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An audit of Organ at Risk (OAR) constraints achieved for carcinoma of the nasopharynx treated with intensity modulated radiotherapy

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SUMMARY

Background: In Nasopharyngeal Carcinomas (NPC), due to its anatomical location and radio sensitivity, the primary treatment modality is radical radiotherapy. Intensity Modulated Radiotherapy (IMRT) provides excellent loco regional control and sparing of Organs at Risk (OARs) and it has become the technique of choice for radiotherapy of NPCs. Still late toxicities can occur in up to 40% of patients. The present study analyses the organ at risk doses achieved in patients with NPC treated with IMRT.

Materials and Methods: A retrospective audit of NPC treated with IMRT from January 2013 to August 2018 was done. The prescription dose for PTV HR, PTV IR and PTV LR were 69.3 Gy, 59.4Gy and 54 Gy respectively in 33 fractions. Concurrent chemotherapy was added for patients with stage II and above with Cisplatin 100 mg /m^2 every 21 days. OAR constraints were restricted to the tolerance doses as per the recommendations. The data was analysed for the degree of adherence to the recommended dose volume constraints for OARs and the correlation of achieved OAR doses against Gross Tumour Volume (GTV) of primary, nodes and total GTV was analysed using Pearson's correlation coefficient.

Results: Plans of 40 patients were analysed. Adequate target dose coverage (D95 for PTV HR, IR and LR) was achieved in the majority (93% of patients for PTV HD, 100% of patients for PTV ID and 98% of patients for PTV LD) of our patients. More than 80% of patients had met the dose constraints for brainstem, spinal cord, v69 of temporal lobe, v75 of mandible, eyes, optic chiasm and optic nerves. The achieved doses for parotids and temporal lobes in particular were higher. Significant positive correlation was noted for OARs close to the primary site against GTV primary and GTV total.

Conclusions: Adherence to the recommended dose volume constraints were achieved for optic and neuronal structures close to the primary site as well as for mandible in majority of patients. But a higher priority needs to be given for parotids and temporal lobes during radiation treatment plannings.

Key words: nasopharyngeal carcinoma, IMRT, OAR doses

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INTRODUCTION

Nasopharyngeal cancers comprise less than 1% of cancers in India [1]. The primary treatment modality for Nasopharyngeal Carcinomas (NPC) is radical radiotherapy as the anatomic location of the cancer provides limited surgical access. Moreover, these are relatively radiosensitive cancers. Intensity Modulated Radiotherapy (IMRT) has evolved as the technique of choice when compared with conventional two-dimensional radiotherapy, as it provides superior normal tissue sparing without compromising on disease control [2, 3].

The severity of adverse effects of radiotherapy is related to the dose to organs at risk (OARs) [4]. Although OARs sparing has improved significantly with IMRT, in up to 40% of patients, grade 2-4 xerostomia and sensorineural hearing loss can still occur [5, 6]. Total radiation doses and fraction size contribute to the development of radiation toxicities.

QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) guidelines are widely used to guide radiation tolerance limits to organs at risk. As the Gross Tumour Volume (GTV) increases the adherence to QUANTEC guidelines can become difficult. In this study we analysed the OAR doses achieved in patients undergoing IMRT for nasopharyngeal carcinoma, their degree of adherence to the recommended dose volume guidelines, and the relationship between OAR dose constraints achieved and GTV volume.

METHODOLOGY

This is a retrospective analysis of patients with nasopharyngeal carcinoma treated at our hospital with Volumetric Modulated Arc Therapy (VMAT) between January 2013 and August 2019. All patients were planned for radical chemo radiotherapy and underwent contrast CT scan for treatment planning. The scans were acquired with slice thickness of 3 mm after immobilising the patient in the planned treatment position, on a dedicated CT simulator (Optima GE). Three Clinical Target Volumes (CTV) were defined as follows. High Risk CTV (CTV HR) including GTV primary and GTV nodes with 1 cm expansion (edited for the normal anatomical barriers), intermediate risk CTV (CTV IR) including GTV primary with 1.5 cm expansion (edited for natural anatomical barriers), the nasopharynx, posterior one third of the nasal cavity, posterior one third of the maxillary

sinus, pterygoid fossae, parapharyngeal spaces, sphenoid sinus (the entire sinus was included only in patients with intracranial extension), foramen ovale, foramen rotundum, and clivus depending on the extent of tumour infiltration. The CTV IR was extended superiorly if there is intracranial extension, and included the cavernous sinuses and occasionally adjacent brain. The nodal regions with gross nodes were also included in the CTV IR. Low risk CTV (CTV LR) included retropharyngeal lymph nodes, bilateral cervical lymph nodes from level II to V in addition to the CTV IR. Three Planning Target Volumes (PTV) were defined. PTV HD (high dose PTV), PTV ID (intermediate dose PTV) and PTV LD (low dose PTV), by expanding the corresponding CTVs by 5 mm. Sample cases depicting the target volumes are shown in figure 1 and figure 2.

After delineation of target and OARs, treatment planning was done with VMAT, using the SIB (Simultaneous Integrated Boost) technique (Eclipse Version 13.6, Varian). The dose prescribed was 69.3 Gy to PTV HD, 59.4Gy to PTV ID and 54Gy to PTV LD given in 33 fractions. Concurrent chemotherapy was given with Inj. Cisplatin at a dose of 100 mg/m^2 every 21days.

Dose volume coverage for PTVs were approved and accepted in accordance with the recommendations from ICRU (International Commission on Radiation Units & Measurements). Ideal coverage is the one where 95% of the PTV receives 100% of the prescribed dose (v95 100%). This is not achievable in all cases and hence a dose distribution where 95% of the PTV received 95% of the dose (v95 95%) was considered acceptable. Dose Volume Histograms (DVH) of each OAR was evaluated, in accordance with the QUANTEC, RTOG 0255 (Radiation Therapy Oncology Group), and RTOG 0615 recommendations,

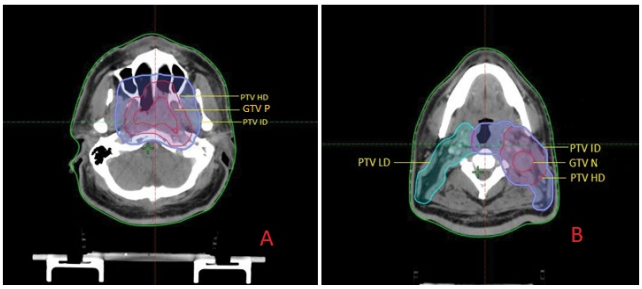

Fig. 1. (A) Axial section of planning CT scan image at the level of nasopharynx showing planning target volumes (PTV). (B) Axial section of planning CT scan image at the level of gross nodes showing PTVs. PTV HD- High Dose PTV, PTV ID -intermediate dose PTV, PTV LD-low dose PTV, GTV P- gross tumour volume primary, GTV N- gross tumour volume nodes

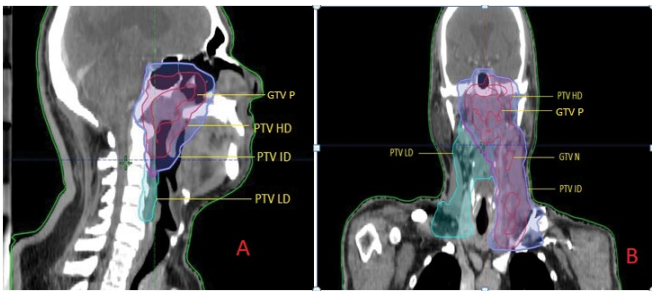

Fig. 2. (A) Sagital section of planning CT scan image showing Planning Target Volumes (PTV). (B)Coronal section of the planning CT scan depicting PTVs. PTV HD- high dose PTV, PTV ID -intermediate dose PTV, PTV LD-low dose PTV, GTV P- gross tumour volume primary, GTV N- gross tumour volume nodes

and the plans satisfying the criteria was approved for treatment. The demographic and clinical data including age, gender, TNM stage, and treatment details were collected from patient's case records. Treatment plans and DVH parameters of PTVs and OARs were retrieved from the treatment planning system (Varian Eclipse).

The patients were categorised according to their total Gross Tumour Volume (GTV) into four groups <30 cc, 30 cc-60 cc, 60 cc-90 cc and >90 cc. The average dose received by OARs in the study population as a whole, and in the four groups were analysed. The degree of adherence to the recommended dose constraint guidelines were analysed according to whether the dose constraint achieved for each OAR is less than or equal to 100%, between 100% and 110% or more than 110% of the recommended dose.

STATISTICAL ANALYSIS

Descriptive statistics were used for expressing the demographic and treatment details. Pearson's correlation coefficient test was used to find out the correlation between dose volume parameters of OARs with GTV primary, GTV nodes and GTV total in the 4 GTV groups and the study population as a whole. The data was analysed using the SPSS statistical software, version 20.0.

RESULTS

Between January 2013 and August 2019, a total of 40 patients with NPC were treated with radical radiotherapy at our centre. The median age was 51.5y (19y - 70y). Among the 40 patients, 22 (55%) patients had a clinical stage 4 disease (Table 1). All patients received concurrent chemotherapy with Cisplatin 100 mg/m^2 every 21 days.

Among the 40 patients, 37 (92.5%) patients were prescribed a PTV Dose of 69.3 Gy/33# and remaining 3 patients (7.5%), 70 Gy/35#. Majority of patients achieved the planning goals of target coverage of at least v95 of 95% (%volume receiving 95% of the prescribed dose of 69.3Gy, 59.4Gy and 54Gy to PTV HD, ID and LD respectively). The target coverage of at least v95 of 95% was achieved for 93% of patients for PTV HD, 100% of patients for PTV ID and 98% of patients for PTV LD. Average v95 was 97.8% for PTV HD, 99% for PTV ID and 97% for PTV LD.

The Dose Maximum (Dmax) was 115% of the prescribed dose of 69.3Gy which occurred in one patient, but the v115 (%volume receiving 115% of the prescribed dose) was only <1% of the irradiated volume. All other patients had a Dmax less than 115% of the prescribed dose (108% to 114.7% of the prescribed dose of 69.3Gy). Only 4 patients had v110 ((% volume receiving 110% of the prescribed dose) >1% (Table 1).

In order to find out the degree of adherence of dose volume constraints achieved for each OAR to the recommended dose volume parameter, and to analyse the excess dose received by each OAR, the dose received by each OAR was classified into whether the achieved dose is </= 100%, 101%-110% or >110% of the recommended dose. Table 2 shows the OAR doses achieved as a percentage of the recommended dose.

Tab. 1. Demographic and treatment details of patients with nasopharyngeal carcinoma treated with concurrent chemo radiation

Age	**Median 51.5y(19y- 70y)**		
		n	%
Age group	<40 yrs.	7	17.5
	41-60 yrs.	24	60
	>60yrs	9	22.5
Stage	I	0	0
	II	9	22.5
	III	9	22.5
	IV	22	55
Dose prescription	69.3 Gy/33#	37	92.5
	70Gy/35#	3	7.5

Tab. 2. Dosimetric parameters and adherence of OAR dose constraints against recommended dose in patients with nasopharyngeal carcinomas

OAR	**DoseVolume Constraint**	**≤ 100% n(%)**	**101%-110% n(%)**	**>110% n(%)**
Brain stem	#Dmax 54Gy	32 (80)	5 (12.5)	3 (7.5)
Spinal cord	#Dmax 45Gy	38 (95)	1 (2.5)	1 (2.5)
Temporal lobe(r)	#Dmax 68Gy	14 (35)	18 (45)	8 (20)
	*V69<1cc	34 (85) (V69<1cc)	6 (15)(V69>1cc)	
Temporal lobe (l)	#Dmax 68Gy	12 (30)	16 (40)	12 (40)
	*V69<1cc	26 (65) (V69<1cc)	14(35)(V69>1cc)	
Mandible	#Dmax 70Gy	4 (10)	32(80)	4(10)
	$V75<1cc	36 (90)(V75<1cc)	4(10)(V75>1c)	
Lens(r)	#Dmax 7Gy	10 (25)	2(5)	28(70)
Lens(l)	#Dmax 7Gy	6 (15)	5(12.5)	29(72.5)
Eye(r)	**Dmean 35Gy	38 (95)	1(2.5)	1(2.5)
Eye(l)	**Dmean 35Gy	38 (95)	1(2.5)	1(2.5)
Parotid(r)	**Dmean 25Gy	3 (7.5)	2 (5)	35(87.5)
	##V30- 50%	21 (52.5)	4 (10)	15(37.5)
Parotid(l)	**Dmean 25Gy	3 (7.5)	1 (2.5)	36(90)
	##V30-50%	11 (27.5)	3 (7.5)	26(65)
Optic chiasm	#Dmax 55Gy	34 (85)	6 (15)	0
Larynx	#Dmax 44Gy	20 (50)	9 (22.5)	11(27.5)
Oral cavity	$$D1cc(Gy)<70	18 (45)(D1<70Gy)	22 (55)(D1>70 Gy)	
Pituitary	#Dmax 45Gy	6 (15)	2 (5)	32 (80)
Optic nerve(r)	#Dmax 55Gy	35 (87.5)	1 (2.5)	4 (10)
Optic nerve(l)	#Dmax 55Gy	36 (90)	4 (10)	0
Constrictors	**Dmean 50Gy	2 (5)	1 (2.5)	37 (92.5)
Middle ear(r)	**Dmean 45Gy	18 (45)	4 (10)	18 (45)
Middle ear(l)	**Dmean 45Gy	21(52.5)	4 (10)	15 (37.5)
Inner ear(r)	**Dmean 4Gy	18 (45)	4 (10)	18 (45)
Inner Ear(L)	**Dmean 45Gy	20 (50)	4 (10)	16 (40)
Esophagus	###V45<33%	9 (22.5)	0	31 (77.5)
Brainstem PRV#$	#Dmax 60Gy	12 (30)	18(45)	10 (25)
Spinal cord PRV #$	#Dmax 50Gy	11(27.5)	23 (57.5)	6 (15)

#Dmax- Dose maximum, *V69-volume receiving 69Gy, $V75-volume receiving 75Gy, **Dmean- dose mean, ##V30-volume receiving 30Gy, $$D1cc (Gy)-dose to 1cc volume, ###V45-volume receiving 45Gy, #$ PRV- planning organ at risk volume

More than 80% of patients had achieved a dose of less than or equal to the recommended dose constraints for brainstem, spinal cord, temporal lobe, mandible, eyes, optic chiasm and optic nerves.

In more than 70% of the patients, the lens received 110% of the recommended dose of 700cGy. Dose to parotids was more than 110% of the recommended dose of Dmean (dose mean) of 25Gy, in more than 85% of the patients. In more than half of the patients, the v30 to 50% of the parotids was more than 110%. Similarly, the doses were more than 110% of the recommended dose in the majority of patients for oral cavity, pituitary, pharyngeal constrictors and esophagus.

The relationship of DVH parameters of OARs with the GTVs including GTV primary (GTV P), GTV nodes (GTV N) and total GTV (GTV T) were analysed. Patients were grouped into 4 groups based on the total GTV (GTV T) volume into Group 1 <30cc, Group 2 30-60cc, Group 3 60-90cc and Group 4 >90cc. The mean doses achieved for OARs in the study population as a whole, and in the four GTV groups are detailed in table 3.

The OARs which showed a significant positive correlation with the three GTVs in the study population as a whole and in the 4 GTV groups are shown in table 4. For the study population as a whole, significant positive correlation was noted with GTV primary for brainstem, brainstem PRV (planning organ at risk volume), spinal cord, spinal cord PRV, lens, parotids v30, pituitary and optic nerves. A positive correlation was also noted

Tab. 3. Mean doses achieved for OARs in patients with nasopharyngeal carcinomas against GTV

		Mean OAR doses(Gy)				
OAR	DoseVolume constraint	Total# (n= 40)	Group1# (n=11)	Group2# (n=13)	Group3# (n=12)	Group4# (n=4)
Brain stem	#*Dmax 54 Gy	51.86	50.95	50.74	51.76	58.34
Spinal cord	#*Dmax 45 Gy	41.96	42.01	40.34	44.22	40.24
	#*Dmax 68 Gy	70.62	70.58	69.63	71.1	72.48
Temporal lobe(r)	*V69<1cc	0.75cc	0.25cc	0.38cc	1.7cc	0.5cc
	#*Dmax 68 Gy	69.45	68.11	67.6	72.41	70.31
Temporal lobe(l)	*V69<1cc	1.3cc	1cc	0.7cc	2cc	1.3cc
Mandible	#*Dmax 70 Gy	74.61	75.17	74.25	74.84	73.57
	$V75<1cc	0.4cc	0.2cc	0.5cc	0.5cc	0.3cc
Lens(R)	#*Dmax 7 Gy	14.29	14.82	12.05	13.2	23.4
Lens(L)	#*Dmax7 Gy	14.9	16.51	10.87	14.21	25.62
Eye(R)	**Dmean 35 Gy	15.24	16.75	10.63	15.25	26
Eye(L)	**Dmean 35 Gy	14.77	17.08	10.41	14.61	23.02
Parotid (R)	**Dmean 25 Gy	39.77	37.89	37.91	41.65	45.3
	##V30-50%	54%	54%	49%	56%	68%
Parotid(L)	**Dmean 25Gy	4248	4842	3624	4283	4535
	##V30-50%	69%	79%	59%	67%	87%
Optic chiasm	#*Dmax 55 Gy	3998	4233	2805	4597	5427
Larynx	#*Dmax 44 Gy	4588	4716	4305	4526	5338
	#*Dmax 30 Gy	47.26	4846	4684	4649	4761
Oral cavity	$$D1cc(Gy) <70	71Gy	71.5Gy	71Gy	70Gy	71.5Gy
Pituitary	Dmax45 Gy	59.55	65.96	48.2	6434	64.39
Optic nerve(r)	#*Dmax55 Gy	39.08	39.98	32.32	4321	48..84
Optic nerve(l)	#*Dmax55 Gy	39.15	43.61	30.11	4223	4705
Contrictors	#*Dmax45Gy	61.45	64.45	60.85	62.91	67.71
Middle ear(R)	**Dmean45Gy	46.84	47.74	43.01	48.73	51.11
Middle ear(L)	**Dmean45 Gy	44.86	44.5	4332	45.93	47.65
Inner ear(R)	**Dmean45 Gy	47.95	48.11	4690	50.61	42..95
Inner ear(L)	**Dmean45 Gy	47.32	48.28	4577	52.16	35.25
Esophagus	###V45<33%	47%	60%	43%	37%	54%
Brainstem PRV#$	#*Dmax60 Gy	62.79	62.63	62.65	62.68	64.27
Spinalcord PRV#$	#*Dmax50 Gy	52.87	51.91	51.13	55.2	54.18

#Total GTV (GTV T) volumes : Group 1 <30cc, Group 2 30-60cc, Group 3 60-90cc, Group 4 >90cc. #* Dmax- dose maximum, *V69-volume receiving 69Gy, $V75-volume receiving 75Gy, **Dmean- dose mean, ##V30- volume receiving 30Gy, $$D1cc(Gy)-dose to 1cc volume, ###V45-volume receiving 45Gy, #$ PRV- planning organ at risk volume

Tab. 4. OARs with significant positive correlation with GTV groups in patients with nasopharyngeal carcinoma

GTV group	GTV primary		GTV total	
	Organ	**p value**	**Organ**	**p value**
Group1 (GTV total<30cc)	Lens	0.02		
	Eyes	0.037	Parotid v30	0.048
	Spinal Cord prv	0.02		
Group2 (GTV total30-60cc)	Eyes	0.036	Mandible	0.009
	Optic nerve	0.04	Oral cavity D1cc(Gy)	0.027
	Spinal cord prv	0.02	Optic nerve	0.04
Group3(GTV total 60-90cc)	Optic nerve	0.04	Eyes	0.047
	Brain stem prv	0.03	Oral cavity D1cc(Gy)	0.036
Group 4 (GTV Total>90cc)	None		None	
Study Population As A Whole	Brain stem	0.02	Eye	0.03
	Brain stem prv	0.003		
	Spinal cord	0.012		
	Spinalcordprv	0.08		
	Lens	0.002		
	Parotid v30	0.036		
	Optic nerve	0.004		
	Pituitary	0.002		

for eyes against GTV total. In group 1, a significant positive correlation was noted for lens, eyes and spinal cord PRV

against GTV primary and parotid v30 against GTV total. In group 2, significant positive correlation was noted for eyes, optic nerve and spinal cord PRV against GTV primary and for mandible, oral cavity D1(Gy) and optic nerve against GTV total. In group 3, significant positive correlation was noted for optic nerve and brainstem PRV against GTV primary; There was also a significant positive correlation between eyes and oral cavity D1cc (Gy)[dose to 1cc volume] with GTV total in this group. In group 4, no positive correlation was noted for any OARs against GTV primary, GTV nodes and GTV total.

DISCUSSION

Though IMRT is the widely used advanced radiation technique for the management of nasopharyngeal carcinoma, its effectiveness in sparing OARs around nasopharynx such as temporal lobe, parotid and cochlea is largely unclear. The data on the relationship between GTV and excess rates of dose to the OARs are also sparse. We did this study to analyse the dose received by organs at risk in patients receiving radiotherapy for nasopharyngeal cancer, the achieved degree of adherence to recommended dose constraints, and also the dose distribution achieved in target volumes.

In the majority of our patients, the desired target coverage was achieved for PTV HD, ID and LD. The target coverage of at least v95 of 95% was achieved for 93% of patients for PTV HD, 100% of patients for PTV ID and 98% of patients for PTV LD. Only 4 patients had a v110 of more than 1%. All except one patient had a dose less than 115% of the prescribed dose of 69.3Gy.

The dose distribution of OARs with respect to various GTVs in NPC patients treated with IMRT was prospectively analysed by Ji-Jin Yao et al in China [7]. The study showed that, with a larger GTV the radiation dose to OARs increased significantly, and GTV was a useful predictor of radiation dose to OARs around the nasopharynx. The OARs like spinal cord,optic nerve, mandible, TM joint, eye, oral cavity and pharynx Constrictors were able to tolerate radiation dose easily.

In our study, recommended doses were achieved for OARs around the nasopharynx (brainstem, spinal cord, optic chiasm, optic nerves, eyes and mandible) in more than 80% of the patients. One reason for the above result could be the high priority given for these OARs, especially the neuronal structures, during radiation treatment planning. Positive significant correlations were noted for OAR doses with volume of GTV primary for those OARs close to the primary site. Hence, as the volume of GTV primary increases, the doses to OARs around the primary site increases. GTV total also correlated positively with the OARs around the primary site.

No significant positive correlations were observed for all OARs with GTV nodes except for brainstem PRV in group 3 patients.

Another observation in our study was that both dose volume constraints for parotids including Dmean and v30 <50% were not achieved in the majority of our patients. One reason for not achieving the dose volume constraint could be the close proximity of the GTVs to parotids, especially so when the primary is large and when there are enlarged jugulodigastric lymph nodes. Assigning a higher priority for the parotids during radiation treatment planning might be effective in reducing parotid doses.

The factors influencing the parotid function in NPC treated with parotid sparing radiotherapy were studied by Wen-Shan Liu et al. They observed that the mean dose to the parotid gland was the most important factor that influenced parotid function. The parotid function could recover one year after parotid sparing radiotherapy [8].

The use of parotid sparing IMRT for preserving the parotid function for NPCs was also studied by Ching-Yeh Hsiung et al. [9]. They used salivary scintigraphy to quantitatively analyse preserved parotid function after IMRT and compared with historical data after conventional radiotherapy. A significant dose-function relationship was noted for the parotid gland. Significant preservation of parotid function was achieved with IMRT for NPC patients.

Another organ which needs more attention is the temporal lobe. A potentially lethal complication of the central nervous system that can occur in patients treated with radiotherapy for NPC is the temporal lobe radiation necrosis [10].The incidence of brain radiation necrosis increases as doses exceed 60 Gy in conventional fractionation. In our study, only 35% of patients achieved a dose of less than or equal to 100% of the recommended maximum dose of 68Gy. However, the constraint of v69<1cc was achieved in 85% of the patients. Hence, a higher priority should be considered for temporal lobes during radiation treatment planning for NPC.

The dose volume parameters of oral cavity, pharyngeal constrictors, pituitary and esophagus were more than 110% of the recommended dose in the majority of patients. But no significant positive correlation could be observed for these OARs against GTV primary, GTV nodes or GTV total. One of the limitations of our study is the small number of patients which is probably the reason for not observing a positive correlation for these instances. Since carcinoma of nasopharynx is rare compared to endemic areas, multicentric studies may be required in order to observe a statistically significant correlation.

CONCLUSIONS

In our study, adequate target dose coverage was achieved in the majority of patients for PTV HD, PTV ID as well as PTV LD. Adherence to the recommended dose volume constraints were noted for neuronal structures close to the primary site as well as for eyes and mandible in the majority of patients. Significant positive correlation was also noted for OARs close to the primary site with GTV primary and GTV total. The achieved doses for parotids and temporal lobes in particular were higher. Hence, a higher priority needs to be given for parotids and temporal lobes during radiation treatment planning.

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