Recurrent Brain Metastases: The Role of Resection of in the Era of Molecular Medicine

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Abstract

Purpose

To evaluate the efficacy of surgical resection for pretreated, recurrent brain metastases (BM) in the era of molecular oncologic medicine.

Patients and Methods:

In a retrospective single center study, patients were analyzed who had undergone surgical resection of recurrent BM between 2007 and 2019. Intracranial event-free survival (EFS) and overall survival (OS) were evaluated by Kaplan-Maier and Cox regression analysis.

Results

In total, 107 patients with different primary tumor entities and individual previous treatment for BM were included. Primary tumors comprised non-small cell lung cancer (NSCLC) (37.4%), breast cancer (19.6%), melanoma (13.1%), gastro-intestinal cancer (10.3%) and other, rare entities (19.6%). The number of previous treatments of BM ranged from one to four; these comprised: resection only, focal or whole brain radiotherapy, brachytherapy and radiosurgery. BM-related symptoms were present in 73.8% of the patients. Median pre-operative Karnofsky Performance Score (KPS) was 70% (range 40–100) which was improved to 80% (range 0-100) after surgery. The complication rate was 26.2% and two patients died during the perioperative period. Postoperative local radio-oncologic and/or systemic therapy regimens were applied in 67 (62.6%) patients. Median postoperative EFS and OS were 7.1 (95%CI 5.8–8.2) and 11.1 (95%CI 8.4–13.6) months, respectively. The clinical status (postoperative KPS ≥ 70 (HR 0.27 95%CI 0.16–0.46; $p < 0.001$) remained the only independent factor for survival in multivariate analysis.

Conclusion

Surgical resection of recurrent BM may improve the clinical status and thus OS, but is associated with a high complication rate; thus, careful patient selection is crucial.

Introduction

Due to rising medical standards and novel therapeutic regimens, the number of patients with brain metastases (BM) is increasing [1–4]. Although BM are considered, in principle, a fatal event for oncological patients, treatment paradigms are changing and affected patients are nowadays frequently treated with repeated non-invasive therapeutic procedures such as radiotherapy and systemic oncological treatments. While the role of neurosurgical resection of primary and symptomatic BM is clearly defined [5,

6], the application of surgery for recurrent BM, especially after previous multimodal treatments, remains an individual decision [7], particularly since underlying studies [8, 9] are scarce.

In the light of the available novel comprehensive oncological treatment regimens, including several types of focused radiotherapy and targeted medical treatments that generally lead to an increased overall survival (OS), the role of surgery in the context of relapse, especially for symptomatic BM, needs to be clearly defined.

Material And Methods

Selection of study population

For this retrospective, monocentric cohort study, we queried our database for patients who had undergone resection of previously treated, recurrent BM in our department between 2007 and 2019. The following parameters were identified: demographic/baseline characteristics (gender, age at time of diagnosis and at time of surgery of the recurrent lesions), tumor characteristics (type of primary tumor, local and systemic tumor status, number and location of recurrent BM, time to recurrence since initial cancer diagnosis, time to recurrence since initial diagnosis of BM), therapeutic interventions (previous treatment, types of adjuvant therapy, number of previous recurrences), clinical status (neurological symptoms, pre- and postoperative Karnofsky-Performance-Scale (KPS)), and outcome measures (surgery-related complications, time to further recurrence after surgery). Data were retrieved from the electronic hospital database and paper charts. The study was approved by the local ethical committee (reference number: 18–089).

Indication for surgery

Indication for surgery was based on suspected recurrent BM detected by magnetic resonance imaging (MRI) or, if required, amino acid positron emission tomography (PET). All decisions were made within an interdisciplinary institutional tumor board comprising board-certified neurosurgeons, neuro-oncologists, medical oncologists, neuro-radiologists, neuropathologists, and palliative care physicians. In general, criteria for (re-)operation were accessibility and size of the lesion allowing safe resection, good clinical condition, adjuvant treatment options (re-irradiation, chemotherapy, or molecular therapy), necessity for obtaining tissue diagnosis, rapid progression leading to neurological complications, or no remaining treatment options other than surgery. Histopathological diagnosis was made by the local Departments of Neuropathology or Pathology.

Surgical treatment and follow-up

The extent of resection was assessed by early postoperative MRI performed within 48 hours after surgery and classified as gross total resection when no residual contrast-enhancing tissue was visible on T1-weighted imaging. Any residual contrast enhancement was defined as subtotal resection. Clinical and radiological follow-up was performed in three-monthly intervals. Intracranial failure was defined as newly developing contrast enhancement in brain MR imaging.

Complications were classified according to the Common Terminology Criteria of Adverse Events (CTCAE) by the National Cancer Institute (NCI) [10, 11] (see Table 3).

Statistical analysis

For descriptive statistics, continuous values are given in median and range, ordinal and categorical variables are stated in numbers and percentages. Post-surgical survival time was calculated from the date of surgery to date of death or last follow-up; patients alive at the time of their last follow up were censored. Event-free survival (EFS) was assumed in the case of no intracranial relapse. Predictive variables for both endpoints were identified by univariate and multivariate analysis. For categorical variables, the log-rank test was used to identify covariates with an influence on EFS and OS and visualized in Kaplan-Meier plots. For continuous variables, Hazard ratios were calculated using Cox regression. P-values < 0.05 were considered statistically significant. Variables with a significant impact were included in a multivariate Cox regression model. All statistical analyses were performed using SPSS Statistics Version 25 (*IBM, Armonk, NY, USA*).

Results

Baseline parameters and demographics

The study included 107 patients with a median age of 61 (range 26–83) years at the time of operation. Forty-three patients (40.2%) were male. Primary tumor entities comprised non-small cell lung cancer (NSCLC) (37.4%), breast cancer (19.6%), melanoma (13.1%), gastro-intestinal tumor (GIT) (10.3%) and other, rare entities (19.6%). At the time of BM relapse, extracranial metastases were present in 61 (57.0%) patients. Detailed demographic and clinical data are displayed in Table 1.

Previous treatment and clinical status at time of recurrence

Previous cerebral treatment comprised one or more local and/or systemic therapies including surgery, whole brain radiation therapy (WBRT), focal/partial brain radiation therapy (fRT), stereotactic radiosurgery (sRS) and brachytherapy (BT). The number and detailed information on previous treatment modalities were recorded (Table 2). At the time of resection, 79 (73.8%) patients suffered from BM-related symptoms including vertigo, hemiparesis, cognitive impairment, epilepsy, and headache. The median preoperative Karnofsky performance scale (KPS) was 70 (range 40–100).

Surgical treatment, complications, and adjuvant treatment

At time of surgery 80 (74.8%) patients suffered from a single recurrent BM, 19 patients (17.8%) from oligo- (2–3) BM and eight patients (7.5%) from multiple (≥ 4) BM. Resection of the target lesion was complete (gross total resection) in 78 (72.9%) patients. Surgery was performed in all patients under general anesthesia with the aid of neuro-navigation, ultrasound, and intra-operative monitoring, if required. Surgery improved the Karnofsky performance scale to a median of 80 (0-100). After resection, adjuvant local treatment was administered in 67 patients (62.6%), comprising WBRT (n = 5), fRT (n = 49),

stereotactic radiosurgery (n = 11), or a combination of the latter two (n = 2). Medical treatment was initiated or continued in 37 (34.6%) patients (Table 2). Surgery-related complications occurred in 28 patients (26.2%) with two patients dying during the acute phase. Details on postsurgical complications and their grading are displayed in detail in Table 3.

Survival

In 51 patients (47.7%), a cerebral treatment failure was detected, resulting in a median EFS of 7.1 (95%CI 5.8–8.2) months. None of the factors analyzed influenced EFS.

At the time of analysis, 73 (68.2%) patients had died. Median OS time was 11.1 (95%CI 8.4–13.6) months. Three patients (2.8%) died within the first 30 days after surgery, two from surgical complications. In the remaining cohort, the causes of death were systemic disease progression in 12 patients (11.2%), cerebral progression in 37 patients (34.6%) and other causes in two patients (1.9%). In the remaining patients, the cause of death was unspecified.

In univariate analysis, a pre- and postoperative KPS ≥ 70 ($p = 0.002$ and $p < 0.001$) and neurological symptoms caused by BM ($p = 0.036$) were prognostic for survival, while all other parameters (age, primary, number of BM, location, previous treatment, application and type of local treatment, ongoing systemic treatment, extracranial status) showed no significant impact. In multivariate analysis only the postoperative clinical status (HR 0.207 95%CI 0.0816–0.3436; $p < 0.001$) remained independent.

Discussion

Due to the availability of effective systemic therapies and closer surveillance during follow-up, the number of patients diagnosed with recurrent BM is increasing [1–4]. However, the inevitable question of how to treat these patients adequately after cerebral progression still remains unsolved, especially for patients maintaining a good clinical condition over a longer period of time before BM recurrence [4]. Most studies with respect to treatment of recurrent BM focus on a single treatment option such as (re-) radiosurgery or re-irradiation [12].

Surgery is well established as a first-line treatment for larger and symptomatic BM. However, the role of surgery for pretreated, recurrent BM is not yet defined, and only scarce data, originating from the pre-molecular era, are available. Only a few studies have reported on the feasibility of (re-)surgery in patients with single or multiple recurrent BM [8, 9, 13, 14]. They included narrowly defined patient cohorts previously treated by either surgery [8, 15] or sRS [14, 16], and reported median survival rates after resection of between 7.5 and 11.5 months. With 11.1 months the survival rate in the present study was within the range of the previously reported data.

The high rate of fatal cerebral progression in this series compared to previous studies may be due to the fact that besides surgery, most therapeutic options are used, leading to a lack of salvage treatment in the case of further cerebral progression. As surgical resection may result in rapid symptom release by reducing the mass effect, the subsequent improvement in the patient’s clinical condition, possibly in

combination with a re-evaluation of the tumor's molecular status, may represent the major benefit of surgery. Since a fair clinical status is a prerequisite for radio-oncological and a tailored adjuvant treatment, this may positively influence the outcome, as observed before [17]. However, this benefit could not be observed with statistical significance for the patients in the present study.

Probably, the specific condition of this study's population offers an explanation since it comprises patients who had already undergone extensive oncological treatment. Possible subsequent development of resistance may leave few remaining therapeutic approaches.

In cases of extensive pretreatment by radiotherapy, resection might therefore be the only local treatment option left. As the cerebral progression partly reflects treatment failure of previous irradiation, the negligible impact of postoperative radiotherapeutic measures on either EFS or OS in this present study is not surprising.

The major argument for surgery in this patient cohort may be seen in the clinical improvement which is, in line with the current literature, the strongest predictor for further survival after recurrent BM treatment [4, 8, 16].

As opposed to the clinical improvement mentioned above, the postoperative complication rate was high and included a critical number of life-threatening complications. This is in contrast to other studies reporting on resection in the setting of initial BM diagnosis, where neurosurgery was usually well tolerated and proved to be feasible and safe [8, 14–16, 18, 19].

The high incidence of complications may be explained by the general condition of oncological patients. The underlying malignancy and/or multiple varied (systemic) pre-treatments would impair wound healing and hemostasis, and increase cardio-pulmonary complications [4, 20]. Furthermore, patient age was described as independently correlating with clinical outcome, since comorbidities are more common in elderly patients [4, 21, 22]. In this context, the indication for re-resection of BM must be based upon multidisciplinary consent that takes into account the patients´ general condition, the possible (and probable) clinical benefit, and the availability of further treatments.

Conclusion

Surgical resection of recurrent BM may improve patients´ clinical status and possibly indirectly prolong survival but carries a high risk for surgery-related complications. Thus, careful patient selection in a multidisciplinary comprehensive setting is mandatory.

Abbreviations

BM: brain metastases

BT: brachytherapy

CSF: cerebrospinal fluid

CTCAE: Common Terminology Criteria of Adverse Events

CTx: chemotherapy

EFS: event free survival

fRT: fractioned radiotherapy

GIT: gastro-intestinal tumor

HR: Hazard ratio

KPS: Karnofsky performance scale

MRI: Magnetic resonance imaging

NCI: National Cancer Institute

NSCLC: non-small cell lung cancer

OS: overall survival

PET: positron emission tomography

RCC: renal cell cancer

SCLC: small cell lung cancer

sRS: stereotactic radiosurgery

TT: targeted therapy

WBRT: whole brain radiation therapy

Declarations

Disclosure

All authors declare no conflict of interests.

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Tables

Table 1: Baseline demographic characteristics and parameters

Parameter	No.	%	Median	Range
Age at operation	75	70.1	61	26–83
≤ 65 years	32	29.9		
> 65 years				
Gender	43	40.2		
Male	64	59.8		
female				
Primary tumor	40	37.4		
non-small cell lung cancer	21	19.6		
Breast cancer	14	13.1		
Melanoma	11	10.3		
Gastro-intestinal tumorOther	21	19.6		
Extracranial disease	46	43.0		
Stable	61	57.0		
Non-stable				
Symptoms (multiple references possible)	19	17.8		
Cerebellar	11	10.3		
Cognitive	25	23.4		
Hemiparesis	14	13.1		
Seizures	22	20.6		
Headache	15	14.0		
Impaired vision	13	12.1		
Aphasia	18	16.8		
Others				

Table 2: Pre- and postsurgical treatment, surgery, and complications

Parameter	No.	%
Previous treatment	44	41.1
Resection	30	28.0
Radiotherapy	24	22.4
Whole brain radiotherapy	53	49.5
Partial brain radiotherapy	8	7.5
Stereotactic radiosurgery		
Brachytherapy		
Number of recurrent BM	80	74.8
1 BM	19	17.8
2–3 BM	8	7.5
≥ 4 BM		
Extent of resection	78	72.9
Gross total	29	27.1
Subtotal		
Adjuvant local treatment	40	37.4
None	67	62.6
Radiotherapy	5	4.7
Whole brain radiotherapy	49	45.8
Partial brain radiotherapy	11	10.3
Stereotactic radiosurgery	2	1.9
Combination	37	34.6
Postsurgical systemic therapy		
Cause of death (n = 73)	37	34.6
Neurological	12	11.2
Systemic	2	1.9
Others	22	20.6
unknown		

Table 3: Complications stratified according to CTCAE (Common Terminology Criteria of Adverse Events)

Complication	CTCAE grade	n
New neurological deficit	2	6
Wound healing disorder	2	5
Wound healing disorder requiring surgery (revision, external drain)	3	4
CSF disorder requiring surgery	3	3
Postoperative haemorrhage requiring intervention	4	1
Cerebral ischemia	4	1
Cerebral edema	4	1
Pulmonary embolism	3	2
Carotic artery dissection	4	1
Pneumonia, sepsis	3	2
Postoperative death	5	2

Figures

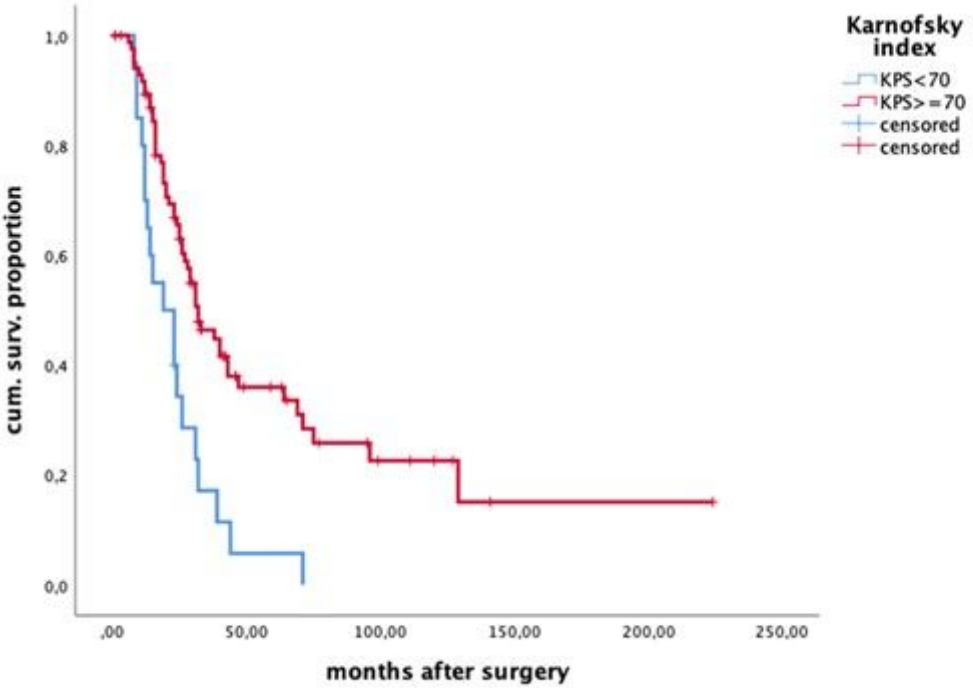

Figure 1

Overall survival (OS), depicting the impact of the clinical status after surgery. Kaplan-Meier plot.