JBUON 2014; 19(2): 484-489
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

The error estimate for contouring the brainstem in radiotherapy of head and neck cancer: A multi-center study from north China

Chengxin Liu[1,2], Guanzhong Gong[2], Tao Zhou[2], Yan Wang[3], Yong Yin[2], Baosheng Li[2]

[1]*Department of Radiation Oncology, Shandong's Key Laboratory of Radiation Oncology, Shandong Cancer Hospital, School of Medicine and Life Sciences, University of Jinan and Shandong Academy of Medical Sciences, JiNan;* [2]*Department of Oncology, Shandong Cancer Hospital, JiNan;* [3]*School of Medicine and Life Sciences, University of Jinan and Shandong Academy of Medical Sciences, JiNan, China*

Summary

Purpose: *To analyze the error in contouring the brainstem for patients with head and neck cancer who underwent radiotherapy (RT) based on computed tomography (CT) and magnetic resonance (MR) images.*

Methods: *20 patients with brain tumor and 17 patients with nasopharyngeal cancer (NPC) were randomly selected. Each patient underwent MR and CT scanning. For each patient, one observer contoured the brainstem on CT and MR images 10 times, and 10 observers from 5 centers delineated the brainstem on CT and MR images only one time. The inter- and intra-observers volume and outline variations were compared.*

Results: *The volumes of brainstem contoured by inter- and intra-observers on CT and MR images were similar ($p>0.05$). The reproducibility of contouring brainstem on MR images was better than that on CT images ($p<0.05$) for both inter- and intra-observer variability. The inter- and intra-observer variability for contouring the brainstem on CT images reached mean values of 0.81±0.05 ($p>0.05$) and of 0.85±0.05 ($p>0.05$), respectively, while on MR images the respective values were 0.90±0.05 ($p>0.05$) and 0.92±0.04 ($p>0.05$).*

Conclusion: *Contouring the brainstem on MR images was more accurate and reproducible than that on CT images. Precise information might be more helpful for the patients whose lesion were closed to brainstem.*

Key words: *brainstem, computed tomography, inter- and intra-observer variability, magnetic resonance, reproducibility*

Introduction

RT has an important role in the treatment of head and neck cancer, although it can cause structural damage and functional impairment of the brainstem [1]. Progressive and irreversible complications of RT to the brain are common, and often occur months or years after treatment [2,3]. The main risk factors for the development of brainstem injury include total radiation dose and fraction size. As a serial organ, the maximum radiation dose to the brainstem represents the most interesting issue. However, great differences still exist among the results of studies regarding the estimations of the dose-volume index for radiation brainstem injury [4-7]. The most important reason is the lack of specificity of conventional CT in distinguishing the brainstem from other brain tissues, mainly in the direction of pedunculus cerebri, due to the poor contrast with the cisterna ambiens that renders difficult its delineation.

The development of advanced computer-aided image techniques have led to the use of MRI for RT planning of NPC and brain tumors as a desirable tool for improving soft tissue delineation and better definition of tumor margins [8]. Furthermore, MR T1-weighted images provide detailed views of the local anatomy of the head

Correspondence to: Baosheng Li, PhD. Department of Radiation Oncology, Shandong Cancer Hospital, JiYan Road 440, Jinan, 250117, China. Tel: +86 13954168847, Fax: +86 0531 67626161, E-mail: baoshli@yahoo.com
Received: 10/01/2014; Accepted: 28/01/2014

and neck tumors and the surrounding structures [9]. Although MR images are always applied for contouring the target and protecting the submandibular gland [9-13], little attention is paid to other organs, including the brainstem. Moreover, no data are available describing the advantages of MRI over CT for soft tissue delineation.

In this study, we investigated the reproducibility of contouring the brainstem on CT and MR images, and determined the intra- and inter-observer variability.

Methods

Patient selection

A total of 37 patients (20 with brain tumors and 17 with NPC) who were hospitalized in the Department of Radiation Oncology, Shandong Cancer Hospital, China, between November 2010 and December 2012, were included in this study. Patient age ranged from 36 to 67 years (median 53); 22 patients were male and 15 female. The Institutional Review Board approved this study, and each patient provided written informed consent.

MR and CT simulation

All MR images were acquired using a 3.0T superconducting MR scanner (Signa CV/I, Philips, Beijing, China). The acquisition parameters were: 400–500 ms repeat time and 3 min to obtain images. CT scans (Brilliance CT Big Bore, Philips Medical Systems, the Netherlands) had a thickness of 3 mm. A thermoplastic film mask was used to immobilize each patient.

CT/MRI fusion

For contouring gross tumor volumes (GTVs) and organs at risk (OARs), all images were transferred to an Eclipse RT treatment planning system (TPS, version 8.6, Varian Medical Systems, Palo Alto, CA, USA). All MR images from each patient were fused with the CT images and the accuracy of registration was visually inspected by the operator using the software provided by the TPS.

Contouring brainstem on MR and CT images

Eleven observers (Table 1) from three centers in Shandong, one center in Hebei and one center from Tianjin were involved in contouring the brainstem on CT and MR images. One contoured the brainstem 10 times on CT and MR images, and the others contoured the brainstem on CT and MR images once. The established contouring criteria were: 1) based on anatomical landmarks, the boundary between the mesencephalon and the telencephalon started from the layer of the pedunculus cerebri; 2) the boundary between the medulla oblongata and spinal cord was at the level of the foramen magnum; 3) the boundary between the ventral surface of the brainstem and surrounding tissues was distinguished from the suprasellar cistern, prepontine cistern, and basilar artery by the CT or MR sign value; 4) the boundary between the back of the brainstem and surrounding tissues was profiled according to the edge of the fourth ventricle; and 5) the boundaries between the right and left sides of the brainstem and the surrounding tissues were differentiated from the edge of the posterior cerebral artery, cisterna ambiens, middle cerebellar peduncle, and cerebellopontine angle by the CT or MR sign value.

Table 1. Observers' and Centers' information

No.	*Center*†	*Age (years)*	*Work time (years)*	*Title*
D1	1	42	16	Senior
D2	1	45	15	Senior
D3	4	33	6	Intermediate
D4	3	37	12	Intermediate
D5	2	30	4	Intermediate
D6	1	27	2	Junior
D7	5	33	4	Intermediate
D8	2	28	4	Junior
D9	4	34	8	Intermediate
D10	3	43	20	Senior
D11	5	26	2	Junior

†The centers of the observers: 1: Shandong Cancer Hospital; 2: TangShan Cancer Hospital; 3: JiNan Hospital; 4: Qianfoshan Hospital; 5: Cancer Hospital of Tianjin Medical University. D stands for Doctor.

Determination of the reproducibility

The reproducibility of contouring the brainstem on the same anatomical section was calculated using MATLAB 2008a software. In every case, four data sets were obtained for each layer. First, an experienced radiotherapist contoured the brainstem 10 times on CT images, and the agreement between the first of brainstem image and the other 9 was considered as the CT intra-observer variability (CT_{intra}). Similarly, 10 radiotherapists contoured the brainstem on the CT images and their data were used to calculate CT_{inter}. The same procedures were carried out for MR images and used to calculate MR_{intra} and MR_{inter}.

Statistics

The delineations were analysed in Matlab R2008a using the open-source tool CERR and in-house code. Data are shown as mean ± standard deviation (SD). All analyses were performed using the Statistical Package for Social Sciences, version 16.0 (SPSS, Chicago, IL, USA). P values less than 0.05 were considered statistically significant.

Results

Brainstem volume

The brainstem volumes according to both CT and MR images were determined using Eclipse TPS (Varian). The mean brainstem volumes for the CT_{inter}, CT_{intra}, MR_{inter}, and MR_{intra} data sets were 24.2±2.4 cm^3, 24.2±1.8 cm^3, 24.2±1.9 cm^3, and 24.2±1.6 cm^3, respectively. The brainstem volume for each patient was found to be similar when estimated from CT vs MR images (F=0.02, p=0.88).

Brainstem reproducibility on CT images

The inter-observer variability for CT imaging of the same anatomical section reached only 0.81±0.05, and the outlining error was not significantly different among the different series (p>0.05). The intra-observer reproducibility for CT imaging was slightly higher at 0.85±0.05, and the contouring error also was not significantly different among different sections (p>0.05). All of these data are shown in Figure 1 and Table 2.

Brainstem reproducibility on MR images

The inter-observer reproducibility for MRI of the same anatomical section reached 0.90±0.04, and the outlining error was not significantly different among the different series (p>0.05). A similar intra-observer reproducibility for MRI of 0.92±0.04 was obtained, and the contouring error also was not significantly different among the different series (p>0.05). These data are shown in Figure 2 and Table 2.

Table 2. Reproducibility data for the four contouring methods in 17 sections

Section	MR_{inter}†	MR_{intra}†	CT_{inter}†	CT_{intra}†
1	0.92±0.04	0.94±0.02	0.79±0.03	0.81±0.04
2	0.92±0.04	0.94±0.02	0.80±0.05	0.82±0.03
3	0.90±0.05	0.94±0.02	0.82±0.05	0.85±0.05
4	0.90±0.04	0.92±0.03	0.82±0.04	0.85±0.04
5	0.89±0.03	0.91±0.03	0.82±0.05	0.86±0.05
6	0.89±0.05	0.91±0.04	0.82±0.04	0.85±0.04
7	0.90±0.04	0.93±0.02	0.82±0.04	0.86±0.04
8	0.90±0.04	0.93±0.03	0.82±0.05	0.86±0.05
9	0.91±0.04	0.94±0.03	0.82±0.06	0.86±0.04
10	0.92±0.05	0.94±0.02	0.83±0.05	0.87±0.06
11	0.90±0.04	0.92±0.03	0.80±0.06	0.82±0.04
12	0.90±0.04	0.92±0.03	0.80±0.06	0.82±0.03
13	0.90±0.04	0.91±0.04	0.79±0.05	0.82±0.04
14	0.90±0.04	0.91±0.04	0.81±0.05	0.86±0.07
15	0.90±0.05	0.91±0.04	0.81±0.04	0.86±0.04
16	0.89±0.05	0.91±0.04	0.81±0.06	0.85±0.05
17	0.90±0.04	0.92±0.05	0.81±0.05	0.85±0.04
Total	0.90±0.04	0.92±0.04	0.81±0.05	0.85±0.05

†*Data are expressed as mean ± standard deviation*

Discussion

It is now accepted that for the effective treatment of head and neck cancer patients, not only GTV plays an important role, but accuracy in determining the critical structures located near the tumor, including the cavernous sinus, pituitary gland, cranial nerve, and brainstem also is critical [14,15]. These regions must be accurately evaluated for disease involvement, or more importantly, must be spared a RT dose if they are deemed to be clear of disease [3,8]. Among injuries to these critical structures, permanent injury to the brainstem can be a devastating complication in patients treated with RT. Furthermore, a few-millimeter shift of the steep dose gradient due to positioning error could overdose the brainstem when intensity-modulated RT, radiosurgery, and stereotactic radiotherapy are used in the treatment; especially stereotactic radiotherapy makes determining the biologically effective dose more complex [3,16-19]. In addition, because of the proximity to the tumor, parts of the brainstem may be included within the radiation portals. Symptoms appear from several months to several years after completion of treatment and can either progress to death or stabilize after partial neurologic loss. Either way, these outcomes are unacceptable for patients who could otherwise obtain long-term survival. In addition, there is an unavoidable potential for brainstem injury if no special attention is given to the brainstem.

To prevent this injury, the maximum irradiation dose to the brainstem on a dose-volume histogram must always be given special attention [20]. However, separate brainstem dose limits are usually absent and dose-volume measures related to toxicity have not generated a uniform dose-response curve from the available data. One of the major reasons is that the brainstem is contoured on the basis of planning CT images. Due to the limits of the CT image-forming principles, CT imaging cannot be used to distinguish the brainstem from the surrounding soft tissue clearly. Hence,

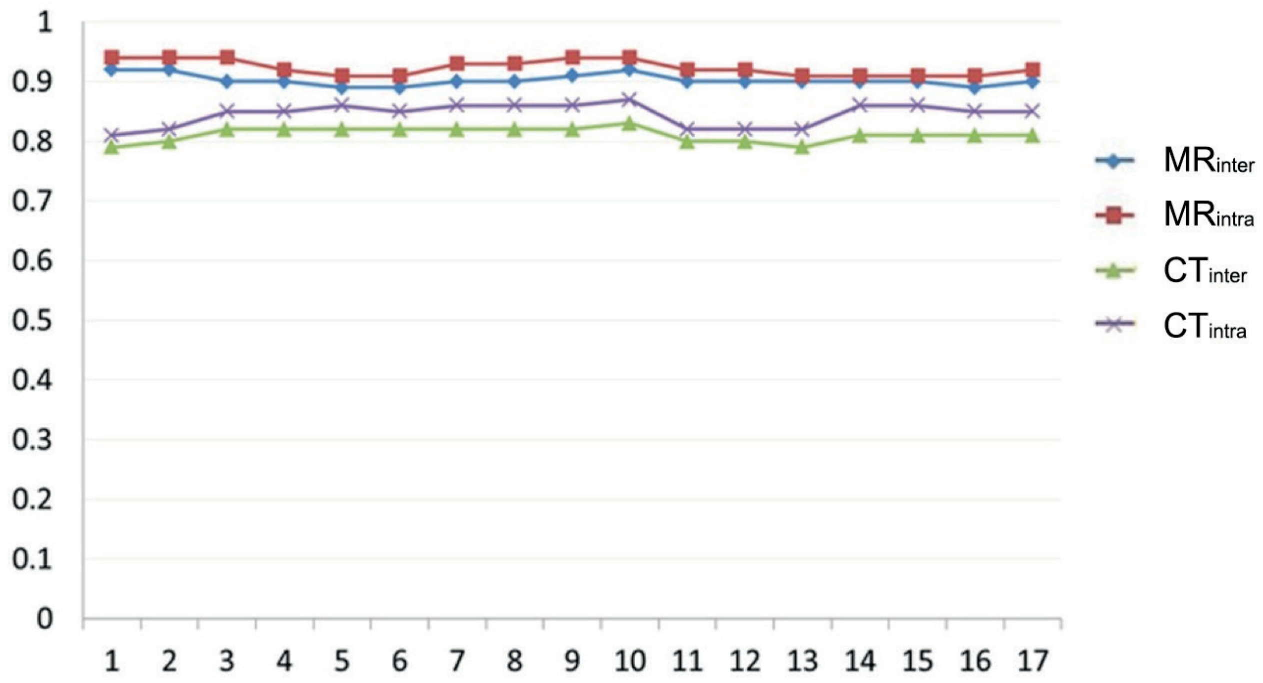

Figure 1. Shown is the reproducibility of every brainstem section (17 sections) obtained from CT and MR images, as well as a comparison of the reproducibility between CT and MR images.

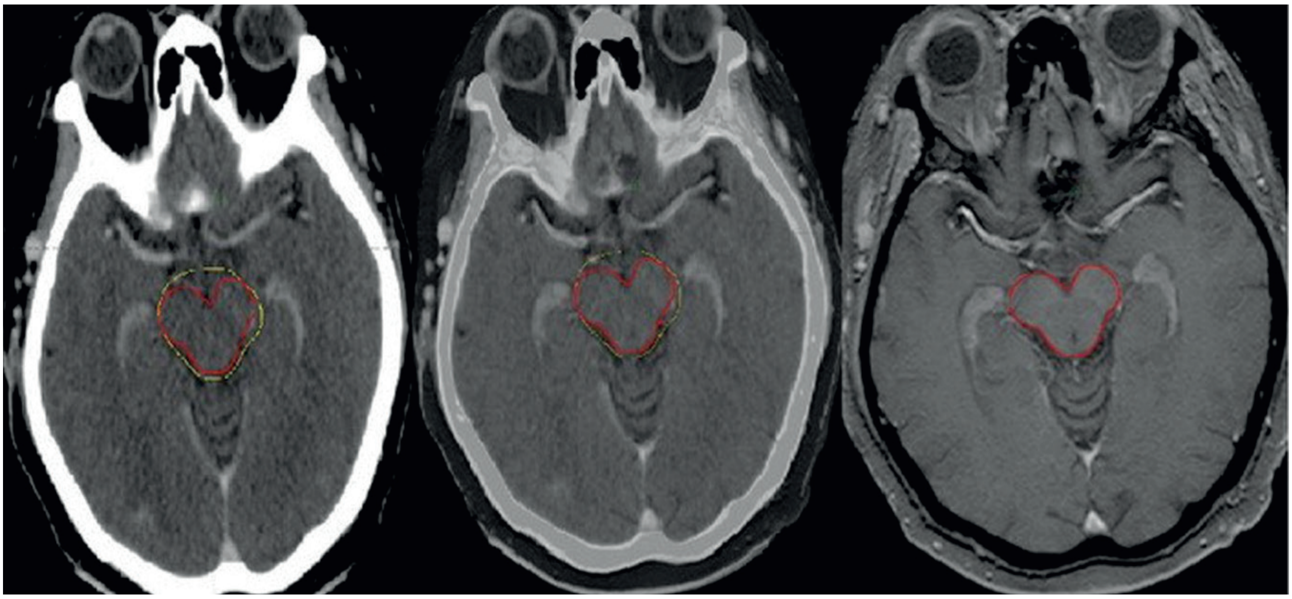

Figure 2. Representative CT and MR images for contouring the brainstem are shown on the left and right, respectively, and the middle image is a fusion image of the two contouring methods. This figure shows that when contouring the brainstem, MR (red line) can distinguish the pedunculus cerebri from the surrounding tissues more easily than CT (yellow line).

these indexes may be impacted by this contouring method, especially for the maximum radiation dose region.

MR provides better tumor definition for nasopharyngeal lesions involving the parapharyngeal space, base of the skull, brain, and oropharynx [21]. Therefore, MR can be considered a valuable tool in staging and outlining the GTV in head and neck cancer patients for RT [22,23]. Also for this reason, MR images may be better for use in contouring the brainstem.

Although poor soft-tissue contrast and visualization of tumors have been noticed on CT images of brain tumors and NPC, there are no indexes to quantify the error and establish appropriate guidelines. Additionally, MR has unique superiority for NPC and brain tumors, but there is a lack of quantitative data regarding how much better MR is for outlining the brainstem. In the present study, the estimated error for contouring the brainstem was investigated on CT and MR images. In addition, the intra- and inter-observer variability was compared.

In the present study, although the brainstem volumes obtained from CT and MR images were not statistically different, it is known that brainstem injury is largely related to the irradiation maximum dose. Therefore, the reproducibility of every layer on the same anatomical section among the different scans in a series of brainstem images must be improved. The intra-observer reproducibility for CT images reached 0.85. Moreover, for inter-observer, the reproducibility was even lower (0.81). In contrast, the intra- and inter-observer brainstem reproducibility for MR imaging were 0.92 and 0.90, respectively. In Figure 1, the first two layers and from the 11^{th} layer to the 13^{th} layer, the inter- and intra-observer reproducibility were almost in the same low level (nearly 0.80). We can conclude that it is difficult to distinguish the brainstem from the surrounding soft tissue in the middle portion. Figure 2 shows that in the first two layers, the brainstem can hardly be differentiated from the pedunculus cerebri and cisterna ambiens. In the 11^{th} layer to the 13^{th} layer, some radiotherapists outlined the posterior cerebral artery, cerebellar peduncle, and part of the middle cerebellar peduncle into the brainstem on CT images. On the contrary, from the first layer to the end, this reproducibility was maintained at a good level for both MR_{inter} and MR_{intra}. Figure 2 also shows that when contouring the start of the brainstem, the MR imaging can be much better than CT imaging for distinguishing the pedunculus cerebri from the surrounding tissues, especially when the brain tumor is near the brainstem. Moreover, with the help of the segmentation or visualization of coronal or sagittal planes, MR imaging can be used to distinguish the brainstem from cerebral and cerebellar peduncles. Hence, between observers, using MR imaging can obviously reduce the outlining error and result in the same contouring guidelines. In addition, Figure 1 shows that the MR_{intra} is better than the MR_{inter} ; therefore, if training for contouring the brainstem could be made uniform, the reproducibility may improve further.

However, MR imaging has not yet seriously challenged CT for RT planning in most sites. The reasons include: a) the lack of electron density information and b) the presence of distortions resulting in geometrical inaccuracies [24]. MR-based RT planning has usually been implemented in conjunction with CT images and has thus involved some form of image registration procedure [25,26]. Therefore, CT/MR fusion must be used for RT planning when MR is used for outlining the brainstem (as shown in the middle graph in Figure 2).

In conclusion, brainstem contouring based on MR has better reproducibility than that based on CT images. Thus, the more accurate and objective maximum radiation dose region could be obtained by applying MR imaging in the treatment planning for NPC and brain tumor patients.

Acknowledgements

This research was supported by the National Science Fund of China (no.81301936 and no.81272501).

During the protocol designing, data collecting and analyzing, and the manuscript writing, tremendous support was offered by the clinical and technique colleagues. Their support and help are greatly appreciated.

References

1. Mayo C, Yorke E, Merchant TE. Radiation associated brainstem injury. Int J Radiat Oncol Biol Phys 2010;76:S36-41.
2. Bayrakli F, Dinçer A, Sav A, Vardareli E, Peker S. Late Brain Stem Radionecrosis Seventeen Years After Fractionated Radiotherapy. Turk Neurosurg 2009;19:182-185.
3. Schipani S, Jain R, Shah K et al. Clinical, dosimetric, and radiographic correlation of radiation injury involving the brainstem and the medial temporal lobes following stereotactic radiotherapy for neoplasms of central skull base. J Neurooncol 2010; 98:177-184.

4. Schoenfeld GO, Amdur RJ, Morris CG, Li JG, Hinerman RW, Mendenhall WM. Patterns of failure and toxicity after intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2008;71:377-385.
5. Hoppe BS, Stegman LD, Zelefsky MJ et al. Treatment of nasal cavity and paranasal sinus cancer with modern radiotherapy techniques in the postoperative setting—the MSKCC experience. Int J Radiat Oncol Biol Phys 2007;67:691-702.
6. Jian JJ, Cheng SH, Tsai SY et al. Improvement of local control of T3 and T4 nasopharyngeal carcinoma by hyperfractionated radiotherapy and concomitant chemotherapy. Int J Radiat Oncol Biol Phys 2002;53:344-352.
7. Daly ME, Chen AM, Bucci MK et al. Intensity-modulated radiation therapy for malignancies of the nasal cavity and paranasal sinuses. Int J Radiat Oncol Biol Phys 2007;67:151-157.
8. Yu E, O'Sullivan B, Kim J, Siu L, Bartlett E. Magnetic resonance imaging of nasopharyngeal carcinoma. Expert Rev Anticancer Ther 2010;10:365-375.
9. Chin SC, Fatterpekar G, Chen CY, Som PM. MR imaging of diverse manifestations of nasopharyngeal carcinomas. Am J Roentgenol 2003;180:1715-1722.
10. Chung NN, Ting LL, Hsu WC, Lui LT, Wang PM. Impact of magnetic resonance imaging versus CT on nasopharyngeal carcinoma: primary tumor target delineation for radiotherapy. Head Neck 2004;26:241-246.
11. Jenghwa C, Ashwatha N. Functional MRI for Radiotherapy of Gliomas. Technol Cancer Res Treat 2010;9:347-358.
12. Emami B, Sethi A, Petruzzelli GJ. Influence of MRI on target volume delineation and IMRT planning in nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2003;57:481-488.
13. Houweling AC, van den Berg CA, Roesink JM, Terhaard CH, Raaijmakers CP. Magnetic resonance imaging at 3.0T for submandibular gland sparing radiotherapy. Radiother Oncol 2010; 97:239-243.
14. Chen L, Liu LZ, Chen M et al. Prognostic value of subclassification using MRI in the t4 classification nasopharyngeal carcinoma intensity-modulated radiotherapy treatment. Int J Radiat Oncol Biol Phys 2012;84:196-202.
15. Lu J, Wei B, Chen W et al. Staging of nasopharyngeal carcinoma investigated by magnetic resonance imaging. Radiother Oncol 2006;79:21-26.
16. Khoo VS, Joon DL. New developments in MRI for target volume delineation in radiotherapy. Br J Radiol 2006;79:2-15.
17. Bhatia KS, King AD, Paunipagar BK et al. MRI findings in patients with severe trismus following radiotherapy for nasopharyngeal carcinoma. Eur Radiol 2009;19:2586-2593.
18. Chang JT, Lin CT, Chen TM et al. Nasopharyngeal carcinoma with cranial nerve palsy: the importance of MRI for radiotherapy. Int J Radiat Oncol Biol Phys 2005;63:1354-1360.
19. Xue J, Goldman H, Grimm J et al. Dose-volume effects on brainstem dose tolerance in radiosurgery. J Neurosurg 2012;117:189-196.
20. Pasciuti K, Iaccarino G, Soriani A et al. DVHs evaluation in brain metastases stereotactic radiotherapy treatment plans. Radiother Oncol 2008;87:110-115.
21. Sharma M, Kondziolka D, Khan A et al. Radiation tolerance limits of the brainstem. Neurosurgery 2008;63:728-733.
22. Chau RM, Teo PM, Kam MK, Leung SF, Cheung KY, Chan AT. Dosimetric comparison between 2-dimensional radiation therapy and intensity modulated radiation therapy in the treatment of advanced T-stage nasopharyngeal carcinoma: to treat less or more in the planning organ-at-risk volume of the brainstem and spinal cord. Med Dosim 2007;32:263-270.
23. Sharma SD, Jalali R, Phurailatpam RD, Gupta T. Does intensity-modulated stereotactic radiotherapy achieve superior target conformity than conventional stereotactic radiotherapy in different intracranial tumours? Clin Oncol 2009;21:408-416.
24. Khoo VS, Dearnaley DP, Finnigan DJ, Padhani A, Tanner SF, Leach MO. Magnetic resonance imaging (MRI): considerations and applications in radiotherapy treatment planning. Radiother Oncol 1997;42:1-15.
25. Yanke BR, Ten Haken RK, Aisen A, Fraass BA, Thornton AF. Design of MRI scan protocols for use in 3-D, CT based treatment planning. Med Dosim 1991;16:205-211.
26. Haken RK, Thornton AF, Sandler HM et al. A quantitative assessment of the addition of MRI to CT based 3-D treatment planning of brain tumors. Radiother Oncol 1992;25:121-133.