disease site. In unilateral diseases, the cochlea on the same side as the primary disease site was given a higher dose of radiation compared to the cochlea on the opposite side. Accordingly, both cochleae were given similar doses in midline diseases like nasopharyngeal malignancy.

Hearing Evaluation

All patients underwent hearing evaluation before the initiation of treatment, at mid-treatment, at completion, at six months and 12 months. High-frequency pure tone audiometry (HFPTA), Impedance audiometry (Interacoustics, Denmark), and otoacoustic emission (OAE) (MAICO, Germany) were used to assess the auditory function at the above-mentioned time interval for all patients.

The HFPTA was performed using the MAICO-MA 42 clinical audiometer (MAICO, Germany). Bone conduction thresholds were obtained at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 hz frequencies.

Hearing level/pure tone average: Average of bone conduction sound thresholds at the following frequency in pure tone audiometer: 500, 1000, and 2000 hz.

Significant hearing loss: Defined as an increase in sound threshold in bone conduction average at 500,1000 and 2000 hz by more than 10 decibels (dB) from baseline reading.

Frequency-specific hearing loss: Increase in sound threshold by more than 10 dB in bone conduction at a specified frequency from baseline reading.

Late toxicity: Other significant late toxicities are dysphagia, change in voice, and xerostomia. The incidence of these symptoms was compared with the dose received [maximum dose within the target volume (D_{max}), mean dose within the target volume(D_{mean})] by the respective anatomical structures, that is, pharyngeal constrictor muscles, larynx, and parotid glands, respectively.

Statistical Analysis

Using median values, ranges, and frequencies, we employed statistical methods to represent patient, disease, and treatment characteristics. For dose-volume histograms, we calculated mean and median values for RT doses, cochlea volume, and cochlear doses (mean, minimum, and maximum) with standard deviations (SDs) and ranges. Right and left cochlear dosimetry was compared among laterality of disease using t test [expressed in t value, degree of freedom (df), p-value]. Repeated measure ANOVA compared hearing thresholds at different intervals, checking covariance equality with Box's test. Wilks' lambda test generated p-values in repeated measure ANOVA. Categorical data were compared using Pearson's chi-square test, and receiver operator characteristic (ROC) curves calculated predicted hearing loss doses. Qualitative data like tympanograms were assessed with the Mann-Whitney U test. Binary logistic regression determined dosimetric parameter odds ratios for late toxicity, and Kaplan-Meier analysis assessed cumulative hearing loss, overall survival (OS), disease-free survival (DFS), local control and regional control (RC), and progression-free survival (PFS), with log-rank tests. Cox proportional hazard models analyzed treatment outcomes. P-values <0.05 were considered significant. SPSS version 25 conducted all statistical tests.

Results

Patient Demography and Clinical Features

The median age was 54 (range: 28-76). The major site of presentation was the oral cavity, and the most common stage of presentation was stage IVa. Other results are detailed in Table 1.

Dosimetry

The dosimetric comparison for both target and OAR is tabulated in Table 2. The dosimetric parameters in the target were comparatively higher in SEQ plans, but the difference was not statistically significant. The dosimetric characteristics of both SEQ and SIB plans were within the guidelines by quantitative analyses of normal tissue effects in the clinic (QUANTEC). There was no statistically significant difference in the OAR constraints between the two plans.

Cochlear Dosimetry and Hearing Loss

Out of the 40 patients who received RT alone as a treatment, 21 underwent the SEQ plan, and 19 underwent the SIB plan

Table 1. Clinical features and demography

Variables	Number	Percentage(%)
Age: median (range) years	54 (28-76)	
Gender		
Male	75	80.6%
Female	18	19.4%
Primary site		
Oral cavity	42	45.16%
Oropharynx	18	19.35%
Hypopharynx	7	7.52%
Larynx	15	16.12%
Nasopharynx	3	3.22%
Nose and PNS	4	4.30%
Salivary glands	4	4.30%
T stage		
T_1	9	9.67%
T_2	16	17.20%
T_3	17	18.27%
T_4	51	54.83%
N stage		
N_0	8	8.60%
N_1	19	20.43%
N_2	49	52.68%
N_3	17	18.27%
Prognostic stage		
I	9	9.67%
II	16	17.20%
III	17	18.27%
IVA	42	45.16%
IVB	9	9.67%
Treatment		
RT alone	40	43.1%
Chemoradiation	53	56.9%
Type of RT		
Adjuvant RT	49	52.6%
Definitive RT	44	47.4%
Plan		
SEQ-VMAT	56	60.3%
SIB-VMAT	37	39.7%

RT: Radiotherapy, SEQ-VMAT: Sequential volumetric modulated arc therapy, SIB: VMAT: Simultaneous integrated boost-Volumetric modulated arc therapy, PNS: Paranasal sinus

VMAT. Statistical analysis of hearing loss for 53 patients who received chemoradiation was performed separately to avoid bias, as cisplatin is already a proven ototoxic drug.

The entire cohort was grouped as right, left, and midline according to the laterality of the primary disease site. The mean doses received by both cochleae were compared and found to be statistically different from each other in right and left-sided diseases, with the ipsilateral cochlea receiving higher doses (Right: p-0.02, df-21, t 3.1) (Left: p-0.04, df-15, t-1.8) (Midline: p-0.76, df-4, t-1.26). The mean dose reaching the cochlea was 8.5±7.8 Gy (right 8.2±7.1 Gy and left 7.9±6.8 Gy).

The mean baseline (n=40) hearing level on the right side was 13.3+/-2.3 dB, and that of the left was 14.2+/-1.5 dB. After 12 months of RT, the mean hearing level on the right side was 18.5+/-2.4 dB, and the left was 19.11+/-1.9 dB. There was no statistically significant difference along the study's bone conduction pure tone average timeline. There was no statistically significant difference in pure tone average between both plans (Box's M-20.12, F-31.62, df_1-8, df_2-1102.3, p=0.0021) (Wilks' Lambda- 0.312, F-21.63, p=0.003) (Table 3).

On analysis of change in frequency-specific hearing thresholds, we found a statistically significant difference at high frequency (4Khz-8Khz) hearing thresholds from baseline reading to 12 months of RT completion (Wilks' Lambda-0.366, F-31.23, p=0.04) in both RT plans (Appendix Table 1). All the threshold shifts observed at bone conduction indicate SNHL. The threshold shift was progressive until the 12th month of the study and was started predominantly at 6 months. However, there was no statistically significant difference between SEQ-VMAT and SIB-VMAT plans at any frequency at any specified study time (Figure 1).

Fifty-three individuals underwent concurrent cisplatin-based chemotherapy in this study. Among these participants, 49 individuals were administered weekly cisplatin concurrently, with an average dosage of 60 mg (ranging from 25 to 45mg/m^2) over a median of three cycles (ranging from 1 to 5 cycles). Additionally, four patients received a single 250 mg dose of paclitaxel in combination with cisplatin as part of their induction chemotherapy.

In the chemoradiation arm, ROC curves were used at each auditory frequency to calculate the minimum dose at which hearing loss occurred when combined with chemoradiation. The results of patients who received radiation alone revealed that the cochlea received maximum doses of up to 28.52 Gy without causing SNHL. But along with chemotherapy (cisplatin), hearing loss occurred at a minimum dose of 9 Gy. The minimum dose cut to predict hearing loss is given in Table 4. Further, we compared the cumulative hearing loss between both plans using the Kaplan-Meier plot. The censorship was kept as the occurrence of hearing loss, and the end of follow-up was kept at 12 months. There was no statistically significant difference between both plans by log-rank test (chi-square- 33, df- 2, p=0.98).

Table 2. Dosimetric characteristics of VMAT

Variables	Parameters	QUANTEC dose-volume constraints for organs-at-risk	SEQ-VMAT	SIB-VMAT	p-value
Target					
PTV high risk	D_{mean} (Gy)		68.5 (68.4 - 69.3)	69.5 (67.5 - 68.4)	0.89
	V95 (%)	>95	98.0 (97.1 - 99.9)	99.1 (98.2 - 99.9)	0.76
	V107 (%)	<1	0.50 (0.00 - 3.10)	0.5 (0.00 - 3.1)	0.45
	D98% (Gy)	>60.8	63.1 (62.0 - 64.2)	64.1 (62.3 - 66.5)	0.32
	HI		11.8 (7.6 - 14.3)	12.1 (7.2 - 14.5)	0.56
	CI1		1.73 (1.62 - 3.12)	1.91 (1.62 - 3.02)	0.21
	% DCI1-2		97.6 (94.9 - 99.2)	98.1 (93.9 - 99.7)	0.08
	% DCI1-3		95.5 (94.9 - 97.4)	96.1 (95.1 - 97.1)	0.33
PTV intermediate risk	V95 (%)	>95	98.9 (97.8 - 99.9)	99.1 (98.8 - 99.9)	0.06
	D98 % (Gy)	>57	58.3 (56.7 - 60.3)	58.9 (57.7 - 60.4)	0.07
	CI2		1.79 (1.63 - 2.51)	1.84 (1.61 - 2.93)	0.09
PTV LR	V95 (%)	>95	98.9 (98.0 - 99.7)	99.1 (98.1 - 99.8)	0.65
	D98 % (Gy)	>50 Gy	53.8 (52.6 - 55.0)	54.1 (52.8 - 55.9)	0.76
	CI3		1.55 (1.49 - 1.81)	1.61 (1.50 - 1.91)	0.09
Organ at risk					
Cochlea	D_{mean} (Gy)	<45 Gy	8.5(8.1-9.2)	9(8.2-10.5)	0.42
	D_{max} (Gy)		9.29(8.3-10.5)	10.3(9.1-11.2)	0.16
Larynx	D_{mean} (Gy)	<44 Gy	44.41(43.6-46.3)	44.8(43.8-45.9)	0.21
Right parotid gland	D_{mean} (Gy)	<26 Gy	23.8(22.6-25.2)	24.76(23.7-26.3)	0.08
Left parotid gland	D_{mean} (Gy)	<26 Gy	24.3(23.1-26.8)	24.8(21.6-25.5)	0.33
Pharyngeal constrictors	D_{mean} (Gy)		52.1(49.2-55.6)	53.2(49.1-54.3)	0.86
Lenses	D_{mean} (Gy)	<55 Gy	1.3 (1.2-4.8)	1.5 (1.1-4.5)	0.27
Brain stem	D1, cc (Gy)	<54 Gy	31.2 (26.0-37.7)	32.2 (26.9-38.7)	0.33
	EUD (Gy)		23.8 (18.9-24.8)	24.1 (19.9-25.5)	0.06
	NTCP (%)		0.0 (0.0-0.0)	0.0(0.0-0.0)	0.17
Spinal cord	D1, cc (Gy)	<45 Gy	36.9 (35.8 - 43.8)	36.4 (35.2 - 44.9)	0.09
	EUD (Gy)		31.8 (24.9 - 33.5)	31.1 (25.9 - 34.5)	0.65
	NTCP (%)		0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.77
Optic nerve	D_{mean} (Gy)		2.8 (1.8 - 14.3)	3.1 (1.9 - 14.9)	0.09
	D_{max} (Gy)	<55 Gy	4.2 (1.4 - 28.9)	4.9 (1.9 - 29.2)	0.98

HI: Homogeneous index, CI: Conformity index, EUD: Equivalent uniform dose, NTCP: Normal tissue complication probability, SEQ-VMAT: Sequential volumetric modulated arc therapy, PTV: planning target volume, SIB-VMAT: Simultaneous integrated boost volumetric modulated arc therapy, QUANTEC: Quantitative analyses of normal tissue effects in the clinic, D_{max}: maximum dose within the target volume, D_{mean}: mean dose within the target volume

Impedance audiometry was analyzed in two domains: compliance and type of graph. 5.6% of the ears exhibited a change in tympanogram (A to B) during treatment, indicative of otitis media, which resolved in 4.1% of ears six months after therapy was completed. There was no statistically significant difference between the SEQ-VMAT and SIB-VMAT plans in impedance parameters.

OAEs were compared between time intervals, and there were no statistically significant differences between baseline and 12 months OAE reading by repeated measure ANOVA (Wilks' Lambda- 0.43, F- 32.13, p=0.86). Similarly, OAE were compared between SEQ-VMAT and SIB-VMAT, and there was no statistically significant difference between the two at the end of the 12- month follow-up in both TOAE (t- 2.81, df- 40, p=0.89) and DPOAE (t- 2.76, df- 40, p=0.43).

Late Toxicities

The dosimetry of parotid glands, pharyngeal constrictor muscles, and larynx were analyzed further to define the dose constraints for late toxicity. There was no statistically

Table 3. Distributions of median (range) hearing thresholds in various frequencies and the results of ANOVA

Frequency	Baseline		Mid-fraction(2 weeks)		Completion		6 months		12 months		p-value
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	
Hearing level(Average of 500,1 Khz, and 2 Khz)	13.1 (11.2-15.2)	13 (11.7-14.4)	13.33 (11.7-14.9)	13.8 (11.2-14.2)	14.8 (13.1-16.2)	14 (13.9-17.1)	16.62 (15.7-18.9)	16 (15-17.3)	19.87 (18.9-21.1)	20.07 (19.1-22.2)	0.45
250	10.1 (8.9-11.2)	11 (9.2-12.3)	10.1 (9.2-12.1)	9.1 (8.9-11.2)	11.2 (10.3-12.7)	12.1 (10.3-12.7)	13.8 (11.9-15.3)	13.33 (11.01-14.9)	15.1 (14.2-16.8)	16.6 (15.1-17.8)	0.89
500	15.2 (12.1-16.4)	14.9 (13.2-16.4)	15.29 (13.2-16.5)	14.2 (12.1-16.4)	15.5 (14.2-17.3)	14.9 (13.9-17.3)	17.2 (15.5-18.8)	17.1 (16.5-18.56)	19.3 (18.2-20.3)	18.9 (17.2-21.3)	0.76
1000	13.5 (11.2-15.2)	12.5 (11.7-13.9)	13.5 (11.7-14.9)	13.3 (11.2-15.2)	14.8 (13.8-16.2)	14 (13.3-17.2)	17.97 (15.7-18.9)	17.71 (16.6-19.9)	20.1 (18.9-21.1)	20 (18.2-22.1)	0.23
2000	10.3 (8.3-12.2)	11.1 (8.9-11.9)	10.3 (8.9-11.8)	11.1 (8.3-12.2)	14.1 (13.3-15.9)	14.1 (12.9-15.8)	15.7 (13.4-16.3)	15.5 (14.4-17.3)	20.2 (19.3-21.4)	21.1 (19.9-22.4)	0.04
4000	15.3 (13.4-16.4)	14.3 (13.6-15.8)	15.3 (13.6-16.8)	13.1 (13.4-16.4)	21.2 (18-22.9)	20.2 (19.1-21.9)	31.3 (29.7-32.5)	30.3 (28.8-33.3)	38.2 (37.2-39.9)	39.2 (37.2-40.9)	0.02
8000	15.6 (13.8-17.3)	14.6 (14.1-16.2)	15.6 (14.1-17.2)	16.1 (14.8-17.3)	23 (21.2-24.9)	22.2 (21.1-24.7)	34.8 (31.7-35.8)	35.8 (32.1-36.3)	41.1 (39.6-42.5)	41.1 (40.6-42.5)	<0.001

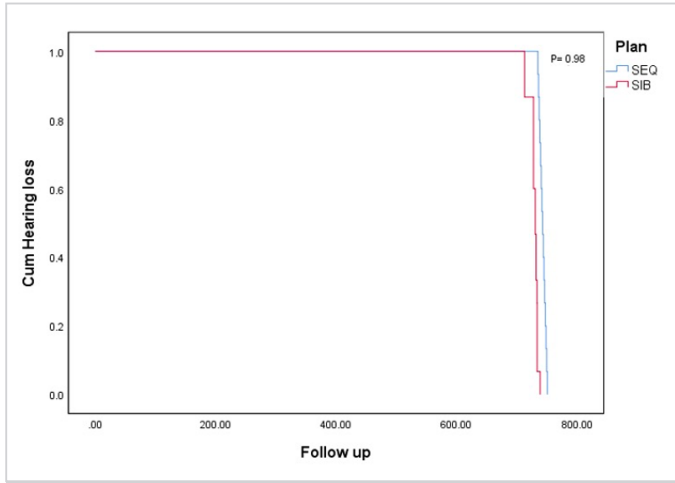

Figure 1. Kaplan-Meier plot for cumulative hearing loss showing the comparison of SEQ vs. SIB plans with p-value generated by log-rank test

SEQ: Sequential, SIB: Simultaneous integrated boost

Table 4. ROC curve values of predicted RT dose causing hearing loss

Frequency (bone conduction) hz	500 hz	1000 hz	2000 hz	4000 hz	8000 hz
Mean dose cut-off by youden's index method (Gy)	6.34	22.2	4.9	7.99	11.91
Area under	0.64	0.621	0.69	0.66	0.61
Sensitivity	63.5	40	77.8	55.8	46.8
Specificity	61.1	90.4	54.6	75.4	80.3
p-value	0.02	0.001	0	0.001	0.01

ROC: Receiver operator characteristic, RT: Radiotherapy, Gy: Gray

Table 5. Binary logistic regression to assess the risk of developing late toxicity as a function of dose received by the target volume

Binary logistic regression	Parameter (Gy)	Odd's ratio (95% CI)	p-value
Constrictor muscles of pharynx	D_{max}	1.41 (0.98-2.12)	0.021
	D_{mean}	1.23 (0.21-3.12)	<0.001
Larynx	D_{max}	0.98 (0.11-2.32)	0.86
	D_{mean}	0.76 (0.18-1.99)	0.45
Right parotid	D_{max}	1.09 (0.23-2.82)	0.09
	D_{mean}	1.04 (0.71-2.31)	0.33
Left parotid	D_{max}	1.12 (0.89-3.21)	0.24
	D_{mean}	0.99 (0.31-1.98)	1

D_{max}: maximum dose within the target volume, D_{mean}: mean dose within the target volume, Gy: Gray, CI: Confidence interval

significant difference between SIB vs. SEQ plans in patients who developed dysphagia (42.3% vs. 40.7%), change in voice (9.4% vs. 8.9%), and xerostomia (51.4% vs. 53.3%). On binary logistic regression, the D_{max} and D_{mean} of pharyngeal constrictor muscles were predictors for dysphagia with statistically significant results (Table 5). The odds ratio for developing dysphagia was 1.4 when D_{max} was above 50 Gy. There was no statistically significant difference between SEQ and SIB VMAT plans in the incidence of late toxicity.

Survival Analysis

The mean follow-up time was 13.5±1.2 (mean±SD) months. The mean survival time was 723.2±1.6 days (Mean±standard error) (95% CI: 710.76-765.6). The OS was 63.8% at the end of 12 months. There was no statistically significant difference between SEQ and SIB in OS (62.8% vs. 60.9%, p=0.89), DFS (62.1% vs. 52.4%, p=0.67), LC (58.7% vs. 57.6%, p=0.57), RC (95.2% vs. 89.3%, p=0.25) and PFS (72.1% vs. 69.2%, p=0.87) (Figure 2). Univariate and multivariate Cox hazard model analysis for the treatment plan is given in Table 6. The subgroup analysis of two-year survival in the RT and chemoradiation groups according to the primary site is given in Appendix Table 2.

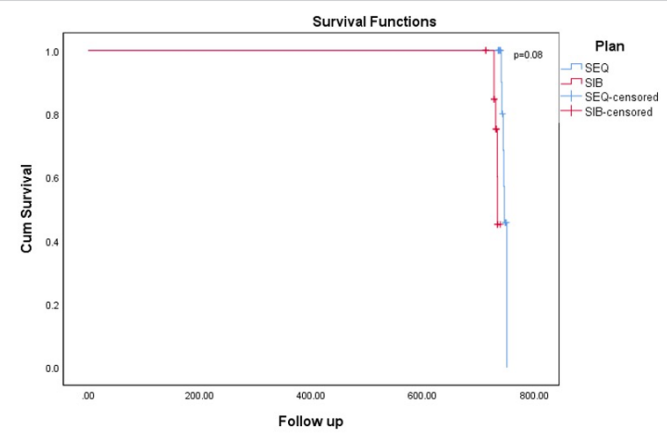

Figure 2. Kaplan-Meier plot for cumulative survival showing the comparison of survival between SEQ vs. SIB. P-value generated by log-rank test

SEQ: Sequential, SIB: Simultaneous integrated boost

Discussion

Advancements in dosimetry accuracy and the need for shorter treatments drive the adoption of novel delivery techniques. Transitioning from 2D RT to IMRT has reduced treatment toxicity, leading to the adoption of advanced methods like VMAT. SIB/SEQ is now the standard for complex malignancies. Research on toxicity profiles is ongoing, including ototoxicity (5, 10-13). In head and neck radiation therapy (RT), precise target dose determination is crucial for effective treatment with minimal side effects. Factors like tumor characteristics, patient-related factors, and potential tissue toxicity must be considered. The study of Morgan and Sher (14) emphasizes the roles of tumor size, location, and stage. Proximity to critical organs like the lenses, the spinal cord, and the salivary glands is vital. Patient health, comorbidities, and prior treatments also impact the dose. Balancing tumor control and tissue preservation enhances outcomes and quality of life for head and neck cancer patients (15).

In this study, the SEQ-VMAT and SIB-VMAT treatment techniques met the prescribed dose requirements for target volumes and effectively spared OAR. While there was no significant difference in achieved dose coverage to the target between the two techniques, the homogeneity index was notably lower in SEQ-VMAT for PTV-intermediate and PTV-low. The SIB-VMAT approach, with its high prescription dose to PTV_1 and attachment of PTV_2 and PTV_3, led to higher dose inhomogeneity in nearby target regions. SEQ-VMAT resulted in more uniform doses to the target structures. Furthermore, patients treated with SIB-VMAT showed lower doses to the pharyngeal constrictors and brainstem, indicating that the SIB technique is advantageous in delivering lower doses to critical structures. However, these findings were statistically not significant. Kachhwaha et al. (16) conducted a prospective comparison of SEQ versus SIB of VMAT in treating 54 oropharyngeal carcinoma patients. Their results were like the presented study.

According to QUANTEC guidelines (17), the recommended safe mean dose constraint for the cochlea is <45 Gy. Our

Table 6. Treatment outcomes, Cox proportional hazard model

Treatment outcomes	Univariable		Multivariable	
	SEQ vs. SIB [hazard ratio (95% CI)]	p-value	SEQ vs. SIB [hazard ratio (95% CI)]	p-value
OS	0.56 (0.32–2.25)	0.87	1.24 (0.24-2.31)	0.76
DFS	0.57 (0.29-1.52)	0.23	0.65 (0.33-1.49)	0.21
LC	0.68 (0.42-1.89)	1.01	0.70 (0.27-1.62)	0.43
RC	0.35 (0.24-1.78)	0.22	0.14 (0.02–2.78)	0.55
PFS	0.42 (0.31-2.13)	0.43	0.12 (0.01-1.13)	0.08

OS: Overall survival, DFS: Disease-free survival, LC: Local control, RC: Regional control, PFS: Progression-free survival, SEQ: Sequential, SIB: Simultaneous integrated boost, CI: Confidence interval

study successfully adhered to this constraint. Lamaj et al. (18) investigated hearing impairment in nasopharyngeal carcinoma patients undergoing chemoradiotherapy (CRT). They aimed to spare the cochlea while using IMRT and VMAT to maintain treatment effectiveness. Re-optimized plans significantly reduced cochlear dose ($p<0.001$) without compromising other quality parameters. Their study demonstrates the feasibility of preserving cochlear function in nasopharyngeal carcinoma patients during CRT. It underscores the importance of considering hearing toxicity in treatment planning due to the absence of a defined dose threshold for CRT-induced hearing impairment.

In a retrospective study by Vlacich et al. (19), researchers conducted a matched cohort analysis on locally advanced head and neck carcinoma patients treated with chemoradiation. A total dose of 69.3 Gy in 33 fractions was administered to 209 patients, 68 receiving SEQ and 141 receiving SIB treatment. Results revealed no significant differences in DFS (63% vs. 69%; p=0.27) and OS (69.3% vs. 76.8%; p=0.13) between the SEQ and SIB groups. However, the SIB group exhibited a higher incidence of grade 3 or 4 acute dysphagia (82% vs. 55%) and acute dermatitis (78% vs. 58%). Interestingly, our study showed no difference in grade 3 dysphagia incidence between the SEQ (11.5%) and SIB (19.2%) groups (p=0.44). The dissimilarity in patient populations may explain this, as Vlacich et al.'s (19) study included oropharyngeal cancer patients, potentially accentuating differences in SIB vs. SEQ techniques due to retropharyngeal node involvement.

Our study, involving 40 head and neck cancer patients treated with RT alone, examined the impact on hearing. We focused on definitive or adjuvant RT without chemotherapy. Our model suggested that the cochlea could tolerate doses up to 28.52 Gy without causing SNHL in this context, with exceptions at 4 Khz and 8 Khz frequencies in the RT-only group. We conducted further investigations and referenced the relevant literature. Regarding treatment plans, there were no statistically significant differences between SEQ and SIB plans, aligning with Pan et al.'s (20) study on 3D CRT planning. Our study found a lower median cochlear dose at 4.2 Gy (range: 0.38 to 56.6 Gy) irrespective of the disease side, with consistent cochlear volume exposure (0.56 cm3 vs. 0.14 cm3) compared to Pan et al. (20). All patients underwent VMAT treatment, ensuring adherence to safe cochlear dose constraints and potentially reducing the risk of immediate SNHL post-RT.

Apart from audiometry, otoacoustic emissions, measured at different intervals, did not significantly differ from baseline or between treatment plans. In a prospective study, Akazawa et al. (21) explored RTs impact on the Eustachian tube and middle ear functions in head and neck cancer patients. They identified Eustachian tube dysfunction as a common complication. Our study examined 186 ears and found a 5.6% change from curve type A to B, mainly on the right side, associated with reduced right tympanic membrane compliance (p=0.029), often occurring mid-treatment. However, 73% of the affected ears recovered within six months. Considering the disease laterality, the skewed data suggests a potential statistical artifact. In summary, radiation-induced middle ear dysfunction may contribute significantly to conductive hearing loss.

Our research revealed no hearing impairment in patients solely treated with VMAT RT. However, when combined with cisplatin, the clinically significant high-frequency hearing loss occurred at an average cochlear RT dose of approximately 9 Gy. Hitchcock et al.'s (22) prospective study involving 62 head and neck cancer patients investigated dose-related hearing loss in patients receiving RT, cisplatin, or both. For RT alone, no significant hearing loss was seen below 40 Gy. In patients receiving cisplatin, even lower radiation doses (10 Gy) led to hearing loss at 8000 hz, worsening with higher doses (40 Gy).

In a randomized phase III study comparing SEQ and SIB intensity-modulated RT for nasopharyngeal carcinoma, grade 3-5 mucositis, and dysphagia were the most common acute toxicities. However, no statistically significant differences were found in the cumulative incidence of grade 3-4 acute toxicities between the two treatment approaches (SEQ and SIB). Late toxicities included hearing loss, temporal lobe injury, cranial nerve injury, and xerostomia, consistent with our findings. Pharyngeal constrictor muscle D_{max} and D_{mean} were predictors for dysphagia (odds ratio 1.4 for D_{max}>50 Gy). Three-year PFS and OS rates showed no significant differences between SEQ and SIB (p0.488 and p=0.938, respectively) during the 41-month median follow-up (23).

Shivananjappa et al. (24) shared their experience using SIB VMAT (SIB VMAT) to treat head and neck cancer definitively. Their prospective randomized study included 50 patients with stage T1-3 squamous cell carcinoma of the oropharynx, hypopharynx, and larynx, with enlarged nodes ≤3 cm. Patients were split into hypo-fractionated SIB (Hypo-SIB VMAT) and conventional boost VMAT (Conv-VMAT). After two years, OS rates were 84% (Hypo-SIB VMAT) and 80% (Conv-VMAT), with no significant differences (p=0.25). DFS was 88% vs. 72% (p=0.12), and locoregional recurrence-free survival (RFS) was 92% vs. 84% (p=0.38). Both arms had similar toxicities, but Hypo-SIB VMAT had a significantly shorter average overall treatment time (39.4 vs. 50.2 days, p=0.00001).

Conclusion

In conclusion, both SEQ and SIB plans met the QUANTEC guidelines with similar dosimetric characteristics, showing no significant differences in target

and organ-at-risk constraints. The RT-alone group had no significant hearing loss, with the cochlea tolerating up to 28 Gy without issues. However, when combined with cisplatin-based chemotherapy, frequency-specific hearing loss emerged at 9 Gy, especially in high frequencies (4 Khz-8 Khz). These findings suggest the importance of stricter cochlear dose constraints when using cisplatin and RT. Late toxicities, specifically dysphagia, were correlated with higher pharyngeal constrictor muscle D_{max} and D_{mean}. Survival outcomes did not significantly differ between the two treatment plans.

Ethics Committee: The study was conducted at All India Institute of Medical Sciences between January 2019 and December 2021. Ethics and research committee approval was obtained from the institution and the study was conducted within the scope of the specialization thesis of the first author (decision number: AIIMS/IEC/2019/1680, date: 21-01-2019).

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.D., S.H.K., V.S., P.P., K.S., A.G., Concept: N.D., S.H.K., V.S., P.P., K.S., A.G., Design: N.D., S.H.K., V.S., P.P., K.S., A.G., Data Collection and/or Processing: N.D., S.H.K., V.S., P.P., K.S., A.G., Analysis and/or Interpretation: N.D., S.H.K., V.S., P.P., K.S., A.G., Literature Search: N.D., S.H.K., V.S., P.P., K.S., A.G., Writing: N.D., S.H.K., V.S., P.P., K.S., A.G.

Informed Consent: In this prospective single-arm interventional study, we enrolled 93 individuals diagnosed with head and neck cancer who had no prior history of otological diseases after obtaining their informed consent.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Main Points

- In this study, we evaluated the effectiveness of modern-day radiotherapy techniques in sparing the organ at risk in the context of early & late radiation toxicity and survival in head and neck cancer patients.
- The cochlea exhibited varying radiation tolerance levels. In the radiation-only group, the cochlea demonstrated tolerance up to 28 Gy without the incidence of hearing loss. However, hearing loss was observed at a minimum of 9 Gy in the chemoradiation group.
- There was no significant difference in ototoxicity between sequential (SEQ) and simultaneous integrated boost plans of volumetric modulated arc therapy.
- The maximum dose (D_{max}) and the mean dose (D_{mean}) received by pharyngeal constrictor muscles can predict late toxicity, such as dysphagia.
- Notably, there were no significant differences in late toxicity or survival outcomes between the SEQ and simultaneous integrated boost plans of volumetric modulated arc therapy.

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Appendix Table 1. Comparison of hearing thresholds among SEQ & SIB across different time interval of the study

Hearing Frequency (hz)	Baseline thresholds (dB)			Mid-fraction Thresholds(dB)			Completion thresholds(dB)			6 months thresholds(dB)			12 months thresholds(dB)		
	SEQ-VMAT	SIB-VMAT	p-value	SEQ-VMAT	SIB-VMAT	p-value	SEQ-VMAT	SIB-VMAT	p-value	SEQ-VMAT	SIB-VMAT	p-value	SEQ-VMAT	SIB-VMAT	p-value
250	10.1 (8.9-11.2)	10 (8.2-11.4)	0.98	10.1 (9.2-12.1)	10 (9.1-11.7)	0.18	11.2 (10.3-12.7)	11 (10.5-13.1)	0.68	13.9 (11.1-14.2)	13.8 (11.9-15.3)	0.72	15.1 (14.2-16.8)	14.3 (12.3-15.6)	0.84
500	15.2 (12.1-16.4)	15.1 (13.1-16.8)	0.06	15.29 (13.2-16.5)	15.1 (14.2-16.9)	0.36	15.5 (14.2-17.3)	15.4 (14.2-16.9)	0.24	17.3 (15.3-19.3)	17.2 (15.5-18.8)	0.37	19.3 (18.2-20.3)	18.6 (17.3-19.3)	0.56
1000	13.5 (11.2-15.2)	13.4 (11.6-15.4)	0.45	13.5 (11.7-14.9)	13.4 (12.1-15.3)	0.25	14.8 (13.8-16-2)	14.57 (13.1-16.7)	0.45	18.2 (17.2-20.1)	17.97 (15.7-18.9)	0.45	20.1 (18.9-21.1)	19.85 (18.4-21.5)	0.66
2000	10.3 (8.3-12.2)	10.2 (9.3-12.1)	0.54	10.3 (8.9-11.8)	10.2 (7.9-12.1)	0.14	14.1 (13.3-15.9)	13.8 (12.1-14.5)	0.65	14.9 (12.9-16.7)	14.7 (13.4-15.3)	0.44	20.2 (19.3-21.4)	20.1 (18.9-21.1)	0.73
4000	15.3 (13.4-16.4)	15.2 (13.6-16.1)	0.22	15.3 (13.6-16.8)	15.2 (12.9-14.6)	0.42	21.2 (18-22.9)	21.08 (19.9-22.3)	0.99	32.2 (30.4-33.3)	31.3 (29.7-32.5)	0.12	38.2 (37.2-39.9)	37.33 (36.2-38.1)	0.37
8000	15.6 (13.8-17.3)	15.5 (12.9-16.8)	0.21	15.6 (14.1-17.2)	15.2 (12.9-14.6)	0.61	23 (21.2-24.9)	22.8 (20.2-23.9)	0.09	35 (30.5-37.5)	34.8 (31.7-35.8)	0.81	41.1 (39.6-42.5)	41 (38.8-42.1)	0.21

SEQ: Sequential, SIB: Simultaneous integrated boost, VMAT: Volumetric modulated arc therapy

Appendix Table 2. Subgroup analysis of 2-year survival

Primary site	RT alone		Chemoradiation		p-value
	2-year survival (%)	p-value	2-year survival (%)	p-value	(RT vs. Chemo RT)
Oral cavity					
SIB	81	0.65	85	0.55	0.99
SEQ	79		81		
Oropharynx					0.06
SIB	72	0.99	79	0.19	
SEQ	75		74		
Larynx					0.11
SIB	69	0.07	72	0.57	
SEQ	72		73		
Hypopharynx					0.29
SIB	79	0.06	76	0.34	
SEQ	81		74		
Nose and paranasal					0.08
sinuses	71	0.23	77	0.09	
SIB SEQ	69		74		
Nasopharynx					0.77
SIB	90	0.09	91	0.44	
SEQ	88		90		
Salivary glands					0.31
SIB	98	0.98	89	0.78	
SEQ	96		90		

SEQ: Sequential, SIB: Simultaneous integrated boost, RT: Radiotherapy