·Clinical Research·

Efficacy of X-ray stereotactic radiotherapy on brain metastases and prognostic analysis

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[Abstract] Background and Objective: X-ray stereotactic radiotherapy (SRT) is one of the effective treatments for brain metastases (BM). This study was to evaluate the efficacy of SRT on BM, and investigate prognostic factors. **Methods:** Between July 1999 and December 2004, a total of 122 intracranial lesions in 78 patients with BM were treated using SRT in our Center. Forty-nine patients had a solitary lesion and 29 had multiple (2–6) lesions. The median SRT dose was 15 Gy (11–24 Gy) in single fraction for 38 lesions, and 24 Gy (11–40 Gy) in 2–6 fractions for 84 lesions. SRT was combined with whole brain radiotherapy (WBRT) of 30–40 Gy for 39 patients. Progression-free survival (PFS) and overall survival (OS) were estimated by Kaplan-Meier method. Univariate and multivariate analyses were performed by the log-rank test and Cox model, respectively. **Results:** The median survival time was 12.9 months (1.7–77.4 months). The 1-year intracranial PFS rate was 87.4%. The 1- and 2-year OS rates were 53.9% and 25.8%, respectively. Univariate analysis showed that the 1-year OS rates were higher in the patients with pretreatment KPS of ⩾ 70, extracranial lesions controlled, or SRT combined with WBRT than in those with KPS of < 70 (60.7% vs. 29.4%, $P = 0.002$), extracranial lesions uncontrolled (69% vs. 44.9%, $P = 0.005$), or SRT alone (64.1% vs. 43.4%, $P = 0.03$). The benefit of treating with WBRT in combination was mainly achieved in the patients with extracranial lesions controlled or with more than one intracranial lesion. Multivariate analysis showed that KPS score and status of extracranial lesions were independent prognostic factors for OS. **Conclusions:** SRT is an effective and safe modality for BM. SRT combined with WBRT may prolong the survival time of the patients with extracranial lesions controlled or multiple intracranial lesions. Independent prognostic factors for OS are KPS score and status of extracranial lesions.

Key words: Brain metastasis, effect, prognosis, stereotactic radiotherapy

Brain metastases is one of the most common malignant intracranial tumors[1,2]. Brain metastases were found by autopsy in 50% of the patients died of cancer[3]. The morbidity of brain metastases is rising with the development of medical imaging techniques and the survival extension of tumor patients[4]. Whole brain radiotherapy (WBRT), as the main treatment of brain metastases, may prolong the median survival of patients to 3–6 months[5,6]. Stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) have also been widely applied to treat brain metastases with advantages of concentrated dose, notable dose gradient around the target volume, and less damage to surrounding normal tissues. This study summarized the experience to treat brain metastases SRT in Sun Yat-sen University Cancer Center, investigated the efficacy of SRT on brain metastases and explored independent prognostic factors through univariate and multivariate analyses.

Materials and Methods

General clinical data

Between July 1999 to December 2004, 78 patients with brain metastases were treated by SRT at Sun Yat-sen University Cancer Center, including 46 men and 32 women, with a median age of 55 (range, 28–75). Of the 78 patients, 60 were aged below 65 and 18 were aged of or above 65; 49 had single lesion and 29 had multiple lesions (2–6 lesions), with a total of 122 lesions; 71 had lesions surrounding the parenchyma and 7 had lesions in midline; as confirmed by pathology, 72 had lesions of epithelial origin and 6 had lesions of non-epithelial origin; 50 (64.1%) had

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lung cancer as primary tumor, 10 had breast cancer, 5 had colorectal cancer, 2 had esophageal cancer, 2 had gastric cancer, 1 had melanoma, 1 had rhabdomyosarcoma, 1 had left subaxillary poorly differentiated metastatic carcinoma, 1 had malignant fibrous histiocytoma (MFH), 1 had ovarian carcinoma, 1 had non-Hodgkin's lymphoma, 1 had thyroid carcinoma, 1 had hepatoma, and 1 had renal carcinoma; 61 had KPS of ≥ 70 and 17 had KPS of < 70; 29 had controlled extra-cranial tumor while 49 had uncontrolled extra-cranial tumor.

SRT technique and planning

CREAT stereotactic radiotherapy system and PHILIPS linear accelerator with 8 MV X-ray were used to provide multi-arc rotation irradiation. in SRT. Special head frame and closed pyrolysis plastic mask were applied to fix the head with a supine position. Continuous enhanced CT scans with a thickness of 3 mm were performed from the head to the lower edge of the second cervical vertebra. The data were transmitted to SRT planning system workstation. The range of lesion on enhanced CT image was delineated as gross target volume (GTV), and an extended 1 mm area to the edge of GTV was defined as planning target volume (PTV). Sensitive organs and structures, such as the brain stem, optic chiasm, optic nerves, eyes and crystal, were also delineated. Iso-center rotation irradiation covering the target volume delineated by 70% –90% iso-dose line was conducted with 4–7 non-coplanar radiation arcs, using 15–50 mm collimator (selected according to the lesion size). Treatment plans were evaluated according to sectional dose distribution and dose-volume histogram (DVH). After confirmation of the plans, SRT was performed once a day, 2–3 times per week.

SRT prescription dose

SRT was given by the 70%–90% iso-dose line covering PTV (the 90% iso-dose line accounted for 90.2% of the volume). The dose and fractionation were determined according to lesion size, lesion number, lesion location, intracranial pressure before treatment, whether the whole brain irradiation was added, systemic status of patient, and so on. The median maximum diameter of GTV was 24 mm (range, 4–47 mm), with the median volume of 3.95 cm^3 (0.14–25.56 cm^3). Forty patients had GTV of ≤ 5 cm^3 and 38 had GTV of > 5 cm^3. Thirty-eight lesions were treated with single SRT, with a median prescription dose of 15 Gy (11–24 Gy); 84 were treated with 2–6 times of SRT, with a median prescription dose of 24 Gy (11–40 Gy) and a median fractionated dose of 12 Gy (5–16 Gy). Biological effective dose (BED) of 122 lesions was converted from physical dose by the following formula: $BED = nd\ [1 + d/(\alpha/\beta)]$ (d for SRT fractionated dose, n for times of SRT, α/β equals to 10 Gy). The median BED was 75 Gy (37.5–100.8 Gy); 56 patients had BED of ≤ 75 Gy and 22 had BED of > 75 Gy.

Whole brain radiotherapy

Thirty-nine patients received WBRT before or within 1 month after SRT. Of the 39 patients in SRT plus WBRT group, 24 had single brain lesion, 15 had multiple (≥ 2) lesions, 15 had controlled extra-cranial lesions; 26 received WBRT before SRT and 13 received WBRT after SRT, with a median interval between WBRT and SRT of 8 days (1–29 days). Bilateral parallel field irradiation was performed using 60Co or 6–8 MV X-ray by linear accelerator (eyes shaded), with prescription dose of 30-39 Gy by 10–13 fractions or 40 Gy by 20 fractions, once a day, 5 fractions per week. Intracranial hypertension occurred during radiotherapy was treated by mannitol dehydration or hormone therapy. The median prescription dose of SRT for these patients was 18 Gy (12–30 Gy), and the median fractionated dose was 12 Gy (6–16 Gy).

Of the 39 patients in SRT alone group, 25 had single brain lesion, 14 had multiple lesions, 14 had controlled extra-cranial lesions; the median prescription dose of SRT was 26 Gy (11–40 Gy), and the median fractionated dose was 13 Gy (5–24 Gy).

Statistical analysis

The overall survival (OS) and intracranial progression-free survival (PFS) were mainly observed. Intracranial progression included primary lesion progression (the product of two diameters increased by above 25% in radiology) and the emergence of new intracranial metastases. OS and intracranial PFS were calculated since the first day of SRT or WBRT till death, intracranial progression or the latest follow-up. OS and PFS were estimated by Kaplan-Meier method using SPSS12.0 software. The difference between the survival curves was tested by log-rank method, and prognostic multivariate analysis was performed in Cox model (two-tailed test, $\alpha = 0.05$).

Results

All patients were followed-up by outpatient visit or telephone interview. The end of follow-up dated January 31, 2007. The median follow-up duration was 14.8 months (1.7–77.4 months). The follow-up rate was 94.9% with 4 patients lost. Sixty-three (80.7%) patients died; among them, 7 had intracranial tumor progression at primary site as diagnosed by pathology or imaging, 4 were found with new intracranial lesions. The median OS was 12.9 months, the 1- and 2-year OS rates were 53.9% and 25.8% (Figure 1), and the 1-year intracranial PFS rate was 87.4% (Figure 2). For the patients received single and multiple (≥ 2 times) SRT, the 1-year intracranial PFS rates were 93.7% and 85.2% ($P = 0.16$); the 1-year OS rates were 55.0% and 53.5% ($P = 0.61$). By recursive partitioning analysis (RPA) grading

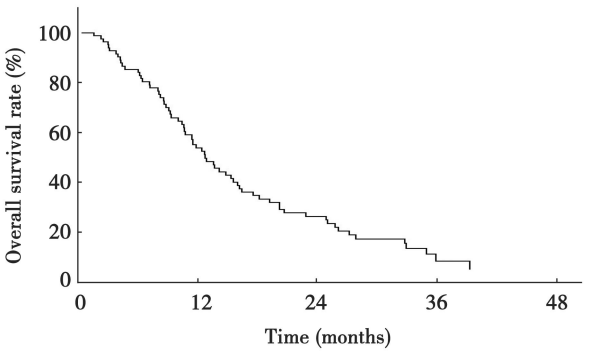

Figure 1 Overall survival curve of the patients after treatment for brain metastases

standards, the patients were graded I, II and III, and the 1-year OS rates were 71.4%, 55.0% and 29.4% ($P < 0.05$) (Figure 3).

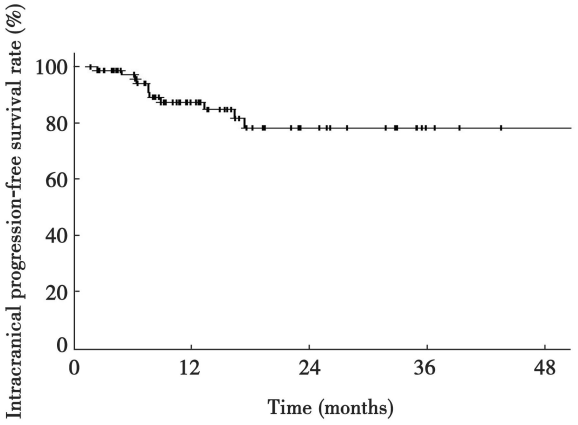

Figure 2 Intracranial progression-free survival curve of the patients after treatment for brain metastases

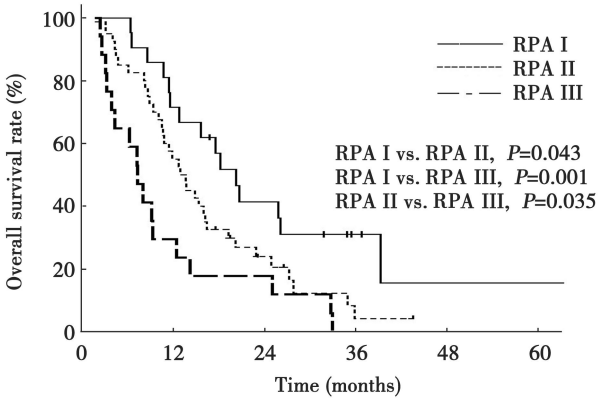

Figure 3 Overall survival curves of the patients with RPA I, II, and III brain metastases

Univariate analysis

The 1-year OS rate was significantly higher in the patients with pre-treatment KPS of ⩾ 70 than in those with KPS of < 70 (60.7% vs. 29.4%, $P = 0.002$), and was higher in the patients with controlled extracranial lesions than in those with uncontrolled extracranial lesions (69% vs. 44.9%, $P = 0.005$) (Table 1, Figures 4 and 5).

The median survival of SRT plus WBRT group and SRT alone group were 16 and 11.4 months, and the 1-year OS rates were 64.1% and 43.4% ($P = 0.03$) (Table 1, Figure 6). For the patients with controlled extracranial lesions, the 1-year OS rate was significantly higher in SRT plus WBRT group than in SRT alone group (80.0% vs. 57.1%, $P = 0.018$); for those with multiple (≥ 2) brain lesions, the rate was also higher in SRT plus WBRT group than in SRT alone group (73.3% vs. 35.7%, $P = 0.033$). However, for the patients with uncontrolled extracranial lesions and single brain lesion, the 1-year OS rates between the two groups had no significant differences (54.2% vs. 36.0%, $P = 0.524$; 58.3% vs. 48%, $P = 0.338$).

Multivariate analysis

Ten factors, sex, age (< 65 or ⩾ 65), primary tumor site (the lungs, breast, digestive tract and others), histological type (epithelial-derived and non-epithelial-derived), pre-treatment KPS score (⩾ 70 or < 70), the status of extracranial lesions (controlled or uncontrolled), the number of brain lesions (1 or ⩾ 2), tumor size (⩽ 5 cm^3 or > 5 cm^3), treatment (SRT plus WBRT or SRT alone) and the BED (⩽ 75 Gy or > 75 Gy), were analyzed by backward stepwise regression using Cox model for factor screening. Results showed that KPS score and the status of extracranial lesions were the independent prognostic factors affecting OS (Table 1).

Table 1 Univariate and Cox multivariate analyses of factors affecting the 1-year overall survival (OS) of the patients with brain metastases

Factor	1-year OS (%)	*P*	Multivariate HR (95% CI)	*P*
KPS scores				
⩾ 70	60.7	0.002	1.888 (1.053–3.385)	0.033
< 70	29.4			
Extracranial leision status				
Uncontrolled	44.9	0.005	1.824 (1.053–3.162)	0.032
Controlled	69.0			
Treatment modality				
SRT alone	43.4	0.030	0.691 (0.420–1.138)	0.146
SRT + WBRT	64.1			
Gender				
Male	54.4	0.787	0.763 (0.453–1.285)	0.308
Female	53.1			
Primary tumor site				
Lung	54.0			
Breast	60.0	0.250	1.145 (0.886–1.479)	0.301
Colorectal	66.7			
Others	33.3			
Number of lesions				
1	53.1	0.786	1.006 (0.590–1.716)	0.982
⩾ 2	55.2			
Age at diagnosis				
< 65 years	55.0	0.290	0.645 (0.329–1.266)	0.202
⩾ 65 years	50.0			
Histological status				
Epithelial	55.6	0.344	2.005 (0.711–5.654)	0.188
Non-epithelial	33.3			
Tumor volume				
⩽ 5 cm^3	52.5	0.920	1.204 (0.684–2.121)	0.520
> 5 cm^3	55.3			
BED				
⩽ 75 Gy	53.6	0.890		0.062
> 75 Gy	54.6			

KPS, Karnofsky performance state; SRT, stereotactic radiotherapy; WBRT, whole-brain radiotherapy; BED, biological effective dose.

Adverse events

All patients received SRT with or without WBRT as scheduled. Headache, nausea and vomiting occurred in a few patients during treatment. These symptoms were relieved by mannitol dehydration and hormone therapy.

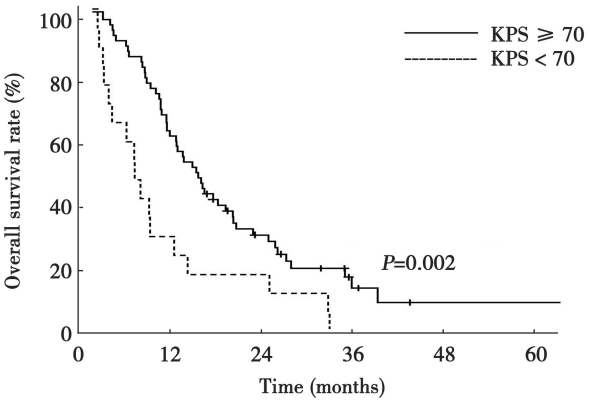

Figure 4 Overall survival curves of the patients with KPS of ⩾ 70 and < 70

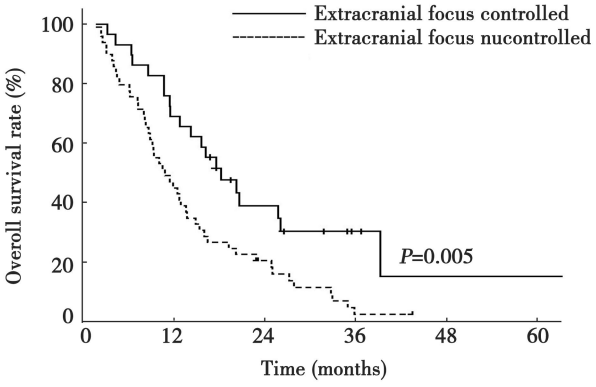

Figure 5 Overall survival curves of the patients with extracranial lesions controlled and uncontrolled

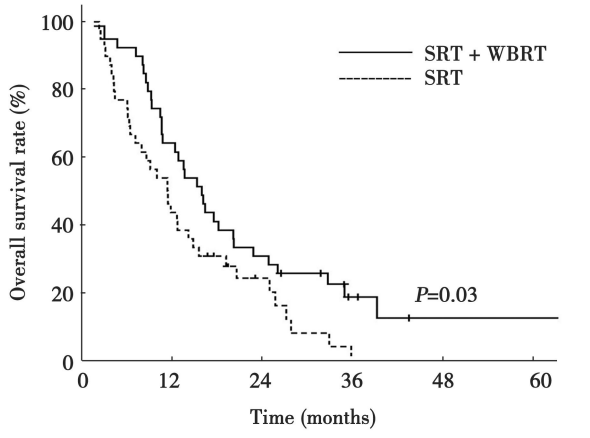

Figure 6 Overall survival curves of the patients with brain metastases treated by SRT plus WBRT and SRT alone

Discussion

SRT, including single high-dose radiotherapy, that is, SRS, and fractionated radiotherapy, that is, fractional stereotactic radiotherapy (FSRT), could be realized by using X-ray-generated linear accelerator to form iso-center muiti-arc rotating irradiation. SRS is often used to treat brain metastases. According to reports, in SRS treatment of brain metastases, the local control rate was up to 85%–96%, and more than 80% of patients with neurological dysfunction got function improved, with a median survival of 3.3–14.2 months[7-10]. In this study, for the patients with brain metastases treated by SRS and FSRT, the 1-year local control rate was 87.4%, with a median survival of 12.9 months. This result was better than those of Zable *et al*.[7] and Kim *et al*.[8], and was similar to the report of Rao G *et al*.[9] with a median survival of 14.2 months.

FSRT, compared with SRS, has the following advantages: (1) the fractionated dose, lower than the dose of SRS, will help to protect the vital structures and organs around the tumor (such as the brain stem and visual pathway), and is particularly suitable for the treatment of brain lesions in midline position; (2) FSRT is more suitable for large lesions, which can reduce damage of the surrounding normal tissue. In this study, the patients treated with FSRT were mainly with lesions located in the midline (7/7) and with large (diameter of > 3 cm) lesions (25/32). The efficacy of FSRT was similar to that of SRS, with no severe acute reaction, suggesting the effectiveness and safety of FSRT as a treatment for midline and large brain metastases.

There is no unified opinion about whether WBRT combined SRT is needed. Pirzkall *et al*.[11] found that the median survival was 8.3 months for the patients underwent SRS and 15.4 months for those underwent WB RT combined SRS, especially, WBRT combined SRS prolonged the survival for the patients without extra-cranial lesions. However, two recent prospective randomized studies showed that the OS rates of patients underwent SRS and SRS plus WBRT were similar, while SRS plus WBRT had advantage in intracranial control as compared with SRS[12,13]. Our results showed that the median survival was longer in SRT combined WBRT group than in SRT alone group, mainly benefiting the patients with controlled extra-cranial lesions and multiple (≥ 2) intra-cranial lesions. The explanation may be as follows: (1) the risk is relatively small for the patients with controlled extra-cranial lesions to occur intracranial re-metastasis or other metastases in a short term, is relatively small for with controlled extra-cranial lesions, moreover, WBRT is helpful in controlling intracranial micro-metastases and prolonging the survival; (2) the occurrence of multiple brain metastases indicates a great chance of intracranial tumor spreading, and combing WBRT could better control brain micro-metastases.

In the studies of prognostic factors in the patients with brain metastases treated by SRT, the results varied due to the variances in case selection, radiotherapy technology, the adoption of statistical methods, and so on, among different tumor centers. It was reported that the prognostic factors for the patients with brain metastases treated by SRT included the age before

radiotherapy, KPS score, the number of brain metastases, the status of extra-cranial primary lesions and metastatic lesions, among these factors, KPS score and control status of extra-cranial lesions were of most importance.[14-16] In our study, because the proportion of patients with intracranial progression after treatment (14%) was not large (which may be associated with some patients' dieing of extra-cranial tumor progression before intracranial progression was detected), univariate and multivariate analyses had failed to screen out factors affecting intracranial PFS (not listed in the results). However, the results confirmed that pre-treatment KPS score and the status of extra-cranial lesions were independent factors affecting OS. The interpretation may be as follows: (1) the patients with higher KPS score were in better general conditions and with better immune function, which led to better therapeutic effect; (2) the controlled extra-cranial lesions could reduce the probability of intracranial re-metastasis and other distant metastases, which would prolong the survival; (3) the primary tumor was one of the main causes of death in patients, while the nervous system-related deaths occurring after SRT treatment of brain metastases accounted for only 38% of all deaths[12]. Therefore, the proper pre-treatment use of dehydrating agent and glucocorticoids to reduce cerebral edema, lower intracranial pressure and prevent neurological impairment, the improvement of functional status before radiotherapy in patients, and active treatment of extra-cranial primary tumor and metastases are all beneficial to extend the survival of patients.

In recent years, to better predict the efficacy of SRT on brain metastases and develop a more reasonable individualized comprehensive treatment program, some researchers proposed concepts about prognostic index and its related grading system, mainly included RPA[17], graded prognostic assessment (GPA)[18], basic score for brain metastases (BSBM)[19], and so on. Among them, the widely applied system in current clinical practice is RPA grading system, which is based on patients' KPS score (< 70 and $\geqslant$ 70), age (< 65 years and $\geqslant$ 65 years) and the existence of extra-cranial primary and metastatic lesions as the three classification factors. Grade I is with the best prognosis, grade III the worst, grade II in between. In our study, as graded according to RPA grading system, the 1-year OS rates of patients at grades I, II and III were 71.4%, 55.0% and 29.4% ($P < 0.05$), proving the predictive value of RPA grading system for evaluating the efficacy of SRT on brain metastases.

In conclusion, treating brain metastases with SRT is effective and safe. For the patients with controlled extra-cranial lesions or multiple ($\geqslant$ 2) intracranial lesions, WBRT combined SRT is beneficial to prolong the survival. Pre-treatment KPS score and the status of extra-cranial lesions are independent factors affecting OS.

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