Clin Oncol Cancer Res (2010) 7: 116-121
DOI 10.1007/s11805-010-0505-0

Observation of Intensity-Modulated Radiotherapy with Different Fractionated Doses Used in 58 Cases with Astrocytoma

Yun-qin LIU
Li-ting QIAN
Hong-yan ZHANG
Jun MA
Yu-fei ZHAO
Wei-wei WU

Department of Radiation Oncology, Anhui Provincial Hospital Affiliated with Anhui Medical University, Hefei 230001, Anhui Province, China.

Correspondence to: Li-ting QIAN
E-mail: money2004@sina.com

The work was supported by a grant from the Foundation of Anhui Provincial Scientific Problem-Tackling Program, China (No. 0701302202).

Received February 26, 2010; accepted April 6, 2010.

E-mail: 2008cocr@gmail.com
Tel (Fax): 86-22-2352 2919

OBJECTIVE To analyze the therapeutic effects and side effects of intensity-modulated radiotherapy (IMRT) with different fractionated doses in treating astrocytoma.

METHODS During a period from October 2001 to December 2006, 58 patients with astrocytoma were treated using IMRT. Based on the World Health Organization (WHO) classification, 32 of the 58 cases were grade-II, 20 grade-III and 6 grade-IV (glioblastoma multiforme, GBM). Thirty-two of the 58 patients (3 with grade IV, 11 with grade III, and the other 18 with grade II who were over 40 years) were treated with hyperfractionated IMRT (Hyper Fr IMRT), and the other 26 patients were treated with standard fractionated IMRT (St Fr IMRT).

RESULTS The 1-, 3- and 5-year overall survival (OS) rates were respectively 86%, 52%, and 45%, and the 1-, 3- and 5-year progression-free survival (PFS) rates were respectively 77%, 38%, and 25%. Using an analytical hierarchy process it was shown that concerning the patients with grade II astrocytoma classified based on WHO grading, the therapeutic effect was much better in the group of Hyper Fr IMRT than in the St Fr IMRT group. There was no statistical significance of the differences in the OS and PFS rates between the 2 groups ($P = 0.049$ and $P = 0.006$). The OS and PFS rates of the patients with grade-III astrocytoma were both higher in the group with Hyper Fr IMRT than in the St Fr IMRT group. However, there was no statistical significance of the differences between the 2 groups. Advanced RTOG grade-III (radiation therapy oncology group, RTOG) neurotoxicity occurred only in 1 of the cases.

CONCLUSION Compared with the St Fr IMRT, the Hyper Fr IMRT may help to prolong the survival of patients with astrocytoma.

KEY WORDS: astrocytoma, intensity-modulated radiotherapy, conformal radiotherapy.

Introduction

Conventional therapy for astrocytoma is surgery followed by adjuvant radiotherapy and/or chemotherapy. Since some of the tumors are close to jeopardized areas which control vital organs, such as eyes, optic nerve, optic chiasm, brain stem and spinal cord, using high-dose radiation is not safe if delivered to the region of the tumor through

conventional radiotherapy. New techniques in radiotherapy, such as 3 dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) can increase the dose delivered to the target area while reducing the dose to the peripheral normal tissue. Recently, it has been shown in a comparative study on the different dose distribution between the plans of 3D-CRT and IMRT, that in the treatment of high-grade gliomas, IMRT can improve the conformality in the target tissue and better protect the normal tissues[1]. The technique of IMRT has been available in more and more clinical settings. However, the proper fractionated dose, treatment outcomes, and toxic reactions produced by IMRT in treating the astrocytomas is still unclear. Since 2001, hyper-fractionated (Hyper Fr) or standard fractionated (St Fr) IMRT for treating astrocytoma began to be applied in our hospital. In this paper, the outcome of survivals and radio-therapeutic reaction of the new technology were retrospectively reviewed.

Materials and Methods

Clinical data

From October 2001 to December 2006, 58 astrocytoma patients, with a KPS of ≥ 60, underwent IMRT. Of these patients, grade-II astrocytoma was found in 32, grade-III malignant astrocytoma in 20, and grade-IV glioblastoma multiforme (GBM) in the remaining 6. Hyper-fractionated IMRT was conducted in 32 patients, including 3 with grade- IV, 11 with grade-III, and the other 18 with grade-II astrocytoma. All these patients were above 40 years of age. At the same time, St Fr IMRT was conducted in the other 26 astrocytoma patients. There were no significant differences in the clinicopathologic features between the 2 groups (Table 1). The median age of the 58 patients was 45 years, with a range from 19 to 74 years. In the patients, 37 were male and 21 female. Before the treatment, none of the patients received any chemotherapy or radiotherapy. Puncture biopsy was performed in only 1 patient and a partial resection of the tumor was performed in all other patients. The foci localized in a temporal lobe were found in 34 of the cases, a frontal lobe in 21, an occipital lobe in 2, and a parietal lobe in 1. The median dose of the radiotherapy was 58 Gy (range from 54 to 60 Gy). Adjuvant chemotherapy was given to 24 patients with grade-III or grade-IV for 4 to 6 cycles after radiotherapy. Salvage chemotherapy was used in 5 of the patients, who developed a recurrence following radiation therapy. A dosage of 150-200 mg/m^2 of temozolomide, an oral chemotherapeutic drug, was given to 4 patients for successive 5 days, and was repeated every 28 days. In 25 patients, an intravenous drip of carmustine at 125 mg/d was administrated for 3 successive days, and repeated every 4-6 weeks.

Treatment

The median interval time between the surgery and radiotherapy was 28 days, with a range of 15 to 39 days. The simulation was conducted 1 to 3 weeks after surgery. A thermoplastic face-mask was correctly utilized for each patient by fixing in on the head and neck during radiotherapy. The enhanced computer tomography scan (CT) was conducted on all of the patients. The range of the scan was from head to neck, with a thickness of 2.5 mm. All image data were transmitted to the NOMOS Peacock planning system for 3 dimensional dose optimization and computation, which produced a dose-volume histogram. The patients underwent a MRI scan a week after the CT examination in order to make a clear delineation of the target area and the vital organs close to the

Table 1. Comparison of clinicopathologic features between the group of St Fr IMRT and group of Hypo Fr IMRT.

Factors	Group of Hypo Fr IMRT (n = 32)	Group of St Fr IMRT (n = 26)	P
Age (years)	46.5 ± 11.5	41.5 ± 16.7	0.305
Sex			
Female	13	8	0.437
Male	19	18	
KPS	80 ± 8.9	80 ± 6.5	0.093
Pathologic types			
WHO grade-II	18	14	0.961
WHO grade-III	11	9	
WHO grade-IV	3	3	
Interval time between surgery and radiotherapy (days)	8.0 ± 6.1	27.0 ± 6.6	0.35
Chemotherapy			
Yes	14	15	0.291
No	18	11	

tumor. The clinical target volume (CTV) of grade-II astrocytoma meant a 1-2 cm extension from the margin of the diseased region (DisR) shown by the enhanced CT and MRI scan conducted after surgery. The total dose of the CTV was 55 Gy /22f in the group with Hyper Fr IMRT, with 2.5 Gy each time, and was 54 Gy/27f in the group with St Fr IMRT, with 2 Gy each time. The CTV of grade-III malignant astrocytoma and grade-IV GBM indicated a 2 cm extension from the margin of the DisR shown by the enhanced CT and MRI scan performed after surgery. The total dose of CTV was 60 Gy/24f in the group with Hyper Fr IMRT, with 2.5 Gy each time, and 60 Gy/30f in the group with St Fr IMRT, with 2 Gy each time. The planning of target volume (PTV) showed a 0.3-0.5 cm extension from the margin of the CTV, and the PTV was surrounded by 90% of the isodose line. In our groups, the delineation of the target area referred to the conventional radiotherapy, i.e., there was a 2 cm extension beyond the gross tumor volume (GTV) for planning the PTV of low potential malignancy astrocytoma, and 2.5-3 cm more extension for PTV of glioblastoma multiforme (GBM). In addition, it was confirmed by previous data that for PTV of GBM with tumor relapse, the exposure field was usually within the GTV of the tumor plus a 2 cm extension[2]. By using the 6-MV X-ray accelerator, radiotherapy was given 5 days a week, and lasted for 5 to 6 weeks in total. The maximum tolerated dose of these vital organs was as follows: 4000 cgy for the spinal cord, 5400 cGy for the optic nerve and the optic chiasm, 1000 cGy for crystal bodies, and 5500 cGy for the brain stem.

Follow-up

The follow-up data of the patients were obtained from the case records kept in the clinic and admission office of the hospital, including the case history, neurologic check, and CT or MRI examination. Call visits were carried out to all patients (to the patients or relatives of the patients). The calculation of the survival time and the time of tumor progression (TTP) started from the first day of the radiotherapy. The level of tumor progression was determined based on the clinical neurologic check and image analysis. The radiotherapeutic reactions were classified based on the grading system of the radiation therapy oncology group (RTOG).

Statistical analysis

SPSS 13.0 statistical software was used for statistical analysis, and the survival rate was computed using the life-table method. The Log rank test was adopted to check the significance of the differences in the survival rate among the groups. Multivariate analysis (Cox regression) was used for evaluating the known factors, such as the gender, age, KPS, mode of fractionation and the impact of tumor staging on the prognosis.

Results

Survival and local control (LC) rates

The median follow-up time was 24 months, ranging from 5 to 73 months. Disease-free survival was found in 24 of the 58 patients (41.4%). Eight of the 58 patients lived well with cancer (13.8%), but 26 patients died of tumor progression (44.8%). The 1-, 3-, and 5-year overall survival (OS) rates were 86%, 52%, and 45% (Fig.1) respectively, and the 1-, 3-, and 5-year progression-free survival (PFS) rates were respectively 77%, 38%, and 25% (Fig.2). The 1-, 3-, and 5-year OS rates were respectively 100%, 63%, and 57% in the patients with grade-II astrocytoma, and 84%, 51%, and 38%, respectively in the patients with grade-III malignant astrocytoma. All 6 GBM patients died, with median survival times (MST) respectively of 10 months and 7 months (Fig.3) in the Hyper Fr IMRT and St Fr IMRT groups.

Different fractionated doses

In comparing the survival and RC rates in the patients treated with different fractionated doses of IMRT, analysis showed using the analytical hierarchy process that the 5-year OS rates of the grade-II astrocytoma patients were respectively 50% and 30% (P = 0.049, Fig.4) in the Hyper Fr IMRT and St Fr IMRT groups. The 5-year PFS rates were 48% and 11%, respectively in the Hyper Fr IMRT and St Fr IMRT groups (P = 0.006, Fig.5). The

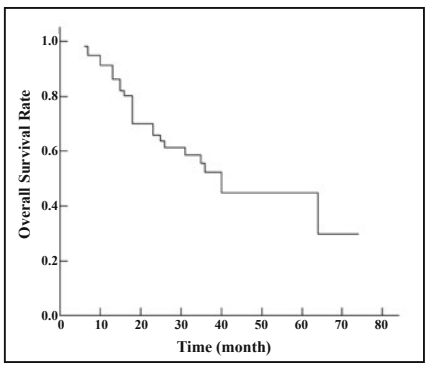

Fig.1. Overall survival curve of all patients in the group.

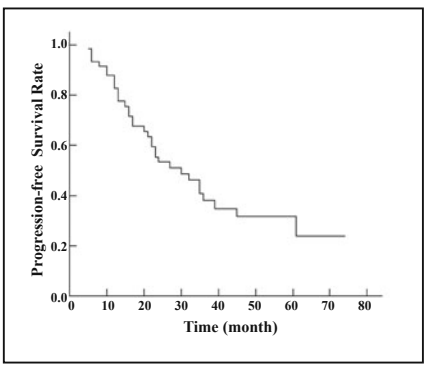

Fig.2. Progression-free survival curve of all patients in the group.

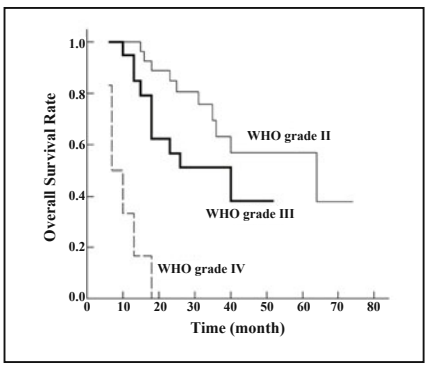

Fig.3. Overall survival curves of all patients with WHO grade II, III and IV GBM in the group.

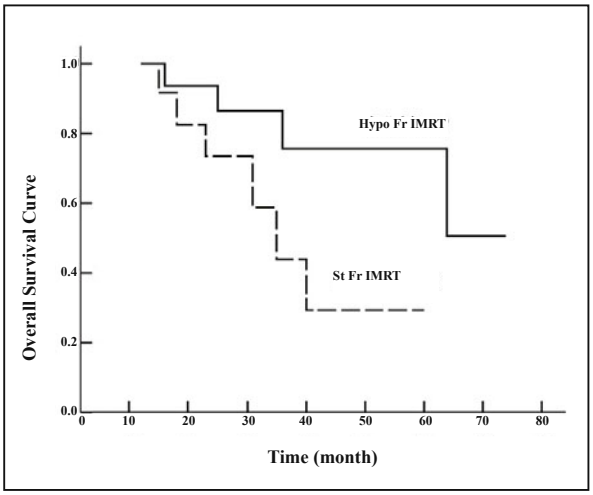

Fig.4. Comparison of the overall survival curves between the patients with grade II astrocytoma respectively treated with Hypo Fr IMRT and St Fr IMRT.

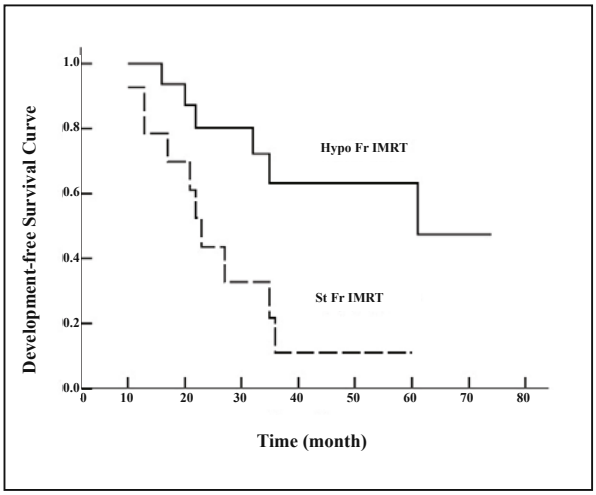

Fig.5. Comparison of the progression-free survival curves between the patients with grade II astrocytoma respectively treated with Hypo Fr IMRT and St Fr IMRT.

OS and PFS rates of grade III patients investigated by WHO were higher in the Hyper Fr IMRT group compared to those in the St Fr IMRT group. However, there was no statistical significance in the differences between the two groups ($P = 0.368$ and $P = 0.356$).

Analysis of prognostic factors

Univariate analysis indicated that the factors predicting poor prognosis of the patients included a high grade of tumor classified based on the WHO grading, age of ≥ 50 years, and the KPS less than 70, with the *P* values of 0.000, 0.000 and 0.012, respectively. The multivariate COX regression analyses of the age (< 50 *vs.* ≥ 50), KPS (< 70 *vs.* ≥ 70), gender (male *vs.* female), grading of tumor (grade II *vs.* III *vs.* IV), and the mode of fractionation (St Fr *vs.* Hypo Fr) were conducted. There were correlations among tumor grading, age, the mode of fractionation, and survival, with the *P* values of 0.000, 0.002 and 0.025, respectively.

Types of relapse

A local recurrence of the primary focus occurred in 31 of the total patients, contralateral recurrence in 2 and dissemination to the cerebrospinal fluid in 1 patient.

Complications

All patients completed the treatment plan, with slight acute toxic reactions. A RTOG grade I reaction was found in 43 of the 58 patients (74.1%) and a RTOG grade II reaction in the other 15 (25.9%). There were no statistical differences in the acute reactions between the Hyper Fr IMRT and St Fr IMRT groups. The RTOG grade-III advanced reaction occurred in one patient with a grade-III malignant astrocytoma from the Hyper Fr IMRT group. The primary tumor was localized in the temporal lobe, and the patient presented a disorder of verbal expression, with an enlarged DisR shown by enhanced MRI scan 11 months after the radiotherapy. In a follow-up after the symptomatic treatment, no further progression of the lesion was found via enhanced MRI examination. The RTOG grade IV/V advanced neurotoxicity was not found, either group.

Discussion

Different radiotherapeutic doses in different target areas can be concurrently given by IMRT. The total dose of St Fr IMRT is lower, within the fixed frequency of irradiation, in the normal tissue compared to the target area of the tumor. Therefore, each fractionated dose in the normal tissue can be reduced, and as a result, normal tissue damage in the late phase reaction is decreased. Compared to the St Fr IMRT, Hyper Fr IMRT possesses superiority with low costs of the treatment, the shortened duration of therapy and a potential of radiobiology. In an application research on a human GBM graft using a nude mouse model, Hasegawa et al.[3] reported that the tumor regression responded most by Hyper Fr radiotherapy.

It was shown in a preliminary result of applying St Fr IMRT to treat astrocytoma patients, that the survival rate was not improved. Narayana et al.[4] reported on the application of the dynamic multi-diaphragm collimator for IMRT of GBM in 58 cases, in which the radiotherapeutic dose was 59.4-60 Gy, 1.8-2.0 Gy each time. MST of the patients with malignant astrocytoma and patients with GBM was respectively 36 months and 9 months. A grade-III late phase toxic reaction occurred in 4 patients, presenting a verbal or cognitive disorder, without grade-IV/V late phase neurotoxicity. Similarly, Fuller et al.[5]

reported the preliminary results of 42 patients who underwent IMRT. In the 42 patients, IMRT was solitarily employed in 72%, and a boost of IMRT was given to the other 28% after 3D-CRT, with a MST of 8.7 months. A nonparametric analysis showed that there were no significant differences in the survivals between the solitary application of IMRT and the IMRT boost after 3D-CRT. The authors believed that employment of the conventional definition of the target area and the St Fr dose of IMRT may not improve the survival and RC rates of GBM.

There have been some reports on the use of Hyper Fr IMRT for GBM, which varied greatly in the results related to whether the mode of treatment could increase the survival rate of the astrocytoma patients. Floyd et al.[6] appraised the therapeutic outcomes of utilizing Hyper Fr IMRT in 20 GBM patients who underwent a total radiotherapeutic dose of 50 Gy/10f/2w. Compared with previous outcomes of using St Fr, this treatment mode failed to improve the overall survival time and failed to delay the time of the progression of disease. The need for surgery in patients with brain cell necrosis is very frequent.

Sultanem et al.[7] reported on the therapeutic outcome of 25 GBM patients undergoing Hyper Fr IMRT. The total therapeutic dose was 60 Gy/20f, 3 Gy each day, and the MST was 9.5 months. This is a safe mode of treatment which shortens the time of therapy. However, it has no improvement in the survival rate compared to conventional therapy. A report of research conducted by Iuchi et al.[8] demonstrated improvement in survival in GBM patients using Hyper Fr IMRT. A delineation of the 3-layered PTV was conducted in 25 GBM patients who underwent Hyper Fr IMRT. The dose of the PTV_1 (the DisR displayed by enhanced CT/MRI plus a 0.5-cm extension) was 48-68 Gy/8f (BED 77-12 Gy). At the same time, the dose of PTV_2 (PTV_1 plus 1.5 cm extension) was 40 Gy/8f and that of PTV_3 (edema area around the enhanced DisR) was 32 Gy/8f. Compared with the therapeutic outcome of 60 GBM cases with conventional external irradiation, the progression-free time of the tumor was obviously longer in the group with Hyper Fr IMRT treatment compared to the group with conventional external irradiation ($P < 0.0001$).

Age is a key prognostic factor for low-grade glioma patients. It was reported by Yeh et al.[9] that the OS and PFS rates of the grade-II astrocytoma patients at an age below 40 years were higher than those of the patients with an age over 40. In our group, Hyper Fr radiotherapy was performed in 18 grade- II astrocytoma patients with an age over 40. The differences in the OS and PFS rates between the Hyper Fr IMRT and St Fr IMRT groups ($P = 0.049$ and $P = 0.006$) was statistically significant. The OS and PFS rates of grade-III malignant astrocytoma patients were higher in the Hyper Fr IMRT group than those in the St Fr IMRT group. However, the differences between the 2 groups were not statistically significant. Death occurred in all 6 GBM patients. The MST of the patients was 10 months and 7 months, respectively in the Hyper Fr IMRT and St Fr IMRT groups. The outcome of the GBM patients in our group was similar to that of the patients with the same treatment method in other reports.

In our group, the CTV was defined as 1-2 cm extension from the boundary of the DisR shown by the enhanced fuci image of CT and MRI scan after surgery. The decision of CTV originated from the data of the studies on multiple types of relapse after radiotherapy. Most of the relapses occurred within the area less than 2 cm away from the primary tumor[10-14]. This indicates that our delineation of the CTV was enough for the treatment. The Hyper Fr dose may increase the therapeutic outcome, nevertheless, the RTOG grade IV/V toxic reactions were not found in our group. To further lower the radiotherapeutic reactions, we started to apply PET-CT to determine the GTV. Application of IMRT can further raise the fractionated dose of GTV, and also protect the normal tissues better. As a result, preferable survival can be reached, and toxic reaction can be reduced.

Whether or not IMRT can extend the field of a low-dose irradiation in the brain tissue remains controversial, and the low-dose irradiated region may increase the risk of a radiotherapy-induced tumorigenesis. A cross-check analysis on comparing the doses of 3D-CRT to IMRT demonstrated that the integral dose of IMRT in the normal brain tissue was cut down at a ratio by 7%-10% ($P < 0.001$), and there was no significant increase of the integral dose in the 0.5-5 Gy cold spot area[1]. In our study, none of 32 patients who survived developed radiotherapy-induced tumorigenesis.

The therapeutic effect of GBM patients can be further enhanced thorugh combined therapy. After surgery of GBM, it was shown in a randomized control study between the synchronized radio-chemotherapy and simple radiotherapy, that the method of radiotherapy plus temozolomide could further increase the survival rate[15]. Fan et al.[16] reported, after studying 64 GBM patients, that following surgery, applying synchronized radiochemotherapy (chemotherapeutic agents was semustine) could improve the RC rate of the GBM patients, and could delay the recurrence time. IMRT of GBM with synchronized chemotherapy deserves further investigation. Wang et al.[17] reported that after a 40 Gy/20f conventional exposure to the high-grade gliomas, the clinical curative effect of the IMRT in hyperfractionated brachytherapy (2.5 Gy/f, median dose 17.5 Gy) combined with chemotherapy was slightly increased, with the 3-year OS rate of 25%. Of the 97 patients, radiation necrosis occurred in only 3 patients.

The modes of Hyper Fr and St Fr IMRT for treating astrocytoma are feasible and safe. This is a retrospective study with fewer cases, however, the preliminary results offers the prospect of applying Hyper Fr IMRT treatment. More investigation is needed for deciding a better

delineation of various targets and optimal dose of Hyper Fr IMRT.

Conflict of interest statement

No potential conflicts of interest were disclosed.

References

1 Hermanto U, Frija EK, Lii MJ, et al. Intensity-modulated radiotherapy (IMRT) and conventional three-dimension conformal radiotherapy for high-grade gliomas: does IMRT increase the integral dose to normal brain? Int J Radiat Oncol Biol Phys 2007; 67: 1135-1144.
2 Yin WB, Gu XZ, Eds. Radio-therapeutics on Cancer. Peking Union Medical College Press, Beijing: 2002; 1018-1023 (Chinese).
3 Hasegawa M, Niibe H, Mitsuhashi N, et al. Hyperfractionated and hypofractionated radiation therapy for human malignant glioma xenograft in nude mice. Jpn J Cancer Res 1995; 86: 879-884.
4 Narayana A, Yamada J, Berry S, et al. Intensity-modulated radiotherapy in high-grade gliomas: clinical and dosimetric results. Int J Radiat Oncol Biol Phys 2006; 64: 892-897.
5 Fuller CD, Choi M, Forthuber B, et al. Standard fractionation intensity modulated radiation therapy (IMRT) of primary and recurrent glioblastoma multiforme. Radiat Oncol 2007; 2: 26.
6 Floyd NS, Woo SY, Ten BS, et al. Hypofractionated intensity-modulated radiotherapy for primary glioblastoma multiforme. Int J Radiat Oncol Biol Phys 2004; 58: 721-726.
7 Sultanem K, Patrocinio H, Lambert C, et al. The use of hypofractionated intensity-modulated irradiation in the treatment of glioblastoma multiforme: preliminary results of a prospective trial. Int J Radiat Oncol Biol Phys 2004; 58: 247-252.
8 Iuchi T, Hatano K, Narita Y, et al. Hypofractionated high-dose irradiation for the treatment of malignant astrocytomas using simultaneous integrated boost technique by IMRT. Int J Radiat Oncol Biol Phys 2006; 64: 1317-1324.
9 Yeh SA, Ho JT, Lui CC, et al. Treatment outcomes and prognostic factors in patients with supratentorial low-grade gliomas. Br J Radiol 2005; 78: 230-235.
10 Aydin H, Sillenberg I, Von Lieven H. Patterns of failure following CT-based 3-D irradiation for malignant glioma. Strahlenther Onkol 2001; 177: 424-431.
11 Wallner KE, Galicich JH, Krol G, et al. Patterns of failure following treatment for glioblatoma multiforme and anaplastic astrocytoma. Int J Radiat Oncol Biol Phys 1989; 16: 1405-1409.
12 Hochberg FH, Pruitt A. Assumptions in the radiotherapy of glioblastoma. Neurology 1980; 30: 907-911.
13 Liang BC, Thornton AF Jr, Sandler HM, et al: Malignant astrocytomas: Focal tumor recurrence after focal external beam radiation therapy. J Neurosurg 1991; 75: 559-563.
14 Chan JL, Lee SW, Fraass BA, et al. Survival and failure patterns of high-grade gliomas after three-dimension conformal radiotherapy. J Clin Oncol 2002; 20: 1635-1642.
15 Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005; 352(10):987- 996.
16 Fan YW, Qi LW, Jiang XD et al. Postoperative concurrent chemo-radiotherapy for 64 patients with high-grade intracranial glioma. Zhongguo Zhongliu Linchuang 2007; 34: 1354-1357 (Chinese).
17 Wang Y, Sheng XF, Dong W, et al. Conventional radiotherapy followed by intensity-modulated radiotherapy combined with chemotherapy for treatment of high-grade gliomas. Zhongguo Zhongliu Linchuang 2009; 36: 184-187 (Chinese).