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# Efficacy observation of radiotherapeutic plans developed according to prognostic factors of brain metastases.

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## Abstract

**This study aimed to assess the efficacies of different radiotherapeutic plans for brain metastases (BM). A total of 110 patients with BM treated from January 2008 to December 2012 were retrospectively included, and divided into the standard group (n=57) and the auxo-dose group (n=53) according to their Karnofsky scores (KPS) and extracranial lesions. The standard group underwent whole brain radiotherapy with 30 Gy in 10 doses over 2 weeks, while the auxo-dose group received an increased local boost dose compared to the standard group, according to the number and invasiveness of the metastases. The follow-up lasted 2 years to observe the effect of local auxo-dosage on the prognosis of BM. The median survival time (17 months *vs.* 5 months), 1-year survival rate (69.8% *vs.* 33.3%), and 2-year survival rate (41.5% *vs.* 0) of the auxo-dose group were higher than those of the standard group. The 1-year complete remission (42.5% *vs.* 13.3%) and 1-year partial remission (48.8% *vs.* 6.7%) rates of BM in the auxo-dose group were higher than that in the standard group; 48 patients of the auxo-dose group died, with the main cause being extracranial tumor (60.4%, 29/48). All patients of the standard group died during the observation period, with the main cause as intracranial tumor (42.1%, 24/57). All of the above comparisons were significant (P<0.05). Compared with standardized whole-brain radiation therapy, radiotherapy with an additional local dose improved remission rates while reducing the long-term mortality of BM.**

**Keywords:** Brain tumor/secondary, Brain tumor/radiotherapy, Stereotactic radiosurgery/radiotherapy, Prognosis.

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## Introduction

Metastatic tumors involving the brain overshadow primary brain neoplasms in frequency and are an important complication in the overall management of many cancers [1]. Brain metastases (BM) are the most common intracranial tumors and their incidence is increasing [2], with an estimated prevalence of new BM in the USA between 7-14 persons per 100,000, based on population studies [3]. Untreated BM are always associated with a poor prognosis and a poor performance status. Metastasis development involves the migration of a cancer cell from the bulk tumor into the surrounding tissue, extravasation from the blood into tissue elsewhere in the body, and formation of a secondary tumor [4].

Lung cancer and breast cancer are the most frequent cancers causing BM. Among the various histologies of lung cancer, small cell lung cancer (SCLC) is the most likely to metastasize to the brain, with an 80% probability of BM within two years after diagnosis [5], and whole-brain radiation therapy (WBRT) continues to be the standard of care for patients with BM from lung cancer [6]. As for breast cancer patients with BM, radiosurgery plus WBRT results in significantly better escape from new BM than radiosurgery alone, but no survival advantage is noted [7].

Current therapeutic approaches for BM include surgery, WBRT, stereotactic radiosurgery (SRS), chemotherapy, systemic therapy, some combination of these treatments, or supportive measures alone [8,9]. Some studies showed no benefit of WBRT for melanoma BM [10-12], while others suggested that WBRT might improve intracranial disease control [13] or survival [14]. Survival for patients with BM treated with WBRT typically ranged from 4 to 6 months, but it also was observed as 12-24 months for some patients [15]. With WBRT, the improvement in BM control might be particularly important in the subset of patients with absent or stable extracranial disease, where the competing risk of death from extracranial disease is low [16].

Radiotherapy occupies an important position in the treatment of BM; however, norms have yet to be developed for individualizing treatment for these patients. We found that prognostic factors provide some guidance for developing radiotherapeutic plans for BM. Based on long-term

observations, we applied different radiotherapeutic plans according to prognostic factors for 80 BM patients from January 2008 to December 2012, and achieved better effects, as reported below.

## Methods

### *Clinical data*

Enrollment period: from January 2008 to December 2012. Inclusion criteria: 1) age: >18 years old; 2) Karnofsky score (KPS) ≥ 50 points (including patients with improved KPS after craniotomy to release intracranial pressure, Table 1); 3) with extracranial lesions; 4) with iconography-confirmed intracranial space-occupying mass; 5) all intracranial lesions were treated during the initial therapy. Exclusion criteria: 1) primary intracranial space-occupying lesion; 2) the extracranial lesion was malignant melanoma or renal cell carcinoma; 3) the presence of anemia or bone marrow failure; 4) having partial brain cortical lesions amenable to radiotherapy; 5) having serious hepatonephric dysfunction. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Nantong University. Written informed consent was obtained from all participants.

*Table 1. KPS score.*

| Physical condition | Score |
|---|---|
| Normal, no symptoms and signs | 100 points |
| Can carry out normal activities, have mild symptoms and signs | 90 points |
| Forced to carry out normal activities, there are a number of symptoms or signs | 80 points |
| Life can take care of themselves, but cannot maintain normal life and work | 70 points |
| Life can take care of themselves, but sometimes it needs help | 60 points |
| Often need to take care of | 50 points |
| Life can not take care of themselves, need special care and help | 40 points |
| Serious life can not take care of themselves | 30 points |
| Seriously ill, need hospitalization and aggressive supportive care | 20 points |
| Heavy danger, near death | 10 points |
| Death | 0 points |

### *Clinical grouping*

The patients meeting the inclusion criteria were enrolled and divided into the standard group and the auxo-dose group according to their KPS scores and brain tumor distributions. The standard group met the following four conditions simultaneously: 1) KPS ≥ 70 points, or <70 points due to the BM-induced compression; 2) ≤ 3 intracranial lesions; 3) without distant extracranial metastasis (not including lymph node metastasis in the drainage region, namely M1 in the TNM staging); 4) the primary lesion (including lymph node metastasis in the drainage region) was completely remitted or basically controlled (definition of "basically controlled": found BM during chemotherapy, radical radiotherapy, or combined radiochemotherapy treatment, and the primary tumor had already reached a PR at or before this time, but the evaluation time was before 4 cycles of the chemotherapy or 56 Gy of radiotherapy). The patients that did not meet all the above criteria were grouped into the auxo-dose group.

### *Treatment*

The treatment of the standard group included low-dose fractionated WBRT, with the head immobilized with a noninvasive mask, level opposing fields, 6 MV X-rays, for a total dose (DT) of 30 Gy delivered in 10 fractions over 2 weeks. The treatment for the auxo-dose group began by using the stereotactic radiotherapeutic positioning device and a noninvasive mask to fix the patient's head, followed by CT scanning. The gross tumor volume (GTV) was the post-WBRT lesion, with a 5 mm margin beyond the region of the GTV as clinical tumor volume (CTV)1 and a 5 mm margin beyond the region of the pre-WBRT lesion as CTV2. Appropriate radiotherapeutic plans were designed depending on the patient's individual situation. Requirements included: 1) the 90% isodose line covered CTV1; 2) for stereotactic fractionated radiotherapy (SFR), the 70% isodose line covered CTV2; for 3 dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT), the 80% isodose line covered CTV2; 3) additional requirements for IMRT: (A) the volume accepted as the GTV receiving >110% of the prescribed dose should be less than 20%; (B) the volume accepted as the GTV receiving <95% of the prescribed dose should be less than 3%; (C) any place outside CTV2 should not receive >100% of the prescribed dose.

Three methods of superadding the additional dose were used, depending on KPS and tumor status. A: For KPS ≥ 70 points, with no extracranial lesion (without distant metastasis, i.e., the primary tumor in a CR or having been removed surgically), after conventional fractionated WBRT, for patients with 1) ≤ 2 metastases having a diameter ≤ 25 mm, they were treated twice with stereotactic radiotherapeutic technology: SFR 8 Gy/ treatment, daily times 2 days. However, if the treatment field was near to the eyeballs, IMRT, with a DT of 56 Gy in 22 fractions within 31 days could be used instead; 2) ≤ 2 metastases having a diameter >25 mm or having 3 metastases, they were treated with 3DCRT, 4 Gy/fraction/day or IMRT, 4 Gy/fraction/day, for a DT of 56 Gy in 24 fractions within 32 days. B: For KPS ≥ 70 points, when the primary tumor was basically controlled, and no extracranial metastasis was present, we performed accelerated, hyperfractionated radiotherapy, 36 Gy in 24 fractions over 16 days, with a time interval ≥ 6 hours between treatments, followed by an additional dose application as in A above, to a DT of 52 Gy within 20 days. C: For KPS <70 points, caused by compression from the BM, and having no extracranial lesion, we

administered an additional dose four times with 3DCRT or IMRT after the conventional WBRT splitting, to a DT of 46 Gy in 14 fractions within 18 days.

### Observation and follow-up

The patients were followed once a month in the outpatient clinic after the radiotherapy to examine and record the changes in their neurological symptoms; they also underwent head magnetic resonance imaging (MRI) or computed tomography (CT) once every 1 to 3 months to observe changes in the lesions. All patients were followed until December 20, 2014; the follow-up rate was 100%.

### Efficacy evaluation criteria

To evaluate symptom remission, the criteria were defined, according to the Radiation Therapy Oncology Group brain tumor radiotherapy evaluation criteria [1], as: CR, meaning that the neurological symptoms completely disappeared within two months of the radiotherapy; PR, meaning that the neurological symptoms were reduced; NC, meaning that the neurological symptoms showed no improvement; or PD, meaning the neurological symptoms became worse.

The evaluation of the BM was divided into CR, PR, PD and NC according to the efficacy criteria of measurable lesions in solid tumors: CR, disappearance of all target lesions; PR, at least 30% decrease in the sum of diameters of target lesions; PD, at least 20% increase in the sum of diameters of target lesions; NC, no improvement of target lesions. Side effects that occurred during treatment were also recorded.

### Statistical analysis

The median survival times of the two groups were compared using the Mann-Whitney non-parametric test. The 1-year and 2-year survival rates were compared using the chi-square test. The difference in the reasons for death between the two groups was also compared.

## Results

### Clinical data

A total of 110 patients were enrolled, 67 men and 43 women, aged 35 to 74 years old, with a median age of 51 years. They included 59 cases of lung cancer, 23 cases of invasive ductal carcinoma, 11 cases of esophageal squamous cell carcinoma, 8 cases of gastric adenocarcinoma, 5 cases of rectal adenocarcinoma, 2 cases of squamous cell carcinoma of the maxillary sinus, 1 case of nasopharyngeal squamous carcinoma, and 1 case of cervical lymph node metastatic squamous carcinoma. According to the grouping criteria, the standard group comprised 57 cases, and the auxo-dose group comprised 53 cases. The clinical data between the two groups showed no statistically significant difference in age, sex, KPS, primary lesions, number of metastases, and extracranial lesions (P>0.05).

### Symptom remission rates

Except for the nine patients who were asymptomatic before radiotherapy (the standard group had five cases and the auxo-dose group had 4 cases), the neurological symptoms for the two groups were remitted to various degrees, with the both remission rates (CR+PR) both 100%. The remission rates of physical dysfunction of the auxo-dose group and the standard group were 85.7% (42/49) and 84.6% (44/52), respectively (P>0.05).

### Remission rates of BM

The comparison of MRI or CT before and after radiotherapy revealed that the auxo-dose group had 22 patients with CR (41.5%), 25 with PR (47.2%), and 6 with NC (11.3%). The standard group had 8 patients with CR (14.0%), 36 with PR (63.2%), and 13 with NC (22.8%). The CR rates were significantly different ($\chi$2=10.452, P<0.001), but there was no difference in CR+PR ($\chi^2$=2.536, P =0.111).

### Long-term efficacies

The median survival time of the auxo-dose group and the standard group were 17 months and 5.0 months, respectively (P<0.01). The 1- and 2-year survival rates were 69.8% (37/53) and 33.3% (19/57) ($\chi^2$=14.623, P<0.001), and 41.5% (22/53) and 0 (0/57) ($\chi^2$=46.422, P<0.001), respectively.

### Causes of death

At the end of the follow-up observation, the cause of death for patients in the auxo-dose group was extracranial tumor, while that in the standard group was intracranial tumor ($\chi^2$=10.06, P<0.01, Table 2).

***Table 2.*** *Comparisons of death causes among the study group, the auxo-dose group, the WBRT group, and the control group.*

| Group | Intra-brain tumor (n,%) | Extra-brain tumor (n,%) | Intra-+extra-brain tumor (n, %) | Non-tumor factors (n, %) |
|---|---|---|---|---|
| Standard (n=57) | 24 (42.1) | 22 (38.6) | 10 (17.5) | 1 (1.8) |
| Auxo-dose (n=48) | 9 (15.8)* | 29 (60.4)* | 8 (16.7) | 2 (4.2) |

Note: Compare with standard group, *P<0.01

### Side effects

The auxo-dose group and the standard group had 21 and 8 cases, respectively, of radiation-induced brain edema; except for 5 cases (auxo-dose group, 4 cases; standard group, 1 case) occurring within 2-4 weeks after radiotherapy, all cases occurred within one week after radiotherapy, presenting with aggravated symptoms such as headache, vomiting, drowsiness, or delirium. Symptoms improved after administration of intracranial decompression drugs, such as dexamethasone and mannitol, and the effects of the radiotherapy were not affected.

No intractable brain edema occurred within either group, nor did late radiation-induced brain injury occur.

## Discussion

Radiotherapy provides a high remission rate for most BM cases, and is a safe and effective means of palliative treatment. The 110 patients included in this study had good short-term efficacies after radiotherapy, and the remission rate was 100%. Since most BM patients experience multiple metastases, the rate of BM diagnosis is expected to rise with continuous improvement in MRI technology, and is likely to reach 80%-90% [17]. WBRT is the conventional treatment for BM, providing a median survival time of 4-6 months; however, many patients still die from BM [17]. Clinical studies have shown that WBRT plus auxo-dose to local lesions could better prolong the survival and/or improve the quality of life of patients with BM than does WBRT and stereotactic radiotherapy alone [18]. However, it is still controversial which method currently provides the best treatment. One study also showed that developing radiotherapeutic plans based on prognostic factors could provide a greater benefit for patients with BM [19].

The factors affecting the prognosis of BM include KPS, controlling the primary tumor or not, presence or absence of extracranial metastases, number of BM, age, and pathological type. Patients with a high KPS normally have a good state, could accept more aggressive treatment, and exhibit stronger resilience towards tumor development. Therefore, a higher KPS correlates with a better prognosis. The most important prognostic factor is the extracranial condition, namely the control of the systemic tumors. Tumor is a systemic disease, and BM and death from BM are only one aspect of the disease. If extracranial lesions are not controlled, the impact of adding additional post-WBRT local dose on the improvement of the survival would be significantly reduced. Patients with better prognostic factors might have a longer survival. However, 10%-20% of the patients receiving 30 Gy over 2 weeks of WBRT might develop radiation-induced dementia 1 year after treatment.

Because patients with poor prognostic factors have shorter survival, analyzing the effect of additional post-WBRT local dose for them would be inconsequential. Therefore, our patients were divided into the auxo-dose group and the standard group according to KPS and the presence of extracranial lesions. The auxo-dose group received different radiotherapy techniques and doses according to the numbers and sizes of BM. The number of multiple BM treated during radiotherapy correlates with prognosis, and the median survival time of patients with 2, 3, and ≥ 4 BM were 10.3, 6.0, and 2.7 months, respectively and the 1-year survival rates were 33.2%, 20.7%, and 0%, respectively [20]. Therefore, the approaches for achieving the best prognosis can be described as follows: A. providing a boost dose according to the BM number and size, after conventional fractionated WBRT, making the DT reach 56 Gy within 31-32 days; B. simultaneously shortening the radiation time based on the premise of not increasing chronic brain injury, administering chemotherapy as early as possible, and providing a boost dose with the A mode after accelerated hyperfractionated WBRT, to a DT of 56 Gy, while the time is shortened by 11-12 days; and C. for patients with relatively poorer prognostic factors among those with good prognostic factors, due to difficulty with patient mobility, lower KPS, and generally larger lesions, less fractionated WBRT should be normally performed, followed by a boost dose provided by 3DCRT or IMRT, to a DT of 46 Gy within 18 days. Because of their short expected survival time, patients with poor prognosis in the standard group received a lower dose of fractionated WBRT alone, DT of 30 Gy over 2 weeks. The results showed that developing and implementing the radiotherapeutic plans according to the prognostic factors of BMs provided better compliance and better short- and long-term efficacies, consistent with the literature [18]. The 2-year survival rate was 0% for the standard group, while that for the auxo-dose group was 41.5%.

BM of lung cancer is the most common type in both men and women. Moreover, BM of breast cancer is the second-most common type in women, as well as the second leading cause of BM along with lung cancer, after melanoma [21,22]. Lung cancer is the most common primary tumor of BM, contributing to the morbidity and mortality due to these cancers, impairment of sensory and motor neural functions, and incidences of headaches, vomiting, and seizures. Patients with lung cancer might develop early BM, within the first 2 years after the primary tumor is diagnosed [23]. One study focusing on non-SCLC (NSCLC) showed that WBRT plus simultaneous in-field boost with image-guided IMRT was a tolerable and effective treatment for patients with NSCLC and inoperable BM [24].

Besides lung cancer, this study also included breast cancer and gastrointestinal tumors, and the results were consistent with the above-mentioned studies. The median survival time and 1-year survival rate of the standard group (5 months and 33.3% respectively) were significantly lower than that of the auxo-dose group (17 months and 69.8%, respectively; $P<0.05$), indicating that for cancer patients with BM, a local boost dose could kill the cancer cells. Thus, a more targeted approach instead of whole brain radiation therapy could be effective. Furthermore, in view of safety, the risks of serious side effects were not significantly increased.

In this study, 29 patients developed radiation-induced brain edema, which improved after intracranial decompression treatment. There were no cases of intractable cerebral edema within the two groups, nor did late radioactive injury occur. Therefore, developing and implementing radiotherapeutic plans according to prognostic factors could offer a better local control rate and control time for patients with BM. The patients' compliance may improve, while side effects would be decreased. Thus, this approach could improve the patients' quality of life, prolong survival, and avoid overexposure for certain patients.

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