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Radiotherapy of NPC

Recommendation for a contouring method and atlas of organs at risk in nasopharyngeal carcinoma patients receiving intensity-modulated radiotherapy

Ying Sun [a,1], Xiao-Li Yu [a,1], Wei Luo [a,1], Anne W.M. Lee [b,1], Joseph Tien Seng Wee [c,1], Nancy Lee [d,1], Guan-Qun Zhou [a], Ling-Long Tang [a], Chang-Juan Tao [a], Rui Guo [a], Yan-Ping Mao [a], Rong Zhang [e], Ying Guo [f], Jun Ma [a,*]

[a] State Key Laboratory of Oncology in Southern China, Department of Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou; [b] Department of Clinical Oncology, The University of Hong Kong-Shenzhen Hospital, People's Republic of China; [c] Department of Radiation Oncology, National Cancer Center Singapore, Singapore; [d] Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, USA; [e] Imaging Diagnosis and Interventional Center; and [f] Department of Medical Statistics and Epidemiology, State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, Guangzhou, People's Republic of China

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ABSTRACT

Background and purpose: To recommend contouring methods and atlas of organs at risk (OARs) for nasopharyngeal carcinoma (NPC) patients receiving intensity-modulated radiotherapy, in order to help reach a consensus on interpretations of OARs delineation.

Methods and materials: Two to four contouring methods for the middle ear, inner ear, temporal lobe, parotid gland and spinal cord were identified via systematic literature review; their volumes and dosimetric parameters were compared in 41 patients. Areas under the receiver operating characteristic curves for temporal lobe contouring were compared in 21 patients with unilateral temporal lobe necrosis (TLN).

Results: Various contouring methods for the temporal lobe, middle ear, inner ear, parotid gland and spinal cord lead to different volumes and dosimetric parameters ($P < 0.05$). For TLN, D1 of PRV was the most relevant dosimetric parameter and 64 Gy was the critical point. We suggest contouring for the temporal lobe, middle ear, inner ear, parotid gland and spinal cord. A CT–MRI fusion atlas comprising 33 OARs was developed.

Conclusions: Different dosimetric parameters may hinder the dosimetric research. The present recommendation and atlas, may help reach a consensus on subjective interpretation of OARs delineation to reduce inter-institutional differences in NPC patients.

Radiotherapy is the preferred therapeutic modality for non-metastatic nasopharyngeal carcinoma (NPC). Intensity modulated radiotherapy (IMRT) is currently the mainstay of radiation oncology. Accurate delineation and precise dosage of the target volume and organs at risk (OARs) are the keys to successful radiotherapy.

Many normal tissues close to the nasopharynx are defined as OARs, including the temporal lobe, brainstem, spinal cord, optic nerve, chiasm, parotid gland, submandibular gland, pituitary et al.; therefore, treatment planning is difficult in NPC. Furthermore, critical normal tissues such as the brainstem and temporal lobe are so close to the target volume that inaccurate delineation will mislead treatment planning, resulting in inadequate target volume coverage or OAR overdose. Thus, accurate and consistent OARs delineation in NPC is critical. However, large variations were observed when contouring OARs [1–3]. Furthermore, significantly different contouring methods are also recommended in the literature. For example, when contouring the inner ear, some clinicians delineate the cochlea alone, the internal auditory canal (IAC) in combination with the vestibule and cochlea, the IAC and cochlea, or the vestibule and cochlea [4–7]. Such diversity in OAR contouring will certainly generate unmatched dosimetric parameters, and prevents side effect correlation studies. Thus, guidelines for OARs delineation are necessary. The considerable variation in OARs delineation mainly originates from the diversity of subjective interpretations and variation in actual contouring. In

* Corresponding author. Address: State Key Laboratory of Oncology in Southern China, Department of Radiation Oncology, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, People's Republic of China.
E-mail address: majun2@mail.sysucc.org.cn (J. Ma).
[1] These authors contributed equally to this study.

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this study, we mainly focused on the various subjective interpretations.

We identified different OARs contouring methods and applied these methods in 41 NPC patients, to compare the volumes and dosimetric parameters. Furthermore, as an example, we retrospectively compared the areas under the receiver operating characteristic (ROC) curves for two temporal lobe contouring methods in 21 NPC patients with unilateral temporal lobe necrosis (TLN) who underwent IMRT. A more reasonable contouring method for temporal lobe was obtained. Finally, we recommend a contouring method and atlas of the OARs in NPC patients, for which we expect to reach a consensus on interpretations of OARs delineation.

Methods and materials

Delineation methods

A review of the literature regarding OARs delineation in head and neck cancer (HNC) revealed two to four contouring methods for the middle ear, inner ear, temporal lobe, parotid gland and spinal cord. Information for this review was identified by searches of PubMed using the name of the organs (such as temporal lobe, et al.) and search terms "contouring", "delineation" or specific radiation injuries (such as temporal lobe necrosis, temporal lobe injury, et al.) and "radiation therapy"/"radiotherapy" in the title/abstract (or radiation injury and "radiation therapy"/"radiotherapy" in title for the spinal cord and parotid gland). References were supplemented with relevant citations from the reference lists of the retrieved papers. Relevant papers were defined as clinical studies or reviews elaborating on the organs contouring or presenting pictures of delineated OARs on sectional CT or MRI. Papers published until the end of November 2012 were included. All papers identified in the searches were selected on the basis of the above criteria by the first author (Sun Y.) after reading the abstract. Totally, 97, 146, 178, 94 and 38 papers were identified and 5, 30, 13, 7 and 7 papers were found to be relevant for the temporal lobe, parotid gland, spinal cord, inner ear and middle ear, respectively (Supplementary References 1). For the other OARs, different contouring methods were few referred [8–10].

Two methods were used to contour the temporal lobe. The first included brain tissue outside the Sylvian fissure and basal ganglia, excluding the parahippocampal gyrus and hippocampus (method 1); the other method contoured the temporal lobe including the parahippocampal gyrus and hippocampus, excluding the basal ganglia and insula (method 2) [11]. Three middle ear contouring methods were identified: contouring the combination of tympanum and Eustachian tube (ET) [5]; the tympanum and bony part of the ET respectively, [12]; or the ET, tympanic cavity and mastoid process, respectively [13]. As described above, four methods were observed for inner ear [4–7]. Spinal cord contouring included the true spinal cord [14], or the bony limits of the spinal canal [15]. Chau et al. split the parotid gland into the gross tumor volume-overlapping, planning target volume-overlapping and non-target-overlapping sub-segments [16]. As no parotid gland involvement was detected in this study, we delineated the complete parotid gland and non-target-overlapping sub-segments. By reviewing atlases of anatomy [8–10], we defined 3D-boundaries for other OARs, and suggested representative contouring according to their anatomic locations on CT–MRI fusion.

Application of different contouring methods

A total of 41 consecutive, newly diagnosed, non-metastatic NPC patients were treated in our hospital between March 2011 and September 2011. The patients' characteristics are presented in Supplementary Table 1.

According to International Commission on Radiation Units and Measurements (ICRU) reports 50, 62 and 83, we contoured the gross target volume (GTV), clinical target volume (CTV) and OARs using the delineation methods described above. Atlas-based auto segmentation (ABAS, Version 2.01, ELEKTA CMS, INC., Stockholm, Sweden) was used to generate primary OARs delineation. Then, the contouring was modified and completed by Sun Y. who specializes in HNC with 11 years work experience, and then was reviewed by a radiologist (Zhang R.) with more than 20 years work experience. The differences were resolved by group discussion. A 3 mm margin was used to generate the corresponding planning target volume and planning organs at risk volume (PTV/PRV). A total dose of 70 Gy at 2.12 Gy per fraction (5 fractions per week) was prescribed. According to the Radiation Therapy Oncology Group (RTOG) protocols 0225 and 0615 and ICRU report 83, we calculated the volume of all organs; the mean dose (Dmean) for the parotid gland, middle and inner ear, D1 of PRV (Dx/xcc, the minimum dose received by the "hottest" x% or x ml of the structure) for the spinal cord and temporal lobe to compare the different contouring methods.

Selection of temporal lobe contouring methods

We retrospectively analyzed the dosimetric parameters in 21 NPC patients with unilateral TLN who underwent IMRT between November 2004 and November 2006. The patients' characteristics are presented in Supplementary Table 1.

The median follow-up time was 45 months (range: 38–63 months) and the latency of TLN was 35 months (range: 25–57 months) after completion of radiotherapy. The patients underwent follow-up (clinical and/or imaging examinations) monthly in the first three months after completion of radiotherapy, every three months in the first three years, every six months in the next two years, and annually thereafter. MRI was required every six months during the first 2 years and annually thereafter, and was also performed when tumor recurrence or TLN was suspected [17]. MRI findings were independently reviewed by two radiologists, and any disagreements were resolved by consensus. A diagnosis of TLN will be made if the MRI presented following signs, (1) WMLs (homogeneous lesions in the white matter); (2) solid, enhanced nodules with or without a necrotic center and finger signs; (3) cysts of round or oval lesions [18–19]. Tumor recurrence or metastasis of tumor was excluded.

Statistical analysis

SPSS 16.0 was used for data analysis. We performed the Friedman test to compare middle/inner ear Dmean; the paired-*t* test to compare parotid gland volume and Dmean, spinal cord volume and D1 of PRV; the Wilcoxon-test to compare temporal lobe the volume, and D1 of PRV for the 41 patients.

For the 21 patients with unilateral TLN, three steps were adopted. Firstly, the paired-*t* test was used to compare all the dosimetric parameters (the D1–D60, D1–D40 cc, V10 [Vx, the percentage volume of the organ which received more than × Gy] to V75, D1–D60 of PRV, and V20–V75 of the PRV at five units intervals) between the temporal lobes with and without radiation-induced damage for every method. All of the significantly different parameters from the paired *t*-tests were separately included in the next analyses. Secondly, multivariate analysis using the binary logistic regression model was used to identify the most relevant parameters associated with TLN. Lastly, the areas under the ROC curves of the most relevant parameters from the two contouring methods were compared to select a more reasonable contouring method. $P < 0.05$ was considered significant.