Postoperative ischemic changes following brain metastasis resection as measured by diffusion-weighted magnetic resonance imaging

Clinical article

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Object. Brain metastases occur in 10% to 40% of patients harboring cancer. In cases of neurosurgical metastasis resection, all postoperative neurological deterioration should be avoided. Reasons for postoperative deficits can be direct tissue damage due to resection, hemorrhage, venous congestive infarcts, or arterial ischemic events leading to tissue infarction. The aim of this study was to evaluate whether postoperative ischemic infarctions occur in surgery for brain metastasis and to determine their influence on new postoperative neurological deficits.

Methods. Patients who underwent resection of brain metastases and had preoperative and early postoperative (within 48 hours) MRI scans, including diffusion-weighted imaging sequences and apparent diffusion coefficient maps, between January 2009 and May 2012 were included in this study. Clinical and histopathological data (histopathological results, pre- and postoperative neurological status, and previous tumor-specific therapy) were recorded.

Results. One hundred twenty-two patients (56 male, 66 female) who underwent resection of brain metastases were included. The patients’ mean age was 60 years (range 21–89 years). The mean time span from initial tumor diagnosis to resection of brain metastasis was 44 months (range 0–338 months). The mean preoperative Karnofsky Performance Status was 80% (exact mean 76% ± 17% [SD]), and the mean postoperative value was 80% (exact mean 78% ± 17%). Twelve (9.8%) of the 122 patients had postoperative permanent worsening of a neurological deficit or a new permanent neurological deficit; 44 (36.1%) of the 122 patients had postoperative ischemic lesions. When comparing patients with and without previous brain irradiation, 53.8% of patients with previous brain irradiation had ischemic lesions on postoperative imaging compared with 31.3% of patients without previous brain irradiation (p = 0.033). There was a significant association between ischemia and postoperative neurological status deterioration (transient or permanent); 13 (29.5%) of 44 patients with ischemic lesions had deterioration of their neurological status compared with 7 (9%) of the 78 patients who did not have ischemic lesions (p = 0.003).

Conclusions. This study demonstrates a high prevalence of vascular incidents in patients undergoing resection for metastatic brain disease. Patients harboring postoperative ischemic lesions detected by MRI have a higher rate of neurological deficits (transient or permanent). Patients who had previous irradiation therapy are at higher risk of developing postoperative ischemic lesions. A large number of postoperative neurological deficits are caused by ischemic incidents.

Key Words • diffusion-weighted imaging • apparent diffusion coefficient • brain tumor surgery • brain metastasis • oncology

Brain metastases occur in 10%–40% of patients harboring cancer. Therefore, metastatic brain tumors are a common problem faced by neurosurgeons, oncologists, and radiotherapists alike. The improvement of overall survival in patients with brain metastases requires the best possible conditions for local tumor control, which means resective surgery for a subset of patients.

Current guidelines recommend the resection of accessible single brain metastases or symptomatic metastases in cases of multiple metastases, followed by irradiation therapy (stereotactic and/or whole-brain irradiation).

In cases of neurosurgical metastasis resection, all

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
postoperative neurological deterioration should be avoided. Possible causes of neurological damage due to surgery are the resection of functional brain tissue, secondary events such as hemorrhages, or, as observed in glioma surgery, arterial ischemic events leading to infarction of eloquent brain tissue. Few authors have dealt with the assessment of vascular incidents following neurosurgical tumor resection.  

Recently, our group evaluated the incidence of postoperative infarctions after glioma resection and its role for the development of neurological deficits. However, a systematic approach dealing with metastatic brain disease has not yet been developed. Additionally, in surgery for brain metastases, the disclosure of causes of postoperative neurological deterioration is an important concern for the treating neurosurgeon, along with knowledge of possible postoperative ischemic lesions that could mimic tumor progression during further follow-up. The aim of this study is to evaluate the incidence of ischemic events following resection of brain metastases, the possible risk factors, and their influence on new postoperative neurological deficits.

**Methods**

Between January 2009 and May 2012, patients who underwent resection of brain metastases in our department and had preoperative and early postoperative (within 48 hours) MRI scans, including diffusion-weighted imaging (DWI) sequences and apparent diffusion coefficient (ADC) maps, as described in detail below, were included. Additionally, clinical and histopathological data (tumor grading, pre- and postoperative neurological status, and previous tumor-specific therapies) were recorded. Regarding the neurological status, a permanent neurological deficit was defined as a deficit still present after 6 weeks or at last follow-up.

This study was approved by the ethics committee of the Technische Universität München.

**Imaging**

MRI studies were conducted with a whole-body 3-T imaging system (Achieva 3T, Philips Electronics NV.) using an 8-channel head coil. Included were DWI and ADC maps. Through single-shot echo planar imaging (EPI) with 2 b values of 0 and 1000 sec/mm², DWI was acquired and isotropic diffusion-weighted images and ADC maps were calculated automatically with the following imaging parameters: repetition time (TR) 3388 or 8413 msec; echo time (TE) 55 msec; image resolution: 2 × 2 × 2 mm³ or 1.6 × 1.8 × 5 mm. The T2-weighted FLAIR images (TR/TE 494/10 msec) with and without intravenous administration of 0.1 mmol/kg of gadopentetate dimeglumine were conducted (27 axial slices, 4-mm thickness, 1-mm gap, plane resolution 0.9 × 0.9 mm²). Tumor location was classified as left- or right-sided and supratentorial, and the number of metastases was classified as single or multiple. Different cerebral lobes for supratentorial lesions (frontal, temporal, parietal, and occipital) were assessed. Location in or close to territories of perforating central arteries was documented.

The evaluation of MRI was conducted by a board-certified neurosurgeon and a neuroradiologist blinded to clinical course.

Postoperative, new DWI-hyperintense and ADC map–hypointense areas were classified as ischemic lesions on early postoperative MRI studies. Areas of restricted diffusion related to methemoglobin and small DWI-hyperintense rims at the resection cavity were excluded. “Arterial territory” (AT) infarctions were defined as areas of restricted diffusion, which resemble territories of the main branches of the anterior cerebral artery, middle cerebral artery, or posterior cerebral artery. Smaller infarctions also related to the tumor cavity were defined as “terminal branch” (TB) infarctions. The DWI-hyperintense areas, not resembling an arterial territory and not displaying a terminal branch infarction, we defined as “venous infarction,” resembling venous congestive infarction with a round or oval area of restricted diffusion, partial bleeding, and perifocal edema (Fig. 1). The approach for definition of infarctions was analogous to that used in our previous published classification for patients with gliomas. In this patient cohort, no other/venous infarctions occurred. Infarct volume was assessed by semiautomatic segmentation with iPlan Net Cranial 3.0.1 (Brainlab). Evaluation of imaging was conducted by a neuroradiologist and a neurosurgeon independently, both blinded to the clinical course and course of the operation.

**Statistical Evaluation**

Descriptive data analysis, Pearson correlation, and Pearson chi-square tests were conducted by IBM SPSS Statistics. We considered a difference with an error probability of less than 0.05 as statistically significant.

**Patients and Clinical Data**

One hundred twenty-two patients of 175 patients who underwent resection of brain metastases between January 2009 and May 2012 had preoperative and early postoperative MRI studies and were included in our study. For the remaining 53 patients imaging data were not available; reasons included MRI not being possible due to implantation of a cardiac pacemaker and other contraindications, surgery having been performed on an emergency basis without preoperative MRI, postoperative imaging having been performed beyond the 48-hour time window, or other MRI contraindications. Of the 122 patients included in the study, 56 were male and 66 were female. Their mean age at the time of surgery was 60 years (range 21 to 89 years). The mean time span from diagnosis of brain metastasis to neurosurgical resection was 3 months (range 0 to 338 months). The mean time span from diagnosis of brain metastasis to neurosurgical resection was 3 months (range 0 to 36 months; mean 5 months for patients already previously treated [radiation and surgery] and 0.8 months for patients without prior treatment).

The origins of neoplasms were as follows: breast cancer in 32 cases; lung in 20 (non–small cell lung carcinoma in 14, small cell lung carcinoma in 6); upper or lower
gastrointestinal tract tumors in 18; melanoma in 17; renal cell carcinomas in 8; and other origins in 27 cases. A total of 65 patients presented with solitary brain metastases; 57 patients had multiple metastases. The mean preoperative Karnofsky Performance Status was 80% (exact mean 76% ± 16%; range 20%–100%) and the mean postoperative value was 80% (exact mean 77% ± 17%; range 20%–100%). Postoperatively, 12 (9.8%) of the 122 patients had permanent worsening of a neurological deficit or a new neurological deficit (worsening of hemiparesis in 4 cases, worsening of arm paresis in 1 case, worsening of facial paresis in 1 case, new hemiparesis in 5 cases, worsening of sensory aphasia in 1 case). Eight (6.6%) of the 122 patients harbored mild postoperative transient deficits (facial paresis in 1 case, hemiparesis in 4 cases, dysarthria in 1 case, arm paresis in 1 case, cognitive dysfunction in 1 case). Seventy-seven (63.1%) of the 122 patients had a preoperative neurological deficit; this was improved postoperatively in 32 patients. Therefore, 26.2% of the patients improved due to the surgery.

Twenty-six patients received brain irradiation therapy prior to surgery; 12 patients had previously undergone resection of brain metastases. The main location of the resected metastases was frontal lobe in 49 cases, parietal lobe in 28, temporal lobe in 15, occipital lobe in 9, frontal-temporal in 1, frontoparietal in 1, and temporoparietal in 1. In 18 patients, infratentorial metastases were resected.

Ischemia and Its Risk Factors

Of the 122 patients, 44 had new postoperative ischemic lesions (36.1%, 6 AT infarctions, 28 TB infarctions, 0 venous infarctions). Mean volume of infarction was 2.26 cm³ (± 6.00 cm³). Mean infarct volume in patients with AT infarctions was 9.4 cm³ (± 15 cm³) and 1.2 cm³ (± 1 cm³) in patients with TB infarctions. The difference was statistically significant according to t-tests (p = 0.002). Comparing patients with and without previous brain irradiation, 53.8% of patients with previous brain irradiation had ischemic lesions, compared with 31.3% of patients without previous brain irradiation. According to the chi-square test, the difference was statistically significant (p = 0.033). Infarct volume had a positive correlation with previous radiotherapy (Pearson correlation coefficient 0.300, p = 0.048 [2-tailed]), which was statistically significant.

Considering only patients without previous surgery, patients who had already undergone brain irradiation (Fig. 2) had a significantly higher prevalence of new postoperative ischemic lesions 55% (10 of 18 patients) compared with 30.3% (28 of 92 patients) of patients without brain irradiation (chi-square test, p = 0.04). The preoperative Karnofsky Performance Status revealed no statistically significant correlation to the rate of ischemic lesions. Age had a significant correlation to the occurrence of postoperative ischemic lesions, according to the Pearson correlation (0.200, p = 0.027).

Previous chemotherapy, infra- or supratentorial tumor location, single or multiple brain metastases, anatomical location according to cerebral lobes, previous surgery, and time span of initial tumor diagnosis to neurosurgical metastasis resection had no statistically sig-
significant influence on the rate of postoperative ischemic lesions. Additionally, histopathological tumor entity had no influence on the rate of ischemic lesions in our patient cohort.

Ischemia and Neurological Deficits

When we compared the rate of postoperative neurological status deterioration (transient or permanent) in patients with and without ischemic lesions on postoperative imaging, the rate was 9% in the patient group without ischemia (7 of 78 patients) compared with 29.5% in the group with ischemia (13 of 44 patients); the between-groups difference was highly statistically significant (chi-square test, \( p = 0.003 \)). The rate of permanent neurological deterioration was 5.1% (4 of 78 patients) among patients without postoperative infarction compared with 18.2% (8 of 44 patients) in the group with postoperative infarctions (Fig. 3); this difference was also statistically significant (chi-square test, \( p = 0.02 \)). In 11 (55%) of the 20 patients with transient or permanent neurological deterioration, neurological impairment was explainable by the infarction and its location. In 7 (58.3%) of the 12 patients suffering from permanent neurological deterioration, the neurological deterioration could be explained by infarction. The remaining 5 patients suffered from either the worsening of a neurological deficit associated with a tumor location in eloquent tissue or a new visual field defect (which are both explainable by direct tissue damage).

Discussion

The present study demonstrates a high incidence of vascular incidents in patients undergoing resective surgery for brain metastases. Patients harboring postoperative ischemic lesions detected by MRI have a higher rate of transient or permanent neurological deficits. Patients who underwent previous irradiation therapy are at higher risk of developing postoperative ischemic lesions. In a substantial number of cases, postoperative neurological deficits are clearly caused by ischemic incidents.

The therapeutic goal in surgery for patients with brain metastases is improvement of clinical symptoms as a result of the removal of space-occupying lesions or a reduction of edema, as well as improvement of local control and subsequent improvement of overall survival. The introduction of any neurological deterioration due to surgery might conflict with this aim. In our patient cohort, permanent neurological deterioration due to surgery was observed in 9.8% of the patients (predominantly aggravations of a preoperative neurological deficits), which is comparable to what has been reported in other publications. Numerous publications on resection of glioma address the issue of preservation of function, whereas for metastatic brain disease, the issue is poorly evaluated, possibly due to the belief that brain metastases have a noninfiltrative growth pattern, and, therefore, the rate of neurological deficits is believed to be lower. Nevertheless, the percentage of patients suffering from postoperative ischemic lesions following metastasis resection was similar to the incidence that we and most other authors have observed for glioma resection. Ulmer and colleagues observed postoperative ischemic lesions in up to 70% of patients, Smith and colleagues found lesions in 64%, Dützmann et al. in 26%, and we found postoperative ischemic lesions in 31% of patients who underwent resection of newly diagnosed glioma and 80% of patients who underwent resection of recurrent glioma. Khan and colleagues evaluated a heterogeneous group of patients harboring different intracranial lesions and found that only 19% had postoperative ischemic lesions. This study included 82 patients in total, with only a small number of intracranial metastases. Considering all publications on new ischemic lesions, the methodological differences (selection of MRI sequences, definition of ischemia) seem to account for most of the differences in the incidence rates for postoperative ischemic lesions.

Factors influencing the occurrence of ischemic lesions in the present study were age and previous radiation therapy. Since the incidence of cerebrovascular disease increases with age, an increase of postoperative infarctions with increasing age could be suspected and was seen in our patient cohort.

Previous radiotherapy significantly increased the risk
for new postoperative ischemic lesions and their size in our patient cohort. These findings are well in line with findings of recent studies dealing with stroke in brain tumor survivor patients, which highlight brain irradiation therapy as a risk factor for cerebrovascular disease as well.3,12

Since nowadays most decisions regarding therapy planning for patients with metastatic brain disease are made by an interdisciplinary board of oncologists, neurosurgeons, and radiotherapists, the potential higher risk of neurological deterioration in patients receiving irradiation therapy before tumor resection might influence the choice of therapeutic modality.

Observing a similar rate of ischemic lesions in patients with metastatic brain disease and patients with glioma could lead to the conclusion that the differences in the pattern of vascular supply and growth of brain metastases and gliomas are less than suspected or that aspects of the neurosurgical procedures (tissue preparation, tumor resection, pressure of spatalia), which are alike in glioma and metastasis surgery, are largely responsible for the origin of postoperative ischemic lesions. A significant influence of postoperative ischemic lesions on the rate of postoperative neurological deficits was seen in the present study, comparable to that seen in patients with intracranial gliomas.10 Therefore, in surgery for metastatic brain disease, perioperative infarction—not only resection of eloquent cortical tissue or fiber tracts—predominantly provokes neurological deficits. Meticulous surgical approaches sparing vascular structures have to be implemented as well as frequent removal of spatalia and irrigation with warm solution. Even elevation of blood pressure or the use of vasoactive substances should be considered.

Comparable to its use in the treatment of glioma patients, postoperative MRI serves as a baseline for evaluation of future tumor progression in patients with brain metastases. The differentiation of tumor progression and treatment-related changes for patients with brain metastases is a subject of ongoing debate.7 Therefore, postoperative DWI might be valuable as a way to differentiate contrast enhancement during follow-up as postoperative ischemic areas/treatment-related changes, and not as tumor progression.7,24

Conclusions

In this study, we demonstrated a high incidence of vascular events in patients undergoing resection of metastatic brain disease. Patients harboring postoperative ischemic lesions detected by MRI have a higher rate of neurological transient and permanent deficits. Patients who underwent previous irradiation therapy are at higher risk of developing postoperative ischemic lesions. A substantial number of postoperative neurological deficits are caused by ischemic incidents. In surgery for metastatic brain disease, avoidance of damage to vascular structures, in addition to preservation of eloquent tissue, is important for reducing the risk of postoperative neurological deterioration. Regarding the timing of radiation therapy, the higher rate of neurological deficits in patients who had already undergone irradiation before brain metastasis resection should be considered in the planning of the therapeutic strategy.

Disclosure

The authors have no financial interest in the subject under discussion, nor did they receive any financial support for the present study.

Author contributions to the study and manuscript preparation include the following: Conception and design: Gempt, Gerhardt, Hüttenger, Ryang, Wostrack, Meyer, Förschler, Ringel. Acquisition of data: Gempt, Gerhardt, Toth, Hüttenger, Wostrack. Analysis and interpretation of data: all authors. Drafting the article: Gempt, Gerhardt, Toth, Hüttenger, Ryang, Wostrack, Meyer, Ringel. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Gempt. Statistical analysis: Gempt, Wostrack, Ringel. Administrative/technical/material support: Ringel. Study supervision: Meyer, Förschler, Ringel.

References

14. Kalkanis SN, Kondziolka D, Gaspar LE, Burri SH, Asher AL,


