Effect of Whole Brain Radiotherapy Dose on Breast Cancer Brain Metastases Survival

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ABSTRACT
This paper sets to study the effect of whole brain radiotherapy (WBRT) dose on the survival after breast cancer brain metastases (BM) in order to reduce the mortality rates of breast cancer. We collect relevant information on the patient, operation, and post-operation systematic treatment, diagnosis and treatment of BM from the medical record inquiry system. The results show that under implications of multiple factors, local supplement dose, to some extent, has good prognosis tendency, but does not extend the intracranial progression free survival (PFS), while the WBRT dose can. It is the conclusion of this paper that WBRT can improve the overall survival (OS) and PFS, but WBRT cannot further extend the OS after exceeding a certain amount.

Key Words: Breast Cancer, Brain Metastases, Whole Brain Radiotherapy
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Introduction
Breast cancer is a common malignant tumor among females in China, and one that has highest brain metastases (BM) rate. Fig 1 shows the typical symptom of breast cancer, which accounts for 10-16% of BM (Lin, 2010). In recent years, with development of extended survival of breast cancer patients and imaging diagnosis techniques, the BM rate is rising over the years and 5% to 21% patients have metastases (Weil et al., 2005). Recent international research shows that the breast cancer BM is on an upward trend to 25% to 34%. Further autopsy results show that the BM rate can be as high as 26% to 30% (Lin et al., 2004). BM is the main reason behind the shortened life span and deteriorated life quality of the patients, and research shows that 20% breast cancer patients die of BM (Halbleib et al., 2006). Since most of the drugs cannot permeate the blood-brain barrier, simple radiotherapy has limited effects. Carbometine, propofol, topotecan and temozolomide can easily permeate the blood brain barrier, while the etoposide, platinum and vincristine have poorer permeability. In addition, the BM cancer typically have multi foci and therefore cannot be properly controlled with surgical operations. The indications are BM patients who have superficial, metastatic foci of 1 or 2 with high KPS scores and no external BM. So brain radiotherapy is the most common and effective palliative treatment used on BM cancers (SEZGİN et al., 2006). Median survival of the untreated patients is 1 month, and for patients receiving supportive treatments, the expected median survival is 1 to 2 months.

The WBRT breast cancer BM patients have expected median survival of 4 to 6.5 months, which fall short of the medical demands of the patients (SEZGİN et al., 2006). The brain radiotherapy treatment includes WBRT, WBRT+...
local supplements WBRT+SRS/SRT, and SRS/SRT. However there is not enough data and research on the treatment effects of brain radiotherapy.

Breast cancer is caused by complicated pathogeny. According to Niwinska, BM patients with different molecular subtypes have varied lengths of survival. As the molecular type varies, the rate of BM and prognosis also vary (Siegal, 2013). Based on estrogen receptor (ER) and progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2), there are three subtypes, Trip-negative breast cancer (TNBC), HER2+ and HR+. HER2+ and HR+ subtypes indicate poorer prognosis and higher tendency of BM in patients (Weber et al., 2014). HER2+ BM has the features of multiple small focus and is often accompanied by leptomeningeal metastases. Those with leptomeningeal metastases tend to have poorer prognosis (Vanan et al., 2015). The HR+ subtype tends to have better prognosis.

Figure 1. A common symptom of breast cancer

Radiotherapy is a local treatment of tumor using radiation. Fig 2 is an example diagram. The radiation used include α, β, γ radial generated by radio isotope, and x radial, electron, proton and other particle beams generated by X radial machine and accelerators. About 70% of the cancer patients receive radiotherapy treatments, and about 40% of the cancers can be cured using this treatment. It has a prominent role in cancer treatment as one of the main methods to treat malignant tumors.

The current WBRT include stereotactic radiotherapy (SRT) and stereotactic radiosurgery (SRS). The SRT requires precise positioning and has faster dose attenuation outside of the target area. This research uses retrospective analysis to understand the effect of WBRT on breast cancer BM patients and the impact of WBRT dose on OS and PFS. At the same time, by taking into consideration of other factors, the results will have referential meanings to the clinical treatment after breast cancer post-BM.

Figure 2. Example diagram of radiation therapy

Methods

Material

This paper collects medical records of breast cancer BM patients hospitalized during January 1, 2013 to December 31, 2015. Those meeting below conditions are excluded: males with breast cancer BM, carcinoma in situ BM. A total of 105 patients meeting selection standards are selected for the experiment. We obtain the information on the patient, operation, and post-operation systematic treatment, diagnosis and treatment of brain metastases from the medical record inquiry system.

Variables

The WBRT dose groups include: 0Gy, <30Gy group, 30-39Gy group, and ≥40Gy group. The after local supplement overall include: 0Gy group, <50Gy group, and ≥50Gy group. Among the record collected, the covariant include: BM-relevant information including BM age, symptom, ECOG score, GPA class, BM (number, position, size), if BM, if external BM, if integrated with cardio cerebrovascular disease, post-BM treatment (operation, radiotherapy, endocrinology, targeting therapy); breast cancer information including: breast cancer history (years), operation method, TNM stage, pathological type, vascular tumor suppository, ER/PR, HER2, Ki-67, and pre- and post- operation systematic treatments (chemotherapy, radiotherapy, endocrine therapy, targeted therapy). This research determines ER/PR positive ≥1+ (rate of positive cells ≥1%) based on recorded histopathological immunohistochemistry information (-, +, ++, +++). Based on the histopathological immunohistochemistry information (-, +, ++, ++++) on HER2, the HER2 negative is (-, +) while the HER2 (++).
categorized and the HER2 positive (+++); the Ki-
-67, based on the histopathological
immunohistochemistry information (-, +, ++, ++++)
or positive cell rate, has high expression at (+, ++, ++++) and low expression at (-) (positive cell rate <14%). The ER/PR positive means HR positive, both ER and PR negative means HR negative. Since HR positive and endocrine therapy has close
relationship, so do HER2 positive and targeted
therapy, this paper, among multiple factors, uses
docrine therapy and targeted therapy to
replace HR positive and HER2 positive in analysis.

Statistical method
The average value (standard deviation) and
median of continuous variable clinical data are
calculated. ANOVA analysis is adopted for
comparison between groups. The percentages are
calculated by classification variables. The
comparison between groups is done with χ2 test
and Fisher’s test. In analysis of OS and PFS, K-M
curve and Log-Rank test are used. Before multi-
factor COX survival analysis on OS and PFS, all the
single variables are selected by single screening
analysis to determine the final multifactor
analysis model, through the risk ratio (HR) and
the corresponding P list of the COX risk ratio
model. Bilateral P < 0.05 is statistically significant.
SAS9.20 is used for statistical treatment.

Results and discussion

Group data
This research is conducted on 105 cases. The
average age of BM is 53 years old (27-82), BM
singular BM group 42.9% (45), 2 BM 11.4% (12),
3 BM 1.9% (2), and ≥4 BM 43.8% (46). The ECOG
score 0-1, 2, 3-4 groups account for 38.1%(40),
32.4%(34), and 29.5% (31). Those have
meningeal metastases account for 17.1% (18),
66.7% (70) with BM, 74.3% (78) with other organ
metastases, 30.5% (32) with cardiovascular and
cerebrovascular diseases, 58.1% (61) with
hyponatremia, and 17.1% (18) with infections.
The median survival period of the groups is 11.3
(2.0-22.9) months (30 days/month), the
cumulative total mortality is 76.2% (80), and the
rate of treatment failure (death + relapse +
metastasis) is 81% (85) (see details in Fig 3 and
Fig 4. Fig 5 is overall survival of all patients by
WBRT schemes).

WBRT group data
WBRT groups (0Gy, <30Gy, 30-39Gy, and ≥40Gy)
have statistical differences in terms of total dose
after local supplementation, chemotherapy after
BM, TNM staging, and Ki-67 expression (P < 0.05). Non-WBRT group: I-II phase 34.8% (8/23), III phase 52.7% (29/55), IV phase 63.6% (7/11). Where the WBRT dose is not 0: I-II phase 65.2% (15/23), III phase 47.3% (26/55), and IV phase 36.4% (4/11). The data show that patients in WBRT groups have earlier staging than those non-WBRT groups, which accords with the tendency of patients opting for WBRT. However, there is no difference in the distribution of HR and HER2 among the radiotherapy groups (P=0.057 and 0.790).

**PFS analysis of radiotherapy treatment groups**

In all the groups, the total treatment failure rate of WBRT groups is 81% (85/105). The failure rates of 0Gy, <30Gy, 30-39Gy, and ≥40Gy groups are 84.3% (43/51), 81.8% (9/11), 84.6% (11/13), and 73.3% (22/30). In the single factor COX analysis of the radiotherapy groups, compared with the 0Gy group, there is a statistically significant difference between the group and the ≥40Gy group (P=0.026), while <30Gy and 30-39Gy groups do not have statistical significance (P=0.05). But in multi-factor analysis, compared with 0Gy, the 30-39Gy and ≥40Gy groups have statistical difference (P < 0.05), while the <30Gy group has no statistical significance (P=0.212). But there is no statistical difference between the 30-39Gy and ≥40Gy groups (P>0.05). It suggests that when WBRT dose > 30Gy, it improves the PFS, but further increased dose of WBRT does not improve PFS (see Fig 6).

![Figure 6. Progression-free survival of all patients by WBRT schemes (P<0.005)](image)

The failure rates in the local supplement group are 82.4% (56/68), 100% (5/5) and 75% (24/32) respectively in 0Gy, <50Gy and ≥50Gy groups. In the single factor COX analysis of local supplement group, compared with 0Gy, there is statistical significance in ≥50Gy group (P < 0.05). But in multi-factor analysis, <50Gy group has statistical significance (P=0.002), there is no statistical significance in ≥50Gy group (P=0.087). It indicates that, impacted by multiple factors, the total dose after local supplementary, when more than 50Gy, has a good prognosis, but cannot improve PFS. The total failure rate of SRS/SRT treatment BM groups is 81% (85/105). The failure rates of groups without SRS/SRT and with SRS/SRT are 80.4% (78/97) and 87.5% (7/8) respectively. Univariate and multivariate COX analysis show no significant difference between SRS/SRT group and non-SRS/SRT group (P>0.05), meaning that SRS/SRT cannot improve PFS in both single and multivariate analysis.

**Conclusions**

The gap of this research is that ER/PR positive set by this research is ≥1%, which is consistent with current standards (2015 St. Gallen International Consensus on Breast Cancer). But since many patients did not receive immunohistochemistry and are therefore categorized as the unknown group, it may have implications when comparing results of this research with other researches. Limited by time and funding, we do not perform re-reading classification on the immunohistochemical staining. In addition, HER2(++) patients, though not being checked with FISH, are not categorized. But we have conducted analysis by listing them as one category to reduce implications to the minimum. This research has considerable number of unknown ER/PR and HER2 cases where they cannot be classified according to the molecular, so sub-type analysis without BM is not conducted. This research has below conclusion:

- WBRT can improve OS and PFS, when the WBRT dose ≥40Gy, it can not further improve OS.
- HER2 treatment can improve OS for breast cancer BM patients.
- The risk factors to the OS include BM age under 35, with meningeal metastases, BM focus ≥4, ECOG ≥2, Ki-67 high expression, HER2+, and HR-.

**References**