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ORIGINAL ARTICLE - BRAIN TUMORS

Outcome after surgery in supratentorial and infratentorial solitary brain metastasis

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Abstract

Background The aim of this retrospective study was to investigate and compare the outcome after surgery in patients with a supratentorial solitary metastasis (SSM) and an infratentorial solitary metastasis (ISM). A worse prognosis has been reported in ISM.

Methods Fifty-two patients with a newly diagnosed solitary brain metastasis on MRI were included to identify risk factors affecting the outcome. Key variables included tumor size, staging of the primary tumor, time span of presurgical work-up, and surgical technique. Outcome variables included postoperative complications, tumor recurrence, and mortality. Kaplan-Meier survival analysis was applied.

Results Thirty patients with a SSM and 22 patients with an ISM underwent gross total resection. The tumor size did not have a statistical significant effect on survival. Presurgical work-up time was similar in SSM and ISM. Postoperative complications were more frequently encountered in ISM. Recurrence rate was comparable in SSM and ISM. Carcinomatous meningitis (CM) was more frequently seen in ISM, and CM was seen more often with the piecemeal resection technique. There was no statistical difference in overall survival between SSM and ISM.

Conclusions This study identified factors that play a role in the outcome after surgery in patients with ISM and SSM on MRI. Postoperative complications seemed to be higher in ISM and CM was more often seen in ISM, but the worse prognosis in patients with ISM compared with SSM could not be confirmed.

Keywords Brain metastasis · MRI · Supratentorial · Infratentorial

Abbreviations

BM	Brain metastasis
CM	Carcinomatous meningitis
CT	Computed tomography
CUSA	Cavitron Ultrasonic Surgical Aspirator
ISM	Infratentorial solitary metastasis
KPS	Karnofsky Performance Status
MRI	Magnetic resonance imaging
SSM	Supratentorial solitary metastasis
WBRT	Whole-brain radiotherapy

This article is part of the Topical Collection on *Brain Tumors*

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Introduction

Brain metastases (BM) are the most frequent brain tumor. After the introduction of magnetic resonance imaging (MRI), multiple lesions have outnumbered single lesions. MRI is crucial in the diagnostic work-up of a suspected solitary BM.

The gold standard for the treatment of a solitary BM is not yet established [9]. Surgery is considered the standard treatment in patients with a good functional status and controlled systemic disease but inevitably the procedure is associated with morbidity and mortality [17]. There is still controversy concerning the most appropriate treatment for solitary BM. Three random clinical trials studied differences between surgery with whole-brain radiotherapy (WBRT) or WBRT alone [18, 22, 37]. Two of these studies showed a significant survival benefit for the surgery group [22, 37]. A meta-analysis, published in 2005, however showed no significant difference in overall survival between surgery and whole-brain

radiotherapy versus whole-brain radiotherapy alone [12]. Survival with surgery and adjuvant radiotherapy has been reported to be better than with stereotactic radiosurgery [3]. One trial compared surgery plus WBRT versus stereotactic radiosurgery and the other trial compared surgery plus WBRT versus stereotactic radiosurgery plus WBRT but no difference in overall survival could be found [19, 25]. Only a small minority of the patients in these trials had an ISM. In a randomized, controlled, phase 3 trial, the authors found no difference in overall survival between WBRT (96 patients) and stereotactic radiosurgery (98 patients) after surgery for BM [4]. Local control and distant brain control were worse in the stereotactic radiosurgery group than the WBRT group, but there was no difference in the development of leptomeningeal disease between the treatment groups. They found more decline in cognitive function in the WBRT group and concluded that stereotactic radiosurgery should be considered one of the standards of care as a less toxic alternative to WBRT. WBRT could be related to cognitive impairment and decreased the quality of life [26]. Considering the longer survival patients with BM, it has been suggested to keep this treatment for possible new episodes of metastases [30]. Surgery and stereotactic radiosurgery are considered effective but a recent meta-analysis could not demonstrate sufficient evidence of the effectiveness of one therapy versus the other [10]. Immunotherapeutic and targeted agents are increasingly being used in patients with multiple BM [13]. Surgery and/or stereotactic radiosurgery followed by systemic immunotherapy in solitary BM remain largely unexplored.

Factors associated with longer median survival are a high Karnofsky Performance Status (KPS)-score, female gender, young age, gross total resection of the metastasis, and supratentorial location [38]. Most studies have shown that ISM has a worse prognosis than SSM but reasons remain unclear [5, 11, 30, 38]. Carcinomatous meningitis (CM) and peritoneal metastases along the shunt tube have been related to a worse outcome [15].

This article reports the author's experience with patients who presented with a supratentorial solitary metastasis (SSM) or an infratentorial solitary metastasis (ISM) on MRI and were treated with surgery and WBRT with the objective to assess differences in outcome between both tumor locations.

Methods and materials

Patients

The IRB approved the retrospective review of a database of patients with brain metastases (BM).

Data were collected from the respective electronic medical records of 114 patients who presented at our institution between 2010 and 2016, with a suspected solitary BM on computed tomography (CT). Fifty-eight patients were excluded: 35 patients with multiple metastases on MRI, 20 patients who had WBRT as first treatment, and 3 patients who underwent urgent tumor resection on the day of admission.

Fifty-two patients with a solitary BM confirmed on MRI, underwent gross total resection. Tissue diagnosis was available. These patients were separated into two groups: 30 patients with a SSM and 22 patients with an ISM. WBRT was applied in 49/52 patients. The WBRT dose was 30 Gy in 10 fractions ($n = 34$) or 20 Gy in 5 fractions ($n = 15$).

Methods

The demographic data of the 52 patients with a single BM on MRI were obtained through medical records.

We reviewed the medical records of 52 patients for data on primary tumor, location of the metastasis, symptoms at presentation, presurgical work-up time, size of the metastasis, staging of the primary tumor at diagnosis of intracranial disease, surgical technique, complications after surgery, timing and location of recurrence, and cause of death.

Kaplan-Meier survival analysis was performed for overall survival analyses.

Results

Twenty-nine patients (44%) were male and 23 female (56%) with a mean age of 59.7 ± 12.5 years. All patients had a preoperative KPS-score > 60–70. The most common symptoms in patients with SSM were cognitive decline, language disturbances, headaches, hemiparesis, and epilepsy. Epilepsy was only seen in SSM. The most common symptoms for patients with an ISM were nausea/vomiting and headache. The mean time between the initial presentation and surgery was 13 days for SSM and 11 days for ISM.

Primary tumor and location of brain metastasis

The final histopathological diagnosis is listed in Table 1. Lung, breast, and melanomas caused 64% of the solitary BM, which is slightly less than what is reported in the literature [36]. Lung cancer was the most common primary tumor (8 SSM and 10 ISM), followed by gastrointestinal cancer ($n = 9$) and breast cancer ($n = 8$). The probability to develop cranial disease for a certain primary tumor is highest for the malignant melanoma, with up to 75% of these cancer patients developing brain metastasis [27, 29]. In our series, there were no patients with ISM from malignant melanoma but 7 patients with a SSM. In one patient, no primary tumor was found despite an extensive diagnostic work-up. According to the literature, up to 15% of the primary tumors can remain undiagnosed [24].

Table 1 Histological diagnosis in 52 patients with a solitary brain metastasis

Primary tumor of SSM	Histology
Lung cancer	8 non-small cell lung cancer (NSCLC):
	- 5 adenocarcinoma
	- 3 squamous carcinoma
Malignant Melanoma	7
Breast cancer	4 adenocarcinoma:
	- 3 invasive ductal adenocarcinoma
	- 1 invasive lobular adenocarcinoma
Colorectal cancer	5 adenocarcinoma
Esophagus	2 adenocarcinoma
Liver cancer	1 hepatocellular carcinoma
Thyroid carcinoma	1 papillary thyroid carcinoma
Ovarian cancer	1 serous papillary ovarian carcinoma
Liposarcoma	1 undifferentiated liposarcoma of the lower leg
Lung cancer	10 NSCLC:
	- 5 adenocarcinoma
	- 4 squamous carcinoma
	- 1 adenosquamous carcinoma
Breast cancer	4 adenocarcinoma:
	- 3 invasive ductal adenocarcinoma
	- 1 invasive lobular adenocarcinoma
Colorectal carcinoma	4 adenocarcinoma
Synovial lung sarcoma	1 high grade synovial sarcoma
Bladder cancer	1 transitional cell cercinoma
Renal cancer	1 renal cell carcinoma
Unknown origin	1

The SSM was located in the frontal lobe (12/30), the parietal lobe (10/30), the temporal lobe (5/30), and the occipital lobe (3/30). Most ISM was located in the cerebellar hemisphere (16/22) while 6 were located in the vermis.

Size of metastasis

MRI was used to measure the metastases in three dimensions. In SSM, the longest diameter had a mean value of 3.1 cm and a median of 2.9 cm (range 3.6 ± 0.90 cm). In ISM, the mean was 3.1 and the median value was 3.1 cm (range 3.2 ± 0.84 cm). We separated the BM in two groups, with a cut-off of 3 cm and calculated the median survival. There was no difference in median overall survival for lesions < 3 cm (16 and 17 months for SSM and ISM, respectively) or lesions > 3 cm (12 and 11 months for SSM and ISM, respectively).

Staging of primary tumor

All patients were classified in one of three groups depending on the stage of primary tumor.

- Group 1 ($n = 12$, 5 SSM and 7 ISM): BM as a first presentation of the primary cancer
- Group 2 ($n = 14$, 6 SSM and 8 ISM): controlled systemic disease at diagnosis of the BM
- Group 3 ($n = 26$, 19 SSM and 7 ISM): progressive systemic disease at diagnosis of the BM

The median overall survival was higher in group 1 and 2, compared with group 3 in SSM and was higher in group 1 than in group 2 for ISM (Table 2). Six patients with SSM (all from group 3) and 2 patients of the group of the ISM (one from group 1, one from group 2) died within 3 months after surgery. We calculated the median overall survival (Table 2) and the Kaplan-Meier curves of these different groups for ISM and SSM (Fig. 1a–c). The results were statistically not significant ($p = 0.363$, $p = 0.291$, and $p = 0.360$ for resp. group 1, 2, and 3).

Surgical technique and postoperative complications

All patients underwent a gross total resection. “En bloc” resection was performed in 26/30 (87%) SSM and in 11/22 (50%) ISM. The piecemeal resection technique was used in 4/30 (13%) SSM and in 11/22 (50%) ISM. Piecemeal resection was defined as resection of the tumor with an ultrasonic aspiration device and/or microsurgical resection of the tumor in different parts.

Postoperative complications were observed in 7/52 (SSM = 1, ISM = 6) patients (13%): postoperative aseptic meningitis with persistent headache, motor aphasia with an increased edema around the resection space on CT, a PICA infarct with mass-effect on the fourth ventricle and hydrocephalus, hydrocephalus due to perilesional edema for which drainage was necessary, ataxia and gait problems after posterior fossa surgery, nystagmus and sensibility problems in trigeminal area after posterior fossa surgery and asthenia, headache, unsteady gait, and vomiting 18 days after surgery. Three patients with an ISM needed a separate operation for treatment of hydrocephalus (two postoperative, one preoperative).

Table 2 Overall survival in patients with brain metastasis in relation to staging of the primary tumor

Stage primary tumor	Median overall survival in SSM (months)	Median overall survival in ISM (months)
Group 1: first diagnosis with a BM	16	15
Group 2: controlled systemic disease	26	10
Group 3: progressive systemic disease	10	17

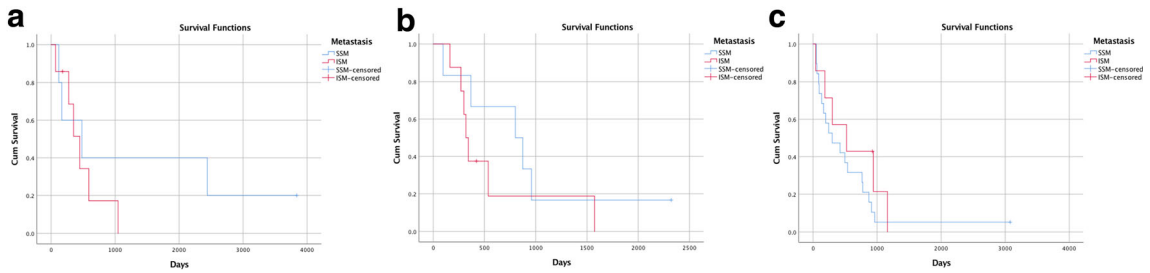

Fig. 1 **a** Kaplan-Meier curve depicting survival in patients with a new diagnosis of solitary brain metastasis (group 1) ($p = 0.363$). **b** Kaplan-Meier curve depicting survival in patients with a controlled systemic disease (group 2) ($p = 0.291$). **c** Kaplan-Meier curve depicting survival in patients with progressive systemic disease (group 3) ($p = 0.360$)

Tumor recurrence

Time between surgery and tumor recurrence was calculated and we distinguished local recurrence (at the resection lodge) from distant recurrence (other central nervous system location).

In our series of 30 SSM, there was no recurrence in 14 patients (46%). A local recurrence was seen in 9/16 patients. Mean time between surgery and recurrence was 11 months, 10 of these patients had recurrences within 8 months. Ten of 16 patients with recurrence died because of neurological deterioration. Three patients who are still alive did not have a recurrence.

Of our 16 patients with recurrence, 3 patients were diagnosed with CM on MRI (2 from lung carcinoma and 1 from transitional cell carcinoma) (Fig. 2).

In our group of 22 patients who underwent surgery for an ISM, there was no recurrence in 9 patients (41%). Two patients were lost on follow up after 421 days and 181 days. Eleven patients (50%) had recurrence. In 4 of them, recurrence was local at the site of resection, 4 had new tumors at a distance, and 3 developed diffuse metastasis.

Mean time between surgery and recurrence was 11 months, 5 of these patients had recurrences before 8 months. Six of 11 patients with recurrence died because of neurological deterioration.

Six patients developed CM (1 from breast carcinoma, 2 from lung carcinoma, 1 from colorectal carcinoma, and 2 from melanoma).

In both groups, cause of death was equally divided in both groups between general and neurological deterioration. Only four patients survived (living more than 3–10 years after surgery).

We calculated median survival and Kaplan-Meier curves of the patients with a SSM vs. ISM. Mean survival was 27 months for SSM and 18 months for ISM. No significant difference in survival time was seen.

Discussion

We compared the outcome in 30 SSM and 22 ISM, diagnosed with MRI, who underwent surgical resection and WBRT. Postoperative complications occurred more frequently in ISM and CM was more often seen in patients with an ISM (27% vs 10%). Although there was a trend showing a better overall survival in SSM, we could not confirm a worse outcome for patients with ISM.

Currently, ISM is considered to have a worse outcome compared with SSM [5, 11, 30, 38]. This has been ascribed to the small and deep surgical field in ISM. It has also been

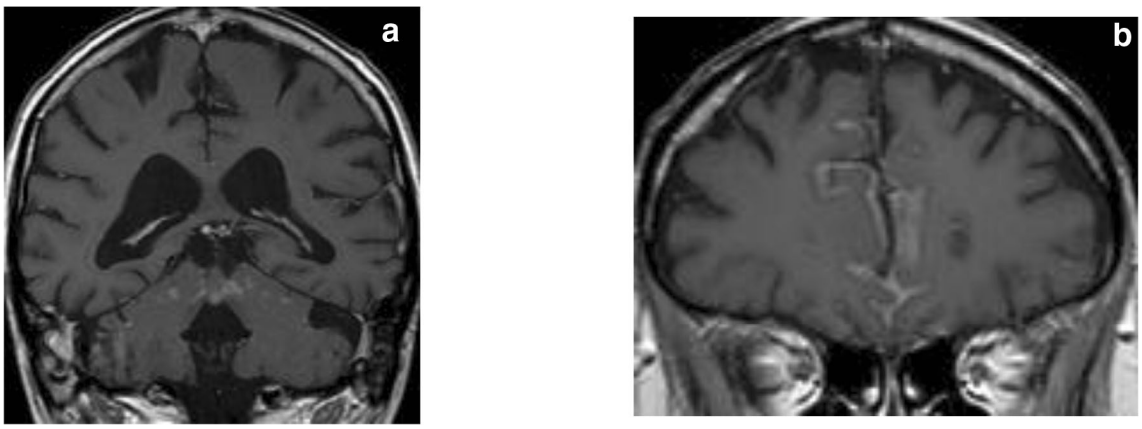

Fig. 2 Coronal T1 weighted spin-echo images after intravenous administration of Gd-DTPA showing infratentorial carcinomatous meningitis (**a**) and supratentorial carcinomatous meningitis (**b**)

suggested in the literature that time between diagnosis and surgery might be one of the explanations for a less favorable outcome in ISM. Patients with ISM would get a less extensive diagnostic work-up and more acute surgery because these tumors are more often associated with acute hydrocephalus and coma [34]. In our series, the mean time between diagnosis and surgery in SSM and ISM was 13 and 11 days, respectively. All our patients underwent a complete staging (including chest/abdominal CT and tumor markers) prior to surgery. Sunderland et al. reported a median interval of 8 days between diagnosis and surgery for patients with an ISM [34].

MRI is superior to CT and plays an essential role in confirming the presence of a solitary BM. In our series, multiple metastases were seen in 35/114 (31%) with a solitary metastasis on brain CT. To our knowledge, there are no studies that compared ISM and SSM diagnosed on high-resolution MRI. The studies reporting a worse outcome for ISM did not routinely use MRI and certainly not high resolution 1 mm slices [5, 11, 30, 38].

According to the literature, the diameter of the metastasis does not have implications on survival [7, 37]. This was confirmed in our series both for SSM and ISM. Tumor size appeared to have some influence on survival of patients, but these differences were not statistically significant. Surgery is certainly a treatment option in patients with controlled primary disease when size of the metastasis exceeds 3 cm or when it produces symptoms. For smaller lesions (less than 3 cm), radiosurgery and microsurgery would have the same benefit on overall survival and local control [21].

A gross total resection is a positive prognostic factor after surgical resection of a solitary BM [31, 35]. The integrality of surgical resection is often based on several operative findings while early postoperative MRI can also be used to support the surgeon's judgment [14]. The surgical technique might also play a role in the outcome. Several reports describe a higher incidence of CM with piecemeal resection (Cavitron Ultrasonic Surgical Aspirator, CUSA), compared with "en bloc" resection [32–34]. Whether CM can be attributed to the surgery is still under debate, and tumor type or location might also play a role [6]. One study compared cerebellar metastases treated with surgery or radiotherapy and found no difference in development of CM [6]. Lung cancer, breast cancer, and certainly melanoma would have a propensity to develop CM [2, 16, 28]. In our series, 9 of 52 patients developed CM. One of the striking observations in our study is the high number of patients (6/22) with an ISM who develop CM, compared with 3/30 patients with a SSM who develop CM. From our patients with an ISM and CM, 4 of 6 had surgery with the CUSA. In total, 5 of 9 patients with CM had a resection with the CUSA. Retrospective studies show that 25–67% of the patients developed CM after resection of the solitary cerebellar metastasis and quickly deteriorated, compared with 1–17% in patients with an SSM [20, 28].

Postoperative complications occur in 15–40% of patients who get surgery for a BM [1, 8]. We found that complications were more often seen in ISM (27%) than SSM (3%). Three patients were shunt-dependent after surgery, all three had an ISM. In a large series of single BM, a higher local recurrence rate was seen in patient who had undergone piecemeal resection and in tumor volumes exceeding 9.7 cm^3 [23]. The frequency of recurrence was similar in SSM (53%) and ISM (50%). Recurrence within 8 months after surgery for SSM and ISM was 27% and 22%, respectively. A reduction in the recurrence rate does not necessarily mean a prolonged survival but recurrence is important because of its influence on functional state of the patient [22, 38].

When classifying the patients according to the stage of the primary tumor, we saw a trend in group 1 (first diagnosis of BM) and group 2 (diagnosis of BM in controlled systemic disease): patients with SSM seemed to have a longer overall survival time than patients with ISM. In group 3 (diagnosis of BM in progressive systemic disease), we found the opposite effect, but perhaps this could be explained by the larger difference in number of patients with SSM and ISM in this group.

In our study, progressive systemic disease and neurological deterioration seemed equally important causes of death. In a large series of patients with BM, 57% died because of progressive systemic disease while 18% died of central nervous system progression [5, 22].

Strengths and limitations

The study design is retrospective and therefore prone to selection bias. Our inclusion criteria consisted of patients with a solitary BM on MRI who were eligible for surgery as first treatment. Therefore, our series does not reflect the epidemiological studies. In most epidemiological studies, the distribution between supratentorial and infratentorial BM is 90% vs. 10% [36]. The relatively small sample size is another limitation although single BM, certainly after the introduction of high-resolution MRI, occurs much less frequently than multiple BM. The heterogeneity of the primary tumor is a limitation due to the relatively low incidence of single BM. But the data quality was satisfactory and little data was lost. The MRI examinations were all obtained with the same state of the art protocol resulting in a reliable diagnosis of a single ISM or SSM.

Conclusion

We identified factors that play a role in the outcome after surgery in patients with ISM and SSM, and we found differences between ISM and SSM. But we could not confirm the worse prognosis in patients with ISM. Surgical resection plays

a major role in the management of solitary BM and the advances in surgical techniques, e.g., high-resolution operative microscopy, neuronavigation, and gross total resection with additional marginal resection may contribute to a better prognosis. Our observations are sufficiently relevant to initiate a prospective multicenter clinical trial to study the value of surgery and stereotactic radiosurgery and/or immunotherapy, in patients with SSM and ISM diagnosed on high resolution MRI, in order to assess the effectiveness of the treatment options on the overall survival in a large patient population with ISM and SSM.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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