CSCO expert consensus on the diagnosis and treatment of breast cancer brain metastasis

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Abstract: Breast cancer is one of the most common malignancies among women worldwide. According to the International Agency for Research on Cancer, breast cancer affected more Chinese women than any other cancer in 2020. The brain is an increasingly common metastatic sites of breast cancer. Although the risk of developing brain metastases (BMs) is lower in breast cancer than in lung cancer and melanoma, due to its high prevalence, it is the second most common cause of BM among solid tumors, being second only to lung cancer. The incidence of breast cancer brain metastasis (BCBM) differs by molecular subtype. Half of patients with advanced human epidermal growth factor receptor-2 (HER2)-positive and one-third of patients with triple-negative breast cancer (TNBC) develop BM. The clinical manifestations of leptomeningeal metastasis (LM) are often non-specific and may manifest as a variety of signs and symptoms, mainly including brain parenchyma involvement and meningeal irritation syndromes cranial nerve involvement, increased

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intracranial pressure, and progressive brain dysfunction. Therefore, the Chinese Society of Clinical Oncology (CSCO) Breast Cancer Committee has developed this expert consensus on BM, in an effort to improve the overall prognosis of BCBM and promote the standardized diagnosis and treatment of this disease. During the development of this expert consensus, we carried out a comprehensive literature review and referred to some of the most authoritative guidelines in China and abroad. In this consensus, we will discuss clinical manifestations, imaging examinations, pathological diagnosis, treatments, prognosis, follow-up and monitoring. We hope this consensus will be of help to all the clinicians majored in breast cancer and other similar professions.

Keywords: Breast cancer (BC); brain metastases (BMs); expert consensus

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Introduction

Breast cancer metastasis to the brain, including breast cancer brain metastasis (BCBM) and leptomeningeal metastasis (LM), occurs in 10% to 20% of breast cancer (BC) cases. About 80% of breast cancer brain metastases (BMs) occur in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brain stem. In a study by Cacho-Díaz *et al.*, 47.6% of the patients had multiple lesions and 26.4% had solitary lesions, most of which were located at the cerebral cortex-medulla junction, where the vascular branches are relatively narrow. Only a small proportion of cases had LM (about 6.9%), and 3.6% had both BMs and LM, which was associated with a poorer prognosis (1,2).

The incidence of BCBM differs by molecular subtype. About 15% of patients are diagnosed with advanced hormone receptor (HR)-positive BC, 50% of patients with advanced human epidermal growth factor receptor-2 (HER2)-positive BC, and one-third of patients with triple-negative breast cancer (TNBC) develop BM (3,4). The occurrence of BCBM is also associated with BRCA1 (BReast CAncer gene 1) and BRCA2 (BReast CAncer gene 2) mutations. BRCA1/2 mutation carriers have been found to have a significantly higher rate of BM (5).

Methods

Professor Zefei Jiang, Vice President and Secretary General of the Chinese Society of Clinical Oncology (CSCO) and Chairman of the CSCO Breast cancer Expert Committee, took the lead in formulating an expert consensus on BCBM. On the 17th March 2022, the BM consensus expert group held an online meeting to define the consensus on the diagnosis and treatment of BCBM from the epidemiological characteristics, clinical manifestations, diagnostic methods, treatment, prognosis, and monitoring follow-up five aspects, and written by the experts' division of labor. Finally, the CSCO expert consensus on the diagnosis and treatment of BCBM was formed through discussion and summary of several online meetings.

Results and discussion

Clinical manifestations

Patients with BCBM experience some common clinical manifestations, which may vary among individual patients due to differences in the histobiological features, location, size, and the number of metastatic lesions. The most common symptoms in patients with BCBM include headache (35%), vomiting (26%), nausea (23%), hemiplegia (22%), visual changes (13%), and seizures (12%) (6). Common clinical manifestations include headache, symptoms related to increased intracranial pressure, focal neurological dysfunction, seizures, and psychiatric disorder.

The clinical manifestations of LM are often non-specific and may manifest as a variety of signs and symptoms, mainly including brain parenchyma involvement and meningeal irritation syndromes (e.g., headache, vomiting, nuchal rigidity, cognitive disorders, clouding of the consciousness, and the onset of symptomatic epilepsy), cranial nerve involvement, increased intracranial pressure, and progressive brain dysfunction. Sometimes it is difficult to differentiate LM from BM or treatment-associated toxicities. In some cases, patients with LM present only with progressive neck and shoulder pain. If the tumor also spreads along the spinal

membrane, spinal cord, and spinal nerve root, stimulation can occur, manifesting as radicular pain, segmental sensory disturbance, limb numbness, sensory ataxia, and reduced or absent deep tendon reflexes (7-10).

Imaging examinations

Magnetic resonance imaging (MRI)

Cranial MRI plays an important role in the diagnosis, response evaluation, and post-treatment monitoring and follow-up of patients with metastases (11). It is the preferred imaging modality for BM and LM due to being radiation-free and offering high-resolution soft-tissue imaging, multi-parameter imaging, and high sensitivity; however, it is not feasible for patients with magnetically sensitive metals in their bodies or those with claustrophobia. Meningeal metastases of breast cancer can be divided into LM, dural metastases, and mixed meningeal metastases. On MRI, dural metastases are shown as a continuous uneven linear meningeal thickening on the convex surface of the brain or tentorium, which typically does not extend into the sulcus or the brain fissure. The involvement can be extensive, and in severe cases, local nodules or irregular masses may form, which are markedly enhanced after contrast application. Leptomeningeal metastases on MRI are mostly arc-like enhancements along the surface of the gyrus, sulci, fissures, cistern, and subependymal zone. They are irregular in shape, and nodules can also form. Invasion of adjacent brain tissues can cause local parenchymal edema. In some cases, meningeal metastases of breast cancer may only manifest as hydrocephalus without meningeal enhancement, which is difficult to diagnose with MRI alone, and cerebrospinal fluid (CSF) examination may be helpful.

Computed tomography (CT)

On CT, BCBM typically manifests as iso- or low-density shadows, although the density may be slightly elevated in the presence of hemorrhage. The typical manifestations of BCBM on contrast-enhanced CT scans are small tumors and large edema with an obvious enhancement of solid components, which are manifested as nodular, annular, or irregular enhancements. In cases where patients have contraindications to MRI, CT remains a valuable adjunct. Notably, small isodense metastases are difficult to detect, and metastases in the posterior fossa are often overlooked due to the presence of surrounding bony structures. Calcification of BM from breast cancer is extremely rare.

Positron emission tomography/computed tomography (PET-CT)

PET-CT can provide both anatomical and metabolic information and is valuable for assessing systemic tumor load. However, due to the predominance of glucose metabolism in cerebral gray matter, the background radioactivity of normal brain tissue is high, which makes the differentiation between brain tumors and the surrounding normal brain tissues difficult. As a result, imaging of local structures is often required. In patients with clinical symptoms of BM, a timely head MRI or CT scan should be performed to determine the systemic tumor load.

Pathological diagnosis

For patients who have a high clinical suspicion of BCBM, a biopsy of the metastatic lesions is recommended, if clinically feasible, to confirm the diagnosis. Histological morphology examination and immunohistochemical staining of the primary tumor and metastases should also be performed to determine whether it is BCBM. Panels of immunohistochemical markers are recommended; these may include cytokeratin 7 (CK7), GATA binding protein 3 (GATA3), gross cystic disease fluid protein 15 (GCDFP-15), mammaglobin, trichorhinophalangeal syndrome 1 (TRPS1), and SRY-related HMG-box (SOX10). For patients from whom biopsy tissue cannot be obtained, CSF detection, along with cytological and immunohistochemical staining, may be performed to identify BCBM.

The high degree of temporal and spatial heterogeneity among advanced breast cancer may result in inconsistent molecular typing results between metastases and primary lesions. Re-assessment of the molecular subtype of a metastatic lesion based on estrogen receptor (ER), progesterone receptor (PR), HER2, and KI67 status is recommended. In particular, the HER2 status of metastases should be determined wherever possible. Immunohistochemistry plus in situ hybridization (ISH) is recommended to detect HER2 status (12): (I) HER2 positivity: IHC 3+ or IHC 2+ AND ISH positive; (II) low HER2 expression: IHC 1+ or 2+ AND ISH negative; and (III) HER2 negativity: IHC 0.

Treatment

Both systemic therapy and treatment of BM are important for the treatment of BCBM, and multidisciplinary treatment is always preferred. Localized treatments including surgery,

whole-brain radiation therapy (WBRT), and stereotactic radiosurgery (SRS) remain the mainstay of treatment for BCBM. Medical therapies have also shown efficacy in treating certain types of breast cancer. The aim of treatment for BCBM is same as that for advanced breast cancer: to improve quality of life and prolong survival.

Surgical treatment

Surgical removal of BM can lower intracranial pressure, relieve symptoms, prevent focal neurological dysfunction and epilepsy, and reduce steroid use. Surgical specimens are useful in making a definite pathological diagnosis, and they can also be used in molecular pathology and targeted therapy. Surgery is an effective treatment for patients with solitary BM, especially those with giant lesions and compressive symptoms, for whom the benefit is higher than it is for patients with multiple BM or systemic symptoms. Patchell *et al.* randomized 48 patients with BM (including 3 BCBM cases) into surgery, whole brain radiation therapy (WBRT), and biopsy with WBRT groups, and found that the recurrence rate in the surgery group was significantly lower than that in the WBRT group (20% *vs.* 52%) and the median survival was significantly longer (40 *vs.* 15 weeks) (13). Patients with two or three BMs whose general condition is satisfactory can also benefit from surgery, with comparable outcomes to those of patients with solitary BMs (level IIIb) (14).

Margin status is an important prognostic factor, with the postoperative residual tumor being significantly associated with tumor recurrence and progression (level IIIb) (15). A meta-analysis (16) found that in patients with posterior fossa metastases, radical resection (R0) reduced the recurrence rate; the rate of leptomeningeal dissemination was only 5 to 6%, which was significantly lower than that after partial resection (level IIIb). In another study, residual tumor after metastasis extirpation was observed on early postoperative MRI in nearly 20% of patients and was significantly correlated with local recurrence (level IIIb). Multimodal imaging and navigation techniques such as preoperative functional MRI, intraoperative neuronavigation, and pyramidal tract reconstruction (level IV) can protect brain function and reduce complications while completely resecting BM.

Magnetic resonance-guided laser-induced thermotherapy (LITT) is an emerging treatment technique. It represents a new treatment opportunity for patients with deep brain lesions, older or frail patients who cannot tolerate a long surgical operation, and those with radiation-induced necrosis. A case-control study reported that laser-induced thermotherapy was as effective as a surgical resection for local control of BM. The 6-month local control rates of recurrent BM and radiation-induced necrosis ranged from 54% to 81.9% and 56.5% to 100%, respectively (17,18). In a meta-analysis and a retrospective clinical trial, the performance of laser-induced thermotherapy was equal or even superior to that of bevacizumab for the control of radiation-induced necrosis in patients with BMs (19,20). Moreover, laser-induced thermotherapy treatment did not reduce the Karnofsky Performance Status (KPS) score or the quality of life of patients (17), and to a certain extent, reduced the use of steroids (17,21). Another multicenter prospective clinical trial showed that laser-induced thermotherapy effectively controlled BMs in areas difficult to reach by surgery (22). Brain edema caused by radiation-induced necrosis can also be effectively controlled by laser-induced thermotherapy therapy. Some self-developed LITT treatment system in China has shown that it is effective in controlling both newly diagnosed and recurrent brain metastases, as well as radiation-induced necrosis. According to the 2021 guidelines on the treatment of BMs jointly released by the European Association of Neuro-Oncology (EANO) and the European Society for Medical Oncology (ESMO), laser-induced thermotherapy is a new technology for the treatment of recurrent BMs and radiation-induced necrosis, but its value needs to be further investigated.

Radiotherapy

Goals

The overall goals of radiotherapy for BCBM include intracranial lesion control, neurological symptom improvement, cognitive function and quality of life preservation, and maximization of survival benefits. In clinical practice, treatment strategies based on different treatment goals are often developed based on individual patients' expected survival. Some non-prospective studies have suggested that the Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) score may improve the treatment decision-making for patients with BM through prognostic stratification (23,24). In a survey on local therapies for multiple BM, one-third of physicians preferred to use the Recursive Partitioning Analysis (RPA) or GPA score as the basis for selecting SRS (25). Therefore, an updated Graded Prognostic Assessment (Breast GPA) is recommended to determine treatment goals and guide the treatment of BM in a stratified, reasonable, and orderly manner. This scoring system will be continuously optimized

with the innovation of medical therapies and local treatment methods.

Currently, radiotherapy for BCBM includes stereotactic radiotherapy (SRT) and WBRT with or without hippocampal avoidance.

SRT

Owing to its advantages including more precise positioning, higher dose, a shorter course of treatment, and lower toxicity, SRT can effectively protect cognitive function while controlling the progression of intracranial lesions and relieving neurological symptoms. Consequently, it has gradually replaced WBRT as a mainstay of local treatment for BM. With regard to dose fractionation, SRT is divided into SRS and fractionated stereotactic radiotherapy (FSRT).

(I) Postoperative SRT

Half of the patients with BMs who undergo surgical resection alone suffer from intracranial local recurrence within the first 6 months after surgery (26). Postoperative WBRT can decrease both the risk of local recurrence and the risk of intra-cranial distant recurrence by 50%, as well as prolong survival (27-29). Several observational studies have explored the efficacy of postoperative SRT (30-33). After single- or multiple-fraction postoperative SRT, the 1-year local control rates of the intracranial surgical bed reached 73% to 90%, which were comparable to the local control rates of lesions after postoperative WBRT. Mahajan *et al.* (34) analyzed 132 patients with one to three BMs who were randomized to receive postoperative SRS or undergo observation and confirmed that postoperative SRS significantly improved the local control of the surgical cavity. The NCCTG N107C/CEC3 study (35) enrolled 194 patients who had undergone surgery for BM (at least one resected BM and no more than three unresected BM). While there was no difference in overall survival between the treatment groups, the median cognitive-deterioration-free survival rate and the cognitive deterioration rate at 6 months were superior in the SRS group. The surgical site control rates were lower in the SRT group than in the WBRT group (80% *vs.* 87% at 6 months, and 61% *vs.* 81% at 12 months), which was likely due to 40% of the patients had an operative cavity width greater than 3 cm.

Therefore, we recommend that for patients with a limited number of BCBM, postoperative radiotherapy is necessary to improve intracranial local control. Compared with postoperative WBRT, postoperative tumor bed SRT can achieve equally effective local control of the surgical cavity while being associated with fewer cognitive impairments without compromising survival. Therefore, if postoperative SRT is technically accessible, it should be the therapeutic choice of priority, followed by WBRT; however, the risk of intracranial recurrence should not be neglected, especially for patients with a surgical cavity larger than 3 cm. Close follow-up is thus required.

(II) SRT alone

The RTOG 9508 study (36) confirmed the efficacy and safety of WBRT + SRS in patients with one to three BMs. Subsequent clinical studies compared the efficacy and toxicity of SRS with WBRT versus SRS alone in the same population (26,37-39). Compared with SRS alone, SRS with WBRT was found to reduce the risk of intracranial disease progression by about 50%; however, it not only failed to prolong overall survival but also increased the risk of toxic effects, such as cognitive decline. Several randomized trials have supported the use of SRS as initial therapy for patients with a small number of BMs who are suitable candidates (*Table 1*). Meanwhile, due to the toxicities associated with WBRT, it is generally preferable to defer the use of WBRT for most patients who have a limited number of BMs and can be initially treated with SRS. Most of these previous randomized clinical trials included patients with no more than 4 BMs of no larger than 3 cm in diameter (*Table 1*).

The strongest evidence currently supporting the use of SRS in patients with more than 4 BMs comes from a Japanese prospective single-arm multicenter study [JLGK0901 (43)] which included 1,194 patients with between 1 and 10 BMs. Compared with patients with 2 to 4 BMs, those with 5 to 10 BMs had similar overall survival, toxicities, and subsequent central nervous system failure rates after SRS. Another randomized controlled study [NCT02353000 (41)] compared the toxicity and efficacy of WBRT versus SRS in patients with 4 to 10 BMs. Although the study was prematurely ended due to poor accrual, analysis of the 29 patients enrolled showed that in the SRS group, the actuarial 1-year brain salvage-free survival rate was 50% and the 1-year survival rate was 57% with good quality of life maintained.

Therefore, we recommend that effective SRT can safely postpone WBRT for patients with a limited number of BMs (i.e., <4) while ensuring survival, thereby allowing them to avoid WBRT-related neurotoxicity. For patients with multiple BMs (>4), SRT has shown good efficacy and may be recommended when technically feasible.

(III) Fractionation

No prospective randomized controlled trials have investigated the clinical benefits of different dose/fractionation regimens of SRT. The dose of postoperative

Table 1 Prospective randomized controlled trials on radiotherapy for brain metastases

Study	n	Inclusion criteria	Groups	Radiotherapy dosage	Intracranial local control (RR or PFS)	OS
Patchell *et al.* (13)	48	>18 y; solitary; KPS ≥70	Surgery + WBRT (n=25); WBRT (n=23)	36 Gy/12 F	5/25 *vs.* 12/23; P<0.02	40 *vs.* 15 w; P<0.01
Vecht *et al.* (28)	63	>18 y; solitary; PS ≤1	Surgery + WBRT (n=32); WBRT (n=31)	40 Gy/20 F	NA	10 *vs.* 6 m; P=0.04
Mintz *et al.* (29)	84	<80 y; solitary; KPS ≥50	Surgery + WBRT (n=41); WBRT (n=43)	30 Gy/10 F	NA	5.6 *vs.* 6.3 m; P=0.24
Patchell *et al.* (27)	95	>18 y; solitary; KPS ≥70	Surgery + WBRT (n=49); Surgery (n=46)	50.4 Gy/28 F	18% *vs.* 70%; P<0.001	48 *vs.* 43 w; P=0.39
NCCTG N107C/CEC3 study; Brown *et al.* (35)	194	≥18 y; PS ≤2; including 1 resected BM with a surgical cavity <5 cm; 0–3 unresectable BMs with max. diameter <3 cm (77% were solitary)	Surgery + SRS (n=98); Surgery + WBRT (n=96)	WBRT: 30 Gy/10 F and 37.5 Gy/15 F; SRS: 12–24 Gy*	6.4 *vs.* 27.5 m; P<0.0001	12.2 *vs.* 11.6 m; P=0.70
Kayama *et al.* (40)	271	PS ≤2 or PS =3 only because of neurological symptoms; 1–4 BMs were surgically removed, and 1 lesion sized >3 cm	Surgery + SRS for residual tumor (n=134); Surgery + WBRT (n=137)	WBRT: 37.5 Gy/ 15 F	4.0 *vs.* 10.4 m	15.6 *vs.* 15.6 m
EORTC22952-26001 (26)	359	PS ≤2; 1–3 BMs; surgical resection (n=199) or SRS (n=160)	WBRT (n=180); Wait-and-see (n=179)	30 Gy/10 F	4.6 *vs.* 3.6 m; P=0.02	10.9 *vs.* 10.7 m; P=0.89
Mahajan *et al.* (34)	132	KPS ≥70; surgical resection of 1–3 BMs	SRS (n=64); Wait-and-see (n=68)	SRS: 12–18 Gy	72% *vs.* 43%; P=0.015	17 *vs.* 18 m; P=0.24
RTOG 9508 (36)	333	≥18 y; KPS ≥70; 1–3 BMs ≤4 cm	WBRT + SRS (n=167); WBRT (n=164)	WBRT: 37.5 Gy/ 15 F; SRS: 15–24 Gy	1 y: 82% *vs.* 71%; P=0.01	6.5 *vs.* 5.7 m; P=0.14
Aoyama *et al.* (38)	132	≥18 y; KPS ≥70; 1–4 BMs ≤3 cm	SRS + WBRT (n=65); SRS (n=67)	WBRT: 30 Gy/ 10 F; SRS: 18–25 Gy	1 y tumor bed recurrence: 46.8% *vs.* 76.4%; P<0.001	7.5 *vs.* 8.0 m; P=0.42
Chang *et al.* (39)	58	≥18 y; KPS ≥70; RPA grade 1–2; 1–2 BMs	SRS + WBRT (n=28); SRS (n=30)	WBRT: 30 Gy/12 F; SRS: 15–20 Gy	1 y: 73% *vs.* 27%	NA
Brown *et al.* (37)	213	≥18 y; PS ≥2; 1–3 BMs ≤3 cm	SRS + WBRT (n=102); SRS (n=111)	WBRT: 30 Gy/12 F; SRS: 18–24 Gy	1 y: 84.6% *vs.* 50.5%; P<0.001	7.4 *vs.* 10.4 m; P=0.92
NCT02353000 (41)	29	≥18 y; KPS ≥70; 4–10 BMs ≤30 cm^3	SRS (n=15); WBRT (n=14)	SRS: 15–24 Gy/1 F and 24 Gy/3 F; WBRT: 20 Gy/5 F	1 y: 50% *vs.* 78% (P=0.22)	1 y: 57% *vs.* 31% (P=0.52)
NRG ONCOLOGY CC001 (42)	518	≥18 y; KPS ≥70	HA-WBRT + memantine hydrochloride (n=261); WBRT + memantine hydrochloride (n=257)	30 Gy/10 F	5.0 *vs.* 5.3 m; P=0.21	6.3 *vs.* 7.6 m; P=0.31

*, surgical cavity SRS (volume/dose): <4.2 cm^3/20–24 Gy; 4.2–7.9 cm^3/18 Gy; 8.0–14.3 cm^3/17 Gy; 14.4–19.9 cm^3/15 Gy; 20–29.9 cm^3/14 Gy; ≥30 cm^3 and not exceeding 5 cm/12 Gy. KPS, Karnofsky Performance Status; PS, performance status; BM, brain metastasis; SRS, stereotactic radiosurgery; RPA, Recursive Partitioning Analysis; WBRT, whole-brain radiation therapy; HA, hippocampal avoidance; RR, regional recurrence; PFS, progression-free survival; NA, not available; m, month; y, year; OS, overall survival; w, week.

single-fraction SRS can refer to the NCCTG N107C/CEC3 study (35) (*Table 1*). Only some non-randomized studies (33,44-46) have explored postoperative multiple-fraction SRT, and a study to evaluate the fractionation regimens of postoperative SRT (NCT04114981) is ongoing.

In a dose-escalation study of SRT alone (RTOG 9005), the maximum tolerated doses of single-fraction SRS were 24, 18, and 15 Gy for BMs with a maximum diameter of equal or less than 20, 21 to 30, and 31 to 40 mm, respectively (47). Meanwhile, in the above-mentioned multiple prospective studies, the single-fraction dose was 20 to 24 Gy for BMs with a maximum diameter of equal or less than 2cm or a volume of less than 4 cm^3 (26,37,38,43). In a large-scale retrospective study, the local control of tumors no larger than 2 cm was satisfactory using a 24-Gy/single-fraction scheme; however, tumors larger than 2 cm were less effectively controlled by a 15 to 18 Gy/single-fraction scheme (48). Multi-fractional SRT has shown a higher local control rate and lower risk of brain necrosis in this population, especially for solitary BMs with a maximum diameter of larger than 3 cm (49). Acceptable fractions of SRT include 27 Gy/3 Fx or 30 Gy/5 Fx and 3,500 cGy/5 Fx (50). In addition to the maximum diameter, the intracranial substructure of the lesion and its tolerable dose also affect the recommended dose of SRS/SRT. Among the different fractionation schemes of SRT, a biologically effective dose (BED10) of equal or more than 50 Gy was associated with better local tumor control (51).

Therefore, we recommend single-fraction SRS of 20 to 24 Gy for BMs with a maximum diameter of equal to or small than 2 cm, single-fraction SRS of 18 Gy, or multi-fraction SRT for lesions with maximum diameter of 2.1 to 2.9 cm, and multi-fraction SRT for lesions with a maximum diameter of 3.1–4.0 cm. Since previous prospective studies using single-fraction SRS for the treatment of BMs have not included lesions larger than 4 cm, we recommend multi-fraction SRT for these lesions if technically feasible. Nevertheless, SRT is currently discouraged for tumors larger than 6 cm due to lack of evidence (52).

WBRT with or without hippocampal avoidance

Although the indications for WBRT are continually challenged by SRT (53). WBRT remains an appropriate and optional treatment for patients with diffuse BMs with or without leptomeningeal involvement. Research has shown that patients with diffuse BMs (arbitrarily defined as 20 or more lesions) have a chance to survive long enough after WBRT (54). The cognitive decline caused by WBRT has been widely recognized, and less than 10% of BMs are within 5 mm of the hippocampus. In the RTOG 0933 study (55), cognitive function deterioration was less significant when the dose of hippocampal irradiation was reduced. The NRG ONCOLOGY CC001 study (42) further confirmed that hippocampal avoidance WBRT (HA-WBRT) combined with memantine therapy could improve cognitive function without affecting local control or overall survival.

In general, for patients with diffused BMs who have a good prognosis and whose closest distance between the lesions and the hippocampus is not less than 1 cm, we recommend the use of HA-WBRT combined with memantine, as this protocol has high efficacy and low toxicity. Also, HA-WBRT combined with SRT for some metastases can be considered to obtain a better local control rate. The dose of WBRT can refer to the NCCTG N107C/CEC3 study (35), with the recommended dose being 30 Gy/10 Fx (*Table 1*).

The QUARTZ study (56) confirmed that WBRT did not show an advantage over supportive care in patients with poor prognosis. For these patients, more reasonable options include palliative or end-of-life care; or, for patients with symptomatic BMs, short-course WBRT (i.e., 20 Gy/5 Fx) may be applied.

Radiotherapeutic strategy for BMs may be particularly important for patients with a limited number of BMs (i.e., patients with 1 to 4 anatomically independent metastases). More treatment options are available for these patients. Stratified and classified treatment may be arranged based on their general conditions, BM prognosis, and treatment willingness. *Figure 1* summarizes the recommendations for local therapy in patients with a limited number of BMs. During SRS, FSRT, or WBRT with or without hippocampal avoidance, the total BED to the metastases always affects local control.

Timing of radiotherapy and systemic therapy

Since the blood-brain barrier (BBB) blocks the entry of therapeutic substances into the brain, medical therapy was previously believed to have a very limited effect on intracranial lesions from breast cancer. However, preclinical studies have shown that exposure to radiation can damage the BBB and enhance drug permeability (57,58), which provides a theoretical basis for the application of drugs combined with brain radiotherapy in the treatment of BMs (59,60). Many clinical studies have demonstrated that small molecule tyrosine kinase inhibitors (TKIs) such as lapatinib, tucatinib, epertinib, and pyrotinib, as well as macromolecular monoclonal antibodies, have certain

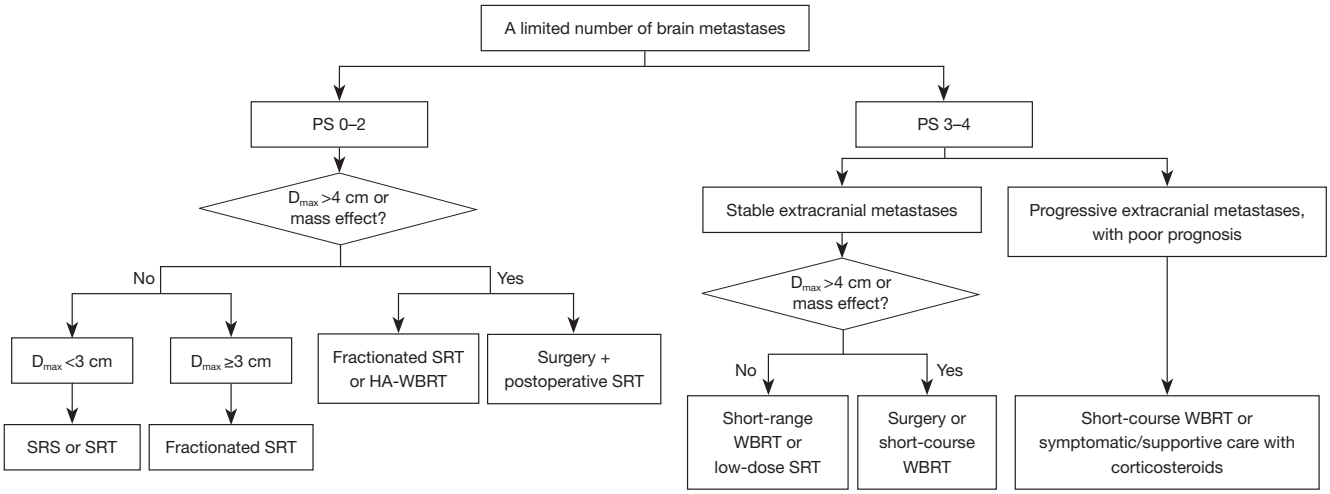

Figure 1 Recommendations on local therapy for patients with a limited number of brain metastases. PS, performance status; HA-WBRT, hippocampal avoidance whole-brain radiotherapy; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy.

therapeutic effects on intracranial lesions from HER2-positive breast cancer (61-67).

In general, targeted therapies with small molecule TKIs, macromolecular monoclonal antibodies, and/or antibody-drug conjugates (ADCs) are effective for HER2-positive BCBM, which also justifies the view that systemic therapy can be used upfront and intracranial radiotherapy may be deferred for HER2-positive patients. Therefore, we recommend for patients with newly diagnosed BMs from HER2-positive breast cancer, anti-HER2 therapy should be the treatment of choice if local symptoms are minor and under control; for patients with other molecular subtypes of BCBM, intracranial radiotherapy should not be postponed due to the lack of effective systemic treatments.

Medical treatment

Chemotherapy

Chemotherapy drugs have poor BBB permeability because they have large molecular weights, carry charges, and can easily bind to albumin. Therefore, chemotherapy alone typically has poor effect in treating BMs. There is no evidence that anthracyclines and taxanes can penetrate the BBB (68). Furthermore, since anthracyclines and taxanes are widely used in adjuvant or salvage therapy, few studies have investigated their roles in BM treatment. Other chemotherapeutic drugs such as capecitabine, platinum, topotecan, methotrexate, and temozolomide, when used alone or in combination, have achieved an objective response rate (ORR) of 4% to 55% in patients with BCBM, and the reported progression-free survival (PFS) is less than 4 months (69-75). However, such evidence has been obtained from clinical exploratory studies with small sample sizes, most of which were single-arm trials that used chemotherapeutic drugs in combination with radiotherapy. Therefore, there is no sufficient evidence to support the use of a single conventional chemotherapeutic agent as the mainstay of treatment for BMs.

HER2-targeted therapy

For patients with BMs from HER2-positive breast cancer, HER2-targeted therapies have shown definite efficacy. Drugs with HER2 inhibitory activity fall into three categories: TKIs, monoclonal antibodies, and ADCs.

(I) Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs)

The four currently approved EGFR-TKIs have achieved good efficacy in patients with BCBM.

Lapatinib is a reversible, dual TKI of human epidermal growth factor receptor type 1 (HER1) and type 2 (HER2). A pooled analysis of 799 patients showed that lapatinib was effective in patients with BMs who have received different lines of different therapies (76). In a prospective single-arm phase 2 study (LANDSCAPE) (77), the combination of lapatinib plus capecitabine in patients who had HER2-positive metastatic breast cancer with BMs who had not previously been treated with WBRT achieved a central nervous system objective response rate (CNS-ORR) of 57.1% and postponed radiotherapy by 8.3 months. The LANDSCAPE study, for the first time, demonstrated the

therapeutic effect of a small-molecule TKI on BMs.

Pyrotinib is an irreversible potent TKI targeting HER1, HER2, and HER4. The prospective, randomized, controlled, phase III PHOEBE study (78) confirmed that pyrotinib was significantly more effective than lapatinib. The phase III PHENIX study showed that pyrotinib could delay the progression of intracranial lesions in patients with asymptomatic BMs (79). In a multicenter, single-arm, two-cohort, phase 2 trial (PERMEATE), pyrotinib combined with capecitabine achieved a CNS-ORR of 42.1% and a PFS of 5.6 months in patients with BMs that progressed after radiotherapy; in patients with radiotherapy-naive HER2-positive BMs, the CNS-ORR was 74.6% and the PFS was 11.3 months, which were comparable to those in patients with extracranial lesions (80). Thus, pyrotinib plus capecitabine can serve as the preferred systemic treatment for EGFR TKI-naïve active BMs with controllable local symptoms.

Neratinib is an irreversible TKI also targeting HER1, HER2, and HER4. The phase III NALA study showed fewer interventions for central nervous system disease occurred in the neratinib group (81). A single-arm study of neratinib in the treatment of BMs that progressed after radiotherapy showed that the CNS-ORR was 33% to 49% and the median PFS was 3.1 to 5.5 months (82).

Tucatinib is a highly selective TKI targeting HER2, which has shown good control of BMs in patients with advanced breast cancer in the second-line and later setting (64). In the phase III HER2CLIMB study that enrolled 291 (47%) patients with BMs, the addition of tucatinib to trastuzumab plus capecitabine significantly prolonged the time to intracranial progression; the CNS-PFS increased from 4.2 to 9.9 months and the overall survival prolonged from 12.0 to 18.1 months (83). Accordingly, tucatinib has been approved for the treatment of BCBM by the US Food and Drug Administration.

(II) Monoclonal antibodies

Macromolecular monoclonal antibodies provide no distinct advantage over small-molecule TKIs in penetrating the BBB. No study has shown that macromolecular monoclonal antibodies can significantly improve brain lesions. Trastuzumab and pertuzumab are monoclonal antibodies targeting the HER2 extracellular domains (ECDs) IV and II, respectively. In the phase III trial CLEOPATRA, the combination with pertuzumab delayed the median time to development of CNS metastases at the first site of disease progression (84); in the PHEREXA study, the addition of pertuzumab to trastuzumab and capecitabine showed a trend in PFS benefit (85); in a single-arm, prospective, phase II study, however, patients with HER2-positive metastatic breast cancer with BMs and CNS progression despite prior radiotherapy received pertuzumab plus high-dose trastuzumab (6 mg/kg weekly), and the CNS-ORR was only 11%, showing a non-significant result (67).

(III) ADCs

ADCs containing trastuzumab and a cytotoxic payload have shown promising therapeutic effects in patients with stable BMs. Trastuzumab emtansine (T-DM1) is an ADC composed of trastuzumab and microtubule polymerization inhibitor DM1. In two phase III studies, a total of 443 patients with asymptomatic BMs were treated with T-DM1, and the median PFS was 5.5 to 5.9 months; in 126 patients with measurable BMs, the best overall response rate was 21.4% (86,87).

Trastuzumab deruxtecan (T-Dxd) is an ADC composed of trastuzumab and the topoisomerase I inhibitor deruxtecan. It has shown excellent efficacy in patients with stable BMs after treatment. In the DESTINY-Breast01 and DESTINY-Breast03 studies, 67 patients with stable, asymptomatic BMs after local treatment were enrolled. The PFS reached 15 to 18.1 months, and in patients with intracranial measurable lesions, the CNS-ORR reached 46.7% to 67.4%, which showed a significant advantage of T-Dxd over T-DM1 (88,89). In existing studies, T-Dxd has shown good efficacy for treating BMs, and efficacy trials in patients with newly-diagnosed BMs or progressive disease after local therapy are still ongoing.

Other targeted therapies

None of the currently approved targeted therapies for HER2-negative advanced breast cancer have shown definite effectiveness in treating BMs. The incidence of BMs is relatively low in patients with HR-positive breast cancer, and BMs usually appear late in the process of tumor recurrence and metastasis. CDK4/6 inhibitors have become a standard of care for patients with advanced HR-positive breast cancer. The CDK4/6 inhibitor abemaciclib was found to be able to penetrate the BBB, resulting in a CNS-ORR of 5.2% in patients with ER+/HER2– BC (90). However, its efficiency is not satisfactory and needs further investigation.

In a substudy from the phase 3 IMpassion130 trial, there was no clinical benefit from the PD-L1 inhibitor atezolizumab in the BM subgroup (91). Two phase III studies of poly (ADP-ribose) polymerase (PARP) inhibitors enrolled patients with HER2-negative metastatic breast cancer and a germline BRCA mutation (92,93). Compared with standard therapy, olaparib and talazoparib prolonged

PFS in patients with BMs (94). Also, the anti-angiogenic drug bevacizumab can relieve brain edema caused by radiotherapy (95). When used in combination with chemotherapy, it yielded a CNS-ORR of 47% to 77% and a PFS of 5.6 to 6.1 months in patients with BCBM who progressed after WBRT (96,97). For patients with HER2-negative BMs, targeted therapies have limited value and there is a paucity of evidence. Local treatment of intracranial lesions is preferred, and medical treatment options may be comprehensively considered based on the systemic conditions.

Intrathecal medications

Intrathecal injection refers to the direct injection of drug molecules into the subarachnoid space, to thereby increase the drug concentration in the CSF to kill tumor cells. Intrathecal therapy is widely used for the treatment of LM. Intrathecal trastuzumab can be considered for patients with LM from HER2-positive breast cancer. In a meta-analysis of 58 patients who received intrathecal trastuzumab, 55% showed clinical remission, suggesting that intrathecal trastuzumab was safe and effective (98). Intrathecal administration of chemotherapy drugs (e.g., methotrexate and cytarabine) can be considered in patients with HER2-negative breast cancer (99,100). However, intrathecal therapy can cause a wide spectrum of adverse effects, such as neurotoxicity; therefore, co-administration with glucocorticoids during chemotherapy may be helpful.

Symptomatic and supportive treatment

During disease diagnosis and treatment, patients with BCBM often suffer from a variety of symptoms, which undermine their quality of life and can even become life-threatening. Therefore, symptomatic and supportive treatment is an important component of the whole-course management of BCBM.

Brain edema caused by BMs increases intracranial pressure, which can lead to symptoms such as headache, nausea, and vomiting, and raise the risk of seizures. Initially, aggressive dehydration and diuretic therapies (e.g., mannitol, glycerol fructose, and furosemide) should be applied to lower the intracranial pressure. For instance, 125 to 250 mL of 20% mannitol may be intravenously administered every 6 to 8 hours according to the patient's symptoms, and plasma electrolyte concentrations and urine output should be closely monitored. Glucocorticoids, especially dexamethasone, can alleviate cerebral edema, improve quality of life, and reduce meningeal irritation, although they do not improve prognosis (101,102). Dexamethasone is widely used, often in combination with mannitol. Glucocorticoids should only be used when specifically indicated, and at the lowest dose possible, for the shortest possible time. Insufficient evidence exists to make a treatment recommendation for patients with BMs who are asymptomatic without mass effect. Glucocorticoid use before surgical resection of BMs can alleviate preoperative and postoperative cerebral edema, and glucocorticoid administration during radiotherapy can mitigate early radiotherapy reactions. Intrathecal chemotherapy is an important treatment for meningeal metastases. Administration of glucocorticoids during intrathecal injection of chemotherapy drugs can reduce chemotherapy-induced neurotoxicities and relieve symptoms. Nevertheless, it is necessary to be alert to possible adverse reactions to glucocorticoids, including peptic ulcers and elevated blood sugar. Furthermore, glucocorticoids must be used with caution in patients with diabetes. Furosemide is administered routinely as a rapid intravenous bolus in doses of 20 to 40 mg, and its dosage is adjusted according to the increased intracranial pressure, clinical symptoms, and 24-h urine output; however, changes in plasma electrolytes, especially hyponatremia and hypokalemia, must be closely monitored. Bevacizumab has also been shown to reduce cerebral edema and improve radiation-induced necrosis (103). A ventriculoperitoneal shunt can provide durable relief for symptomatic hydrocephalus. For headaches, nausea, and vomiting that are not promptly relieved after the above treatments, symptomatic treatments such as antiemetics and analgesics can be administered.

Managing epilepsy is integral to the diagnosis and treatment of BM. Since antiepileptic drugs cannot lower the risk of seizures in patients with BM without epilepsy symptoms, they are generally only used in patients who exhibit symptoms of epilepsy and are not recommended as primary prevention (101-104). Seizures should be treated with anticonvulsants that do not interact with systemic therapy (e.g., levetiracetam, lamotrigine, and lacosamide, which are superior to phenytoin, carbamazepine, and valproic acid). Secondary prophylaxis may be considered for patients who experience seizures. Medical staff must be alert to the potential side effects of antiepileptic therapy, such as abnormal liver function, cognitive impairment, and ataxia.

Antitumor therapy can also cause symptoms. For example, patients may experience dizziness, headache, nausea, loss of appetite, and fatigue after radiotherapy, and the risk of infection can be high in bedridden patients. Symptomatic management including nutritional support,

Table 2 MD Anderson Cancer Center Graded Prognostic Assessment scoring system

Prognostic factors	0 point	0.5 points	1.0 points	1.5 points
KPS score	≤50	60	70–80	90–100
Molecular subtype	TNBC	HR+	HER2+/HR–	HER2+/HR–
Age	>50	≤50	–	–
No. of lesions	>3	1–3	–	–

KPS, Karnofsky Performance Status; TNBC, triple-negative breast cancer; HR, hormone receptor; HER2, human epidermal growth factor receptor-2.

moderate exercise, monitoring of electrolyte balance, and infection prevention can be offered. The risk of *Pneumocystis jiroveci* pneumonia (PJP) may be increased in patients who have received glucocorticoid therapy for a few weeks. Trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis should be considered if additional systemic immunosuppressive therapy is administered. Thromboprophylaxis should be considered for patients who are hospitalized or bedridden with acute illness. Low-molecular-weight heparin or unfractionated heparin is recommended for the primary prevention and treatment of venous thromboembolic events. Risk factors for thromboembolic events in patients with BM include specific primary tumors, glucocorticoid use, chemotherapy, high body mass index, and prolonged bed rest or immobilization. The risk of intracranial hemorrhage may not be increased in patients treated with low-molecular-weight heparin, and other risk factors for bleeding should be considered. Data on direct oral anticoagulants in patients with BM are lacking (101-104).

Prognosis

The prognosis of BCBM is closely related to the molecular subtype of the primary cancer. In a study of 1,147 patients with invasive breast cancer, OS was significantly shorter in patients with triple-negative (TN) breast cancer than in those with HER2-enriched tumors (P<0.001). The median duration of survival following brain metastasis (SFBM) was 386, 310, and 147 days in patients with luminal, HER2-enriched and TNBC, respectively (P=0.029). Patients with luminal breast cancer had a lower risk of developing BMs and the longest BMFS, whereas those with HER2-positive or TNBC had a significantly higher risk of developing BMs. Compared with that in the TNBC group, the duration of SFBM was doubled in the HER2-enriched group (105). Another study that included 206,913 breast cancer patients in the Surveillance, Epidemiology, and End Results (SEER) 18 registry showed that the median survival of patients with luminal A, luminal B, HER2, and TNBC and BM was 12, 23, 10, and 6 months, respectively (P<0.001), and in patients with BM without visceral metastasis it was 14, 34, 17, and 8 months, respectively (P<0.001). On multivariate analysis, among all patients with BM, the subtype order by favorable prognosis was luminal B, luminal A, HER2, and TNBC, while for those with BM without visceral metastasis, the order was luminal B, HER2, luminal A, and TNBC (106).

Previous studies have shown that the prognostic factors for patients with parenchymal BM from breast cancer include systemic organ and nervous system functional status (KPS score), age, primary tumor (location and extent, pathological type, and control), the number and location of BMs, surgical resection, extracranial metastases, recurrence, and the time from primary diagnosis to development of BM (107). Several prognostic indices have been developed accordingly. The value of the Breast GPA, which was proposed by Sperduto *et al.* on top of the GPA, has been well documented (108). In the original Breast GPA, the prognostic grade of BCBM was divided into three grades, and the prognostic factors included the KPS score, molecular subtype of breast cancer, and age (only for patients with a KPS score of 60–80). In 2015, researchers from the University of Texas MD Anderson Cancer Center modified the Breast GPA to develop a new index, the MDACC-GPA, in which a four-tiered grading system refined the prognostic grade of brain BCBM to grade 4. After the number of BMs was added as a prognostic factor, the concordance index was increased from 0.78 (95% CI, 0.77 to 0.80) to 0.84 (95% CI, 0.83 to 0.85) (*Table 2*) (109). In 2020, Sperduto *et al.* updated the Breast GPA, into which the extracranial metastasis and the time interval from primary diagnosis to development of BM were incorporated as prognostic factors, and the four-tier grading system was still used (*Table 3*) (110). Sperduto *et al.* have published their scoring tools on the following website: https://brainmetgpa.com/.

LM is an uncommon complication of breast cancer; however, it is highly fatal. It indicates that the disease is already in its advanced stage and the prognosis is extremely poor. Without proper treatment, the median survival is only 6 weeks to 2 months. After therapeutic interventions, the median survival may reach 3 to 6 months; only 15% of

Table 3 Updated Breast-GPA scoring system

Prognostic factors	0 point	0.5 points	1.0 points	1.5 points
KPS score	≤60	70–80	90–100	–
Molecular subtype	TNBC	Luminal A	–	HER2+ and Luminal B
Age, years	>60	≤60	–	–
No. of lesions	>1	1	–	–
Extracranial metastasis	Yes	No	–	–

GPA, Graded Prognostic Assessment; KPS, Karnofsky Performance Status; TNBC, triple-negative breast cancer; HER2, human epidermal growth factor receptor-2.

Table 4 Recommendations on the treatment of breast cancer brain metastasis in the CSCO BC Guidelines 2022

Stratification	Level I recommendations	Level II recommendations
For patients presenting with 1–3 BMs	(I) Well-controlled extracranial disease and KPS ≥60 points: (i) Surgical resection (1A); postoperative SRS to the resection cavity; (ii) Due to the lack of survival benefit data and the risk of neurocognitive impairment, WBRT is not routinely recommended after surgery or SRT. (II) Poorly controlled extracranial disease, with a low KPS score: consider WBRT or supportive care	(I) SRT may be considered for lesions sized ≤3–3.5 cm (1B); (II) SRT may be considered for inoperable lesions (1B); (III) Medical therapy may be considered for patients with HER2+ BC (2B)
For patients presenting with >3 BMs	WBRT or SRT	Medical therapy may be considered for patients with HER2+ BC (2B)
Meningeal metastasis	Radiotherapy (1A)	Intrathecal injection (2B)

CSCO BC, Chinese Society of Clinical Oncology Breast Cancer; BM, brain metastasis; KPS, Karnofsky Performance Status; WBRT, whole-brain radiotherapy; SRT, stereotactic radiotherapy; BC, breast cancer; HER2, human epidermal growth factor receptor-2.

patients survive for more than 1 year. Death is often caused by progressive neurological disorders. The prognosis is related to disease grade, CSF protein level, molecular subtype of the primary cancer, age, tumor size, metastasis to other sites, and KPS score at the time of diagnosis (111).

Follow-up and monitoring

Although the incidence of BMs is rising annually, guidelines on breast cancer do not recommend routine screening for patients with BMs due to the lack of evidence of survival benefits. Therefore, most BMs are detected based on neurological symptoms, and further active measures are required. HER2 positivity is a widely recognized risk factor for BM. Nearly half of all patients with HER2-positive breast cancer eventually acquire BMs. BMs from HER2-positive breast cancer seem to be an ongoing event that can occur even years after diagnosis. Furthermore, about half of patients with HER2-positive BCBM die due to central nervous system progression even after treatment. Therefore, given the high incidence of BMs in HER2-positive breast cancer and the complexity of BM treatment, brain MRI should be performed timely in patients with this subtype who present with neurological symptoms, to achieve early diagnosis and early treatment, although routine screening with brain MRI for these patients is not recommended by the current guidelines.

It is generally believed that BCBM patients should be regularly followed up after diagnosis and treatment and receive a series of examinations including history-taking, physical examinations, testing of serum tumor markers, and medical imaging. Follow-up visits should be arranged at 1- to 2-month intervals after treatment, and the patient should seek medical treatment if an abnormality is detected. For stable craniocerebral metastases, the intervals between visits can be extended to 3 to 6 months (*Table 4*).

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Footnote

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