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CLINICAL ARTICLE

Proof of principle: supramarginal resection of cerebral metastases in eloquent brain areas

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Abstract
Background Cerebral metastases are not sharply delimitatable; therefore, microsurgical circumferential stripping of intracerebral metastases is often insufficient for preventing local tumor recurrence. Supramarginal resection significantly improves local tumor control but was suggested not to be suitable for metastases in eloquent brain areas. Therefore, we retrospectively analyzed a series of patients with cerebral metastases situated in eloquent areas for newly occurring neurologic deficits after supramarginal resection performed as awake surgery.
Methods A retrospective analysis was performed for all patients who underwent supramarginal resection for a cerebral metastasis performed as awake surgery between June 2011 and April 2012. All metastases were localized in eloquent brain areas. Pre- and postsurgical neurologic status was documented as well as data regarding the primary cancer and histopathologic data. Postoperative MRI within 72 h was scheduled routinely to verify complete resection.
Results A total of 19 patients underwent awake surgery for a cerebral metastasis in eloquent brain areas. Surgery was well tolerated in all patients. Neurologic symptoms improved in five patients after surgery. In three patients, neurologic deficits existing before surgery worsened. The postoperative median National Institute of Health Stroke Scale (NIHSS) score did not differ from the preoperative value.
Conclusions Awake surgery is a feasible tool for metastases in eloquent areas, minimizing postoperative neurologic deficits and morbidity. Therefore, eloquently situated metastases may also be eligible for supramarginal resection. Further studies are needed in order to analyze the benefit of this method in achieving better tumor control.

Keywords Awake surgery · Cerebral metastases · Resection · Function

Introduction

Cerebral metastases were initially believed to be sharply delimitated from the surrounding tissue. Neurosurgical standard therapy is a microsurgical circumferential stripping

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from the surrounding brain tissue, which is often followed by whole brain radiation. However, the vast majority of cerebral metastases do not clearly border surrounding brain tissue, but exhibit a tongue-like expansion into the adjacent brain tissue, in some cases displaying an infiltrative growth pattern [2, 8, 11]. Yoo and co-workers extended resection to a depth of about 5 mm after complete microsurgical resection of cerebral metastases, achieving significantly improved tumor control [24]. This concept, referred to as microscopic resection or supramarginal resection, improves local tumor control but was deemed unsuitable for eloquently situated metastases, as the risk of neurologic deficits was estimated as being too high [24].

Awake surgery including functional brain mapping by cortical and subcortical stimulation is a tool in glioma surgery to prevent new postoperative neurologic deficits and to maximize the extent of surgical resection. However, the impact of awake surgery in metastasis resection has yet to be evaluated. Here, we retrospectively analyzed a series of 18 patients with eloquently situated metastases for newly occurring neurologic deficits after microsurgical supramarginal resection performed as awake surgery (Fig. 1).

Material and methods

We reviewed the charts of patients who underwent awake surgery for a cerebral metastasis between June 2011 and April 2012 at our tertiary care center. All patients included in the this analysis fulfilled the following criteria: (1) indication for surgical resection of an intracranial mass; (2) eloquent location; (3) intraoperative supramarginal extension to a depth of about 5 mm after complete microsurgical resection; (4) postoperative confirmation of complete surgical resection by an early MRI within 72 h after surgery; (5) histopathologic diagnosis of a cerebral metastasis. Systematic biopsy sampling of the margins was not performed as it was thought to be too risky. Intraoperatively, an eloquent brain region was defined according to the literature as a cortical or subcortical brain area at which we expect intraoperative stimulation to elicit changes in neurologic conditions (particularly regarding speech, movement and tactile sensation) or to elicit a response in electrophysiological recordings in corresponding areas [6].

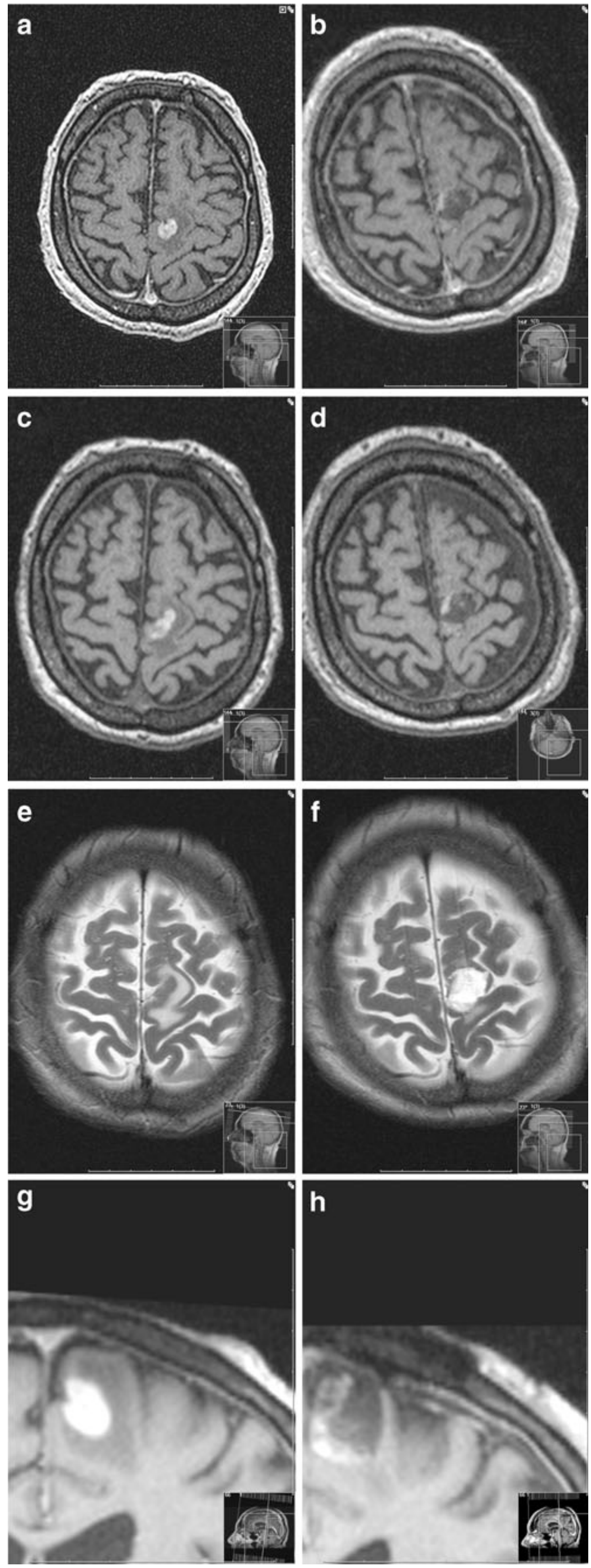

Fig. 1 Supramarginal resection of a precentrally situated metastasis. ▶ MRI scans of a 71-year-old patient suffering from a precentrally situated metastasis of a malignant melanoma. The patient underwent supramarginal resection. Postoperatively, he suffered from a temporary supplementary motor area syndrome, which completely improved within 3 weeks. Axial preoperative non-contrast-enhanced and contrast-enhanced T1 images (**c**, **a** respectively), axial postoperative non-contrast-enhanced and contrast-enhanced T1-images (**d**, **b** respectively), and axial pre- and postoperative T2 images (**e**, **f**) are shown. Supramarginal resection becomes obvious in the pre- and postoperative coronal MPR images (**g**, **h**)

Technique of awake surgery

Preoperative preparation was performed by neurosurgeons. 5-ALA was administered 3 h prior to surgery at a dose of 20 mg/kg body weight p.o. as described elsewhere [8, 21]. Before surgery, patients were positioned in the park bench position. The head was fixed in a Mayfield fixation device after administration of local anesthesia. Surgery was performed in an asleep-awake-asleep protocol. For the asleep phases, total intravenous anesthesia with propofol and remifentanil was administered under controlled ventilation via laryngeal mask. After opening of the dural skin, patients were wakened. During the surgical approach and resection, cortical and subcortical levels were electrically stimulated with standardized 60-Hz stimulation, and, more recently, a frequency train of five stimulations was implemented. Motor, sensory and language functions were monitored. A standard white-light-assisted, microsurgical circumferential resection of the cerebral metastasis was performed. Resection was extended to a depth of about 5 mm after complete microsurgical resection if no new neurologic deficit could be induced by cortical and subcortical stimulation. The cerebral metastasis as well as the surrounding tissue was examined for 5-ALA-derived fluorescence.

Control of extent of surgical resection within 72 h after surgery

The extent of surgical resection was verified by an early postoperative contrast-enhanced MRI within 72 h after surgery.

Data collection and statistical analysis

The standard neurologic status and National Institute of Health Stroke Scale (NIHSS) score was evaluated before surgery, the first day after surgery and before discharge. Epidemiological data (age, gender) and data regarding the tumor location, primary tumor (first diagnosis, other metastases), extent of surgical resection and complications associated with awake surgery were collected if available. Descriptive statistics were performed using the IBM SPSS Version 19. P values of less than 0.05 were considered significant (chi^2 test). Adjustment for multiple testing was not performed.

Results

Patients

Between June 2011 and April 2012, 92 patients with cerebral metastases were treated in our department, of which 19 (7 female; 12 male) underwent extended resection of their cerebral metastases as awake surgery. The median age of the patients was 59 years (range: 36–83 years). Clinical data are summarized in Table 1. One patient had two eloquently situated metastases, which were both removed in one awake surgery procedure.

Seven metastases showed ALA-derived fluorescence whereas 11 metastases were ALA negative. ALA-derived fluorescence data of one patient were not available. Sixteen of 19 patients were scheduled for subsequent radiotherapy; 3/19 patients declined subsequent radiotherapy. In five patients not included in this study, supramarginal resection of eloquently situated metastases was initially attempted but could not be achieved intraoperatively. Here, intraoperative testing (sub-cortical stimulation) revealed that further extension of resection to a supramarginal resection would have most likely led to new neurologic deficits. None of these five patients displayed a worsening of the NIHSS scoring postoperatively.

Twelve patients suffered from an adenocarcinoma, five from a malignant melanoma, one from a small cell neuroendocrine tumor and one from an embryonal carcinoma. The primary tumor was identified as a bronchial carcinoma in six patients; a malignant melanoma in five patients; a mamma carcinoma in two patients; and an endometrial cancer, a cancer of the sublingual gland and a germ cell tumor in one patient each. In one further patient, the primary tumor could not be identified (carcinoma of unknown primary) despite extensive diagnostic procedures.

Pre- and postoperative neurologic deficits

After supramarginal resection of eloquently situated metastases, none of the patients suffered from new permanent neurologic deficits. Extensive neurologic examination was performed to evaluate neurologic deficits at the time of admission and discharge: Before surgery, six patients suffered from hemiparesis, four patients from dys- or aphasia, three patients from disturbances of coordination, one patient from seizures and one from Gerstmann syndrome. Some patients exhibited more than one neurologic symptom while five patients displayed no neurologic deficits. In these patients, the cerebral tumor was detected during standard tumor staging. Median preoperative NIHSS score was 1 (range: 0–12, standard deviation: 2.8).

None of the patients suffered from new permanent neurologic deficits after surgery of masses in eloquent brain regions; however, 3/19 patients (15.7 %) displayed temporarily worsened neurologic deficits [hemiparesis due to supplementary motor area (SMA) syndrome and disturbances of fine motor skills], which we could not detect intraoperatively. Additionally, the median postoperative NIHSS score measured on the first postoperative day was unchanged.

Table 1 Summary of clinical data

No.	Age	Gender	Histopathological diagnosis	Primary site	Location	Side	AIF	Preoperative deficite	New postop. deficit	Pre NIHSS	Post NIHSS
1	63	F	Small cell neuroendocrine tumor	BC	Precentral	Left	Pos	Dysphasie, hemiparesis	None	12	9
2	72	F	Amelanotic malignant melanoma	Malignant melanoma	Parieto-temporal	Left	Pos	Gerstmann syndrome, sensoric aphasia	None	0	0
3	42	F	Adenocarcinoma	BC	Parietal	Left	Neg	Dysphasia	None	0	0
4	83	M	Adenocarcinoma	CUP	Central	Left	Neg	Hemiparesis	None	4	4
5	59	F	Adenocarcinoma	Mamma	Central	Right	Neg	Seizure, hemiparesis right	None	1	1
6	53	F	Adenocarcinoma	BC	Postcentral	Right	Pos	None	None	0	0
7	71	M	Malignant melanoma	Melanoma	Central	Left	Neg	Apraxia, coordination deficit	None	1	0
8	42	F	Adenocarcinoma	Mamma	Parietal	Right	Pos	Dysdiadochokinesis	None	3	2
9	55	M	Adenocarcinoma	BC	Central	Left	Pos	Apraxia, coordination deficit	None	1	1
10	63	M	Adenocarcinoma	BC	Precentral	Left	Pos	Hemiparesis	Worsened hemiparesis	4	6
11	45	F	Malignant melanoma	Malignant melanoma	Parietal	Right	Neg	Aphasia	More aphasia	0	1
12	58	F	Adenocarcinoma	Glandula sublingualis cancer	Precentral	Right	Neg	Hemiparesis	None	4	2
13	67	F	Malignant melanoma	Malignant melanoma	Temporo-occipital	Right	Neg	None	None	0	0
14	57	F	Adenocarcinoma	Endometrial cancer	Fronto-Opercular	Left	Neg	None	None	0	0
15	61	M	Adenocarcinoma	BC	Precentral	Right	Neg	None	None	0	0
16	61	F	Adenocarcinoma	BC	Central	Right	Pos	None	None	0	0
17	36	M	Embryonal carinoma	Germ cell tumour	Fronto-opercular	Left and right	N.d.	Hemiparesis	None	4	3
18	56	M	Adenocarcinoma	BC	Central	Right	Neg	Hemiparesis	None	2	2
19	71	M	Malignant melanoma	Malignant melanoma	Precentral	Left	Neg	None	Hemiparesis	2	6

NIHHS National Institute of Health Stroke Scale

Postoperative NIHSS scores worsened in 3 patients, improved in 5 patients and were unchanged in 11 patients.

Extent of tumor resection

Complete tumor resection was verified in all patients by a postoperative MRI within 72 h after surgery.

Discussion

Awake surgery is an established procedure in surgery of malignant gliomata in eloquent areas minimizing perioperative morbidity and maximizing the extent of surgical resection [3, 14, 15]. Despite differences in surgical techniques of malignant glioma and metastasis resection, this tool also was recommended for resection of cerebral metastases in eloquent areas [20]. This study provides the first data on the outcome of supramarginal resection of eloquently situated metastases performed as awake surgery.

Morbidity associated with awake surgery in our series

Thirty-day mortality of patients who underwent craniotomy for cerebral metastases was suggested to be as high as 3.8 % [10, 17, 19]. Overall morbidity was 32 % and neurologic morbidity was 8.5 % in a series of 400 craniotomies for intra-axial neoplasms including 194 cerebral metastases [19]. For standard microsurgical resection of cerebral metastases, perioperative morbidity ranges below 10 % [9, 10]. For metastases situated in eloquent brain areas, perioperative morbidity is likely higher. However, the present data reveal that awake surgery of cerebral metastases located in eloquent brain areas could be a useful tool in preventing neurologic deficits. In our study, no patients died within 30 days after surgery, and only 3 out of 19 patients (15.7 %) displayed worsened neurologic deficits after surgery. These deficits were temporary and improved within 1 week. Therefore, no patients suffered from new permanent neurologic deficits after surgery of masses in eloquent brain regions. One patient developed supplementary motor area syndrome after surgery. Surgeries of gliomata in the SMA frequently lead to SMA syndrome, which usually has a good prognosis [1, 7, 18, 22]. Onset of neurologic deficits due SMA syndrome is usually 30 min after tumor resection and therefore cannot be detected intraoperatively [4, 5].

Awake surgery as a tool for cerebral metastases?

Local recurrence of cerebral metastases at their original site is usually related to failure of the initial therapy to completely remove and destroy the metastasis [12]. Therefore, local recurrence of cerebral metastases after surgery is the consequence of incomplete surgical resection. Studies systematically investigating the extent of surgical resection of cerebral metastases by an early postoperative MRI are needed. However, local recurrence of surgically resected cerebral metastases without subsequent radiation therapy was estimated to be about 50 % [13, 24]. The high rate of local recurrence of cerebral metastases is likely due to their previously described growth pattern, which renders complete circumferential resection difficult. Achievement of tumor control by surgical resection without additional therapy is in the range of 50 %, disastrous and the reason for the recommendation of subsequent whole-brain radiation. Whole-brain radiation significantly improves local tumor control but can elicit severe neurocognitive deficits [12, 13, 16, 23]. Improving the extent of surgical resection may enable better local tumor control superseding that of resection with subsequent whole-brain radiation. Therefore, incomplete resection of cerebral metastases represents a serious problem and complete resection of cerebral metastases a surgical challenge.

Recently, the impact of 5-ALA fluorescence-guided resection of cerebral metastases in detecting tumor tissue locally infiltrating adjacent brain tissue was evaluated [8]. The tumor could be verified in the fluorescent tumor bed after circumferential metastasis resection in only one third of patients [8]. However, less than 40 % of metastases showed ALA-induced fluorescence in the present study. Therefore, ALA-fluorescence does not allow reliable identification of infiltrating tumor tissue.

The effect of supramarginal resection in achieving better tumor control has been shown in a retrospective single-center study including 94 patients [24]. Extended resection to a depth of about 5 mm after complete microsurgical resection of cerebral metastases enables significantly improved local tumor control compared to standard gross total resection [24]. Interestingly, the local recurrence rate of local metastases in patients who underwent supramarginal resection without subsequent radiotherapy did not significantly differ from those patients who underwent standard resection with subsequent radiotherapy [24]. However, this was deemed unsuitable for metastases in eloquent brain areas. Our present analysis reveals that awake surgery may represent a promising approach for patients with metastases in eloquent brain areas. However, one must note that supramarginal resection is not suitable for all patients with metastases in eloquent brain areas (19 out of 24 patients in this study). Nevertheless, the efficiency of this method in improving local tumor control must be evaluated in greater detail by future studies.

Conclusion

Awake surgery is a feasible tool for resection of metastases in eloquent areas, minimizing postoperative neurologic deficits and morbidity. Therefore, eloquently situated metastases may also be eligible for supramarginal resection. Further studies are necessary in order to evaluate the efficiency of this method in improving tumor control.

Conflicts of interest None.

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