RESEARCH ARTICLE

Therapeutic Regimens and Prognostic Factors of Brain Metastatic Cancers

Wen-Guang Song[1]*, Yi-Feng Wang[2], Rui-Lin Wang[1], Yin-e Qu[3], Zhi Zhang[1], Guo-Zhong Li[1], Ying Xiao[1], Fang Fang[1], Hong Chen[1]

Abstract

Objective: This work aims to investigate the therapeutic regimen of brain metastatic cancers and the relationship between clinical features and prognosis. Methods: Clinical data of 184 patients with brain metastatic cancers were collected and analysed for the relationship between survival time and age, gender, primary diseases, quantity of brain metastatic foci, their position, extra cranial lesions, and therapeutic regimens. Results: The average age of onset was 59.1 years old. The median survival time (MST) was 15.0 months, and the patients with breast cancer as the primary disease had the longest survival time. Females had a longer survival time than males. Patients with meningeal metastasis had extremely short survival time. Those with less than 3 brain metastatic foci survived longer than patients with more than 3. The MST of patients receiving radiotherapy only and the patients receiving chemotherapy only were all 10.0 months while the MST of patients receiving combination therapy was 16.0 months. Multiple COX regression analysis demonstrated that gender, primary diseases, and quantity of brain metastatic foci were independent prognostic factors for brain metastatic cancers. Conclusions: Chemotherapy is as important as radiotherapy in the treatment of brain metastatic cancer. Combination therapy is the best treatment mode. Male gender, brain metastatic cancers originating in the gastrointestinal tract, more than 3 metastatic foci, and involvement of meninges indicate a worse prognosis.

Keywords: Brain metastatic cancers - prognosis - treatment - radiation therapy - chemotherapy

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Introduction

Brain metastasis is the most common complication of advanced tumors. There're about 200,000 new cases only one year in America, which is ten times more than primary intracranial tumors (Patchell, 2003; Gavrilovic et al., 2005). Some reported that brain metastasis might occur in the pathological process of 20-40 percent of patients with malignant tumors (Newton, 1999). Gradual upward trend in recent years may be induced with the longer overall survival of cancer patients since the improving level of comprehensive cancer treatments, as well as more and more asymptomatic brain metastases were diagnosed due to the developed diagnostic imaging techniques (Abd-El-Barr et al., 2011). The prognosis of patients with brain metastases is generally poor, and it would even be about 4 weeks, if without positive treatment (Sundstrom et al., 1998). Therefore, the treatment of brain metastases, for physicians, cannot be ignored.

Whole brain irradiation has always been considered as the standard treatment of brain metastases (Bradley et al., 2004). Over the last decade, stereotactic radiotherapy (including gamma-knife) technology, which can provide higher radiation dose in the localized nidi and with relatively lighter damages in surrounding normal tissues at the same time, highlight its position in the treatment of brain tumors (Matsunaga et al., 2010). Unlike radiation therapy, which cannot be repeated applications and is ineffective for recurrence after radiotherapy or some uncontrolled lesions, chemotherapy can be applied repeatedly, but also take into account the systemic diseases.

However, the traditional view is that most chemotherapy drugs cannot reach the lesions of brain metastases, or form the localized effective therapeutic concentrations, because of the impact of the blood-brain barrier, so that chemotherapy has little effect for brain metastases (Pardridge, 2005). But some researchers found that enhanced contrast agent, which cannot pass the blood-brain barrier, could make sharp strengthening in brain metastasis lesions on CT or MRI, which means that brain metastases may be able to destroy the blood-brain barrier (Mehta et al., 1995), and demonstrated that chemotherapy might be positive for the treatment of brain metastases. Therefore, we can often see the reports about chemotherapy or other drugs used in the treatments of

*[1]Department of Radiotherapy and Chemotherapy, [2]Department of Obstetrics and Gynecology, Workers' Hospital, Tangshan, Hebei, [3]Basic Medical College, Hebei Union University, Tangshan, China *For correspondence: wenguangsong@163.com*

brain metastases (Moscetti et al., 2007; Lee et al., 2008; Neuhaus et al., 2009). In a word, so far there're no standard treatments of brain metastases at all.

In addition to treatment factors, the prognosis of patients with brain metastases affected by many factors such as: age, body condition, the number of intracranial lesions, as well as the primary disease (Gaspar et al., 1997; Lagerwaard et al., 1999). Therefore, a retrospective analysis of the clinical data from January 2002 to December 2010 in our hospital for treatment of 184 patients with brain metastases was carried on. The purpose of this study is to analyzing the relationship between clinical features and prognosis of patients with brain metastases and also to exploring the status of cancer radiotherapy, chemotherapy and combined radiotherapy and chemotherapy in treatment.

Materials and Methods

Clinical data

From January 2002 to December 2010, the department of radiotherapy and chemotherapy in our hospital treated patients with brain metastases totally 184 cases, 109 cases were male and 75 cases were female. The age of them were between 29 years old and 84 years old, with an average of 59.1 years old. The sources of tumor are as follows: 138 cases of lung cancer, 25 cases of breast cancer, gastrointestinal cancer, 11 cases, and 10 cases of other sources (including 2 cases of liver cancer, 2 cases of kidney cancer, 1 case of thyroid cancer, a case of lymphoma, and unknown primary tumor 4 cases).

Analytical methods

Clinical data including quantity of brain metastasis focus, position of brain metastasis focus, extra cranial lesions, treatment situation and so on are collected as the independent variable. Appropriate statistical methods are applied to analyze the relationship between the independent variables and the dependent variable -- survival time. Therapeutic regimens involved in this study include: (1) surgery, referring to the implementation of intracranial tumor resection but not excluding the postoperative radiotherapy and chemotherapy; (2) radiotherapy, including whole-brain irradiation with or without stereotactic radiotherapy in lesions; (3) chemotherapy, including anticancer drug therapies such as systemic chemotherapy, targeting therapy and so on; (4) supportive therapies, merely including lowering the intracranial pressure by hydration, nutritional support and so on but not implementing the targeted anti-cancer therapy (excluding the anti-cancer traditional Chinese medicine). Survival time (OS) is defined as the time from diagnosis of brain metastasis to death or last follow-up of the patients.

Statistical methods

Use SPSS 17.0 (Chinese Edition) software to analyzing the group constituent ratio by chi-square test. The differences in age of onset are analyzed by the univariate analysis of variance (one-way ANOVA), F test. Survival statistics are analyzed by using Kaplan-Meier method. The differences of Lifetime are analyzed by the log-rank test. Survival correlation is analyzed by single factor or multiple factors COX analysis.

Results

Incidence of the brain metastases from different sources

The age, gender, the number and position of metastases and extra cranial metastases are showed in chart one (Table 1). The incidence of brain metastases from lung cancer is 75% (138/184), 13.6% (25/184) from breast cancer, 6.0% (11/184) from gastrointestinal cancer and total 5.4% (10/184) from liver cancer, renal cancer and thyroid cancer. Overall average age of onset is 59.1 years of age, where the average age of onset of brain metastases

Table 1. The Characteristics of Patients with Brain Metastases from Different Sources

	brain metastases sources				*P*
	Lung n=138	Breast n=25	GIT# n=11	other n=10	
Age (years)					0.002
average	59.4	50.9	55.8	57	
range	32-84	29-68	31-71	41-78	
gender					0.933△
male	95	0	7	7	
female	43	25	4	3	
MPBM§					0.013
cerebrum	91	13	4	6	
cerebellum	26	6	3	1	
brain stem	19	4	1	2	
meninges	2	2	3	1	
Number of position					0.709
1-3	56	12	6	5	
>3	82	13	5	5	
ECM*					0.234
No	61	8	2	7	
Yes	77	17	9	3	

#GIT, gastrointestinal tract; §MPBM, the main position of brain metastases; *ECM, extra cranial metastases; △Breast cancer patients, all women, it is not included in the statistics of the gender differences

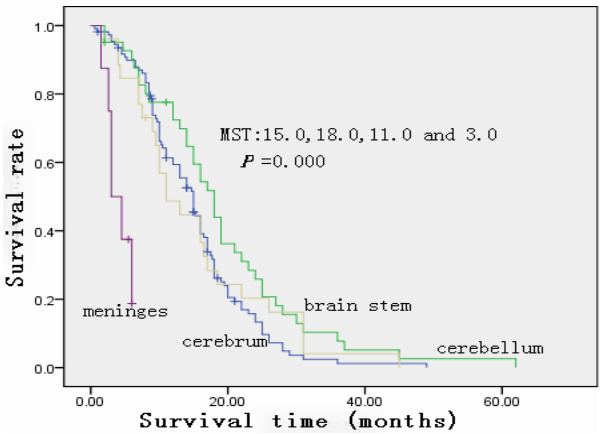

Figure 1. Intracranial Metastatic Sites Related Survival Curves. The survive time of patients with cerebrum metastases is showed by the blue curve, while cerebellum metastases by green, brainstem metastases by yellow and meninges metastases by perple curve. Their MST were 15.0, 18.0, 11.0 and 3.0months respectively

Table 2. The Main Therapeutic Method and Overall Survival Time in Different Source

	brain metastases sources				*P*
	Lung n=138	Breast n=25	GIT# n=11	other n=10	
Main therapy	9	2	0	2	0.899
surgery	16	5	2	1	
Radiotherapy	14	3	2	1	
chemotherapy	89	13	6	5	
R+C△	10	2	1	1	
SC▲					
ST& (months)					0.000
Mean	16.6	17.6	4.6	12.9	
Medie	15.3	16	4.5	11	
Range	0.6-62	4.5-36	1.5-8.5	6-25	

#GIT, gastrointestinal tract; △R+C, radiotherapy and chemotherapy; ▲SC, supportive care only; &ST, survival time

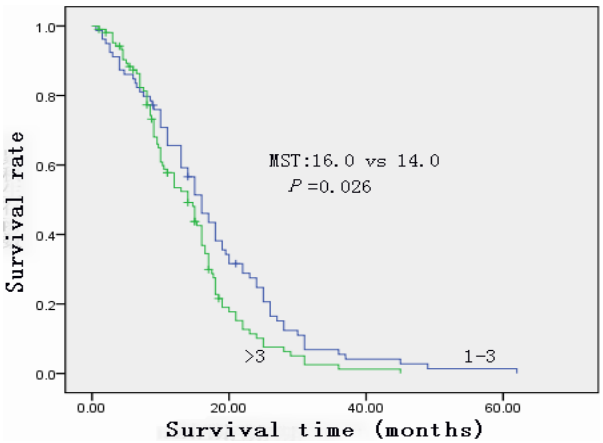

Figure 2. Intracranial Metastatic Number Related Survival Curves. The survive time of patients with 1-3 metastases is showed by the blue curve, with >3 metastases is showed by the green curve. The MST for the former is 16.0 months and the latter is 14.0 months

from lung cancer is 59.4 years (95% CI 57.7~61.0), 50.9 from breast cancer (95% CI 46.6~55.3), 55.8 from gastrointestinal cancer (95% CI 47.87~63.8), and 57.0 from other cancers (95% CI 49.4~64.6), through one-way ANOVA (F = 5.332, P = 0.002). Except that from breast cancer, there is no significant difference among the brain metastases from other sources (χ^2 = 0.138, P = 0.933). Transfer quantity and extra cranial metastases from various tumors have no significant differences. However, about the metastatic sites, the proportion of brain metastases from gastrointestinal cancer which meninges involvement is higher, up to 27.3% (3/11), then 8% from breast cancer and lower, 1.4% (2/138), from lung cancer, whole of which have significant difference (χ^2 = 20.994, P = 0.013).

Commonly used treatment methods and the overall prognosis of brain metastases

As shown in Table 2, only 13 patients underwent surgical treatment in 184 patients, accounting for 7.1%; the chemotherapy and radiotherapy are 113 cases, accounting for 61.4%; radiotherapy, chemotherapy alone and only supportive care accounted for 13.0%, 10.9% and 7.6%, respectively; between different sources of tumor treatment

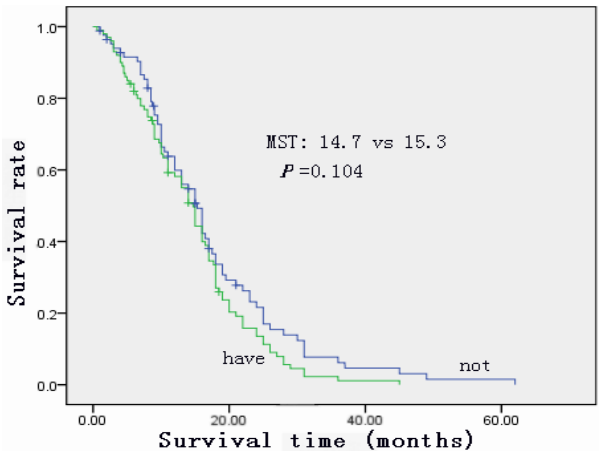

Figure 3. If or not have Extracranial Metastasis Effect on the Survival Time. The blue curve represents the patients with extracranial metastasis besides the intracranial metastasis, and the green curve for those not have extracranial metastasis. Their MST is 15.3 and 14.7 months respectively

constitutes no significant difference (χ^2 = 6.328, P = 0.899). The patients of this group overall average survival time is 15.8 months (95% confidence interval: 14.3 to 17.3), the overall median survival time (Median Survival Time, MST) is 15.0 months (95% confidence interval, 13.5 to 16.5). MST of lung cancer sources is 15.3 months, MST of breast cancer, gastrointestinal cancer and other tumor sources by are 16.0,4.5 and 11.0 months, by the log-rank test, χ^2 = 81.102, P = 0.000, there is a significant statistical difference. Between-group pairwise comparisons show that the survival time of brain metastasis that is come from gastrointestinal was significantly shorter than lung cancer, breast cancer, and other sources; P values are less than 0.001.

Analysis of prognostic factors in brain metastases cancer

Analyze the patients' information basing on general clinical information by Univariate analysis, we found that the female patient survival is slightly better than men, MST were 16.0 months and 13.0 months, but the difference has no statistically significant (χ^2 = 2.232, P = 0.135). The survive time of patients with meningeal metastases is shorter than the patients with brain, cerebellum or brainstem metastases; MST were 3.0 months, 15.0 months, 18.0 months and 11.0 months respectively. (χ^2 = 42.903, P = 0.000), see Figure 1. The MST of patients with 1-3 metastases is 16 months and the MST of patients with metastases more than 3 is 14 months. There is a statistically significant between them, see Figure 2. Whether patients associated with extracranial lesions or not have no significant effect on survival; the MST is 14.7 and 15.3 months, respectively. (χ^2 = 2.644, P = 0.104), see Figure 3. The survival time that is affected by main treatment illustrate, MST of the patients accept surgical treatment is 18 months. MST of patients accepts radiotherapy and chemotherapy respectively is 10 months. MST of patients accepts chemotherapy and chemotherapy combined is 16 months. While MST of patients only accepts supportive care is 2.6 months, overall comparison (χ^2 = 176.876, P = 0.000), see Figure 4. The five main treatment methods pairwise comparisons showed that

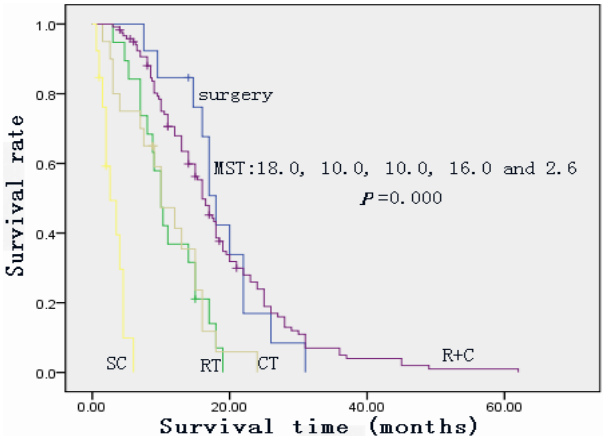

Figure 4. Main Therapies Effect on the Survival time of BM Patients. In this diagram, the five different colour on behalf of the survival curve of the surgery, radiotherapy, chemotherapy, radio-chemotherapy and support care of brain metastasis patients, blue curves represent the surgery, green for radiotherapy, bronze for chemotherapy, purple for radio-chemotherapy, yellow for supported care. The MST is 18.0, 10.0, 10.0, 16.0, and 2.6 months respectively

the combination therapy of surgery and chemotherapy compared with radiotherapy alone, chemotherapy alone, and supportive treatment showed significant survival advantage. The difference has not statistically significant between surgical treatment and radiotherapy or chemotherapy alone.

Involve general clinical patient survival data information into multivariate COX analysis found that the primary disease, intracranial metastases number and gender is an independent prognostic factor, *P* values were 0.001, 0.007 and 0.048. That means male patients, the source of gastrointestinal, metastatic lesions more than 3 more are bad factors for prognosis.

Discussion

Metastatic brain tumors aren't the malignancy originating from the nerve tissue, but its morbidity is the highest among malignant brain tumors and would be more complicated in treatments compared with the primary tumors in brain (De Angelis et al., 2001). It's known that brain metastases result from the hematogenous metastasis of extra cranial tumors into the brain. Since lung cancer cells can directly transfer to the left atrium, the internal carotid artery, the vertebral artery, and then to the brain via the pulmonary vein systems, rather than the pulmonary capillary filtration (Rahmathulla et al., 2012), in addition to the increasing incidence of lung cancer, just as shown in present study, most of brain metastases derive from lung cancer, followed by breast cancer and gastrointestinal cancer. Consistent with our data (Fabi et al., 2011), however, no one cases of malignant melanoma among 184 patients, significantly different with some western literatures that malignant melanoma accounts for 5-20% of the total number of brain metastases (Rades et al., 2007), which may be associated with higher incidence of malignant melanoma in the west. Similar to the age of onset and the distribution of literature of other literatures, the age of onset of brain metastases from breast cancer is slightly lower than lung and gastrointestinal cancer. Among brain metastases from different sources, there're no significant difference in the number of metastatic lesions in the brain and extra cranial lesions, however, in intracranial metastatic sites, as this study shown, brain metastases to the meninges from gastrointestinal cancer are significantly higher (27.3%), compared with other groups (less than10%). This phenomenon has not been reported, in which the mechanism is unclear.

Currently, treatment of brain metastases has no fixed pattern. All the factors as follows should be taken into considerations: the patient's general condition, the site of primary disease and its pathological type of brain metastases, number and presence of extra cranial original, secondary lesions. Basing on the traditional view, radiotherapy is the preferred treatment for brain metastases. Affected by many factors, however, surgery is only suitable for very little patients with single shot of brain metastases and the general condition of them are good. Because of the blood-brain barrier, the literature on the role of chemotherapy in the treatment of brain metastases recognize different. Some people think that the most chemotherapy drugs cannot through the blood-brain barrier hence the treatment effect of cerebral metastatic carcinoma by chemotherapy drugs is not obvious (Fabi et al., 2011). Opposite views insist that brain metastasis cancer cells, tissue and blood capillary keep the characteristics of the primary tumor, its permeability is also consistent with primary tumors and they do not have the basic conditions of forming blood-brain barrier. Basing on the opposite view, the drugs that cannot be through the blood-brain barrier can also be used for brain metastasis cancer treatment in clinical application (Butowski, 2011). This clinical data showed that 61.4% patients accept chemotherapy and radiotherapy at the same time, in addition, 10.9% patients only accept the chemotherapy without radiotherapy. So combine the chemotherapy and radiotherapy is the main treatment of cerebral metastasis carcinoma. The survival analysis showed that the median survival time (MST) of patients who accept radiotherapy alone is 10 months and the median time survival of patients who accept radiotherapy alone is also 10 months. Besides that, the survival analysis showed that the median survival time of patients who accept combination treatment is 16 months. According to the data we can draw a conclusion that chemotherapy and radiotherapy in the treatment of brain metastases is equally important. This set of data also shows, the MST of patients who accept the surgery can be extended to 18 months, but the general condition of patients who accept the surgery is better than the other patients. Affected by a number of objective and subjective factors, a very small proportion of patients underwent clinical surgery and most of these patients are also accepted postoperative chemotherapy and radiotherapy. So compared with radiotherapy and chemotherapy, the status of surgery in the treatment of brain metastases is still not obvious.

According to the literature, which was reported before, we know that the impact factors of survival prognosis for patients with brain metastases are organic energy status (KPS), age, the control of the primary lesion and other

extra cranial lesions. Besides that related symptoms of brain metastasis, histological type, as well as the sensitivity of various treatments are also the important impact factors (Gaspar et al., 1997; Lagerwaard et al., 1999; Meyers et al., 2004). The patients` overall median survival time of this group is 15.0 months. Univariate analysis found that the survival rates of female patients are slightly better than male patients, but there was no statistical difference. For the patients with meningeal metastasis, prognosis of them is poor and the survival time of them is only 3 months. The MST of patients with metastatic lesion that is less than three is superior to the patients with metastatic lesion that is more than three. Whether associated with extracranial lesions has no significant effect on survival time. After the multivariate COX analysis, results show as follows: (1) primary disease, intracranial metastases number and gender is an independent factor that can affect the prognosis; (2) There is poor prognosis in patients who is suffer from brain metastases transferred from gastrointestinal cancer; (3) the patients with intracranial metastases lesion that is less than three is superior to the patients with intracranial metastases lesion that is more than three; (4) Furthermore, female patients have slight advantages in the aspect of survival rate. A bit bizarre, this study shows the main treatment for non-independent prognostic factors. When we combine the analysis of clinical practice, the result show other clinical features maybe restrict the choice of treatment particularly in primary disease and intracranial and extracranial lesions, and therefore become secondary factors.

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