Original Article

Skin Sparing in Intensity-Modulated Radiation Therapy of Nasopharyngeal Carcinoma

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Abstract

Background and Purpose: Radiation therapy of nasopharyngeal carcinomas (NPCs) involves high doses to the target structures which are superficial to the skin surfaces. As a result, the skin toxicities involved are higher and sometimes worsens to such an extent that radiotherapy needs to be interrupted unplanned. This leads to a break in radiation therapy which overall affects the local control and cure rates. The aim of this study is to decrease the skin dose by contouring skin as an organ at risk (OAR) to include in inverse planning calculation. **Materials and Methods:** Seventy-three cases of nasopharyngeal cancers were planned for 60 Gy to intermediate-risk planning target volume ($PTV_{Intermediate)}$ and 70 Gy to high risk ($PTV_{High)}$, by three different modes of Intensity-modulated radiation therapy (IMRT)- namely conventional sequential intensity-modulated radiation therapy (S-IMRT PH-I and PH-II), Skin Spared sequential intensity-modulated radiation therapy (SS-IMRT PH-I and PH-II), and Skin Spared simultaneously instantaneous boost intensity-modulated radiation therapy (SS-SIB IMRT). The plans were compared by dose volume histograms and dose statistics to the PTV as well as to the OAR's. For PTV, mean dose (Dmean), maximum dose (Dmax), and minimum dose (Dmin) were compared to check the homogeneity index (HI) while sparing the skin. For other OAR's Dmean, Dmax and dose to to 1 cubic cm was used for comparison. The skin doses to various volumes from volume to receive 5 Gy (V5) to volume to receive 70 Gy (V70) were evaluated and compared between the three techniques. Statistical analysis was done using one away ANOVA on the data editor SPSS Version 26.0 (SPSS Inc., Chicago, Illinois, USA) to evaluate the results. Continuous variables were expressed as mean ± standard deviation, and categorical variables were summarized as frequencies and percentages. Survival analysis was done by Kaplan–Meier Estimator. **Results:** When the skin was considered as an OAR, the skin volume to receive 5, 10, 15, 20, 30, 40, 50, 60, 70 Gy was reduced by 6.5%, 6.5%, 6%, 11.5%, 7%, 6%, 6%, 5%, 2%, respectively, by SS-IMRT PH-I and II and 2%, 4.05%, 4%, 7%, 5%, 3%, 6%, 5%, 1%, respectively, by SS-SIB IMRT when both the SS techniques were compared with S-IMRT PH-I and II. Volume of skin to receive 20 Gy showed maximum reduction in SS-IMRT PH-I and II. A one-way ANOVA was carried out to find the differences in the skin doses between the three techniques. The skin dose in the two SS techniques, i.e., SS-IMRT PH-I and PH-II and SS-SIB IMRT was found significantly lower than that of IMRT plans without skin as an OAR, i.e., S-IMRT PH-I and PH-II ($P = 0.000$). The PTV doses were well within the 95%–107% of the prescribed dose (HI) and there were no significant differences in the means of the prescribed dose between the simple and skin spared IMRT techniques. The other OARs doses were also evaluated and there were no significant differences between the means of the doses among the techniques. **Conclusions:** SS IMRT for NPC has demonstrated reduction in skin dose while using skin as an OAR in the optimization. Moreover, decreased skin dose can decrease the skin related toxicities provided there is no compromise on Target dose coverage and OAR dose. We recommend that skin should be contoured as an OAR for NPC, provided PTV is minimally 3–5 mm beneath skin surface, in order to have a better disease control with lesser toxicities and less unplanned treatment interruptions.

Keywords: Nasopharyngeal carcinoma, organ at risk, simultaneously instantaneous boost, skin sparing

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Introduction

Nasopharyngeal carcinoma (NPC) is an uncommon cancers that is endemic to east and southeast Asia (70% of the cases).[1] It is the 23rd most common type of cancer worldwide. Although rare the men are at higher risk to develop nasopharyngeal cancers than females and are

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approximately twice as common in men as in women. It is the 18th most commonly occurring cancer in men and the 22nd most commonly occurring cancer in women. There were an estimated 133,354 cases of NPCs with a mortality of about 80,008 in 2020[2] and the projected 5-year prevalence is 382,507 cases. Overall incidence rates are three times higher in middle- to low-income countries than in high-income countries. Among Asian countries, India has the fourth most common incidence of carcinoma nasopharynx.[3] In addition to geographic diversity, it seems that some ethnic groups are prone to nasopharynx cancer. These groups include the Bidayuh in Borneo, the Nagas in northern India, and the Inuits in the North pole. The highest rates are found in South-East Asia, in particular among Cantonese people living in the central region of Guangdong Province in southern China.[4] The risk factors include dietary products such as consuming Cantonese-style salted fish,[5,6] red meat, processed meat, and preserved nonstarchy vegetables. In addition to the findings on diet, nutrition, physical activity, other established causes of nasopharyngeal cancers include, smoking,[7] occupational exposure, infectious agents like Epstein–Barr virus, family history.[8,9] Nasopharyngeal cancer as per our hospital based cancer registration is not common in our region. It accounts only for 2% of the total cases registered in our hospital. The incidence varies from 1% to 5% per year.[10] Treatment options and recommendations depend on several factors, including the type and stage of cancer, possible side effects, and the patient's preferences and overall health. The main treatment for NPC recommended by the American Society of Clinical Oncology (ASCO) is the radiation therapy. It is usually given in combination with chemotherapy as concurrent chemoradiation.[11-13] Surgery is sometimes needed mainly to remove lymph nodes after chemoradiation or in case of recurring disease. Radiation therapy to nasopharynx is usually best delivered by intensity-modulated radiation therapy (IMRT) that allows more effective doses of radiation to be delivered, at a better sparing of organs at risk (OAR's) surrounding the nasopharynx. ASCO, the European society for medical oncology recommends concurrent chemoradiation as a treatment of choice as a treatment of choice for all the stages from stage II to stage IV disease.[14,15] Brachytherapy is also used to treat NPCs but as the procedures being invasive and cumbersome in nature only few radiotherapy centers offer this treatment.[16] As the external beam radiation therapy curative doses for NPCs are as high[17] as 70 Gy to the target structures, i.e., nasopharynx and nodes which are superficial and near to the skin surfaces, the skin toxicities becomes the major cause of unplanned treatment interruption during the course of radiotherapy, which can affect the local control as well as the overall survival of the patient. In this study, we aimed to decrease the skin dose to some extent by contouring skin as an organ at risk (OAR), which usually is not contoured as an OAR for head and neck irradiations. Few authors have recently published on the feasibility of skin sparing (SS) in NPC and thus an attempt was made by us to achieve few benefits from the same using the available resources for a resource limited radiotherapy center like ours.

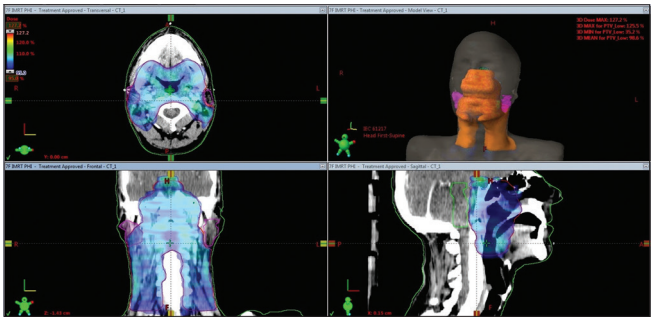

Figure 1: A representative case for radiotherapy of nasopharynx planned using Intensity modulated radiotherapy

Materials and Methods

Patient selection and radiotherapy planning

Seventy-three cases of NPC patients registered from 2016 to 2021 receiving adjuvant radiation therapy of 70 Gy were selected for the study. Computed tomography scanning-based simulation of all the patients was done using a head and neck thermoplastic cast from Klarity® on the wide bore computed tomography (CT) scanner (M/s Semiens Somatom Sensation) with contrast dye. The slice thickness of the scan was 3 mm for IMRT. All the scans were taken in supine position. The CT datasets in digital imaging and communications in medicine format were transferred to the Eclipse™ treatment planning system (Ver. 13.6) in which the Somavision workstation was used to delineate the targets and OAR's. The targets and OAR's volumes were defined as per international

Table 1: Volume of skin to receive different doses by conventional sequential (sequential intensity modulated radiation therapy PHI and II), skin spared simultaneously instantaneous boost intensity modulated radiation therapy and skin spared sequential intensity modulated radiation therapy PHI and II) ($P<0.05$)

Dose (Gy)/ volume (%)	Mean±SD			*P*
	S-IMRT PHI and II	SS SIB-IMRT	SS-IMRT PHI and II	
5	92.75±1.70	90.00±0.82	85.00±0.82	0.000
10	78.75±0.50	75.00±0.82	73.60±0.58	0.000
15	70.72±0.53	66.45±0.53	63.50±1.29	0.000
20	65.23±0.71	60.83±1.09	53.29±1.26	0.000
30	50.50±0.58	45.50±0.5	42.75±0.50	0.000
40	34.75±0.50	32.75±0.50	29.50±0.58	0.000
50	27.50±0.58	25.00±0.80	22.50±0.82	0.000
60	20.50±0.58	15±0.80	14.25±0.96	0.000
70	7.25±0.50	6.00±0.00	5.00±0.00	0.000

S-IMRT: Sequential intensity modulated radiation therapy, SS SIB-IMRT: Skin spared simultaneously instantaneous boost intensity modulated radiation therapy, SS-IMRT: Skin spared sequential intensity modulated radiation therapy, SD: Standard deviation, PH: Phase

commission on radiation units and Measuremen Reports 50 and 62 recommendations.[18] The doses were optimized according to the dose recommendations from radiation therapy oncology group (RTOG) and qualitative analysis of normal tissue effects in the clinic.[19] Usually, skin is not contoured as OAR for NPCs, but for these 73 patients 3 mm skin inside the body was contoured as an OAR. Study patients were divided in three planning groups namely Group I that received 70 Gy by conventional sequential IMRT (S-IMRT PHI and PHII), Group II-Skin Spared sequential IMRT (SS-IMRT PHI and PHII), and Group III-Skin Spared simultaneously instantaneous boost IMRT (SS-SIB IMRT).

All the plans were planned using Eclipse™ Treatment Planning System Version 13.6 by Varian Medical System, Inc., Palo Alto, CA USA. Volume dose was calculated using Anisotropic Analytical Algorithm (Version 13.6.23) with a calculation grid size of 0.25 cm and fluence was optimized using Dose Volume Optimizer (Version 13.6.23). Figure 1 shows a representative plan of an NPC planned using (IMRT).

Dosimetric evaluation

The plans were compared by dose-volume histograms (DVHs) and dose statistics to the planning target volume (PTV) volumes as well as to the OAR's. For PTV, Dmean, Dmax, Dmin, were compared. For OAR's Dmean, Dmax/Dmax and dose to one centimeter cube were used for comparison. The skin doses to various volumes from volume to receive 5 Gy (V5) to skin volume receiving 70 Gy (V70) were evaluated and compared.

Sample analysis

The evaluated dose was analyzed using data editor of IBM® SPSS® V-26 (SPSS Inc., Chicago, Illinois, USA). A one-way-ANOVA analysis was used to access the difference in the skin doses between the three techniques. The comparative datasets were evaluated on a 5% level of significance i.e., $P < 0.05\%$ was considered statistically significant. The other OAR's doses were also analyzed by one-way ANOVA. The PTV dose coverage and homogeneity was also calculated and analyzed by one-way ANOVA.

Table 2: ANOVA descriptives for the Mean volume of skin receiving 20Gy

V20								
	n	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
S-IMRT PHI&II	73	65.23	0.71	0.08	65.06	65.39	64.00	67.00
SS-SIB IMRT	73	60.84	1.09	0.13	60.58	61.09	59.00	62.90
SS-IMRT PHI&II	73	53.29	1.26	0.15	53	53.59	51.00	55.00
Total	219	59.79	5.05	0.34	59.12	60.46	51.00	67.00

Table 3: Test of significance between three techniques for volume of skin to receive 20 Gy

Multiple Comparisons						
Dependent Variable: V20						
Least significant difference (LSD)						
(I) TEC	(J) TEC	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
S-IMRT PHI&II	SS-SIB IMRT	4.39*	0.17	0.000	4.05	4.73
	SS-IMRT PHI&II	11.93*	0.17	0.000	11.59	12.28
SS-SIB IMRT	S-IMRT PHI&II	-4.39*	0.17	0.000	-4.73	-4.05
	SS-IMRT PHI&II	7.55*	0.17	0.000	7.20	7.89
SS-IMRT PHI&II	S-IMRT PHI&II	-11.93*	0.17	0.000	-12.28	-11.59
	SS-SIB IMRT	-7.55*	0.17	0.000	-7.89	-7.20

* The mean difference is significant at the 0.05 level.

Table 4: Overall ANOVA results for skin volume to receive 20 Gy

ANOVA					
V20					
	Sum of Squares	df	Mean Square	*F*	Sig.
Between Groups	5320.40	2	2660.20	2431.75	0.00
Within Groups	236.29	216	1.09		
Total	5556.70	218			

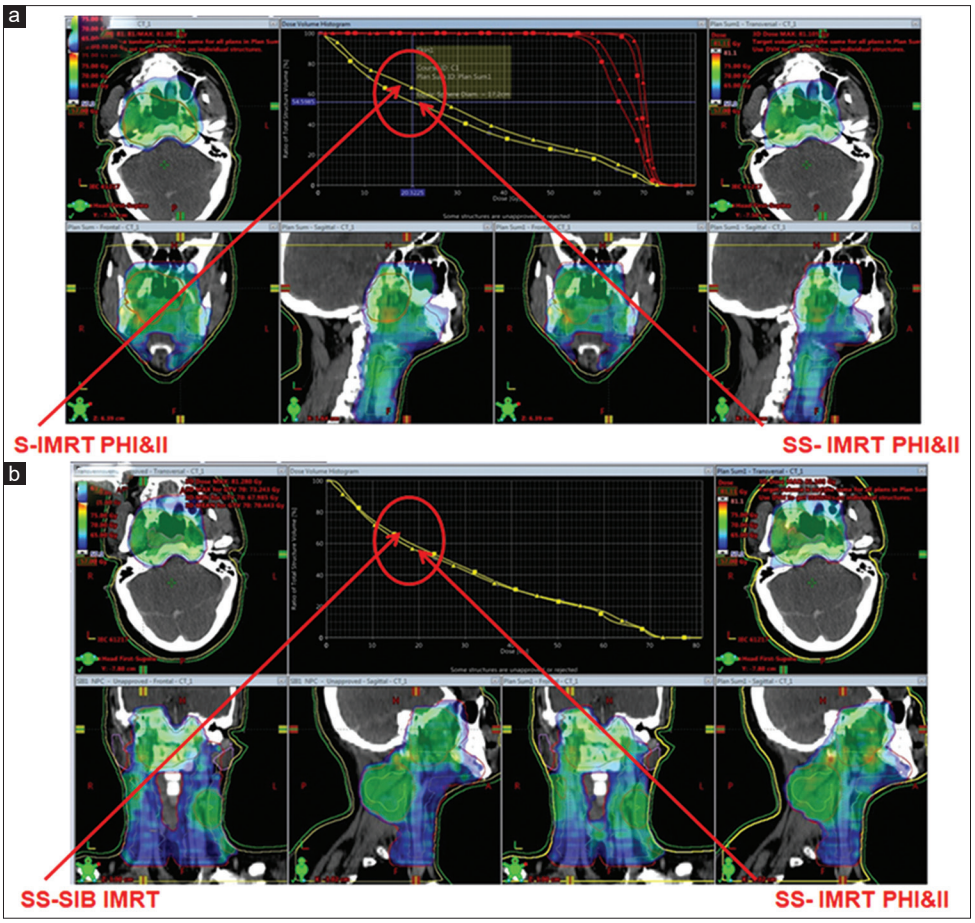

Figure 2: DVH and plan comparisons in multiplanner view (a) Conventional versus skin sparing IMRT plan (b) Skin spared IMRT versus skin spared SIB IMRT (SS-SIB) Plan, IMRT: Intensity modulated radiation therapy, SS-SIB: Skin Spared simultaneously instantaneous boost, DVH: Dose volume histogram

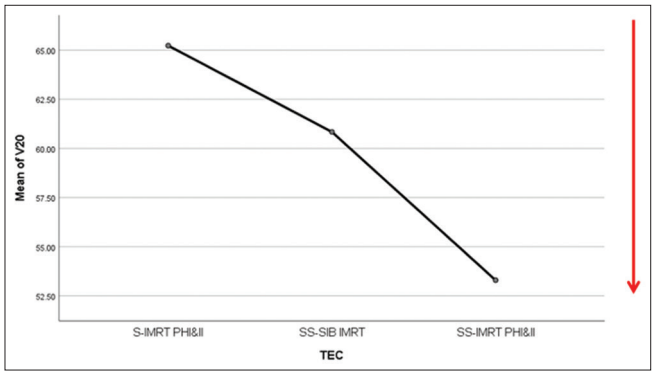

Figure 3: Graph showing the Mean Volume of skin to receive 20 Gy by three techniques

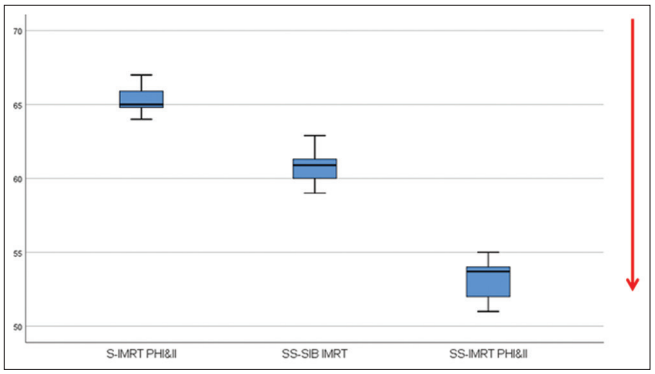

Figure 4: Box plot showing volume of skin to receive 20 Gy dose by three techniques

Results

Skin dose

When the skin was considered as an OAR the skin volume to receive 5, 10,15, 20, 30, 40, 50, 60, 70 Gy was reduced by 6.5%, 5%, 6%, 11.5%, 7%, 6%, 6%, 5%, 2%, respectively, by SS-IMRT PHI and II and 2%, 4.05%, 6%, 7%, 5%, 3%, 3%, 5%, 1%, respectively, by SS-SIB IMRT when compared with S-IMRT PHI and II. Table 1 shows percent volume of skin (Mean ± standard deviation [SD]) to receive different doses of radiation by the three IMRT techniques. Table 2 shows a one-way ANOVA result for Skin volume to receive 20 Gy. Table 3 describes test of significance between three techniques for volume of skin to receive 20 Gy. Table 4 shows overall ANOVA results for skin volume to receive 20 Gy. Figure 2 shows DVH comparisons as well as the IMRT plans in multiplanner view (a) Conventional versus SS IMRT Plan, (b) Skin Spared sequential IMRT versus skin

Table 5: Organs at risk dose in three techniques of intensity modulated radiotherapy were almost same ($P>0.05$)

	Mean dose (Gy)	SD	Significance (P)	95% CI for mean	
				Lower bound	Upper bound
Brain stem					
S IMRT	58.06	8.12	0.917	47.98	68.14
SS SIB IMRT	55.84	7.33		46.74	64.95
SS IMRT	56.54	10.02		44.09	68.99
Total	56.81	7.99		52.39	61.25
Chaism					
S IMRT	25.11	21.75	0.985	−1.89	52.12
SS SIB IMRT	22.85	19.75		−1.67	47.38
SS IMRT	24.28	21.15		−1.98	50.54
Total	24.08	19.37		13.35	34.81
Left choclea					
S IMRT	39.90	23.62	0.766	10.58	69.22
SS SIB IMRT	38.69	14.16		21.12	56.27
SS IMRT	32.10	14.63		13.92	50.28
Total	36.90	17.04		27.46	46.34
Right choclea					
S IMRT	35.90	19.92	0.980	11.16	60.64
SS SIB IMRT	36.38	19.24		12.48	60.27
SS IMRT	34.10	18.13		11.59	56.61
Total	35.46	17.72		25.64	45.27
Left eye					
S IMRT	24.26	20.74	0.912	−1.49	50.01
SS SIB IMRT	19.24	15.80		−0.38	38.86
SS IMRT	21.84	18.27		−0.85	44.53
Total	21.78	17.15		12.28	31.27
Right eye					
S IMRT	20.48	18.53	0.954	−2.53	43.49
SS SIB IMRT	17.01	18.04		−5.39	39.41
SS IMRT	19.08	17.23		−2.32	40.48
Total	18.86	16.68		9.62	28.09
Left lens					
S IMRT	4.078	2.36	0.854	1.15	7.01
SS SIB IMRT	3.346	1.63		1.32	5.37
SS IMRT	3.732	2.09		1.14	6.33
Total	3.718	1.92		2.65	4.78
Right lens					
S IMRT	3.348	1.64	0.974	1.31	5.38
SS SIB IMRT	3.145	1.36		1.45	4.84
SS IMRT	3.336	1.64		1.30	5.37
Total	3.276	1.44		2.48	4.07
Left optic nerve					
S IMRT	22.78	21.36	0.887	−3.74	49.30
SS SIB IMRT	16.96	16.54		−3.58	37.50
SS IMRT	21.36	20.37		−3.94	46.66
Total	20.37	18.27		10.25	30.48
Right optic nerve					
S IMRT	17.96	20.16	0.999	−7.07	42.99
SS SIB IMRT	17.88	20.87		−8.03	43.79
SS IMRT	17.46	20.21		−7.63	42.55
Total	17.77	18.90		7.30	28.23
Left parotid					
S IMRT	28.90	13.66	0.547	11.94	45.86
SS SIB IMRT	22.50	2.69		19.16	25.84
SS IMRT	26.25	7.09		17.44	35.06
Total	25.88	8.78		21.01	30.75
Right parotid					
S IMRT	20.84	5.49	0.921	14.02	27.66
SS SIB IMRT	21.09	6.29		13.27	28.90
SS IMRT	22.33	6.75		13.94	30.71
Total	21.42	5.78		18.22	24.62
Pitutary					
S IMRT	35.20	20.58	0.977	9.64	60.76
SS SIB IMRT	32.61	18.66		9.44	55.77
SS IMRT	34.56	20.53		9.07	60.05
Total	34.12	18.50		23.88	44.37
Spinal cord					
S IMRT	48.74	4.26	0.709	43.45	54.03
SS SIB IMRT	46.43	4.30		41.10	51.77
SS IMRT	48.22	5.06		41.93	54.51
Total	47.80	4.34		45.39	50.20

(Contd...)

Table 5: Contd...

S-IMRT: Sequential intensity modulated radiation therapy, SS SIB-IMRT: Skin spared simultaneously instantaneous boost intensity modulated radiation therapy, SS-IMRT: Skin spared sequential intensity modulated radiation therapy, SD: Standard deviation, CI: Confidence interval, PH: Phase

Table 6: Dose homogeneity index±standard deviation to planning target volume in three techniques of intensity modulated radiotherapy ($P>0.05$)

HI	S-IMRT PHI and II	SS SIB-IMRT	SS-IMRT PHI and II
Mean±SD	0.82±0.07	0.94±0.16	1.20±0.20
P		0.095	

SD: Standard deviation, HI: Homogeneity index, S-IMRT: Sequential intensity modulated radiation therapy, SS SIB-IMRT: Skin spared simultaneously instantaneous boost intensity modulated radiation therapy, SS-IMRT: Skin spared sequential intensity modulated radiation therapy, PH: Phase

spared SIB IMRT (SS-SIB) plan. Figure 3 shows graphically the difference in the mean volume of skin to receive 20 Gy by three techniques. Figure 4 depicts the volume of skin to receive 20 Gy dose by three techniques along with the Q1, Median and Q3 values of all 73 patients.

Other organs at risk dose

Rest of the OAR's dose was also analyzed by one-way ANOVA. There was no significant difference ($P > 0.05$) between the doses to OAR's among the three techniques. Table 1 shows the Mean ± SD, 95% confidence interval and significance values. Table 5 shows the dose received by different OARs by three techniques and the differences in the mean as P value.

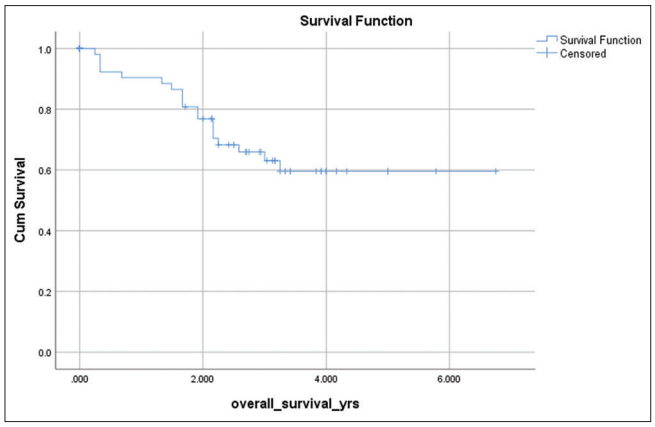

Figure 5: Overall survival of nasopharyngeal carcinoma

Figure 6: *In vitro* verification of dose difference to the skin by skin spared IMRT using Gafchromic film dosimetry, IMRT: Intensity modulated radiation therapy

Table 7: Dose confidence interval±standard deviation to planning target volume in three techniques of intensity modulated radiotherapy ($P>0.05$)

CI	S-IMRT PHI and II	SS SIB-IMRT	SS-IMRT PHI and II
Mean±SD	1.21±0.20	1.25±0.11	1.32±0.21
P		0.074	

SD: Standard deviation, CI: Confidence interval, S-IMRT: Sequential intensity modulated radiation therapy, SS SIB-IMRT: Skin spared simultaneously instantaneous boost intensity modulated radiation therapy, SS-IMRT: Skin spared sequential intensity modulated radiation therapy, PH: Phase

Planning target volume dose

The target dose was evaluated using Homogenity Index, described by RTOG formula given below, D2%, D98%, and D50%. There were no significant differences in the dose homogeneity between the three techniques. Table 6 shows the dose homogeneity indexes (HI) to PTV in three techniques. Target dose was also evaluated for conformity using the RTOG Formula described below, and there were no significant differences in dose conformity. Table 7 shows the dose conformity indexes to PTV in three techniques.

Homogeneity index=, Where D2%, D98%, D50% is the dose to 2, 98 & 50% volume of the target.

Conformity index $_{RTOG}$ = V_{RI}/TV, Where V_{RI} = Reference isodose volume (D95) and TV = Target volume.

Discussion

NPC accounts for the 2% of all the head and neck cancers.[2,10] Treatment modality is mostly radiotherapy[20] with a good survival rate.[21,22] During 2016–2021, a total of 114 NPC patients were registered at our institution, 73 out of 114 patients were enrolled in this study and were treated by intensity-modulated radiation therapy. The overall survival was 74% with a mean survival of 4.731 years [Figure 5 KP-survival]. All the patients received 60 Gy to PTV Intermediate and 70 Gy to PTV High at 2 Gy per fraction as recommended by various protocols.[17] Further, the feasibility of SS was assessed by re-planning all the 73 cases with skin as an OAR by skin spared IMRT and SIB IMRT and the differences in the various volumes to receive various doses from DVHs were quite significant. Skin volume to receive 5, 10, 15, 20, 30, 40, 50, 60, 70 Gy all reduced significantly when skin was considered as an OAR in the two SS IMRT techniques, but the volume to receive 20 Gy was maximally reduced by 11.5% in SS-IMRT PHI and II and 7% by SS-SIB IMRT (2, 3 and 4). Our results are consistent with a study done by Liao *et al*.[23] to evaluate the feasibility of a skin dose reduction in the treatment of NPC by comparing the skin dose reduction obtained by three different treatment modalities, i.e., IMRT, Volume modulated arc radiation therapy (VMAT) and helical tomotherapy with skin as an OAR without compromising the PTV dose. They concluded when skin was considered as an OAR the skin volume to receive more than 30 Gy was reduced by 3.7% by IMRT, 4.1% by VMAT, and 4.3% helical tomotherapy. In our case as we are not having higher state of art of radiotherapy delivery than IMRT, and our center being a resource limited center, we compared the simple IMRT plans with skin spared IMRT plans to reduce the dose to skin by some amount and found a significant decrease in the same. Another study on SS IMRT by Saibishkumar *et al*.[24] performed for early-stage breast cancer suggests that doses delivered to skin were significantly lower in plans with skin as an OAR and there was an overall reduction in skin dose from 57.8% to 12.2%. The reduction in dose was evaluated dosimetrically by thermoluminescence detectors measurements on anthropomorphic phantom. We also confirmed the dose reduction *in vitro* on anthropomorphic phantom by Gafchromic film dosimetry and found the dose differences of 10.9% ± 0.12% between simple IMRT and Skin Spared IMRT Plans [Figure 6]. The PTV dose evaluated for the HI to justify the SS without compromising the target dose also remained unvaried ($P > 0.05$). OARs other than skin also remained unvaried between the skin spared and nonskin spared IMRT techniques ($P > 0.05$) which is similar to the study done by Liao *et al*.[23]

Conclusions

SS IMRT for head and neck cancers can be useful to bring down the skin dose as well as the toxicities to some extent. This study also tried to apply the SS in IMRT and we found that a good amount of skin dose decreased in SS IMRT. Therefore,

we conclude that the skin should be contoured as an OAR for the IMRT planning of NPC s where the target is minimally 3–5 mm below the skin. The same strategy could be useful in other head and neck irradiations as far as the disease is not on the skin. Furthermore, this technique can yield lesser toxicities and less unplanned treatment interruptions which otherwise affects the overall treatment time and disease control

Limitations/future scope

The drawbacks of our study were that in this study we compared only treatment planning system calculated dose for SS by three techniques. In future SS IMRT irradiations for NPC could be evaluated for locoregional disease control, skin toxicities as well as the overall survival. Furthermore, TPS calculated skin doses can be measured *in vivo* to find the difference in the calculated and measured doses.

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Conflicts of interest

There are no conflicts of interest.

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