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MINI REVIEW

A systematic approach to the management of patients with brain metastases of known or unknown primary site

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Abstract
Purpose To establish an empirical systematic approach for the management of brain metastases from a variety of cancers.
Methods The English literature was reviewed from 2000 to 2011 and all clinical trials (phase II, phase III and retrospective studies) regarding therapy of brain metastases were selected for more detailed review. Some key articles published prior to 2000 were also included in the review as are supplemental recommendations based on our clinical experience.
Results Patients with brain metastases from small cell lung cancer (SCLC) at the initial cancer diagnosis can be treated with concomitant whole-brain radiation therapy (WBRT) and chemotherapy or first with chemotherapy followed by WBRT. In all other cases, brain metastases are currently treated independently of the management of the extracranial disease with surgery or radiosurgery followed by WBRT. In radioresistant tumors (melanoma, sarcoma, renal cell carcinoma), WBRT may be omitted initially but administered at recurrence. Where surgery or radiosurgery is not an option for patients, WBRT should be administered. Prophylactic WBRT should be given in patients with SCLC and considered in patients with non-small cell lung cancer. Apart from its use in SCLC, chemotherapy for the treatment of brain metastases is reserved for patients enrolled in clinical trials.
Conclusion Brain metastases should be treated aggressively and independently of the primary site tumor especially if the performance status of the patient is good. The role of chemotherapy should be addressed in the context of clinical trials.

Keywords Brain metastasis · Surgery · Radiotherapy · Stereotactic radiosurgery · Chemotherapy

Introduction

Cerebral metastases occur in approximately 10–30% of patients with systemic cancer depending on the primary tumor diagnosis [1, 2]. Cancer cells reach the brain through the vasculartur with mechanisms involved in their growth in the brain including cell adhesion, angiogenesis, cellular signaling, and blood–brain barrier alterations [3].

The frequency of brain metastases is highest for lung cancer, followed by breast carcinoma, malignant melanoma, renal cell carcinoma, gastrointestinal carcinoma, gynecological cancer, and metastases of unknown primary carcinoma [4]. Some primary tumors such as malignant germ cell neoplasms, although rare, frequently metastasize to the brain [5]. Brain metastases can be sometimes solitary but most commonly are multiple. Malignant melanoma and lung primaries often result in multiple metastases, while renal carcinoma and gastrointestinal malignancies are often

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Table 1 General management of symptoms and findings related to brain metastases

Finding	Symptoms	Etiology	Management
Increased ICP [6]	Headache, nausea, vomiting, decreased mental status, focal weakness [36]	Tumor (s)	Dexamethasone, 4–16 mg/day [6]
Epilepsy [110]	Partial complex seizures	Tumor, paraneoplastic, metabolic, infections, chemotherapy [23, 111]	First choice: Levitiracetam, valproic acid Second choice: Oxcarbazepine, topiramate [110]
Neurocognitive dysfunction [25, 112]	↑ Sleepiness ↓ Memory Communication deficit Dementia [25, 112]	Tumor, brain radiotherapy[a] [113]	Methylphenidate, 10–20 mg/day in two divided doses [6] or Modafinil, 100–200 mg/day [35]
Radiation necrosis [37, 38]	↑ Sleepiness ↓ Memory Dementia Bilateral spasticity Focal weakness	Brain radiotherapy[a]	Dexamethasone, 4–16 mg/day Bevacizumab, 5–7.5 mg/kg every 2–3 weeks [37, 38]

ICP intracranial pressure

[a] Brain radiotherapy includes whole-brain radiotherapy, stereotactic radiosurgery, brachytherapy, or combination of the above

associated with single metastatic lesions [6]. Occasionally multifocal glioma resembles brain metastases requiring biopsy for correct diagnosis and appropriate treatment [7, 8]. In fact, multifocal glioma may coexist in patients with a variety of systemic cancers [9], especially in patients with a genetic cancer predisposition [10, 11]. In such cases, imaging characteristics may help to establish the correct diagnosis [12] and institute the appropriate therapy [8].

Patients with brain metastases may clinically present with symptomatology related to increased intracranial pressure such as headache, nausea, vomiting, and mental status changes, partial complex seizures, or focal motor and sensory findings. Several prognostic indices exist to evaluate patients suitable for clinical trials or patients that will benefit from aggressive therapy [13]. Among them, the recursive partitioning analysis (RPA) grades patients in 3 classes (1–3) with grade 1 the best and grade 3 the worst [14]. The most recently developed diagnosis-specific graded prognostic assessment (DS-GPA) appears to be more subjective and more quantitative than the RPA and grades patients with scores 1–4 and patients with best prognosis having a score of 4 [15–17]. Rarely, the first manifestation of a brain metastasis or even the first cancer manifestation may be an acute stroke-like syndrome particularly with metastatic tumors that have the tendency to hemorrhage spontaneously, such as choriocarcinoma, melanoma, and renal cell carcinoma. In such cases, Tc-99 m Tetrofosmin SPECT may aid in the differentiation of a plain hemorrhage mimicking a brain metastasis from a hemorrhagic metastasis [18]. Contrast-enhanced MRI is the diagnostic modality of choice when brain metastases are suspected or as a screening procedure for the presence of brain metastases [19].

In the present paper, we provide an evidence-based practical approach to the management of brain metastases depending on the tumor type, number and size of metastases, state of the extracranial disease, and performance status of the patient. We reviewed the last decade of publications, selected older key clinical trials, and our personal experience.

Management of patients with brain metastases

Non-specific management of tumor-related symptoms

Increased intracranial pressure and epileptic seizures

Patients with brain metastases may have symptoms and findings related to increased intracranial pressure (ICP) secondary to the total intracranial tumor burden and vasogenic edema. In addition, epileptic seizures can occur in approximately 50% of cases and require antiepileptic therapy. Since approximately half of the patients will never develop seizures and antiepileptic drugs may result in toxicity and interactions with someantineoplastic therapies, prophylactic antiepileptic treatment is ususally justified only for a period of 2–6 months after surgical excision of a cerebral metastasis [20–22]. The management of increased ICP and epilepsy is depicted in Table 1.

Neurocognitive dysfunction

In patients receiving whole-brain radiation therapy (WBRT) or neurotoxic chemotherapy such as methotrexate for metastases [23], prolongation of survival may be associated with neurocognitive deterioration [24]. In some cases, frank dementia, incontinence, and death have been reported [25]. In other studies, however, regression of brain metastases after WBRT correlated with better survival and improved neurocognitive function [24, 26]. In addition, while certain parameters of quality of life may deteriorate after WBRT, patients whose brain metastases respond favorably to WBRT may actually show improvement in quality of life scores [27]. Further confusing the situation, it has been shown that patients with brain metastases who receive WBRT and show stable or improved status of their intracranial disease may actually demonstrate decline in neurocognitive function due to radiation therapy to an extent that is proportional to the extend of their survival [28, 29]. The fact that deterioration in neurocognitive function precedes quality of life decline suggests that delaying neurocognitive decline may be a therapeutic goal in patients in whom a long survival is expected [30].

A recent Radiation Therapy Oncology Group phase III trial in non-small cell lung cancer (NSCLC) showed no overall survival benefit for prophylactic WBRT but a significant decrease in the frequency of developingbrain metastases. Further analysis of the data from that study demonstrated no significant differences in global cognitive function or quality of life except for a significant decline in memory at 1 year. This data underlines the need to use sensitive neurocognitive assessments during clinical trials of WBRT in the cancer patients [31]. Most patients with limited-stage small cell lung cancer (SCLC) have already mild cognitive dysfunction prior to prophylactic WBRT due to a variety of reasons [32]. In such patients, prophylactic WBRT with either 25 or 36 Gy resulted in mild deterioration of communication deficit as well as mild weakness of legs and memory dysfunction, over a 3-year time period [33]. In patients with neurobehavioral slowing and fatigue related to cancer or its treatment, methylphenidate in doses of 10–20 mg in divided daytime dosing can be helpful [34]. Modafinil at 100–200 mg daily may be also an effective alternative regimen [35].

Radiation necrosis

Radiation necrosis may occur in 5–30% of cases depending on the radiation dose and type [36]. It is more common in patients that have received several different forms of radiotherapy, such as combination of WBRT with stereotactic radiosurgery (SRS) or bracytherapy or all of the above [6]. Depending on the radiation type, radiation necrosis can be focal and limited or diffuse. When it is focal and highly symptomatic, the necrotic tissue can be sometimes removed by surgery if the patient's condition and prognosis allows such a procedure. Otherwise, or if it is diffuse, a trial of steroids may control the patient's symptoms. Other interventions that have been used in the past with limited success have been use of pentoxifylline and anticoagulation with warfarin. Recently, use of anti-VEGF therapy with bevacizumab has been found to be an effective therapy for symptomatic radiation necrosis based on class 1 evidence [37, 38].

Specific management of brain metastases

The specific management of patients with brain metastases involves various combinations of surgery, WBRT, SRS, and brachytherapy depending on various factors, such as the number, size and location of brain tumors, as well as histology of the primary tumor and extent of systemic extracranial disease (Table 2) [39–42].

Surgery

Surgery has an indispensable role in the management of brain metastases [39]. In fact, for solitary brain metastasis, surgical resection should be the initial standard of care complemented with WBRT [43]. A phase III trial in 195 patients with solitary brain metastasis from predominantly NSCLC and breast cancer demonstrated that surgery plus WBRT improved survival and local control compared with WBRT alone [44]. Similarly, a retrospective study in 250 patients with NSCLC and brain metastases showed that patients with solitary metastasis that underwent surgical resection followed by WBRT had improved survival compared with WBRT alone [45]. Resection of a single brain metastasis followed by 60 Gy brachytherapy was reported in one study to have comparable results to surgery plus WBRT [46]. Several other small retrospective studies have also indicated that surgery for solitary metastasis resulted in improved local control when combined to WBRT [47–49]. Insertion of carmustine wafers after resection of a single brain metastasis may be an option in selected patients [50], but it has not enjoyed widespread use.

Resection of a solitary brain metastasis without postoperative WBRT resulted in 15% risk of a local recurrence independently of the primary cancer site of origin. The factors that influenced risk of local recurrence included piecemeal rather than en bloc resection and tumor volume > 9.7 cm^3 [51]. Furthermore piecemeal resection carries an additional risk of tumor dissemination into the cerebrospinal fluid which represents an ominous complication [52].

Table 2 Characteristics and therapy of the brain metastases according to primary site

Primary site	Frequency (+ to ++++)[a]	Single/multiple	Surgery	Stereotactic radiosurgey (SRS)	Whole brain radiotherapy (WBRT)	Chemotherapy for brain metastases	Prognosis
Germ cell tumor	++++	Multiple Frequently hemorrhagic [80]	Infrequently	Occasionally	Yes [5]	Yes [5]	Variable Occasionally cure [5]
SCLC	++++	Multiple	Infrequently	Occasionally	Yes [76, 79, 92]	Yes [76, 79]	Variable Initially good response [76, 79]
NSCLC	+++	Usually multiple May be hemorrhagic	(1) Resection if lesion (s) are ≤4, surgically accessible and systemic disease stable, or if significantly symptomatic [44, 45, 48]	(2) In combination with surgery or as alternative to surgery [49, 61, 63–66, 71, 74]	(3) All patients after surgery or SRS or as the only therapy [44, 48, 66]	(4) Only as part of a clinical trial	Surgery or SRS plus WBRT improves survival [44, 49, 61, 64, 66]
Breast	+++	Single or multiple	Resection as in (1) [44, 48]	SRS as in (2) [61, 63–65, 71, 74]	Yes, as in (3) [44, 48, 61, 63, 64]	As in (4)	Better with surgery or SRS plus WBRT [44, 48, 61, 64]
Melanoma	+++	Usually multiple Some may be hemorrhagic	Resection as in (1) [58]	SRS as in (2) [61, 67, 97–99]	On individual basis [61, 67, 97–99]	On individual basis [58]	Better with surgery, SRS or TMZ [58, 61, 97–99]
Renal cell	+++	Usually single May be hemorrhagic Tends to metastasize to the choroids plexus	Resection as in (1) [44]	SRS as in (2) [65, 68, 69, 97, 98]	On individual basis [98, 99]	On individual basis	Surgery or SRS effective therapies [44, 65, 68, 69, 97, 98]
Gastrointestinal	++	Usually single	Resection as in (1) [44, 48]	SRS as in (2) [64, 65]	Yes, as in (3) [44, 48, 64, 65]	As in (4)	Surgery or SRS plus WBRT improves survival [44, 48, 64, 65]
Unknown primary	++	Single or multiple	Resection as in (1) [54]	SRS as in (2) [109]	Yes, as in (3) [107, 108]	As in (4)	Surgery or SRS plus WBRT effective therapy [44, 54, 64, 109]
Uterine, vulvar, ovarian	+	Single or multiple	Resection as in (1) [44, 47, 101]	SRS as in (2) [57, 64]	Yes, as in (3) [44, 47, 101]	As in (4)	Surgery or SRS plus WBRT improves survival [44, 47, 57, 64, 101]
Sarcoma	+	Single or multiple	Resection as in (1) [44, 48]	SRS as in (2) [97, 99]	On individual basis [97, 99]	As in (4)	Better with surgery or SRS [44, 48, 97, 99]
Prostate	±	Usually multiple during end stage disease	Rarely [103]	Occasionally [103]	Yes [103]	As in (4)	Poor [103]

Table 2 continued

Primary site	Frequency (+ to ++++)[a]	Single/multiple	Surgery	Stereotactic radiosurgey (SRS)	Whole brain radiotherapy (WBRT)	Chemotherapy for brain metastases	Prognosis
Bladder	±	Usually multiple during end stage disease	Rarely	Occasionally [101]	Yes [101]	As in (4)	Poor [101]
Hepatocellular	±	Usually multiple during end stage disease May be hemorrhagic [100]	Rarely	Occasionally [100]	Yes [100]	As in (4)	Poor [100]

SCLC small cell lung cancer, *NSCLC* non-small cell lung cancer, *WBRT* whole-brain radiotherapy, *SRS* stereotactic radiosurgery

[a] Frequency reflects how often the patients develop brain metastases if they have the specific diagnosis

Early studies have recognized the efficacy of surgery in the management of even multiple brain metastases. Thus, it has been reported that, in selected patients with multiple brain metastases and stable systemic disease or good patient performance status, surgical removal of all lesions resulted in significantly increased survival time similar to that of patients undergoing surgery for a single metastasis [53]. Patients with multiple brain metastases may also benefit from resection of selected lesions that are symptomatic [54]. For example, a large posterior fossa metastasis with mass effect endangering herniation should be resected prior to the administration of WBRT. In any event, surgery should be considered in every case of brain metastases, especially in patients with good performance status and stable extracranial disease.

Stereotactic radiotherapy

The role of radiosurgery for management of brain metastases has been extensively studied (Table 2) [55]. Apart from the standard techniques for routine SRS, interstitial SRS with a miniature X-ray generator (Photon Radiosurgery System, PRS) allows for an efficient immediate treatment for patients with small solitary metastasis [56]. The indications for SRS are essentially the same as for surgical resection of brain metastases. In most cases, SRS is offered as an alternative to surgery in cases where the patient is not a good surgical candidate or refuses surgery or the lesions in question are not surgically amenable. In addition, SRS can be used in addition to surgery, and with or without WBRT [49, 57–59]. Radiosurgery improves local tumor control and may improve quality of life and survival [60, 61], especially in younger patients with up to 3 brain metastases and low systemic tumor burden [62].

A phase III randomized clinical trial in 132 patients with 1to 4 brain metastases from various primary cancers tested the effectiveness of SRS plus WBRT to only SRS. Although the MST was not different between the 2 groups, more intracranial recurrences were observed in the patients that received only SRS, requiring further salvage therapies [63]. Another randomized phase III trial in 333 patients with up to 3 brain metastases concluded that for unresectable solitary metastasis, SRS followed by WBRT should be the standard form of management and considered in patients with 2–3 brain metastases [64]. Employment of gamma knife SRS in 237 patients with solitary brain metastasis from various cancers (NSCLC, breast, renal cell, melanoma and colorectal) resulted in a median survival time (MST) of approximately 10 months. Favorable prognostic factors were Karnofsky performance score $\geq$ 70, good neurological function prior to SRS, no active extracranial systemic metastases and histologic diagnosis of renal cell or breast carcinoma [65]. Various

retrospective studies have also indicated that SRS is an effective therapy for brain metastases when administered either before WBRT [66–69], after WBRT [68, 70] and with WBRT [67, 70]. A phase III study of SRS versus surgery plus WBRT was prematurely discontinued secondary to poor accrual, but in the 64 patients that they were accrued, it suggested that SRS alone was associated with increased frequency of distant brain metastases [71].

Hypofractionated stereotactic radiotherapy with 5 daily fractions of 6–7 Gy may be used as an equally effective therapy for brain metastases not amenable to radiosurgery [72]. In cases of multiple and cystic brain metastases, a combination of stereotactic drainage and radiosurgery may offer some extra benefit [73].

Whole-brain radiotherapy

WBRT used to be the mainstay of treatment in patients with brain metastases. However, the benefit from surgery when the metastases are either single or few and resectable, and from SRS if surgery is contraindicated, has changed the management of brain metastases [71]. Although adjuvant WBRT is used in a high percentage of cases of brain metastases, patients with resectable brain metastases and stable extracranial disease should be treated first with surgery or SRS prior to WBRT [64]. Alternatively, if WBRT is used initially, SRS could be used as salvage therapy at recurrence [66, 74]. WBRT only should be used in cases when the brain metastases are multiple and not amenable to resection or SRS.

Chemotherapy

Apart from SCLC, chemotherapy is rarely a first-line treatment for brain metastases. Chemotherapy is usually administered intravenously although some studies have reported increased benefit from intraarterial administration with concomitant blood–brain barrier disruption [75]. For patients with SCLC who exhibit brain metastases along with systemic metastases, chemotherapy may be an acceptable option (Table 3). Thus, a combination of irinotecan with carboplatin in patients with systemic metastases including brain resulted in a MST of 6 months [76]. A phase III study in patients with NSCLC and inoperable brain metastases compared the effectiveness of either a combination of WBRT with chemotherapy (cisplatin and vinorelbine), to only chemotherapy initially, adding WBRT if there was no response or after six courses of chemotherapy. This study showed that the timing (early or delayed) of WBRT did not influence survival [77]. In a phase II trial of a combination of WBRT and gefitinib for brain metastases from NSCLC was well tolerated and had a promising activity and a significant improvement of quality of life in a Chinese population [78].

Previously, a chemotherapy combination was designed to improve the cytotoxicity and overcome the tumor cell resistance to lomustine (CCNU), a drug mainly used for gliomas due to its good penetration through the blood–brain barrier [79]. This drug combination involved administration, at specific times, of 6-thioguanine, procarbazine, dibromodulcitol, CCNU, fluorouracil, and hydroxyurea (TPDC-FuHu) [79]. Use of this regimen in a multicenter prospective study in 97 evaluable patients with progressive or recurrent metastatic brain tumors that failed to respond to surgery and/or radiation therapy showed an overall response rate of 52, 66, 60, and 22% in patients with NSCLC, SCLC, breast cancer, and melanoma and median time to progression (MTP) of 12, 26, 12, and 6 weeks, respectively. This study showed some of this regimen against brain metastases from SCLC followed by breast cancer and NSCLC but no activity against melanoma [79].

Table 3 Published chemotherapeutic regimens, with or without WBRT, for recurrent brain metastases

Chemotherapy regimen	Primary cancers	MST (weeks)	Authors' comments
Irinotecan plus carboplatin [76]	SCLC	25.7 [76]	Effective therapy [76]
Combination of thioguanine, procarbazine, dibromodulcitol, CCNU, fluorouracil and hydroxyurea	SCLC, NSCLC, breast, melanoma, other cancer	25 [79]	Patients with SCLC had better response followed by breast Ca and NSCLC
Cisplatin and vinorelbine with different timing of WBRT [77]	NSCLC	21–24 [77]	Timing of WBRT did not influence survival [77]
Gefitinib plus WBRT [78]	NSCLC	55.7 [78]	Promising activity [78]
Intra-arterial carboplatin and IV etoposide and cyclophosphamide [75]	Lung, ovarian, breast, systemic lymphoma	128.8	Promising results [75]
Temozolomide plus WBRT [82, 83, 85–87]	Melanoma, NSCLC, breast cancer	24–55	Active regimen, under investigation [82, 83, 85–87]

SCLC small cell lung cancer, *NSCLC* non-small cell lung cancer, *WBRT* whole-brain radiotherapy, *MST* median survival time

Brain metastases from non-seminomatous germ cell tumors can be managed with either WBRT or standard induction chemotherapy without WBRT [5]. The chemotherapeutic combinations used are similar to those employed for primary intracranial germ cell tumors [80].

Temozolomide (TMZ), an oral methylating imidazotetrazinone, is the main drug used against malignant gliomas [81]. However, TMZ has exhibited antitumor activity against malignant melanomas and brain metastases from several solid tumors. Combination of WBRT with TMZ for brain metastases from various solid tumors showed an objective response of 57.6% and overall MST of 12 months and mild side effects [82]. Another study employing a similar treatment in patients with brain metastases from solid tumors demonstrated a RR of 45%, MTP of 9 months, and MST of 13 months [83]. Treatment of brain metastases from breast or non-small cell lung cancers showed an overall MST of 8.8 m durable stabilization or response months and median PFS of 6 months [84]. While TMZ treatment in patients with brain metastases from melanoma had limited antitumor activity [85], a small subset of patients with systemic melanoma and brain metastases who did show a systemic response to TMZ also had a durable stabilization or response of the brain metastases that allowed cranial irradiation to be deferred or withheld for sometime [86]. Some other studies have indicated a little better result of concomitant TMZ and radiotherapy with median PFS of 5 months and MST of 7 months in patients with concurrent WBRT and 9 months in patients with concurrent stereotactic radiotherapy [87]. In the contrary, another study using a combination of TMZ, thalidomide, and WBRT in metastatic brain melanoma had a poor response rate of 7.6%, MTP of 7 weeks, and median OS of 4 months [88]. The effect of TMZ is still under intense testing in brain metastases but it appears that there is no dose response and the currently standard doses used are equally effective to higher doses [89].

Prophylactic WBRT

Prophylactic WBRT in patients with SCLC significantly decreases the risk of brain metastasis and has a marginal beneficial effect on survival [90]. Although the overall beneficial effect of WBRT is established in patients with limited-stage SCLC, its role in patients with extensive stage disease has not been clearly defined [91]. In addition, for limited-stage disease, the standard dose of 25 Gy seems to have the same benefit as the higher dose of 36 Gy [92] and similar mild neurotoxicity [33].

The brain seems to be the most common site of isolated recurrence in NSCLC after aggressive induction chemoradiotherapy followed by surgical resection of the primary tumor, suggesting that either routine brain scans should be performed frequently [93] or the use of prophylactic WBRT should be considered [94, 95]. In a phase III clinical trial, 356 patients with stage III NSCLC without disease progression after initial induction therapy were randomized to receive either prophylactic WBRT or no further therapy. The results of the study showed that prophylactic WBRT reduced approximately 2.5 times the risk of brain metastasis after 1 year but it did not improve the overall survival [96].

Management of brain metastases from some specific cancers

Radioresistant tumors

Management of brain metastases from radioresistant primary tumors such as melanoma, sarcoma and renal cell carcinoma can be performed with either surgery or stereotactic radiosurgery followed by WBRT (Table 2). Sometimes the WBRT may be omitted in the initial plan and reserved for future recurrences. Such therapy can result in MST from 20 to 35 weeks depending on the number of metastases, performance status, and extend of systemic disease [58, 67, 68, 97–99].

Tumors that rarely metastasize to brain

Brain metastases from hepatocellular carcinoma occur in approximately less than 1% of cases, associated with previous hepatitis B infection and tend to bleed in half of cases. Their prognosis is poor with a MST of 7 weeks but some patients with a single metastasis and relatively stable primary tumor may show better survival with appropriate therapy such as surgery, SRS, and WBRT [100].

Brain metastases from bladder carcinoma usually occur when the systemic disease is extensive. At this point, the survival of patients receiving only WBRT appears to be poor [101], but if there is only one lesion and the systemic disease controlled longer survival can be attained [102]. Similarly, brain metastasis from prostate carcinoma is a rare event. A large retrospective study in 16,280 patients treated at the University of Texas M. D. Anderson Cancer Center documented 103 patients (0.63%) within traparenchymal metastases. Almost all of these patients had extensive systemic metastases at the time of brain metastases. The risk of brain metastasis from prostate carcinoma although overall very low, it was found approximately 20 times higher when the histologic diagnosis was small cell carcinoma or cribriform carcinoma compared with adenocarcinoma. Since the development of brain metastasis was a late event, the prognosis was poor with a MST without treatment of 1 month, treatment with WBRT of

4.5 months, and treatment with SRS in five cases of 9 months [103].

Ovarian carcinoma is another tumor that rarely metastasizes to the brain (0.9%). However, when it is documented the most appropriate therapy is a combination of surgery with WBRT, if the tumors are surgically accessible or WBRT [47]. Substitution of SRS in nonsurgical cases may be also a viable alternative [57].

Brain metastases from cancer of unknown primary site

A retrospective study on 342 patients presented with brain metastases showed that 64% of patients had a known primary site and 36% had an undiagnosed primary site [104]. Further diagnostic workup in the patient group with the unknown primary site revealed that the lung was the primary site in 60% of cases, other organs in 14% of cases, but in 26%, no primary site was revealed despite extensive workup. The investigators of that study recommended biopsy of a brain lesion if a radiological lung investigation failed to demonstrate a primary site in the lung [104]. Although treatment of brain metastases should not be delayed in search for detection of the primary site, whole-body 18FDG PET scanning is a sensitive tool for establishing the primary site in most cases allowing early and focused histological confirmation from suspicious lesions [105]. In a retrospective study on 342 patients with CT-diagnosed brain metastases, there was no statistically significant difference in survival between patients with an undiagnosed primary lesion and those with a diagnosed primary tumor (6 and 4.5 months, respectively). Favorable prognostic factors for the entire group included treatment, age less than 65 years, absence of systemic metastasis, and asymptomatic cerebral metastasis [106]. Another study on 916 patients with brain metastases treated with WBRT reported 5.1% incidence of unknown primary site. This study found median overall survival (OS) of 4.8 months for patients with cancer of unknown primary site (7.3 vs. 3.9 months for patients with a single or multiple brain metastases, respectively) [107]. Some investigators recommend even short-courses WBRT with 5 daily fractions of 4 Gy each that may provide similar intracerebral control and survival as the regular course with 10 fractions of 3 Gy each for the treatment of brain metastases in cancer of unknown primary site since it is more convenient for patients [108]. However, in patients with both single and multiple brain metastases from an undetected primary site, surgical removal of the metastases if it is technically feasible followed by WBRT enables better control of the [5] brain disease and prolongs survival [54]. Radiosurgery is also an effective option for patients with brain metastases from an unknown primary site. Radiosurgery in 29 patients who had solitary or multiple brain metastases without a detectable primary site showed a local tumor control rate of 88.5% and a median survival of 12 months [109].

Conclusions

Brain metastases can occur in up to 30% of patients with various systemic cancers. Some cancers such as lung carcinoma, breast carcinoma, melanoma and renal cell carcinoma do frequently metastasize to the brain, and others, such as hepatocellular carcinoma, bladder, prostate carcinoma, and ovarian carcinoma are among tumors that rarely metastasize to the brain. In addition, after the initial basic workup, the site of origin of brain metastases is not obvious in approximately 33% of patients. Extensive workup reveals the lung as the site of origin of most of these cases. In SCLC, induction chemotherapy should be given initially

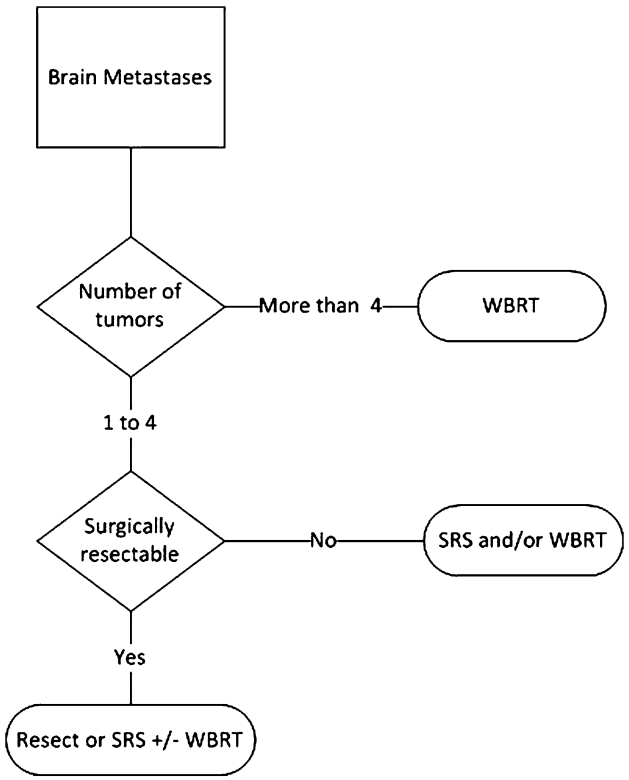

Fig. 1 A flow diagram for management of brain metastases. This is a general approach for a patient with brain metastases of any known or unknown primary site. If the patient has few metastases (1–4), the aggressive approach of surgery/SRS is advocated when the extracranial disease is stable and the performance status of the patient is relatively good. If the patient has multiple brain metastases (>4), the option of SRS could be evaluated for all or the symptomatic brain metastases. In any event, WBRT should follow except in cases of radioresistant tumors (renal cell carcinoma, sarcoma, melanoma) where it can be postponed until the other treatment employed has failed. Management of brain metastases as shown in the flow diagram is in addition to other systemic treatment that the patient may be receiving for the primary tumor and extracranial metastases

with WBRT or followed by WBRT. In all other cancers, brain metastases should be treated with either surgery if few and resectable or radiosurgery in nonsurgical cases followed by WBRT (Fig. 1). In some cases of radioresistant tumors (melanoma, sarcoma, renal cell carcinoma), WBRT may be omitted initially and administered at recurrence. In all other cases, WBRT should be administered. After therapy, all patients should be followed with MRI scans every 3 months for the first post-treatment year, or earlier if they become symptomatic. If they remain in remission for a year, the periods of MRI scans can be gradually extended to 4 and 6 months. Prophylactic WBRT should be given in patients with SCLC and considered in patients with NSCLC. Apart from its use in SCLC, chemotherapy for treatment of brain metastases should be reserved for patients enrolled in clinical trials.

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