·Intensity-Modulated Radiotherapy Column·

Concurrent control study of different radiotherapy for primary nasopharyngeal carcinoma: intensity-modulated radiotherapy versus conventional radiotherapy

Yu Zhang,[1] Zhi-An Lin,[2] Jian-Ji Pan,[1] Zhuo Zheng,[1] Ling Yang,[1] Shao-Jun Lin[1] and Fei Zheng[1]

[1]Department of Radiation Oncology, Teaching Hospital of Fujian Medical University, Fujian Provincial Tumor Hospital, Fuzhou, Fujian, 350014, P. R. China; [2]Department of Radiation Oncology, Zhongshan Hospital, Xiamen University, Xiamen, Fujian, 361004,P. R. China

[Abstract] Background and Objective: Intensity-modulated radiotherapy (IMRT) has recently gained popularity in the treatment of nasopharyngeal carcinoma (NPC) and improved the local-regional control rate. This study was to explore whether IMRT could improved the survival rate while reduce the radiation-related injury for primary NPC patients compared with conventional radiotherapy (CRT). **Methods:** From Nov. 2003 to Dec. 2005, 190 patients with NPC treated with IMRT in a single hospital were retrospectively analyzed. Another 190 patients treated with conventional radiotherapy at the same period were matched by prognostic factors respectively. The survival status and treatment-induced adverse effects were investigated. Treatment results, the occurrence and severity of adverse effects of two groups were compared. **Results:** In the treatment of NPC, IMRT was superior to CRT in term of 4-year local regional control rate, relapse-free survival rate without reducing the overall survival rate. But there were no significant differences in the 4-year progress-free survival rate and distant metastasis-free survival rate between the two groups. Significant reductions of the occurrence rates and severity of acute skin reaction, neck fibrosis, trismus and xerostomia were noted in IMRT arm. But there were no differences in mucositis, hematological toxicity, hearing loss and radiation induced cranial neuropathy between IMRT arm and CRT arm. **Conclusions:** IMRT could improve the local regional control rate and relapse-free survival rate while reduce some radiation-related complications in patients with NPC. But the improvement of overall survival rate did not reach significant level.

Key words: nasopharyngeal neoplasm, intensity-modulated radiotherapy, prognosis, radiation damage

In recent years, the application of intensity-modulated radiotherapy (IMRT) in nasopharyngeal carcinoma (NPC) has been increased gradually, with 2- and 3-year local control rates of above 90% ,[1-3] and the efficacy has improved significantly compared with conventional radiotherapy (CRT).

Some scholars think there may be bias in the comparison of treatment efficacy in different periods due to stage change caused by advances of diagnostic imaging, changes of comprehensive treatment modalities, as well as the use of adjuvant radiotherapy equipment.[4] In IMRT, will longer time required from preparation to treatment, extended duration of each irradiation and the reduced dose rate affect the efficacy? Will increased fraction dose of GTV and volume of low-dose region in normal tissues increase radiation damage? Can improved local control rate of NPC be translated into survival advantage? All these questions need to be confirmed by clinical research.

In this study, matched cohort study[5] was used to analyze the survival, acute and late toxicity in two groups of newly diagnosed patients with NCP treated by IMRT or CRT in the same period, and explore the efficacy of IMRT for newly diagnosed NPC.

Patients and Methods

Case selection

From November 2003 to December 2005, 197 newly diagnosed patients with NPC were treated by IMRT at Fujian Provincial Tumor Hospital, among which 7 patients were excluded according to the following criteria, and 190 patients were selected as IMRT group. In the same period, 639 newly diagnosed patients with NPC treated by CRT were eligible,

Correspondence to: Jian-Ji Pan; Tel: +86-591-83617526; Fax: +86-591-83928767; Email: panjianji@126.com

This paper was translated into English from its original publication in Chinese by *CJC* Medical Translation and Wei Liu on 2009-09-26.

The original Chinese version of this paper is published in *Chinese Journal of Cancer* 28(11); http://www.cjcsysu.cn/cn/article.asp?id=16453.

Submitted: 2009-08-11; Revised: 2009-08-25.

Grant: Natural Science Foundation of Fujian Province (No. C0310034,No. 2006J0331)

among which 190 patients were selected as CRT group by 1∶1 matching with IMRT group.

Enrollment criteria Patients with pathology of NPC, age of less than 75 years, Karnofsky score of more than 70, treatment interruption of no more than 5 days, and without previous radiotherapy, distant metastasis, and second primary cancer were enrolled.

Exclusion criteria Patients with relapse after radiotherapy, incomplete treatment, or other serious medical disorders such as stroke, diabetes, hypertension, heart disease, and so on, or pathology of non-poorly differentiated squamous cell carcinoma were excluded.

Matching conditions Gender was matched by male or female. Stage was matched by T stage, N stage and M stage according to the '92 Fuzhou staging system. Age was matched by less than 30 years, 30–50 years or more than 50 years old, with a difference of no more than 10 years. Hemoglobin was matched by no less than 110 g/L or less than 110 g/L. Chemotherapy were matched by induction or concurrent chemotherapy, with the same cycles and dose.

Matched control patients were determined after the screening by Excel according to above matching conditions in the database of patients with NPC.

Comparison of equilibrium between two groups There was no significance in sex, age, stage, treatment, follow-up time from treatment starting, the application of comprehensive treatment and hemoglobin between the two paired groups, as shown in Table 1.

Table 1 Clinical status of patiects with primary nasopharyngeal carcinoma treated with IMRT arm and CRT arm

Variate	IMRT(cases)	CRT(cases)	χ^2	*P*
Sex				
Male	146	146		
Female	44	44		
Age(years)				
<30	23	13		
30–50	102	110	3.11	0.211
>50	65	67		
Time after treatment (months)	41.7	41.5	0.283(*t* value)	0.777
T stage				
T1	2	2		
T2	78	78		
T3	57	57		
T4	53	53		
N stage				
N0	22	22		
N1	79	79		
N2	79	79		
N3	10	10		
Clinical stage('92 Fuzhou)				
Ⅰ	1	1		
Ⅱ	32	32		
Ⅲ	97	97		
Ⅳa	60	60		
Chemotherapy				
Induction	113	115	0.701	0.951
Induction+concurrent	3	3		
Induction+adjuvant	14	12		
Concurrent	5	5		
Adjuvant	23	18		
Hemogrobin (g/L)				
≥110	186	186		
<110	4	4		

IMRT, intensity-modulated radiotherapy; CRT, conventional radiotherapy.

Treatment

IMRT was performed as stated in reference [1]. In CRT, facio-cervical field, small facio-cervical field and bilateral pre-auricular field with or without pre-nasal field were used for primary tumor, with a total dose of 68–72 Gy. After receiving external irradiation of 56–60 Gy, 36 patients with stage I-II NPC received intracavitary treatment by 2.5–3.0 Gy/fraction, twice a day for 3 days. Electron beam irradiation was boosted for the upper neck after sparing the spinal cord, and tangent field was used for the lower neck. Dose of 64–70 Gy was given to all positive cervical lymph nodes, and the prophylactic dose was 50–54 Gy. Induction chemotherapy was performed as stated in reference [1]. Concurrent and adjuvant chemotherapy regimens were as follows: intravenous infusion of paclitaxel (135 mg/m^2) on day 1 and intravenous infusion of cisplatin (80 mg/m^2 given in 3 days) on days 1–3, with 21 days for a cycle; concurrent chemotherapy was given for 1–2 cycles and adjuvant chemotherapy for 2–3 cycles.

Follow-up

Examination was carried out repeatedly after treatment, every 3 months in the first year, every 6 months in the second year, and every year thereafter, including general physical examination, nasopharyngoscopy, chest radiography, abdominal B-ultrasound, and CT or MRI of the nasopharynx, skull base and neck. Follow-up ended on July 31, 2008. Endpoints included local or regional relapse, distant metastasis and death, as well as irradiation-related adverse events. Survival time was calculated from the day the treatment started.

Evaluation criteria

WHO Response Evaluation Criteria in Solid Tumors was used for clinical efficacy evaluation. RTOG/EORTC Criteria[6] was used for toxicity evaluation.

Statistical analysis

SPSS15.0 software was used for statistical analysis. Normal distribution test was performed firstly for measurement data. *t* test was used for normal distribution data, and non-parametric test for non-normal distribution data. Survival rate was calculated by Kaplan-Meier method, and log-rank test was used for intergroup comparison. The radiation toxicities were compared by non-parametric test of two samples. Two-sided test was adopted, and a *P* value of less than 0.05 was considered significance.

Results

Follow-up results

The median follow-up time was 39 months (range, 3-61 months) in IMRT group with 13 cases lost, and it was 38 months (range, 3-55 months) in CRT group with 11 cases lost. The total lost rate in two groups was 6.33%, with lost data as censored data. In IMRT group, 1 patient died of car accident, also as censored data.

Of the patients with local relapse, 7 were in IMRT group, and 3 in CRT group. Of those with regional lymph node relapse, 2 were in IMRT group, and 5 in CRT group. Of those with locoregional relapse, 3 were in IMRT group, and 14 in CRT group. Of those with distant metastasis, 21 were in IMRT group, and 15 in CRT group. All the 6 patients with local failure and distant metastasis were in CRT group.

Long-term efficacy

The 4-year local relapse-free survival rate was significantly higher in IMRT group than in CRT group (89.8% vs. 80.7%, χ^2=4.781, *P*=0.029) (Fig. 1). The 4-year locoregional control rate was also significantly higher in IMRT group than in CRT group (90.4% vs. 78.3%, χ^2=7.400, *P*=0.011) (Fig. 2).

Stratified analysis showed that the differences in 4-year local relapse-free survival rate and locoregional control rate of stage I-II patients between two groups had no significance (97.0% vs. 86.8%, *P*=0.290; 89.0% vs. 78.5%, *P*=0.167). The differences in 4-year local relapse-free survival rate and locoregional control rate of stage III-IV patients between two groups were significant (88.2% vs. 75.2%, *P*=0.049; 89.0% vs. 78.5%, *P*=0.017).

The difference in 4-year progression-free survival rate, distant metastasis-free survival rate and overall survival rate between two groups had no significance (79.4% vs. 64.8%, χ^2=1.315, *P*=0.251; 88.6% vs. 83.4%, χ^2=0.032, *P*=0.857; 88.9% vs. 75.8%, χ^2=1.347, *P*=0.246) (Fig. 3).

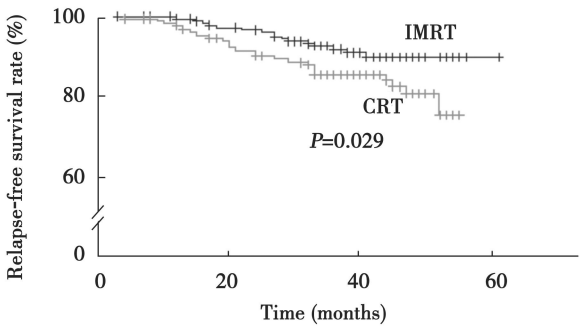

Figure 1 Relapse-free survival rate of patients with primary nasopharyngeal carcinoma treated with intensity-modulated radiotherapy (IMRT) arm and conventional radiotherapy (CRT) arm

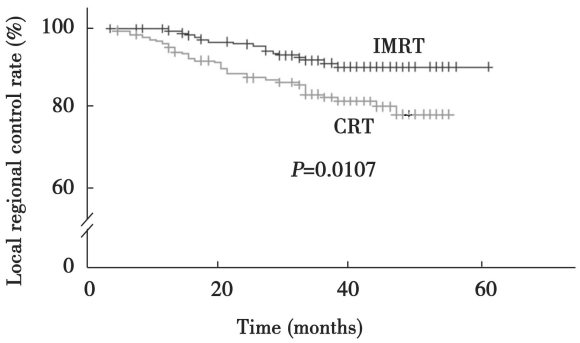

Figure 2 Local regional control rate of patients with primary nasopharyngeal carcinoma treated with IMRT arm and CRT

Table 2 Acute radiation reaction of IMRT arm and CRT arm on patients with primary nasopharyngeal carcinoma (number)

Grade	acute skin reaction		Radiation mucositis		Hematological toxicity		Xerostomia	
	IMRT	CRT	IMRT	CRT	IMRT	CRT	IMRT	CRT
0	3	0	0	0	31	22	18	3
I	145	85	49	54	71	76	125	85
II	35	83	100	95	80	77	47	97
III	7	22	41	41	8	13	0	5
IV	0	0	0	0	0	2	0	0
Z	−6.528		−0.494		−0.938		−6.505	
P	<0.001		0.622		0.348		<0.001	

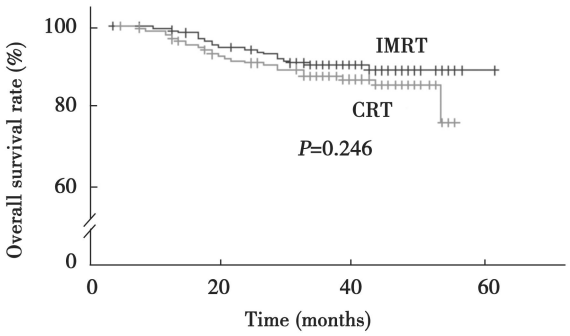

Figure 3 Overall survival rate of patients with primary nasopharyngeal carcinoma treated with IMRT arm and CRT arm

Comparison of acute radiation toxicity

As shown in Table 2, the incidences of acute skin reaction in radiation field and acute serostomia in IMRT group and CRT group had significant difference, while the incidences of acute oral mucositis and bone marrow suppression had no significant difference.

Comparison of late radiation toxicity

As shown in Table 3, the incidences of neck fibrosis and severe trismus were lower in IMRT group than in CRT group, while the difference in hearing loss had no significance. One patient in IMRT group and 2 in CRT group had radiation-induced brain injury. The difference in the incidence of radiation-induced cranial nerve injury between two groups was not significant. Second primary tumor was not observed in radiation area. As shown in Table 4, the incidences of serostomia at 6 months, 1 year, 2 years, 3 years and 4 years after treatment were lower in IMRT group than in CRT group. As time went on, serostomia alleviated gradually in two groups, but more quickly in IMRT group. Most patients in IMRT group had no significant serostomia at 3 years after radiotherapy.

Table 3 Radiation-related damages of IMRT arm and CRT arm on patients with primary nasopharyngeal carcinoma (number)

Grade	Neck fibrosis		Trismus		Hearing loss		Radiation induced cranial neuropathy	
	IMRT	CRT	IMRT	CRT	IMRT	CRT	IMRT	CRT
0	101	73	149	111	125	113	152	145
Ⅰ	53	63	6	32	30	32		
Ⅱ	2	12	1	5	1	4	4	4
Ⅲ	0	1	0	1	0	0		
Ⅳ	0	0	0	0	0	0		
Z	−3.158		−5.037		−0.981		0.004	
P	0.020		<0.001		0.327		0.948	

Note: Apart from withdrawal of cases died and recurrent cases.

Table 4 Xerostomia of patients with primary nasopharyngeal carcinoma after radiotherapy of IMRT arm and CRT arm (number)

Grade	6 months		1 years		2 years		3 years		4 years	
	IMRT	CRT	IMRT	CRT	IMRT	CRT	IMRT	CRT	IMRT	CRT
0	48	8	74	12	77	20	71	17	34	10
Ⅰ	119	80	101	102	87	93	63	81	19	26
Ⅱ	22	93	11	65	6	46	6	31	1	12
Ⅲ	0	5	0	3	1	6	0	5	0	1
Ⅳ	0	0	0	0	0	0	0	0	0	0
Z	−9.178		−9.262		−8.163		−7.670		−4.866	
P	<0.001		<0.001		<0.001		<0.001		<0.001	

Discussion

Radiotherapy has always been the main treatment of NPC. In recent years, IMRT is expected to give patients more benefits. In this study, IMRT was compared with CRT performed in the same period, so that stage change caused by advances of diagnostic imaging, changes of comprehensive treatment modalities, and the use of adjuvant radiotherapy equipment were comparable in the two groups; at the same time, through matching prognostic factors except for radiotherapy method, no other significant difference exists between the two groups in order to explore the difference of radiotherapy.

The study showed that the differences in local relapse-free survival rate and locoregional control rate of stage III-IV patients between IMRT and groups had significance, which was consistent with recent reports.[7,8] In our opinion, in patients with advanced NPC, the target volume is always large with irregular shape, and is closely adjacent to the brain stem and other important organs. In IMRT, multi-field irradiation technology is

often used, and the target volume can be better covered by high-dose region with reasonable dose distribution, 95% of which achieve the prescribed dose with conversion between high-dose region and low-dose region, and normal tissues are better protected. Large target volume has large central hypoxic region, which requires high doses, while CRT is limited by simple beam direction and low tolerance dose for organs at risk, resulting in obvious contradiction of increasing the dose for target volume and reducing the dose for normal tissue. In CRT, in order to protect the organs at risk, the target volume can not receive due high-dose irradiation, and low dose of the beam edge is also a major flaw. Kam et al.[9] compared IMRT with CRT for NPC, and found that the doses to 95% of target volume were 68 Gy in IMRT and 57.5 Gy in CRT.

In the stratified analysis, the difference in local relapse-free survival rate and locoregional control rate of stage I–II patients between two groups had no significance. There are two main reasons: firstly, the target volume in early stage NPC patients was small, and can be clearly indicated by MRI and well covered by conventional two-dimensional irradiation technique, with small possibility of missing; secondly, 33.1% (27/80) of stage I-II patients in CRT group received intracavitary treatment after planned external irradiation. Intracavitary therapy can be considered as a small local IMRT, and can also increase the dose of target volume well for tumors in the nasopharyngeal cavity. Therefore, conventional external beam irradiation plus intracavitary therapy is also a good treatment for patients with early stage NPC, which would cut down the advantage of IMRT.

The study showed that the difference in distant metastasis-free survival and progression-free survival rate between two groups had no significance. Twenty-one (11.1%) patients in each group had distant metastasis. In this study, induction, concurrent and adjuvant chemotherapy were balanced in the two groups, and had no direct influence on the outcome. We also found that the 4-year overall survival rates were 88.9% in IMRT group and 75.8% in CRT group with no significant difference, but overall survival curve had shown the advantage trend of IMRT. The insignificant difference between the two groups might be related to insufficient follow-up time. As to whether IMRT reduces distant metastasis rate and improves survival rate ultimately, or only as a means of local treatment, long-term follow-up and large sample analysis are needed.

In regard to acute and late radiation toxicity, the study showed IMRT can reduce radiation reactions, including acute and chronic xerostomia. The recent extensive literatures have proved this point. It was reported that irradiation of more than 45 Gy can cause almost irreversible damage to the parotid gland.[10] Eisbruch et al.[11] found that if the median parotid dose was no more than 26 Gy, the secretory function of the parotid gland could be well protected and gradually improved over time. Zhang et al.[12] measured the uptake and secretion function changes of the parotid gland in two groups, and found that the incidences of grade I, II, III, IV and V radiation-induced parotid gland injury at six months after radiotherapy were 50.0%, 38.4%, 9.6%, 2.0%, 0 in IMRT group and 22.2%, 22.2%, 55.6%, 0, 0 in CRT group, respectively; parotid function recovered better in IMRT group than in CRT group. With emphasis on the protection of the parotid gland, at the same time, people have begun to focus on the issue of submandibular gland protection.[13] We will do in-depth research on the radiation doses of the parotid and submandibular glands in the next step.

The incidence of neck fibrosis and the incidence and severity of trismus between two groups had significant difference. In IMRT, lymphatic drainage area is selectively irradiated, and local muscle and other soft tissues are less exposed; hot spots are controlled within the target volume by dose optimization, and generally cervical soft tissue does not expose to high dose, so the late radiation toxicity is mild. In CRT, high-dose regions are located in both sides of the temporomandibular joint with masticatory muscles affected by large doses, leading to a high incidence of trismus after radiotherapy. In IMRT, the temporomandibular joint are well protected due to reasonable dose distribution. This study showed that the incidences of grade I-II trismus were 3.6% in IMRT group and 19.7% in CRT group, which was similar with the findings of Liu et al.[14]

Cranial nerve injury was observed in4 patients in each group, with the earliest one occurring at 16 months after IMRT. Damage was found in the IX to XII pairs of cranial nerves. Cranial nerve injury mostly occurred within 3–7 years after radiotherapy, therefore, further follow-up is needed in this study. In our opinion, because cervical lymph node metastasis often occurs around the carotid sheath, part of which will also be irradiated when the target volume of lymph nodes is irradiated by IMRT, with large dose in each fraction, hence, injury to late response tissue is also likely to increase.

The two groups had no difference in hearing loss, and the cases of grade I and II hearing impairment were 30 and 1 in IMRT group, 32 and 4 in CRT group, probably because the inner and middle ear were not regarded as organs at risk and irradiated by low dose at early stage of IMRT application. Kuijper et al.[15] pointed out that hearing could be protected if the target volume was more than 0.6 cm away from the inner ear, or involved no more than 10% of the middle ear. Recently, we have limited irradiation doses to the inner and middle ear.

In conclusion, although this is a retrospective non-randomized controlled study, the main factors affecting prognosis are balanced in the two groups. As preliminary conclusions, IMRT increases local relapse-free survival rate and locoregional control rate in patients with newly diagnosed NPC, but does not improve distant metastasis-free survival, progression-free survival and overall survival rate; some radiation toxicities caused by IMRT are less severe than those by CRT, which helps to improve patients' quality of life; long-term toxicity of IMRT needs further observation.

References

[1] Pan JJ, Lin SJ, Zhang Y, et al. Preliminary research on nasopharyngeal carcinoma treated with intensity-modulated radiotherapy [J]. Chin J Cancer Prev Treat, 2006, 13(20):1553–1555. [in Chinese]

[2] Lee N, Xia P, Quivey JM, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience[J]. Int J Radiat Oncol Biol Phys, 2002,53(1):12–22.

[3] Kam MK, Teo PM, Chau RM, et al. Treatment of nasopharyngeal

carcinoma with intensity-modulated radiotherapy: the Hong Kong experience[J]. Int J Radiat Oncol Biol Phys, 2004,60(5):1440-1450.
[4] Lee AW, Sze WM, Au JS, et al. Treatment results for nasopharyngeal carcinoma in the modern era: The Hong Kong experience [J]. Int J Radiat Oncol Biol Phys, 2005,61(4): 1107-1116.
[5] Liu XQ, Luo W, Tang YQ, et al. A matched cohort analysis of three-dimensional conformal radiotherapy versus conventional radiotherapy for primary nasopharyngeal carcinoma [J]. Chin J Cancer, 2008, 27(6):606-611.[in Chinese]
[6] Yin WB, Gu XZ. Radiation oncology [M]. 3th Edition.,2002:1108-1111.[in Chinese]
[7] Chau RM, Teo PM, Kam MK, et al. Dosimetric comparison between 2-dimensional radiation therapy and intensity modulated radiation therapy in treatment of advanced T-stage nasopharyngeal carcinoma: to treat less or more in the planning organ-at-risk volume of the brain and spinal cord [J]. Med Dosim, 2007,32(4):263-270.
[8] Waldron J, Tin MM, Keller A, et al. Limitation of conventional two dimensional radiation therapy planning in nasopharyngeal carcinoma [J]. Radiother Oncol, 2003,68(2):153-161.
[9] Kam MK, Chau RM, Suen J, et al. Intensity-modulated radiotherapy in nasopharyngeal carcinoma: dosimetric advantage over conventional plans and feasibility of dose escalation [J]. Int J Radiat Oncol Biol Phys, 2003,56(1):145-157.
[10] Valdés Olmos RA, Keus RB, Takes RP, et al. Scintigraphic assessment of salivary function and excretion response in radiation-induced injury of the major salivary glands[J]. Cancer, 1994,73(12):2886-2893.
[11] Eisbruch A, Ten Haken RK, Kim HM, et al. Dose, volume,and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer [J]. Int J Radiat Oncol Biol Phys, 1999,45(3):577-587.
[12] Zhang C, Pan JJ, Zhang Y, et al. Scintigraphic assessment of parotid function prior to and after IMRT for patients with nasopharyngeal carcinoma [J]. Pract J Cancer, 2007,22(4):380-383.[in Chinese]
[13] Jellema AP, Doornaert P, Slotman BJ, et al. Does radiation dose to the salivary glands and oral cavity predict patient-rated xerostomia and sticky saliva in head and neck cancer patients treated with curative radiotherapy? [J]. Radiother Oncol, 2005,77(2):164-171.
[14] Liu Y, Chen M, Zhao C, et al. Radiantion-induced temporomandibular joint damage in nasopharyngeal carcinoma patients after intensity-modulated radiotherapy [J]. Chin J Cancer, 2007, 26 (1):64-67.[in Chinese]
[15] Lamers-Kuijper E, Schwarz M, Rasch C, et al. Intensity-modulated vs. conformal radiotherapy of parotid gland tumors: potential impact on hearing loss[J]. Med Dosim, 2007,32(4):237-245.