Methods and results of local treatment of brain metastases in patients with breast cancer

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This article presents methods and results of surgical treatment and radiation therapy of brain metastases in breast cancer patients (brain metastases from breast cancer BMF-BC). Based on the literature data, it was shown that patients with single BMF-BC, aged less than 65 years, with Karnofsky score (KPS) of 70 or more and with cured or controlled extracranial disease are the best candidates to surgical treatment. Irrespective of the extracranial disease control status, there are indications for surgery in patients with symptomatic mass effect (tumour diameter larger than 3 cm) and patients with obstructive hydrocephalus from their BMF-BC. Stereotactic radiosurgery (SRS) has some advantages over surgery, with similar effectiveness: it may be used in the treatment of lesions inaccessible to surgery, the number of lesion is not a limiting factor if each lesion is small (< 3) and adequate doses can be delivered, it is not contraindicated in patients with active extracranial disease, it does not interfere with ongoing systemic treatment, and it does not require general anaesthesia or hospitalisation. A disadvantage of SRS, as compared to whole brain radiotherapy (WBRT), in patients with BMF-BC is the possibility of subsequent development of new lesion in the non-irradiated field. Thus the majority of the BMF-BC patients are not good candidates to surgery or SRS; WBRT alone or combined with a systemic treatment still plays a major role in the treatment of these patients.

Key words: breast cancer, brain metastases, surgery, radiotherapy.

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Introduction

Breast cancer (BC) is the second, after lung cancer (40–50%), most common cause of brain metastases (brain metastases from breast cancer – BMF-BC) (15–25%), and in this respect it comes before melanoma (5–15%) and renal and colorectal cancers [1–6]. At diagnosis of a BC of a locoregional extent, the risk of BMF-BC development is about 5% [4, 7–9], but in patients with a generalized BC it reaches 7–17% [1, 2, 4, 7, 9–12], and in 1.3% of patients BMF-BC are the first symptom of a metastatic disease [7, 9]. At autopsy, BMF-BC are found in about 30% of patients who died of BC, and in the group of patients with metastatic disease in 6 or more locations this percentage rises up to 86% [1, 2, 4]. The incidence of BMF-BC is systematically increasing due to: increasing incidence of cancers related to population ageing, improved survival of BC patients associated with adjuvant treatment and better efficacy of systemic treatment of generalised BC, and also due to the progress in imaging technology (CT, MRI, PET) [1, 3, 5, 10, 13].

BMF-BC usually develop in late, advanced stages of the neoplastic process and in general they are preceded by extracranial distant metastases, e.g. bone, liver or lung metastases [2, 4, 5, 14]. Median time between BC diagnosis and BMF-BC occurrence is 2–3 years and varies significantly between different BC subtypes, as follows: 28, 36, 47 and 54 months for triple negative, HER2+, luminal B and luminal A disease, respectively [1, 15–19].

Particular molecular subtypes of breast cancer have different predilection for brain metastasis (BM) and thereby different effect on life expectancy. TNBC and HER2+ patients have the worst prognosis [20, 21]. The situation has changed recently when the transtuzumab therapy has become widely available, that improves OS in this group of patients. Both these types of cancer show particularly high incidence of intracranial spread, reaching: 25–46% in the TNBC population and 15–44% in the HER2+ population [21–24].

Numerous risk factors for BMF-BC occurrence are known, such as: age less than 50 years, negative hormone receptor status, HER2 over-expression, high (G3) tumour grade, regional lymph node metastases, advanced extracranial disease (distant metastases in more than 2 locations), presence of BRCA 1 mutation, high level of Ki-67 expression, etc. [1–4, 7, 10, 12, 25–29]. In the group of patients with generalised BC, the risk of BMF-BC occurrence is clearly related to the histological BC subtype and is 35% for HER2+ tumours, 20% for triple negative disease and only 3% for luminal A breast cancer [30, 31].

In general, anty-HER 2 treatment does not reduce the incidence of BMF-BC, however it delays their occurrence (13 months vs. 2 months) and improves survival (11.6 vs. 6.1 months) [13, 32].

General treatment results

Development of BMF-BC is associated with unfavourable prognosis [1, 3–5, 7, 15, 33–36], and median survival ranges from 2 to 16 months, depending on many prognostic factors (age and performance status of the patient, molecular cancer subtype, extracranial disease extent, number of BMF-BC, BMF-BC-free survival and treatment used [1–3, 5, 12, 15, 16, 35, 36]. Recursive partitioning analysis (RPA) index, developed by Gaspar *et al.* [37], is also a prognostic factor. Aoyama performed analysis of 16 publications presenting the results of brain metastases treatment with various methods; 7 publications pertained to metastases from various cancers, among which BMF-BC constitutes only 10–18%, 2 publications included only non small-cell lung cancer (NSCLC) metastases, and next 7 publications – only BMF-BC [38]. Aoyama's analysis has shown that the median survival time for breast cancer and other cancers was similar and was: 17.6 and 14.6 months for RPA class I, 10.6 and 10.1 month for RPA class II, and 3.0 and 4.4 months for RPA class III, respectively (Table 1). It should be stressed that about 20% of patients with BMF-BC survive 12 months since their occurrence [3–5, 16, 33, 34].

Median survival of untreated patients with BMF-BC is slightly more than 1 month, of patients receiving palliative corticosteroid treatment – up to 2 months, of patients subject to WBRT – 3–6 months, and extends to 10–12 months in the group of patients with 1–3 BMF-BC treated with surgery or stereotactic radiosurgery (SRS) with or without subsequent whole brain radiotherapy (WBRT) [1, 16, 39].

Treatment methods

The following methods are used in the treatment of BMF-BC: surgery, SRS, WBRT, systemic treatments and various combinations of these methods (Tables 2, 3) [5, 7, 26, 38–50]. In general, local (surgery, SRS) [5, 7, 38, 40, 46–49] or regional (WBRT) [5, 7, 38, 39, 42, 43, 50] treatment is preferred, or combination of surgery and radiotherapy. There is a growing role of systemic treatments, in particular of targeted therapies [5, 7, 26, 43–47].

Local treatment

There are no controlled clinical studies entirely dedicated to the treatment of BMF-BC; in phase III studies conducted so far, the most prevalent group, 52.4–77% was the group of patients with brain metastases from NSCLC, and only 6.8–19% of patients had BMF-BC [7, 38]. These studies have shown that local treatment (surgery, SRS) used as an add-on to WBRT improves local control in patients with 1–3 BMF-BC and survival of patients with single BMF-BC. It was also found that WBRT adjuvant to the local treatment in patients with 1–3 BMF-BC significantly increases brain disease control but has no significant effect on patients' survival.

Surgery

The best candidates for surgery are patients:
- with a single BMF-BC at a surgically accessible location,
- aged < 65 years,
- with Karnofsky score (KPS) of 70 or more,
- with cured or controlled extracranial disease.

Table 1. RTOG devised prognostic groups

Classes		Median survival (months)
Class I	K ≥ 70 < 65 years of age with primary control no extra cranial metastases	7.1
Class II	all others	4.2
Class III	K < 70	2.3

Table 2. Single brain metastasis ASTRO guideline

Survival time – 3 month or more				Survival time – less than 3 month
Resectable Good prognosis		Not resectable Good prognosis		Poor prognosis
Metastasis size ≤ 3–4 cm	Metastasis size > 3–4 cm	Metastasis size ≤ 3–4 cm	Metastasis size > 3–4 cm	
Surgery and WBRT	Surgery and WBRT	Radiosurgery and WBRT	WBRT	WBRT
Radiosurgery and WBRT	Surgery with radiosurgery/ radiation boost ± WBRT	Radiosurgery		Palliative care
Radiosurgery				
Surgery with radiosurgery/radiation boost ± WBRT				

Table 3. Multiple brain metastasis ASTRO guideline

Survival time – 3 month or more		Survival time – less than 3 month
Good prognosis	**Good prognosis**	**Poor prognosis**
All brain metastases ≤ 3–4 cm	Brain metastases causing mass effect	
Radiosurgery and WBRT	Surgery and WBRT	WBRT
Radiosurgery	WBRT	Palliative care
WBRT		

Irrespective of the extracranial disease control status, there are indications for surgery in:
- the rare breast cancer patients with an isolated BMF-BC (the only evidence of the disease),
- patients with symptomatic mass effect (tumour diameter larger than 3 cm),
- patients with obstructive hydrocephalus from their BMF-BC or at high risk for obstructive hydrocephalus from a large posterior fossa BMF-BC abutting the fourth ventricle [42, 51, 52].

Stereotactic radiosurgery

Similarly as for surgical treatment, patients with a single BMF-BC, with a KPS of 70 and more, with cured or controlled extracranial disease are the best candidates for SRS; in this setting, the efficacy of SRS is similar to that of surgery [51]. SRS has however some advantages:
- it is not limited by BMF-BC location in the brain and it may be used in all cerebral regions, including those not accessible to surgery (e.g. the brainstem),
- the number of lesions is not a limiting factor for SRS if each lesion is small and adequate doses can be delivered (15–24 Gy),
- possible active extracranial disease is not a contraindication for SRS,
- multiple BMF-BC may be treated in one outpatient session,
- it does not interfere with ongoing systemic treatment,
- it does not require general anaesthesia or hospitalisation,
- there is no risk of craniotomy-related complications.

A limitation of SRS, in contrast to surgery, is its unsuitability for the treatment of BMF-BC lesions exceeding 3–3.5 cm in the largest diameter. Additionally, surgery can immediately relieve symptomatic mass effect and it usually guarantees more complete and faster resolution of vasogenic edema [4, 38, 48–52].

A disadvantage of SRS, as compared to WBRT, in patients with BMF-BC, is the subsequent development of new lesion in the non-irradiated field [7, 49, 53]. On the other hand, WBRT causes the problem of late neurotoxicity [7, 54, 55]; Chang *et al.* compared the neurocognitive results of SRS alone versus SRS plus WBRT in a randomized controlled trial of 1–3 newly diagnosed brain metastases; patients who underwent SRS plus WBRT were at a greater risk of a significant decline in learning and memory function by 4 months [54]. Abe and Aoyama tried to define patients with brain metastases with a longer survival prognosis, in whom it would be possible to avoid adjuvant WBRT following SRS [55, 56].

In the analysis of 17 publications cited above, Aoyama [38] has shown that:
- the percentage of patients with RPA III (very poor outcome) was higher in studies including breast cancer patients than in those including brain metastases of any origin (median percentage 42% vs. 10%),
- the percentage of patients with RPA III was low in studies in which SRS was the predominant treatment method, as compared with those in which WBRT was the main method; it is clear that SRS was used only for highly selected patients.

Aoyama suggests using SRS alone only in patients with single BMF-BC and KPS ≥ 70, provided that the patient remains under regular and frequent follow-up [7, 38].

The risk of distant brain failure after SRS alone seems to be much higher in patients with triple negative breast carcinoma [57].

Leptomengeal disease (LMD) in breast cancer patients with CSN metastases is associated with poor prognosis and represents the terminal stage of the disease. LMD diagnosis is confirmed by cerebrospinal fluid cytology or MRI images. There were attempts to identify the risk factors of disease spread (to the CSN). The analyses performed have shown that only the presence of active disease within the chest (i.e. lung metastases) is associated with disease spread to the CSN. Some authors suggest a secondary hematogeneous spread from pulmonary reservoir. Receptor status, active liver and bone metastases, tumour morphology, tumor size, number of brain metastases and history of WBRT showed no correlation with LMD [58]. SRS offers good local control and reduces the risk of late toxicity, as compared to other treatment methods but it cannot protect the patient from meningeal spread [59–61]. Mean overall survival from LMD diagnosis is approximately 6 months [58].

Whole brain radiotherapy

When WBRT is used as adjuvant treatment of BMF-BC after surgery or SRS, two aspects should be taken into consideration: on one hand, this is late neurotoxicity of WBRT, and on the other hand – the risk of development of brain metastases outside the region treated locally; the latter one is of particular importance in breast cancer patients [7, 38, 51, 55, 62, 63].

WBRT alone is indicated first of all in patients not amenable to surgery or SRS, with KPS < 70, with numerous BMF-BC, and with uncontrolled extracranial disease [7, 50, 51, 64]. None of the WBRT fractioning regimens has shown a clear advantage; however fraction doses exceeding 3 Gy are decidedly avoided, due to an increased risk of late post-irradiation neurological damage [7, 50, 51, 65]. The regimen of 30 Gy administered in 10 fractions over a period of 2 weeks is the most commonly used [7, 50, 51]. In the group of patients with BMF-BC some authors use lower

fraction doses, administering the total dose of 40 Gy in 20 fractions (fraction dose – 2 Gy) [50, 51]. The rationale for such fractionation is the possibility of reduction of the risk of late radiation-induced encephalopathy with neurocognitive disturbances that is main late complication of WBRT [50, 51, 66, 67]. It should be stressed that breast cancer is a relatively radiosensitive tumour; additionally, patients with generalised breast cancer live currently much longer, owing to effective systemic treatment which increases the risk of emergence of late post-irradiation injuries [50, 51].

Median survival after WBRT ranges from 3 to 6 months, and objective response to the treatment of BMF-BC is achieved in 30–60% of patients [7, 41, 50, 68].

However in about one half of patients undergoing WBRT it is not effective enough and these patients die of BMF-BC progression [50, 51, 64]. Nieder *et al.* suggest that frequency and duration of response to WBRT is higher in patients with breast cancer, as compared to patients with e.g. non small cell lung cancer, renal cancer or melanoma [68]. There are ongoing studies on reduction of WBRT toxicity by using e.g. irradiation technique with hippocampus shielding, intensity modulated radiotherapy, neuroprotectors, and on enhancement of WBRT efficacy by its combination with systemic treatment [7, 26, 45, 50, 64].

One year or more after WBRT patients treated with this method start to present symptoms of late radiation toxicity to the white matter. This includes demyelination and injury to the population of periventricular stem cells responsible for repair processes within the CSN. White matter changes (WMC) manifest as neurocognitive decline, memory and behaviour disturbances, reaction slow-down and predilection for substances of abuse [69]. WMC diagnosis is based on imaging findings. White matter damage is visible T2 – weighed or FLAIR MRI scans in more than 70% of (irraditated) patients. In patients receiving SRS these lesions occur significantly less frequently [70]. Women with 1–3 intracranial metastases demonstrated remarkably higher neurotoxicity after WBRT plus SRS than women who were treated with SRS alone [71]. Some recent reports show that the irradiated volume has a higher effect on survival than the number of irradiated metastases [72]. Along with metastatic breast cancer patient survival prolongation, availability of new treatment technologies and possibility to combine or repeat treatments, the issue of neurotoxicity becomes more and more serious [73].

In conclusion, the majority of the BMF-BC patients are not good candidates to surgery or SRS, and WBRT alone or combined with a systemic treatment still plays a major role in the treatment of these patients.

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References

1. Gachet J, Giroux J, Girre V, et al. Métastases cérébrales dans les cancers du sein. Épidémiologie et histoire naturelle. Expérience de l'Institut Curie à travers deux études: les patientes HER2- de moins de 65 ans et les patientes de plus de 65 ans. Bull Cancer 2011; 98: 357-69.
2. Dayan A, Koca D, Akman T, Oztop I, Ellidokuz H, Yilmaz U. The factors that have an impact on the development of brain metastasis in the patients with breast cancer. J Cancer Res Ther 2012; 8: 542-8.
3. Kwon H, Oh S.Y, Kim SH, et al. Clinical outcomes and breast cancer subtypes in patients with brain metastases. Onkologie 2010; 33: 146-52.
4. Arslan UY, Oksuzoglu B, Aksoy S, et al. Breast cancer subtypes and outcomes of central nervous system metastases. Breast 2011; 20: 562-7.
5. Braccini AL, Azria D, Thezenas S, Romieu G, Ferrero JM, Jacot W. Prognostic factors of brain metastases from breast cancer: impact of targeted therapies. Breast 2013; 22: 993-8.
6. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. Curr Oncol Rep 2012; 14: 48-54.
7. Tallet A. Métastases cérébrales de cancer du sein. Cancer Radiother 2013; 17: 708-14.
8. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. J Clin Oncol 2004; 22: 2865-72.
9. Pestalozzi BC, Zahrieh D, Price KN et al. Identifying breast cancer patients at risk for Central Nervous System (CNS) metastases in trials of the International Breast Cancer Study Group (IBCSG). Ann Oncol 2006; 17: 935-44.
10. Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. J Clin Oncol 2004; 22: 3608-17.
11. Boogerd W. Central nervous system metastasis in breast cancer. Radiother Oncol 1996; 40: 5-22.
12. Lin NU, Claus E, Sohl J, Razzak AR, Arnaout A, Winer EP. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases. Cancer 2008; 113: 2638-45.
13. Leyland-Jones B. Human epidermal growth factor receptor 2-positive breast cancer and central nervous system metastases. J Clin Oncol 2009; 27: 5278-86.
14. Graesslin O, Abdulkarim BS, Coutant C, et al. Nomogram to predict subsequent brain metastasis in patients with metastatic breast cancer. J Clin Oncol 2010, 28: 2032-7.
15. Minisini AM, Moroso S, Gerratana L, et al. Risk factors and survival outcomes in patients with brain metastases from breast cancer. Clin Exp Metastasis 2013; 30: 951-6.
16. Distefano A, Yong Yap Y, Hortobagyi GN, Blumenschein GR. The natural history of breast cancer patients with brain metastases. Cancer 1979; 44: 1913-18.
17. Lee YT. Breast carcinoma: pattern of metastasis at autopsy. J Surg Oncol 1983; 23: 175-80.
18. Gavrilovic IT, Posner JB. Brain metastases: epidemiology and pathophysiology. J Neurooncol 2005; 75: 5-14.
19. Sperduto PW, Kased N, Roberge D et al. The effect of tumor subtype on the time from primary diagnosis to development of brain metastases and survival in patients with breast cancer. J Neurooncol 2013; 112: 467-72.
20. Soni A, Ren Z, Hameed O, Chanda D, Morgan CJ, Siegal GP, Wei S. Breast cancer subtypes predispose the site of distant metastases. Am J Clin Pathol 2015; 143: 471-8.
21. Duchnowska R, Jassem J, Goswami CP, et al. Predicting early brain metastases based on clinicopathological factors and gene expression analysis in advanced HER2-positive breast cancer patients. J Neurooncol 2015; 122: 205-16.
22. Kennecke H, Yerushalmi R, Woods R, Cheang MC, Voduc D, Speers CH, Nielsen TO, Gelmon K. Metastatic behavior of breast cancer subtypes. J Clin Oncol 2010; 28: 3271-7.
23. Brufsky AM, Mayer M, Rugo HS, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence , treatment , and survival in patients from regist HER. Clin Cancer Res 2011; 17: 4834-43.
24. Lin NU, Claus E, Sohl J, Razzak AR, Arnaout A, Winer EP. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases. Cancer 2008; 15: 113: 2638-45.

25. Evans AJ, James JJ, Cornford EJ, et al. Brain metastases from breast cancer: identification of a high-risk group. Clin Oncol 2004; 16: 345-9.
26. Niwińska A, Murawska M, Pogoda K. Breast cancer brain metastases: differences in survival depending on biological subtype, RPA RTOG prognostic class and systemic treatment after whole-brain radiotherapy (WBRT). Ann Oncol 2010; 21: 942-8.
27. Gabos Z, Sinha R, Hanson J, Chauhan N, Hugh J, Mackey JR, Abdulkarim B. Prognostic significance of human epidermal growth factor receptor positivity for the development of brain metastasis after newly diagnosed breast cancer. J Clin Oncol 2006; 24: 5658-63.
28. Albiges L, André F, Balleyguier C, Gomez-Abuin G, Chompret A, Delaloge S. Spectrum of breast cancer metastasis in BRCA1 mutation carriers: highly increased incidence of brain metastases. Ann Oncol 2005; 16: 1846-7.
29. Arvold ND, Oh KS, Niemierko A, et al. Brain metastases after breast-conserving therapy and systemic therapy: incidence and characteristics by biologic subtype. Breast Cancer Res Treat 2012; 136: 153-60.
30. Yan M, Lü HM, Liu ZZ, Liu H, Zhang MW, Sun XB, Cui SD. High risk factors of brain metastases in 295 patients with advanced breast cancer. Chin Med J 2013; 126: 1269-75.
31. Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer 2003; 97: 2972-7.
32. Dawood S, Broglio K, Esteva FJ, et al. Defining prognosis for women with breast cancer and CNS metastases by HER2 status. Ann Oncol 2008; 19: 1242-8.
33. Shaffrey ME, Mut M, Asher AL, et al. Brain metastases. Curr Probl Surg 2004; 41: 665-741.
34. Chang EL, Lo S. Diagnosis and management of central nervous system metastases from breast cancer. Oncologist 2003; 8: 398-410.
35. Berghoff A, Bago-Horvath Z, De Vries C, et al. Brain metastases free survival differs between breast cancer subtypes. Br J Cancer 2012; 106: 440-6.
36. Kim HJ, Im SA, Keam B, et al. Clinical outcome of central nervous system metastases from breast cancer: differences in survival depending on systemic treatment. J Neurooncol 2012; 106: 303-13.
37. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, McKenna WG, Byhardt R. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 1997; 37: 745-51.
38. Aoyama H. Radiation therapy for brain metastases in breast cancer patients. Breast Cancer 2011; 18: 244-51.
39. Boogerd W, Vos VW, Hart AA, Baris G. Brain metastases in breast cancer; natural history, prognostic factors and outcome. J Neurooncol 1993; 15: 165-74.
40. Niwińska A, Rudnicka H, Krajewski R, Murawska M. Surgery and radiotherapyof brain metastases in breast cancer patients – an analysis of survivaland prognostic factors. Nowotwory J Oncol 2007, 57: 140-5.
41. Niwińska A, Tacikowska M, Murawska M. The effect of early detection of occult brain metastases in HER2-positive breast cancer patients on survival and cause of death. Int J Radiat Oncol Biol Phys 2010; 77: 1134-9.
42. Dutertre G, Pouit B. Les métastases cérébrales des cancers du sein : qui, quand, et comment les opérer ? Bull Cancer 2011; 98: 433-44.
43. Soffietti R, Trevisan E, Ruda R. Targeted therapy in brain metastasis. Curr Opin Oncol 2012; 24: 679-86.
44. Renfrow JJ, Lesser GJ Molecular subtyping of brain metastases and implications for therapy. Curr Treat Options Oncol 2013; 14: 514-27.
45. Niwińska A, Murawska M, Pogoda K. Breast cancer subtypes and response to systemic treatment after whole-brain radiotherapy in patients with brain metastases. Cancer 2010; 116: 4238-47.
46. Kaplan MA, Isikdogan A, Koca D, et al. Clinical outcomes in patients who received lapatinib plus capecitabine combination therapy for HER2-positive breast cancer with brain metastasis and a comparison of survival with those who received trastuzumab-based therapy: a study by the Anatolian Society of Medical Oncology. Breast Cancer 2014; 21: 677-83.
47. Bachelot T, Le Rhun E, Labidi-Gally I, Heudel P, Gilabert M, Bonneterre J, Pierga Y-l, Gonçalves A. Traitements systémiques des métastases cérébrales des cancers du sein: chimiothérapies cytotoxiques et thérapies ciblées. Bull Cancer 2013; 100: 7-14.
48. Matsunaga S, Shuto T, Kawahara N, Suenaga J, Inomori S, Fujino H. Gamma Knife surgery for metastatic brain tumors from primary breast cancer: treatment indication based on number of tumors and breast cancer phenotype. J Neurosurg 2010; 113: 65-72.
49. Kondziolka D, Kano H, Harrison GL, et al. Stereotactic radiosurgery as primary and salvage treatment for brain metastases from breast cancer. Clinical article. J Neurosurg 2011; 114: 792-800.
50. Kirova YM, Chargari C, Mazeron J-J. Métastases cérébrales multiples d'un cancer du sein et leur prise en charge en radiothérapie: quelle est l'attitude thérapeutique la mieux adaptée? Bull Cancer 2011; 98: 409-15.
51. Schwaiki A, Ratanatharathorn V, Hutchins LF, Elshihabi S, Linskey ME. Management of central nervous system metastases from breast carcinoma. In: Berger MS, Prados MD. Textbook of neuro-oncology Elsevier, Inc., Philadelphia 2005; 404-29.
52. Wroński M., Arbit E, Mc Cormick B. Surgical treatment of 70 patients with brain metastases from breast carcinoma. Cancer 1997; 80: 1746-54.
53. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 2006; 295: 2483-91.
54. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol 2009; 10: 1037-44.
55. Aoyama H, Tago M, Kato N, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. Int J Radiat Oncol Biol Phys 2007; 68: 1388-95.
56. Abe E, Aoyama H. The role of whole brain radiation therapy for the management of brain metastases in the era of stereotactic radiosurgery. Curr Oncol Rep 2012; 14: 79-84.
57. Vern-Gross TZ, Lawrence JA, Case LD, et al. Breast cancer subtype affects patterns of failure of brain metastases after treatment with stereotactic radiosurgery. J Neurooncol 2012; 110: 381-8.
58. Trifiletti DM ,Romano KD ,Xu Z ,Reardon KA , Sheehan J. Leptomeningeal disease following stereotactic radiosurgery for brain metastases from breast cancer. J Neurooncol 2015; 124: 421-7.
59. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 2004; 363: 1665-72.
60. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomized controlled trial. Lancet Oncol 2009; 10: 1037-44.
61. Huang AJ, Huang KE, Page BR, et al. Risk factors for leptomeningeal carcinomatosis in patients with brain metastases who have previously undergone stereotactic radiosurgery. J Neurooncol 2014; 120: 163-9.
62. Soffietti R, Kocher M, Abacioglu UM, et al. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. J Clin Oncol 2013; 31: 65-72.
63. Tallet AV, Azria D, Barlesi F, Spano JP, Carpentier AF, Gonçalves A, Metellus P. Neurocognitive function impairment after whole brain radiotherapy for brain metastases: actual assessment. Radiat Oncol 2012; 7: 77.
64. Tallet A, Kirowa Y. Métastases cérébrales de cancer du sein: facteurs pronostiques et prise en charge intégrée. Bull Cancer 2013; 100: 63-67.

65. Rades D, Lohynska R, Veninga T, Stalpers LJ, Schild SE. Evaluation of 2 whole-brain radiotherapy schedules and prognostic factors for brain metastases in breast cancer patients. Cancer 2007; 110: 2587-92.
66. Ricard D, Taillia H, Renard JL. Brain damage from anticancer treatments in adults. Curr Opin Oncol 2009; 21: 559-65.
67. Soussain C, Ricard D, Fike JR, Mazeron JJ, Psimaras D, Delattre JY. CNS complications of radiotherapy and chemotherapy. Lancet 2009; 374: 1639-51.
68. Nieder C, Berberich W, Schnabel K. Tumor-related prognostic factors for remission of brain metastases after radiotherapy. Int J Radiat Oncol Biol Phys 1997; 39: 25-30.
69. Hopewell JW. Late radiation demage to the central nervous system: a radiobiological interpretation. Neuropathol App l Neurobiol 1979; 5: 329-43.
70. Stokes TB, Niranjan A, Hideyuki K, et al. White matter changes in breast cancer brain metastases patients who undergo radiosurgery alone compared to whole brain radiation therapy plus radiosurgery. J Neuroonkol 2015; 121: 583-90.
71. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irraditation: a randomized controlled trial. Lancet Oncol 2009; 10: 1037-44.
72. Baschnagel AM, Mayer KD, Chen PY, et al. Tumor volume as a predictor of survival and local control in patients with brain metastases treated with gamma knife surgery. J Neurosurg 2013; 119: 1139-44.
73. Hall WA, Djalilian HR, Nussbaum ES, Cho KH. Long term survival with metastatic cancer to the brain. Med Oncol 2000; 17: 279-86.

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