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Assessment of feasibility of cochlear sparing optimized radiotherapy in nasopharyngeal squamous cell carcinoma using high conformal radiation technique

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ABSTRACT

Background: One of the most prevalent head-and-neck tumors in Southeast Asia is nasopharyngeal carcinoma (NPC). Each year, NPC causes 84,400 new cases and 51,600 fatalities worldwide. Intensity-modulated radiation therapy (IMRT), which has good local control and few side effects on healthy tissue, is being used to treat NPC. **Aims and Objectives:** Our study aims to assess the feasibility of cochlear sparing using volumetric-modulated arc therapy/IMRT technique. **Materials and Methods:** Radiotherapy plans of 20 patients diagnosed with NPC who received curative concurrent chemoradiation (Weekly Cisplatin dose of 40 mg/m^2) with RT dose of 66 −70 Gy at 1.8–2 Gy/# to a total of 33–35# delivered using True beam LINAC between the year 2020 and 2022 were analyzed retrospectively. **Results:** Cochlea sparing reoptimization led to a considerable reduction in radiation dose for both cochleae as compared to the original treatment plans. The median D mean and D max for the left and right cochlea was found to be decreased. The difference in planning target volume (PTV)-D mean between the original and reoptimized plans was negligible. After reoptimization, the median PTV CI remained unchanged. The sparing of the left and right parotids and brain stem was not improved by reoptimization. A similar event was noted for the spinal cord, where the change from the median D max was not statistically significant. **Conclusion:** Our investigation showed that a much-increased cochlea sparing is possible in the majority of patients while maintaining PTV dosage coverage and the other organs at risk. Clinical trials in the future, both retrospective and prospective, should examine the effects of this optimization.

Key words: Nasopharyngeal carcinoma; Radiotherapy; Cochlea; Organs at risk

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INTRODUCTION

One of the most prevalent head-and-neck tumors in South-east Asia is nasopharyngeal carcinoma (NPC). Each year, NPC causes 84,400 new cases and 51,600 fatalities worldwide.[1] Intensity-modulated radiation therapy (IMRT), which has good local control and few side effects on healthy tissue, is being used to treat NPC. It is difficult to protect the organs at risk (OARs) when developing IMRT for locoregionally established NPC without sacrificing the tumor coverage in advanced lesions.

Due to the location of the tumor, radiation-induced sensorineural hearing loss (SNHL) is a common side effect of radiotherapy (RT) and has a significant detrimental influence on the quality of life of patients with NPC. In a recent study, radiation-induced SNHL occurred in 37% of patients receiving IMRT.[2]

Even though the mean or median cochlear dose has been discussed in many trials, but the exact threshold dose has not been set.[3] Prospective findings revealed that the overall radiation the inner ear receives was related to hearing loss.[4]

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Patients have experienced the synergistic ototoxic impact of radiation along with ototoxic drugs especially cisplatin.[5]

Aims and objectives

A clear and unequivocal "safe" dose to the cochlea has not yet been determined due to its small volume. With this study, we want to assess the feasibility of cochlear sparing using volumetric-modulated arc therapy (VMAT)/IMRT technique.

MATERIALS AND METHODS

After getting approval from the institutional review board, 20 RT plans of patients diagnosed with NPC who received curative concurrent chemoradiation (Weekly Cisplatin dose of 40 mg/m^2) with RT dose of 66–75 Gy at 1.8–2 Gy/# to a total of 33–35# delivered using True beam LINAC between the year 2020 and 2022 were analyzed retrospectively.

Patients received care using the dynamic IMRT (n=15) or VMAT (n=5). One VMAT plan and four dual arc plans were completed. Six MV photons with single doses of 1.8–2.0 Gy and a mean administered dose of 67.2 Gy (range 66–70 Gy). Individual thermoplastic masks were used to keep the patient still during the planning CT, which was collected with a 2 mm slice thickness. In every case, the cochleae were recontoured in accordance with an international consensus recommendation.[6] All other OAR, as well as target volumes, remain unaltered. As part of a PRV strategy, the cochlea structures were extended by a margin of 3 mm. To protect the cochlea as much as feasible without sacrificing planning target volume (PTV) coverage or any other aspect of a high-quality plan, the original treatment plans were then optimized and generated in Eclipse treatment planning system (Version 15.6, Varian, Palo Alto, USA). Each patient received a unique VMAT/IMRT treatment plan with a maximal dosage rate of 600 monitor unit (MU)/min and photon energy of 6 MV. All plans were treated in sequential boost technique.

With VMAT/IMRT, the initial plans that sought a mean cochlear dosage of 45 were reoptimized without sacrificing the target volume coverage.

Statistical analysis

Mean cochlea dosage, PTV coverage, D2%, D98%, D max, Homogeneity Index (HI) (defined as [D2–D98%]/D prescribed), RTOG's Conformity Index (CI: Conformity Index=VRI/TV),[7] and dose to different OARs were compared with the reference plans. P<0.05 was regarded as significant when using the Wilcoxon signed rank test to assess the difference. In IMRT, seven or nine fields with an increment of 50 or 40 degrees gantry angle were employed, however in PTV, one or two coplanar arcs were used depending on the complexity and location of the PTV (Figure 1). On the basis of Beams Eye vision, various collimator angles and jaw openings were also built (BEV). VMAT and IMRT schemes both employed jaw tracking.

Figure 1 provides an illustration of how the initial and reoptimized plans might be compared.

RESULTS

In our study, we analyzed a total of 20 RT plans of NPC patients who received curative concurrent chemoradiation (Table 1). The median total volume of cochlea outlines was 0.156 mL, which is in line with the literature's range of 0.13–0.56 cc.[4,8]

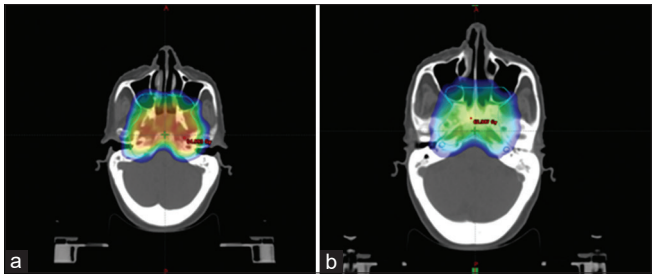

Figure 1: Comparison of original (a) and cochlea reoptimized plan (b)

Table 1: Data from the radiotherapy plans of patients diagnosed with NPC

Characteristic	Value
Total (n)	20
Age	(16–65)
Gender	
Male	11
Female	9
Mean cochlea volume (cm^3)	
Left cochlea	0.15
Right cochlea	0.16
Mean prescription dose	67.20 (66–70 Gy)
CCRT	20
Performance status	
ECOG 1	15%
ECOG 2	85%
T stage	
T1	0
T2	25%
T3	40%
T4	35%
N stage	
N0	15%
N1	30%
N2	40%
N3	15%
M status	
M0	100%
M1	0

The median D mean for the left cochlea decreased from 53.901 Gy (range: 17.7–73.1 Gy) to 30.747 Gy (range: 2.435–66.6 Gy, P=0.005) and right cochlea from 47.9 Gy (range 17.7–69.9 Gy) to 29.082 Gy (range.1.544–66.162 Gy, P=0.001). The median D max for the left cochlea was decreased from 59.119 to 38.8445 Gy (P=0.001), D max for the right cochlea from 54.55 to 37.858 Gy (P=0.0002). For 18/20 patients, it was possible to attain bilateral cochleae doses at 45 Gy in the optimum programs. The difference in PTV-D mean between the original and reoptimized plans was negligible (67.897 and 67.98 Gy, P=0.347). The median PTV HI was 0.095 for the original plans and 0.070 for re optimized plans (P=0.001). After reoptimization, the median PTV CI of 0.93 remained unchanged. The additional OARs had to adhere to the same restrictions as the original plans because the reoptimized plans were to be suitable for clinical application. Table 2 offers a comparison of the most significant OARs. The sparing of the left and right parotids and brain stem were not improved by reoptimization from a median D mean of 38.15–38.374 Gy (left parotid, P=0.872) and 43.25–37.608 Gy (right parotid, P=0.0.596), D mean of the brainstem (median of 50.59–50.81 Gy=0.965). A similar event was noted for the spinal cord, where the change from the median D max of 27.95 Gy–29.519 Gy was not statistically significant (P=0.109). Cochlea sparing reoptimization led to a considerable reduction in radiation dose for both cochleae in contrast to the original therapeutic strategy (Table 2).

DISCUSSION

In the present era of therapeutic treatments aiming at greater quality of life for cancer patients, reducing late treatment-related complications is becoming increasingly significant. One of the main adverse long-term consequences of radiation therapy for the nasopharynx is severe hearing damage, which is influenced by a number of variables, including chemotherapy, age, fractionation, and dosage to the auditory system. The cochlea is shown to be the component that is most radiosensitive with a 2/3 ratio. Tinnitus and radiation-induced SNHL are two potential side effects of radiation exposure to the cochlea. Significant SNHL has been shown to occur in up to 50% of radiation therapy patients for the nasopharynx, according to serial audiological examinations. The primary cause of this phenomenon is the irreversible degeneration of the auditory sensory hair cells of the organ of Corti, especially the higher-frequency outer hair cells. Despite significant investigation, there are still no data that clearly define the dose threshold for cochlea toxicity.

Nasopharyngeal cancer has a convex and concave tumour target, which makes IMRT preferable for NPCs with variable tumor shapes as IMRT produces a dosage distribution that conforms to the contour of the tumor, which enhances local tumor control and lessens damage to OARs. The advantages of IMRT, however, are not without drawbacks because, when attention is focused on delivering a high dose to the tumor site, an additional high dose will be delivered to surrounding tissues.

Hearing loss is a common and serious effect following NPC radiation because it is widely known that the cochlea functions as a crucial component of the acoustic system. Patients' quality of life is still at risk even if cochlea dose limits were taken into account in the QUANTEC data,[9] which revealed that the incidence of SNHL was 30% higher when the cochlea's average dosage was under 4500 cGy. QUANTEC proposed a minimum cochlea dosage

Table 2: Comparison of cochlea sparing in optimized and original treatment plans

Organ dosimetry	Original treatment plan (Median value)	Optimized treatment plan (Median value)	P-value
Left cochlea D mean	53.901 (17.1–73.1)	30.747 (2.435–66.6)	<0.0005
Right cochlea D mean	47.9 (17.7–69.9)	29.082 (1.544–66.162)	0.001
Left cochlea D max	59.119 (17.7–70.2)	38.8445 (3.238–65.6)	<0.0001
Right cochlea D max	54.55 (17.7–74.7)	37.858 (1.89–68.925)	<0.0002
PTV D mean	67.897	67.98	0.34
PTV CI	0.93 (0.91–0.94)	0.94 (0.92–0.96)	0.046
PTV HI	0.095 (0.05–0.13)	0.075 (0.05–0.13)	0.003
PTV D2%	71.586 (70.136–79.398)	71.413 (69.34–79.398)	0.756
PTV D98%	66.985 (63.033–70.897)	67.288 (60.18–78.4)	0.347
Brainstem D mean	25.545 (8.9–37.7)	31.6 (0–36.071)	0.362
Left parotid D mean	38.15 (15.6–72.9)	38.374 (15.6–65.1)	0.872
Right parotid D mean	43.25 (15.4–70.1)	37.6085 (15.5–65.039)	0.596
Spinal cord D max	27.95 (09–34.5)	29.51 (12.6–36.08)	0.109
Left optic nerve D mean	33 (03–72.621)	29.63 (3.2–72.35)	0.638
Right optic nerve D mean	26.95 (03–55.6)	25.05 (3.1–55.229)	0.779
Left eye D mean	09 (1.9–63.2)	8.373 (2.3–64.753)	0.596
Left eye D mean	7.3 (1.9–25.2)	8.042 (2.2–34.445)	0.197
Mandible D max	44.45 (25.2–69.00)	42.824 (0.00–61.20)	0.936

P<o.o5=Significant

restriction of 4500 cGy or less because the cochlea has not previously been thought of as one of the important OARs to administer a lower dosage to maintain the ability to hear.

Cochlea damage has not been considered as endangering the quality of life of patients like OARs such as the brainstem, spinal cord, ocular organs, and salivary glands. Cochlear sparing cannot be done uniformly in all cases of NPC due to its dependence on distance from the tumour location. Also the dose to the cochlea changes significantly based on the tumor's bulk and various T stages. Theunissen et al.,[10] reported that in IMRT for head-and-neck malignancies, the mean dosage to the cochlea was 1780 cGy (100–6660 cGy), but we noticed a mean dosage of 4460±1230 cGy and a D max of 5780±1880 cGy in the cochlea in our IMRT practice practice for NPC.

Wang et al.,[5] studied the association between hearing loss and cochlea dose and found that a substantial rise in the occurrence of SNHL was seen in individuals who received cumulative cisplatin doses, secretory otitis media, and a minimum radiation dosage to maximal dosage volume (D=0.1 mL) in the cochlea, which was 3980 cGy. Contrarily, in some other studies, it was recommended that the cochlea be limited to 5% of its volume to be below 5500 cGy for the treatment of other brain illnesses. However, it appears that these findings were not appropriately applied to radiation treatment for all patients with NPC.

Yao et al.,[11] examined the dose distribution of OARs in an effort to maintain hearing ability while receiving NPC IMRT treatment. The cochlea was identified as an OAR, along with the parotid glands, which met tolerance in NPC patients with difficulty. They also discovered that radiation exposure to OARs was related to the T stage and, particularly, gross tumor volumes. Gao et al.,[12] discovered a statistically significant distinction between both the groups in the cochlea mean dosage when they compared Smartarc-based VMAT-S with step-and-shoot IMRT for locoregionally advanced nasopharyngeal cancer, which was 4380±360 cGy and 4780±400 cGy, respectively. By reducing the typical dose given to the auditory system or putting on more protective weight, Wang et al.,[5] attempt to reduce the dose to the auditory organs was successful in lowering the mean dose to the auditory system from 3855–5391cGy to 2960–4560cGy and from 3855–5391cGy to 2730–4270 cGy, respectively.

The improved homogeneity and conformity of VMAT-S, RapidArc, or tomotherapy compared with IMRT in Gao et al.,[12] and Lee and Fang[9] study, as well as greater cochlea preservation, may be attributable to the excellent feature of how modern machines distribute dose. However, in a situation without volumetric-modulated RT equipment, IMRT can still yield results for CI and HI that are almost identical to or acceptable. Both the VMAT and IMRT plans employed in our investigation considerably decreased the cochlea dose.

Wang et al.,[5] found that the subregion dose restrictions group had a better dose distribution than the weight upgrading group because the subregion dose constraints group's isodose lines had shifted, exposing the hearing organs to a lower dose than in the weight upgrading group. In our study, there was no discernible difference between the target coverage criteria for the cochlea-sparing plan and the standard plan, including D98%, D95%, D50%, D2%, and D mean (mean dose). There was no discernible difference in the effects of cochlea sparing on the spinal cord and brainstem in terms of D2%, D mean, or D max, and the same was true for other OARs such as the parotid, optical nerve, lens, and optical chiasm.

The best target coverages, such as maximum dosages to the mandible or brainstem or the average dosage to the oral cavity, were attained without sacrificing the cochlea. These target coverages were not substantially different between the original and reoptimized treatment plans. Importantly, the cochlea-optimized designs contained no measures of lesser quality. The beam-on time and median MU count for the cochlea-optimized plans were both satisfactory. These results show that stringent cochlea sparing is feasible in daily activities.

For advanced NPC, recent large, and randomized studies have demonstrated the superiority of additional induction chemotherapy,[13,14] and a meta-analysis has previously supported this.[15] Radiation-related ototoxicity must be kept to a minimum, especially in the current era of improved systemic therapy, which almost usually contains a high-dose cisplatin component. In a trial conducted by the University of Utah[16] to assess the relative contributions of RT and cisplatin to hearing loss in patients with head and neck cancer, patients getting comparatively lesser doses of cisplatin — in contrast to the actual recommendations for advanced nasopharyngeal cancer, which already showed damage after 10 Gy of exposure. The investigation of patients with medulloblastoma who received concurrent chemotherapy and modern RT procedures revealed that the potential for hearing loss below 35 Gy is essentially non-existent.[17] This is consistent with several NTCP-models[18-20] as well as the clinical information from Lee et al.,[21] and Wang et al.[5]

Limitations of the study

All optimization has been done retrospectively. The Tinnitus assessment did not include NTCP analysis. The added value of our results could be more accurately

assessed using objective audiometric analysis and patient-reported results.

CONCLUSION

Our investigation showed that a much-increased cochlea sparing is possible in most of the patients while maintaining PTV dosage coverage and the other OAR. Clinical trials in the future, both retrospective and prospective, should examine the effects of this optimization.

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NPC- Acquisition of data, original draft preparation, preparation of manuscript, interpretation of results, and revision of final manuscript; **GMPB-** Review of literature, statistical analysis, review, and editing; **SB-** Interpretation of results; **JS-** Concept and design of the study, review of literature, original draft preparation, review and editing, and revision of final manuscript; **NM-** Review of literature and interpretation of results; and **SKA-** Original draft preparation.

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