Clinics in Oncology

Research Article
Published: 24 Oct, 2019

GTV Cochlea Distance to Predict the Feasibility of Dose Limiting in Cochlea Sparing during Intensity Modulated Radiation Therapy for Nasopharyngeal Carcinoma

Chao Zhang[1], Ling-xiang Liu[1], Wei-zhan Li[1], Wen Liang[2], Zhao-hui Chen[1], Xian-hai Huang[1] and Juan Qi[3]*

[1]Department of Radiation Oncology, Panyu Central Hospital, China

[2]Department of ENT, Panyu Central Hospital, China

[3]Department of Medical Affairs, Panyu Central Hospital, China

Abstract

Introduction: This study was to investigate factors related to dose limiting in cochlea sparing in IMRT with nasopharyngeal carcinoma, and to evaluate GTV-cochlea distance used to predict the feasibility of cochlea sparing.

Methods: During April 2016 to April 2018 fifty one cases of nasopharyngeal carcinoma patients were enrolled, we designed a cochlea sparing plan (C-Plan) compared with non cochlea sparing plan (R-Plan). The dose radiated to the ipsilateral cochlea and contralateral cochlea was recorded. Among 102 cochleas of fifty one cases we measured and calculated its clinical T stage, GTV volume, PGTV dose and G-C distance in order to explore the relationship between these factors and dose to cochlea.

Results: For all T stages, there was a significant difference with cochlea dose limited under 45 Gy between C-Plan and R-Plan (p=0.010). Univariate analysis revealed cochlea dose was associated with its clinical T stage, GTV volume, G-C distance and PGTV dose (p<0.05), multivariate analysis revealed that only G-C distance was related to cochlea dose (p<0.05), and ROC analysis suggested that regarding G-C distance the area under ROC curve was 0.827, the threshold of G-C distance for possible cochlea sparing to limit cochlea dose under 45 Gy was 15.3 mm.

Conclusion: Our results demonstrated that the feasibility of cochlea sparing was associated with G-C distance, if G-C distance was more than 15.3 mm it was feasible to spare the ipsilateral or contralateral cochlea. This might help physicists and radiation doctors to make a judgment on whether or not the specific cochlea could be spared.

Keywords: Cochlea sparing; GTV volume; GTV-cochlea distance; Intensity Modulated Radiotherapy (IMRT); Nasopharyngeal Carcinoma (NPC)

OPEN ACCESS

Correspondence:
Chao Zhang, Department of Radiation Oncology, Panyu Central Hospital, Guangzhou, China, Tel: +86-020-34859206, +86-18926220659; Fax: +86-020-84818098;
E-mail: cbsenglish@163.com

Received Date: *27 Sep 2019*
Accepted Date*: 18 Oct 2019*
Published Date*: 24 Oct 2019*

Citation:
Zhang C, Liu L-X, Li W-Z, Liang W, Chen Z-H, Huang X-H, et al. GTV Cochlea Distance to Predict the Feasibility of Dose Limiting in Cochlea Sparing during Intensity Modulated Radiation Therapy for Nasopharyngeal Carcinoma. Clin Oncol. 2019; 4: 1665.

Introduction

Nasopharyngeal Carcinoma (NPC) is one of most commonly seen malignant tumors in head and neck, epidemically in Southeast Asia, particularly in southern China. IMRT has already been main modality for treatment of NPC, with its unique technique used in radiation therapy for NPC the Disease Free Survival (DFS) has increased by an extent of 12.4%, and the 5-year overall survival has even been 80%, compared with era of 2-dimensional radiation therapy [1]. Nevertheless, while gaining benefits the employment of radiation therapy also produces a number of side-effects on the surrounding organs where treatment beam is involved, since specific dose to these organs causes more or less injuries to normal tissues even though the accuracy of treatment dose is assured.

Among all these side-effects hearing loss is listed as one of major complications which constitute a threat to patients' quality of life after radiotherapy, it comprises Sensorineural Hearing Loss (SNHL), Conductive Hearing Loss (CHL) and both of them [2]. For NPC patients, while a satisfactory disease control is obtained, these complications induced by radiation therapy have gradually become the main concerns, to which we are required to pay more attention. Bhandare N et al. [3] initially studied the relationship between incidence of SNHL and high dose radiated to cochlea, some other authors thereafter explored the possible ways on how to preserve the hearing

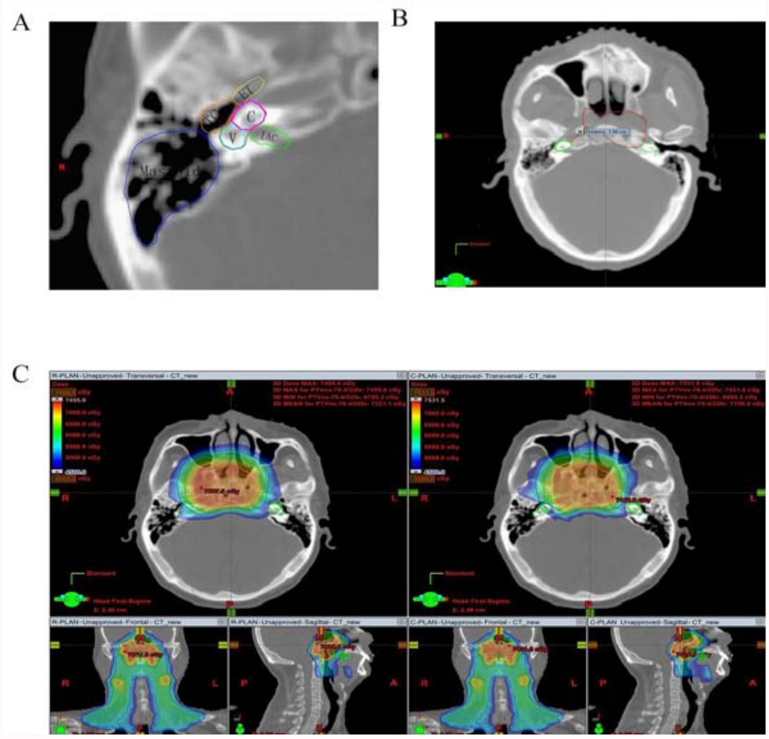

Figure 1: A) Hearing apparatus delineation in cochlea sparing plan (C-Plan) for NPC. B) The illustration of G-C distance measurement. C) Comparison of dose distribution in target volume between R-Plan and C-Plan.

apparatus during radiation therapy [4,5].

With popularity of IMRT employed in cancer treatment, it does not only improve local control with curative purpose, but also makes it possible to preserve the surrounding organs and tissues with its intensity modulating features [6]. Due to anatomic space and irregular invasion of nasopharyngeal cancer the tumor is usually very close to the ipsilateral or even contralateral cochlea [7,8], on the other hand, for radical treatment purpose different dose is needed in order to treat the tumor in nasopharynx, which may have different characteristic in its volume and shape, and its relative spatial relation to ipsilateral or contralateral cochlea [9,10].

In accordance with Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) it is suggested that dose radiated to the cochlea should be less than 45 Gy so that better preservation of hearing function is acquired [11]. In our former report we studied a stratified scheme of sparing cochlea based on T stage and it demonstrated that the cochlea-sparing radiation plan was applicable and practical for both radiation doctors and physicists, in addition, we also found that even with a stage T4 case it was still possible to spare contralateral cochlea as the curve of isodose 45 Gy was not involved in the contralateral cochlea, even though the ipsilateral cochlea could not be spared [12]. The feasibility of cochlea sparing may depend on not only the feature of tumor and factors related to treatment, but also the inherent structure adjacent to the tumor in individual patient, based on this, in this study we further tried to investigate factors related to dose radiated to cochlea, including clinical T stage, GTV volume, PGTV dose and GTV-cochlea distance (G-C distance), in order to help physicists and radiation doctors communicate more effectively in making judgment whether or not the specific cochlea could be spared.

Methods

Inclusion criteria

1) diagnosis was confirmed by nasopharyngeal biopsy; 2) patients were treated with IMRT technology, both cochlea sparing plan (C-Plan) and non-cochlea sparing plan (R-Plan) were designed in our study group; 3) clinical data and follow-up information was collected for further study; 4) all patients were informed with their consent prior to inclusion in the study.

Study cases information: during April 2016 to April 2018 fifty one cases of nasopharyngeal carcinoma patients with 102 cochleas were enrolled, with its clinical T stage, GTV volume, G-C distance and PGTV dose was recorded. The basic information is shown in (Table1).

Radiation therapy protocols: PGTVnx was obtained with a margin of 3 mm to 5mm from GTVnx which was defined as the visible tumor and whole membrane in nasopharynx on CT or MRI images, PCTV1 was obtained with a margin of 3 mm from CTV1 which covered nasopharynx and high-risk local structures, and PCTV2 was obtained with a margin of 3 mm from CTV2 which covered low-risk local structures and prophylactic area of lymph nodes. The dose prescriptions were described as follows: a total dose of 66 Gy to 74 Gy in 30 to 33 fractions at 2.12 to 2.25 Gy/fraction to the planning gross target volume (PGTVnx) of the primary GTV, 60 Gy to the PCTV1 of CTV1 which is high-risk regions in NPC, and 54 Gy to the PCTV2 of CTV2 which is relatively low-risk regions in NPC, and 60 Gy to 70 Gy to the PGTVnd of nodes in neck.

In our practice we try to reduce the dose to cochlea to protect its function, it includes situation as follows: i) for a stage T1 or T2, when the tumor is still small and “far” from cochlea, the isodose curve of

45 Gy dose does not intrude cochlea area, so it is easy to make the dose of cochlea under 45 Gy, we can reach a goal of dose limit as low as possible by delicate contouring and planning design; ii) for a stage T3 or T4, or a large tumor volume and "near" to cochlea, accordingly the isodose curve of 45 Gy intrudes cochlea area, we can reach a goal of limiting high dose at certain volume inside cochlea by delicate contouring and planning design in order to reduce the mean dose of cochlea; iii) for T4 stage, cochlea is already encircled by PTV, we can set maximal dose under percentage of prescribed dose, like Dmax <103% PGTV dose, and/or upgrade protection weight of cochlea to the same level as salivary glands on the condition of best tumor control and other OARs preserved, and/or slightly change beam angle at the extent of ± 5 degree; iv) for T4 stage, even if ipsilateral cochlea is encircled by PTV, so unable to preserve it, but it is still able to protect contralateral cochlea as situation in T2, T3 stage.

About delineation of cochlea in C-Plan and R-Plan: some essential technical in delineating cochlea include in details as follows: a) CT scanning with a slice thickness and slice increment of 2.5 mm; b) appropriate bone window of 1600 and bone level of 450; c) identifying cochlea by comparing its surrounding structures such as vestibule, internal auditory canal, eustachian, and tympanic cavity. An example of hearing apparatus delineation in cochlea sparing plan (C-Plan) for NPC is shown in Figure 1A.

G-C distance measurement: we used the MEASURE tool in the menu of Varian Eclipse TPS system, to measure the distance between the margin of GTV and cochlea on every slice of treatment planning where there appeared both GTV and cochlea and to select the shortest one as G-C distance in our study. The illustration of G-C distance measurement is shown in Figure 1B.

Statistical analysis

SPSS19.0 software was applied to analyze the data; the chi-test was used to compare the effect on the possibility of reducing the dose to be under 45 Gy to cochlea in C-Plan group versus R-Plan group. Univariate analysis and multivariate analysis were used to analyze the correlation between cochlear dose and clinical T stage, GTV volume, G-C distance and PGTV dose. The ROC curve was applied to analyze thresholds; the optimal threshold value was calculated by YOUDEN. The threshold for statistical significance was set at p<0.05.

Results

Comparison of cochlea dose under 45 Gy in C-Plan *vs.* R-Plan

Comparison of effect of C-Plan versus R-Plan on possibility of cochlea dose being under 45 Gy is shown in Table 2, and comparison of dose distribution in target volume between R-Plan and C-Plan is shown in Figure 1C.

Univariate analysis on the correlation between cochlea dose and clinical T stage, GTV volume, G-C distance and PGTV dose

The result of analysis is shown in Table 3.

Multivariate analysis was employed on the correlation between cochlear dose and clinical T stage, GTV volume, G-C distance and PGTV dose

The result of multivariate analysis is shown in Table 4.

ROC analysis was used to predict the potential threshold of G-C distance for possible cochlea dose being under 45 Gy. For G-C distance the area under the ROC curve was 0.827, the threshold of G-C distance for possible cochlea sparing was 15.3 mm, with sensitivity being 83.3%, specificity being 54.2%. The ROC analysis is shown in Figure 2.

Table 1: Characteristic of T stage, GTV volume and PGTV dose in 51 cases of NPC patients with cochlea dose and G-C distance in 102 cochleas.

Variable	Parameter	Notes
Cochlea dose (cGy)	4837.44 ± 979.78	X ± s, N=102
G-C distance (mm)	19.26 ± 13.75	X ± s, N=102
T stage		n(%), N=51
T1	7(13.73)	
T2	11(21.57)	
T3	23(45.10)	
T4	10(19.61)	
GTV volume (cm^3)	42.55 ± 30.06	X ± s, N=51
PGTV dose (cGy)	6993.00 ± 223.00	X ± s, N=51

Table 2: Comparison of cochlea dose below or not below 45 Gy between C-Plan and R-Plan.

Group	cochlea dose		X2	P
	<45 Gy	≥ 45 Gy		
C-Plan	49	53	6.66	0
R-Plan	31	71		

Table 3: Analysis of correlation between cochlea dose and GTV volume, G-C distance, PGTV dose and T stage.

Variables	Cochlea dose (Dm)
GTV volume	0.585**
G-C distance	-0.698**
PGTV dose	0.526**
T stage	0.598**

Table 4: Logistic analysis of T stage, GTV volume, G-C distance and PGTV dose.

Category	B	S.E	Wals	Sig.	Exp (B)	EXP(B) 95% CI	
						LSL	USL
T stage T1			1.854	0.603			
2	-0.42	1.22	0.118	0.731	0.657	0.06	7.189
T3	-0.473	1.465	0.104	0.747	0.623	0.035	11.004
T4	1.248	2.044	0.373	0.541	3.484	0.063	191.198
GTV volume	0.004	0.019	0.041	0.839	1.004	0.967	1.042
G-C distance	-0.108	0.035	9.59	0.002	0.898	0.839	0.961
PGTV dose	0.273	0.222	1.506	0.22	1.313	0.85	2.029

Discussion

Radiation therapy is the main modality in the treatment of nasopharyngeal carcinoma, while patients benefit from radiotherapy they are also at risk of radiation-induced hearing injuries. Apparently hearing function is essential to quality of life for NPC patients, thus it is a critical task to obtain both cochlea sparing and best tumor control during the treatment planning process, and also it has been under research regarding the ways on how to limit radiation dose to cochlea. Some literature reported that the higher dose irradiated to cochlea was associated with the severer injures to the hearing function [13,14]. Lee

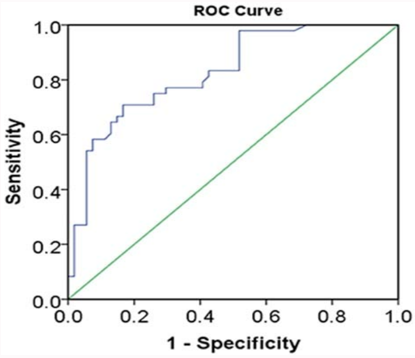

Figure 2: The ROC Analysis.

TF et al. [15] reported that according to Normal Tissue Complication Probability (NTCP), in order to avoid 50% incidence of audiological complications the mean dose to cochlea should be constrained below 46 Gy, and if the incidence of audiological complications be controlled below 20% then the mean dose to cochlea should be reduced below 32 Gy. QUANTEC data also indicated that when the average dose to cochlea was less than 45 Gy, the incidence of SNHL would be less than 30%, so it was suggested in QUANTEC guidelines that a dose for cochlea should be less than 45 Gy in order to preserve the hearing function [3].

By means of IMRT which produces a superior dose distribution even if the tumor is convex and concave in shape, it is likely to acquire best tumor control and least injuries in surrounding tissue if Organ at Risk (OAR) is involved [16,17], on the other hand, even with the superiority of IMRT it is not without any disadvantages because when we focus on delivering high dose to gross tumor and low dose in OARs as much as possible, but meanwhile an extra high dose may possibly be transferred to surrounding normal tissues which we don't concentrate on [18,19]. Ji-Jin Yao et al. [20] reported a prospective study on radiation dose to OARs during IMRT for NPC patients, they found that the radiation dose to OARs increased significantly with increasing GTV volume, and concluded that GTV volume might be a useful prognostic factor for radiation dose to OARs around nasopharynx. Moreover, the spatial correlation between GTV and cochlea poses an effect on dose to cochlea. According to some authors [21,22], the minimal dose irradiated to cochlea varied from 45 Gy to 70 Gy. For some tumors like glioblastoma and other cancers in head and neck [23-25], it was easy to limit cochlea dose under 35 Gy to 45 Gy or even lower, but obviously nasopharyngeal cancer had different scenarios [26], since cochlea was just very close in the vicinity of tumor in nasopharynx.

Usually when we design a Cochlea Sparing Plan (C-Plan) with satisfactory Conformity Index (CI) and Homogeneity Index (HI) [27], we employ some techniques to reduce the dose to cochlea while delivering a radical dose to tumor, in order to obtain a balance of best tumor control and best preservation of hearing function. The techniques usually include: setting a maximal dose limit for cochlea, and/or upgrading cochlea protection weight, and/or changing slightly beams angle. If cochlea is involved in PTV partially, we would divide cochlea into two parts: the part inside PTV we limit maximal dose to be less than 103% of prescribed PGTV dose, if there is a high dose region in this part, we use a ring to set a constraint of limiting dose at certain percentage of volume in this part; the part outside PTV we limit maximal dose to be less than prescribed PGTV dose, as well as setting a constraint of limiting dose at certain percentage of volume in this part. If the cochlea is involved in PTV totally, then apply this strategy to it just the same as the part inside PTV. These techniques were also used to reduce the dose to cochlea by some other authors [28,29]. In our current study, the differences between C-Plan and R-Plan lay in whether or not there is consciousness of techniques of cochlea preserving mentioned above. From Table1 we could see in C-Plan the dose to cochlea could be limited under 45 Gy at 48% (49/102), while in R-Plan the dose to cochlea could be limited under 45 Gy at only 30% (31/102), P=0.01, this suggested these techniques were effective.

In this study, we found that there were more benefits and challenges in making treatment plan with T3, if we compared C-Plan with a regular plan, as for patients with T1, T2 there may not be any planning challenges, and for patients with T4 in which the PTVs may have extended into the ipsilateral cochlea's region [12], which may not generate any planning benefits at all. Since every individual NPC patient has his own different body features and tumor characteristic, including inherent structure relationship inside organs, involvement of tumor invasion [30], the feasibility of cochlea sparing may depend on not only tumor's T stage, but also GTV volume, prescribed PGTV dose, and spatial correlation between GTV and cochlea. In our study univariate analysis demonstrated the correlation between cochlea dose and clinical T stage, GTV volume, G-C distance and PGTV dose, while with multivariate logistic analysis, the results showed that feasibility of dose limit under 45 Gy was associated with G-C distance only, this suggested the fact that there may exist a functional relationship between these factors which influenced on the feasibility. And intrinsically, it suggested that the G-C distance was in reflection of the tumor's T stage and GTV volume, in terms of the spatial relationship between tumor in nasopharynx and cochlea. And also, PGTV dose was just accordingly responding to the tumor's T stage and GTV volume, prescribed by radiation doctors for the treatment purpose.

We used ROC to analyze the potential threshold of G-C distance for possible cochlea dose being under 45 Gy, the area under the ROC curve was 0.827; the threshold of G-C distance for possible cochlea sparing was 15.3 mm. This could explain why it was easy to limit a constraint of dose 45 Gy or less to cochlea for a stage T1 case, with which its GTV volume was not large and its G-C distance was not small, and as a result its PGTV dose should be moderate; On the contrary it became hard when T came to be an advanced stage like T4 to preserve the ipsilateral cochlea, as it was shown in Figure 1B. But interestingly, our findings in this study demonstrated that even for a stage T4, it was not possible to spare ipsilateral cochlea but we could still preserve the contralateral cochlea as much as possible, as it was the case with stage T2 or T3, which was possible to preserve both cochleas.

Conclusion

Our results demonstrated that the feasibility of cochlea sparing was associated with clinical T stage, GTV volume, PGTV dose and G-C distance, while basically G-C distance was the only independent variable to predict the feasibility of cochlea sparing with a threshold of 15.3 mm, if G-C distance was more than 15.3 mm it was feasible to spare ipsilateral or contralateral cochlea. This might help physicists and radiation doctors to make a judgment on whether or not the specific cochlea could be spared.

Ethics

Since this study was focused on IMRT treatment plan to evaluate the relationship between the dose to cochlea and clinical T stage, GTV volume, PGTV dose and G-C distance, there was no disclosure of privacy of any patients. The study was approved by the Ethics Committee in the hospital during applying for provincial project. All patients were informed with their consent prior to inclusion in the study.

References

1. Yi JL, Gao L, Huang XD, Luo JW, Xiao JP, Li SY, et al. Nasopharyngeal carcinoma treated with intensity-modulated radiotherapy: long-term results of 416 patients. Chin J Radiat Oncol. 2012;21:196-99.
2. Pan CC, Eisbruch A, Lee JS, Snorrason RM, Ten Haken RK, Kileny PR. Prospective study of inner ear radiation dose and hearing loss in head-and-neck cancer patients. Int J Radiat Oncol Biol Phys. 2005;61(5):1393-402.
3. Bhandare N, Jackson A, Eisbruch A, Pan CC, Flickinger JC, Anternelli P, et al. Radiation therapy and hearing loss. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S50-57.
4. Chen WC, Jackson A, Budnick AS, Pfister DG, Kraus DH, Hunt MA, et al. Sensorineural hearing loss in combined modality treatment of nasopharyngeal carcinoma. Cancer. 2006;106(4):820-9.
5. Rosenthal DI, Chambers MS, Fuller CD, Rebueno NC, Garcia J, Kies MS, et al. Beam path toxicities to non-target structures during intensity-modulated radiation therapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 2008;72(3):747-55.
6. Muren LP, Wasbø E, Helle SI, Hysing LB, Karlsdottir A, Odland OH, et al. Intensity-modulated radiotherapy of pelvic lymph nodes in locally advanced prostate cancer: planning procedures and early experiences. Int J Radiat Oncol Biol Phys. 2008;71(4):1034-41.
7. Li WF, Sun Y, Chen M, Tang LL, Liu LZ, Mao YP, et al. Locoregional extension patterns of nasopharyngeal carcinoma and suggestions for clinical target volume delineation. Chin J Cancer. 2012;31(12):579-87.
8. Sun Y, Yu XL, Luo W, Lee AW, Wee JT, Lee N, et al. Recommendation for a contouring method and atlas of organs at risk in nasopharyngeal carcinoma patients receiving intensity-modulated radiotherapy. Radiother Oncol. 2014;110(3):390-7.
9. Shen C, Lu JJ, Gu Y, Zhu G, Hu C, He S. Prognostic impact of primary tumor volume in patients with nasopharyngeal carcinoma treated by definite radiation therapy. Laryngoscope. 2008;118(7):1206-10.
10. Jian JJ, Cheng SH, Prosnitz LR, Tsai SY, Tsai MJ, Huang AT. T classification and clivus margin as risk factors for determing locoregional control by radiotherapy of nasopharyngeal carcinoma. Cancer. 1998;82(2):261-7.
11. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. The use of normal tissue complication probability (NTCP) models in clinic. Int J Radiat Oncol Biol Phys. 2010;76(30 Suppl):S10-19.
12. Zhang C, Liu LX, Li WZ, Liang W, Chen ZH, Huang XH, et al. Cochlea sparing with a stratified scheme of dose limitation employed in intensity-modulated radiotherapy for nasopharyngeal carcinoma: A dosimetry study. Med Dosim. 2019;44(3):226-32.
13. van der Putten L, de Bree R, Plukker JT, Langendijk JA, Smits C, Burlage FR, et al. Permanent unilateral hearing loss after radiotherapy for parotid gland tumors. Head Neck. 2006;28(10):902-908.
14. Honoré HB, Bentzen SM, Møller K, Grau C. Sensori-neural hearing loss after radiotherapy for nasopharyngeal carcinoma: individualized risk estimation. Radiother Oncol. 2002;65(1):9-16.
15. Lee TF, Yeh SA, Chao PJ, Chang L, Chiu CL, Ting HM, et al. Normal tissue complication probability modeling for cochlea constraints to avoid causing tinnitus after head-and-neck intensity-modulated radiation therapy. Radiat Oncol. 2015;10:194-201.
16. Chan MF, Schupak K, Burman C, Chui CS, Ling CC. Comparison of intensity-modulated radiotherapy with three-dimensional conformal radiation therapy planning for glioblastoma multiforme. Med Dosim 2003;28(4):261-65.
17. Lee FK, Yip CW, Cheung FC, Leung AK, Chau RM, Ngan RK. Dosimetric difference amongst 3 techniques: TomoTherapy, sliding-window intensity-modulated radiotherapy (IMRT), and RapidArc radiotherapy in the treatment of late-stage nasopharyngeal carcinoma (NPC). Med Dosim. 2014;39(1):44-9.
18. Neill CJ. Dosimetric comparison of intensity-modulated solutions for intact prostate cancer. Med Dosim. 2014;39(4):366-72.
19. Saw CB, Li S, Battin F, Mckeague J, Peters CA. External beam planning module of Eclipse for external beam radiation therapy. Med Dosim. 2018;43(2):195-204.
20. Yao JJ, Chen FP, Zhou GQ, Zhang WJ, Xu L, Wang XJ, et al. A prospective study on radiation doses to organs at risk (OARs) during intensity-modulated radiotherapy for nasopharyngeal carcinoma patients. Oncotarget. 2016;7(16):21742-52.
21. Hirsch A, Noren G. Audiological findings after stereotactic radiosurgery in acoustic neurinomas. Acta Otolaryngol. 1988;106(3-4):244-51.
22. Mujica–Mota M, Waissbluth S, Daniel SJ. Characteristics of radiation-induced sensorineural hearing loss in head and neck cancer: A systematic review. Head Neck. 2013;35(11):1662-68.
23. Briere TM, McAleer MF, Levy LB, Yang JN. Sparing of normal tissues with volumetric arc radiation therapy for glioblastoma: single institution clinical experience. Radiat Oncol. 2017;12(1):79.
24. Theunissen EA, Zuur CL, Yurda ML, van der Baan S, Kornman AF, de Boer JP, et al. Cochlea sparing effect of intensity modulated radiation therapy in head and neck cancer patients: a long-term follow-up study. J Otolaryngol Head Neck Surg. 2014;43:30.
25. Bhandare N, Antonelli PJ, Morris CG, Malayapa RS, Mendenhall WM. Ototoxicity after radiotherapy for head and neck tumors. Int J Radiat Oncol Biol Phys. 2007;67(2):469-79.
26. Raaijmakers E, Engelen AM. Is sensorineural hearing loss a possible side effect of nasopharyngeal and parotid irradiation? A systematic review of the literature. Radiother Oncol. 2002;65(1):1-7.
27. Shao yan, Wang hao, Chen hua. Clinical application of conformity index and homogeneity index. Chin J Radiol Med Prot. 2017;37:(9)717-21.
28. Ni XC, Wang SZ, li J, Wang WF, Yang G. Effects of dose limitation and increased protective weight on dose distribution in auditory organs during intensity-modulated radiotherapy for nasopharyngeal carcinoma. Chin J Radiat Oncol. 2013;22(6):478-81.
29. Guo M, Wang SZ, Wu ZX, Ma CM, WangL, Ni XC, et al. The research of IMRT plan optimization on dose limitation of sub regional auditory organs. Chin J Radiat Oncol. 2015;24(4):438-42.
30. Mao YP, Yin WJ, Guo R, Zhang GS, Fang JL, Chi F, et al. Dosimetric benefit to organs at risk following margin reductions in nasopharyngeal carcinoma treated with intensity-modulated radiation therapy. Chin J Cancer. 2015;34(5):189-97.