Review Article

Neurosurgical Interventions for Cerebral Metastases of Solid Tumors

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Summary

Background: Metastases are the most common malignant tumors affecting the central nervous system and occur in 20–40 percent of patients with solid systemic tumors. The aim of this review is to discuss the role of neurosurgical procedures in a modern, multidisciplinary treatment approach.

Methods: An expert panel of neurosurgeons, neurologists, and radio-oncologists conducted a selective literature review on neurosurgical interventions for the diagnosis and treatment of cerebral metastases. Original articles, meta-analyses, and systematic reviews were included.

Results: There is a lack of prospective randomized studies. Based on retrospective case series, international guidelines recommend the harvesting (if required, stereotactically guided) of tissue for histological and molecular diagnosis in cases of unknown or possibly competing underlying systemic malignant diseases, in cases of suspected tumor recurrence, and with regard to the evaluation of targeted therapies taking into account molecular heterogeneity of primary and secondary tumors. Surgical resection is particularly valuable for the treatment of up to three space-occupying cerebral metastases, especially to achieve clinical stabilization to allow further non-surgical treatment. For cystic metastasis, a combination of stereotactic puncture and radiotherapy may be useful. Meningeal carcinomatosis can be treated with intrathecal medication via an intraventricular catheter system. Ventriculo-peritoneal shunts represents an effective treatment option for patients with tumor-associated hydrocephalus.

Conclusion: Neurosurgical procedures are of central importance in the multimodal treatment of cerebral metastases. The indications for neurosurgical interventions will be refined in the light of more effective radiation techniques and systemic treatments with new targeted therapeutic approaches and immunotherapies on the horizon.

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Metastases of solid tumors are the most common tumors in the brain, with an incidence ten times that of primary brain tumors (1, 2, e1–3). The most common entities are lung cancer (40–60%), breast cancer (10–41.5%), and melanoma (10–30%) (e3). Brain metastases are already found at the time of initial diagnosis in 23–28% of cases (1, 2, e1). The rising incidence of brain metastases can be explained by the aging of the population, better treatment of primary tumors (particularly with new pharmacotherapeutic approaches), and better diagnostic imaging. The median survival of patients with brain metastases has improved over the past 30 years from five to 8–16 months, depending on the entity (3).

The main therapeutic modalities are open microneurosurgery, radiosurgery, fractionated stereotactic radiotherapy, and antitumor pharmacotherapy. These are increasingly used in combination (4, 5). Radiation techniques have been progressively refined to

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mitigate their side effects and complications, and new types of drug treatment are available, including immune modulation. The continuing evolution of the available therapies necessitates a critical risk-benefit analysis of the role of neurosurgery within a multimodal approach to treatment (6, e4). Surgery plays a well-established role in the alleviation of acute manifestations due to solitary space-occupying brain metastases in patients whose extracerebral tumor status is stable (either without current treatment, or under ongoing treatment) (4, e5). Yet surgery can also be useful under some circumstances in patients with advanced cancer, and may even be a prerequisite to further treatment as part of a multimodal treatment plan (3–5). The histopathological and molecular genetic characterization of metastases, and especially of recurrent metastases, is becoming increasingly important in the context of new options for targeted therapy (7, 8, e6). Interdisciplinary coordination of treatment in tumor boards and a profound understanding of the available treatment options are needed in order to determine the optimal treatment for each individual patient. In this review, we discuss the role of neurosurgical procedures in the context of the multimodal management of brain metastases.

Methods

A selective literature search in the PubMed and Cochrane databases was carried out by three independent experts with the search terms "brain," "CNS," "central nervous system," "metastasis," "secondary," "tumor," "cancer," "lung cancer," "melanoma," "surgery," "resection," "operation," "radiotherapy," "radiosurgery," "outcome," and "survival." The final reference list was compiled by consensus between the authors. Only articles in German or English were included in the literature search.

Results

The histological and molecular characterization of brain metastases

In a number clinical situations, neurosurgical intervention is primarily useful for diagnostic purposes:

- if the clinical and imaging findings do not yield a clear diagnosis;
- if the primary tumor is unknown;
- if the patient has more than one kind of cancer;
- and if the patient has a type of cancer that only rarely metastasizes to the brain (4, 5).

Obtaining tissue for histopathological diagnosis may also be indicated when the imaging studies do not alone suffice to distinguish treatment sequelae, such as radionecrosis or pseudoprogression after immunotherapy, from tumor progression (9, 10, e7). For deep-seated tumors in areas of the brain where resective surgery would entail high risk, tissue can be obtained in minimally invasive fashion with stereotactically guided serial biopsy, under either general or local anesthesia. The probability of establishing a diagnosis from 1 mm^3 tissue samples is over 95%, and the risk of complications is acceptably low even for lesions located in the brainstem (2.6% transient morbidity). (11, e8). Seeding of tumor cells along the biopsy trajectory has only been reported only in very rare cases (e9, e10).

TABLE 1

Molecular markers for prediction and for drug therapy of brain metastases*

Primary tumor	Molecular markers
NSCLC	*ALK, BRAF, EGFR, KRAS, MET, NTRK, PD-1/PD-L1, RET, ROS1*
Breast cancer	*BRCA1/2, CDK4/6, ER/PR, HER2, PD-L1, PIK3CA*
Melanoma	*BRAF, KIT, NF1, NRAS, PD-L1*
Colon cancer	*BRAF, KRAS, NRAS, MSI, PD-L1*
Upper gastrointestinal tract cancer	*HER2, MET*

* Exemplary listing of the clinically most relevant molecular markers that serve as therapeutic guideposts for targeted therapy, or as prognostic markers.
These markers can be expressed both in the primary tumor and in the corresponding brain metastasis. Expression in the primary tumor is not perfectly correlated with expression in the brain metastasis.
NSCLC, non-small-cell lung cancer

Comprehensive molecular genetic tissue analysis now increasingly provides the basis for treatment with new types of targeted drug that cross the blood-brain barrier to enter the central nervous system (CNS) *(Table 1)* (7, 8, 12). Approximately 53% of brain metastases manifest clinically relevant mutations that are not found in the primary tumor (13, e6). The mutational status of a tumor can change because of treatment-induced selection pressure or tumor progression. In non-small cell lung cancer with an anaplastic lymphoma kinase (ALK) translocation or an EGFR mutation, there are discordance rates of up to 13% and 33%, respectively, between the primary tumor and the brain metastasis, in the untreated setting (e11). A similar discordance rate of 14% for HER-2/new-status in brain metastases of breast cancer has been reported in two independent studies (e11, e12). The molecular signature of some other tumor entities appears to be more stable: for example, a BRAF mutation in an extracranial melanoma is almost certainly predictive of a BRAF mutation in the associated brain metastasis (e11, e13). The detection of predictive biomarkers in metastatic tumor tissue is also becoming increasingly important for immune therapies, just as it already has an established role to play in the immune therapy of primary tumors (e.g., PD-L1 expression).

The surgical resection of brain metastases

Patient selection

Aside from the need to obtain tissue for diagnostic purposes, the following indications for the surgical resection of brain metastases are internationally accepted:

TABLE 2a

Clinical trials concerning the neurosurgical resection of solitary brain metastases* (prospective trials only)

Trial design, reference number	Intervention (number of patients)	Primary tumor	Inclusion criteria	Outcome with respect to tumor control and survival (resection vs. other treatment)
RCT (e30)	resection→WBRT (n = 10) vs. SRS→WBRT (n = 11)	lung Ca: n = 10 (48%) colon Ca: n = 4 (19%) other: n = 7 (33%)	diameter ≤ 4 cm; ≥ 18 years old; KPS ≥ 70% (except tumor-related)	PFS (incl. local PFS): 3.1 vs. 1.7 months (HR: 0.55; p = 0.2) OS: 2.8 vs. 6.2 months (HR 0.53; p = 0.2)
RCT (27)	resection→WBRT (n = 33) vs. GKRS (n = 31)	lung Ca: n = 22 (34%) breast Ca: n = 11 (17%) urogenital Ca: n = 10 (16%) melanoma: n = 9 (14%) CUP: n = 6 (9%) breast Ca: n = 4 (6%) liver Ca: n = 2 (3%)	diameter ≤ 3 cm; age 18–80 years; KPS ≥ 70%; stable systemic disease with life expectancy ≥ 4 months	1-year local recurrence: 82% vs. 96.8% (HR: n.a.; p = 0.06) survival without distant recurrence: 3% vs. 25.8% (HR: n.a.; p < 0.05) OS: 9.5 vs. 10.3 months (HR: n.a.; p = 0.8)
RCT (e31)	resection→WBRT (n = 41) vs. biopsy→WBRT (n = 43)	lung Ca: n = 45 (54%) gastrointest. Ca: n = 13 (16%) breast Ca: n = 10 (12%) melanoma: n = 4 (5%) CUP: n = 4 (5%) Renal Ca: n = 3 (4%) head and neck Ca: n = 1 (1%) other: n = 4 (5%)	age ≤ 80 years; KPS > 50 %	OS: 5.6 vs. 6.3 months (HR: n.a.; p = 0.24)
RCT (e32)	resection→WBRT (n = 32) vs. biopsy→WBRT (n = 31)	lung Ca: n = 33 (52%) breast Ca: n = 12 (19%) melanoma: n = 6 (10%) renal Ca: n = 4 (6%) other: n = 8 (13%)	age ≥ 18 years; ECOG ≤ 2; life expectancy > 6 months	survival with ECOG ≤ 1: 7.5 vs. 3.5 (HR: n.a.; p = 0.06) OS: 10 vs. 6 months (HR: n.a.; p = 0.04)
RCT (e33)	resection→WBRT (n = 25) vs. biopsy→WBRT (n = 23)	lung Ca: 37 (77%) breast Ca: 3 (6%) gastrointestinal Ca: 3 (6%) urogenital Ca: 2 (4%) melanoma: 3 (6%)	age ≥ 18 years; KPS ≥ 70 %	local recurrence up to data cutoff: 20 vs. 52% (RR: n.a.; p < 0.02) local PFS: > 59 vs. 21 weeks (RR: 7.1; p < 0.001) OS: 40 vs. 15 weeks (RR 2.2; p < 0.01)

* Available prospective studies on resective surgery for solitary brain metastases compared to alternative treatments.
Ca, cancer; CUP, cancer of unknown primary; ECOG, Eastern Cooperative Oncology Group; GKRS, Gamma Knife radiosurgery; HR, hazard ratio; KPS, Karnofsky Performance Score; n.a., not available for review; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; RR, relative risk; SRS, stereotactic radiosurgery; vs., versus; WBRT, whole-brain radiotherapy

- a solitary brain metastasis, even in an eloquent area of the brain, especially if it is too large to be treated with radiosurgery;
- a metastasis causing acute neurological manifestations by mass effect, especially in the posterior cranial fossa;
- a dominant brain metastasis that can be resected in a patient with other brain metastases for which there are other therapeutic options;
- and in cases of suspected local tumor recurrence in a surgically accessible location after previous surgery, radiosurgery, or radiotherapy (4, 5).

No reliable figures are available on the percentage of patients with brain metastases who undergo surgery, but retrospective studies indicate that the rate of resection of metastases has declined over time (from 30.8% in the 1990s to 19.5% in the past decade) in favor of single-session irradiation, particularly with radiosurgery, with small brain metastases being diagnosed at an earlier stage than before (3).

In general, the surgical resection of brain metastases is an option only for patients who are in adequate physical condition (Karnofsky Performance Score ≥ 70%) or whose condition is expected to improve after resection (e.g., after the relief of intracranial hypertension) so that they can undergo further oncological treatment (e5). Clinical nomograms are available as aids to prognostication on the basis of the type of primary tumor and the intra- and extracranial tumor burden (14). Old age and the presence of neurological manifestations are unfavorable prognostic factors whatever the tumor entity (15,16). In cases of acute neurologic deterioration because of mass effect, resection can improve and stabilize the patient's clinical condition, enabling further therapy (17). Frailty must be considered in the assessment of operability: In a retrospective study of 3500 patients with brain metastases, a Modified Frailty Index of ≥ 2 points was associated with higher mortality after hospital discharge (odds ratio 2.79; 95% confidence interval: [1.6; 4.9]) (18). The histological type of the primary tumor is also relevant to the indication for surgery: for example, chemo- and radiosensitive tumors that are prone to diffuse seeding (e.g., small-cell lung cancer) should not be primarily resected if the patient is clinically stable. This illustrates the importance of a

TABLE 2b

Studies on the neurosurgical resection of multiple brain metastases*

Study design, reference no.	Size of patient cohort	Primary tumor	Inclusion criteria	Outcome with respect to quality of life, tumor control, and survival
Retrospective (e34)	n = 704 (n = 372 with solitary metastasis, n = 122 with two metastases, n = 142 with three metastases, n = 68 with > 3 metastases)	breast Ca, lung CA, other (precise number not stated)	histopathologic diagnosis of brain metastasis; surgical resection of ≥ 1 brain metastases; pre- and postoperative MRI	OS: 6 months (postoperative tumor volume with HR 1.02, p = 0.004)
Retrospective (e35)	n = 216 (n = 129 with solitary metastasis, n = 64 with 2–3 metastases, n = 23 with ≥ 4 metastases)	non-small-cell lung Ca: n = 216 (100%)	> 18 years; surgical resection of brain metastases of non-small cell lung cancer	KPS: significant improvement postoperatively (raw data n.a.; p < 0.001) local PFS: 38% of patients with radiological local progression after median radiological follow-up of 8 months (the metastasis count had no significant effect on HR) OS (entire cohort): 12.7 months (the metastasis count had no significant effect on HR)
Retrospective (17)	n = 750 (n = 462 with solitary metastasis, n = 185 with 2–3 metastases, n = 103 with ≥ 4 metastases)	lung Ca: n = 318 (42%) melanoma: n = 114 (15%) breast Ca: n = 116 (16%) gastrointest. Ca: n = 72 (10%) renal Ca: n = 24 (3%) CUP: n = 33 (4%) other: n = 73 (10%)	> 18 years; surgical resection of brain metastases	KPS: 80% preoperative vs. 90% postoperative (p < 0.001) RTOG groups (pre- vs. postoperative): 1: 18.5 vs. 19.3%; 2: 62.9 vs. 70.1%; 3: 18.5% vs. 10.5% (p < 0.001) OS (entire cohort): 10.9 months (HR 0.63 for 1–3 metastases vs. ≥ 4 metastases, p < 0.001)
Retrospective (e24)	n = 127 (n = 81 with 2–3 metastases, n = 24 with 4–5 metastases, n = 22 with ≥6 metastases)	lung Ca: n = 44 (35%) melanoma: n = 22 (17%) gastrointest. Ca: n = 16 (13%) breast Ca: n =15 (12%) renal Ca: n = 15 (12%) CUP: n = 8 (6%) other: n = 7 (6%)	tumor volume ≥ 27 cm^3 ± posterior fossa mass effect ± progression despite prior radiotherapy ± CUP syndrome	KPS: improved in 23% of patients postoperatively, worsened in 16% (p-value not stated) RTOG groups: improved in 12% of patients postoperatively (p-value not stated) OS (entire cohort): 6.5 months (HR 1.81 for ≥ 5 metastases vs. ≤ 4 metastases, p = 0.019)
Retrospective (e36)	n = 208 (n = 132 with solitary metastasis, n = 76 with ≥ 2 metastases)	lung Ca: n = 105 (51%) breast Ca: n = 28 (14%) melanoma: n = 18 (9%) colon Ca: n = 12 (6%) renal Ca: n = 13 (6%) other: n = 25 (12%) CUP: n = 15 (7%) (note: in the paper, the numbers of patients do not add up to the stated total)	surgical resection of brain metastases	KPS: improved postoperatively in 30% of patients with solitary metastasis vs. in 37% of patients with ≥ 2 metastases (HR: not significant) OS (entire cohort): 8 months (8 months in patients with solitary metastasis vs. 11 months in patients with ≥ 2 metastases; p = 0.77)
Retrospective (e37)	n = 56 (all with ≥ 2 metastases)	melanoma: n = 25 (45%) breast Ca: n = 11 (20%) lung Ca: n = 7 (13%) sarcoma: n = 5 (9%) colon Ca: n = 3 (5%) renal Ca: n = 2 (4%) ovarian Ca: n = 1 (2%) CUP: n = 2 (4 %)	presence of multiple brain metastases; surgical resection	local PFS: local recurrence in 4% (1/26) of patients with resection of all brain metastases OS: 10 months (6 months with some brain metastases still present postoperatively vs. 14 months with resection of all brain metastases, p = 0.003)

* No prospective studies are available for multiple brain metastases, so retrospective studies that included more than 50 patients with multiple brain metastases who underwent surgical resection are listed here.

Ca, cancer; CUP, cancer of unknown primary; HR, hazard ratio; KPS, Karnofsky Performance Score; MRI, magnetic resonance imaging, n.a., not available for review; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; RR, relative risk; RTOG, Radiation Therapy Oncology Group; vs., versus

critical assessment of the indications for surgery and of proper patient selection. The available evidence regarding the value of surgery for brain metastases is of low quality (level IV). There are no prospective trials evaluating the effect of the extent of resection on clinical outcome, neither for primary (intrinsic) brain tumors nor for brain metastases, as such trials cannot be performed for ethical reasons.

The timing of surgery

Acute neurological deterioration (e.g., due to intracranial hypertension) can be an indication for urgent or emergency surgery. This is especially true of metastases in the posterior fossa. For surgical procedures that can be planned electively, the timing should accord with the overall treatment plan. Proper timing may require weighing the risks of operating earlier or later: poor wound healing, perioperative bleeding, and infections are more likely if surgery is preceded by longer-term steroid treatment, or if it is closely preceded by radio- or chemotherapy (nadir of the blood counts), or even by anti-angiogenic drug treatment (e.g., the VEGF inhibitor bevacizumab); on the other hand, if surgery is delayed for these or other reasons, the metastasis can grow larger during the interval (e14, e15). The optimal timing of radiotherapy in relation to the surgical resection of metastases is being studied in prospective clinical trials (e.g., NCT04474925). A trial that is now recruiting patients in Germany and elsewhere is also investigating neoadjuvant radiotherapy (NCT03368625).

Technical aspects of surgery for brain metastases

As metastases in the brain grow, they usually remain well circumscribed, displacing rather than invading the surrounding brain tissue. However, autopsy studies have shown that brain metastases can infiltrate a few millimeters into the adjacent brain tissue, regardless of the histology of the primary tumor (19). If the metastasis is located at the surface of the brain, tumor cells can spread along the sulci (local meningeosis). Brain metastases are of highly variable consistency: some are hard, some are soft or even deliquescent, while others are primarily cystic. Brain metastases can be resected "supramaximally," i.e., together with adjacent brain tissue that may contain infiltrating tumor cells, when this is judged to be acceptable in terms of brain function (20, e16, e17). The surgeon should avoid the accidental transfer of tumor cells via the CSF to decrease the risk of further distant metastases or leptomeningeal seeding. Brain metastases should thus be resected en bloc whenever possible, if they are of suitable consistency and at an accessible location (21–24). A magnetic resonance (MR) scan of the brain should be performed early, i.e., within 72 hours, to assess the extent of resection (4, 25). It is not known at present whether supramarginal resection beyond the visible boundary of the tumor might lessen the need for postoperative radiotherapy (see below) (10).

The preservation or restoration of neurologic function has priority; clinical worsening may affect the timing and extent of further treatment with chemotherapy and/or radiotherapy 15, e18). Brain metastases can now routinely be treated safely and effectively in major neurosurgical centers, with a refined approach to surgical indications together with modern technical aids to microsurgery, including the routine use of the high-power surgical microscope, image-guided neuronavigation, and pre- and intraoperative electrophysiological functional testing (26). Depending on the site of the metastasis, a transient morbidity of 10–20% has been described, particularly when the tumor is a recurrence or is located in an eloquent brain region; most complications are mild, mainly consisting of wound-healing disturbances, wound infections, or concomitant systemic illnesses, such as infections (17, 26). In general, an appropriate assessment of the benefits and risks of resection is a key element of the overall oncological approach.

The role of resection for solitary brain metastases

Surgery plays a well-established role in the treatment of solitary brain metastases as well as oligometastatic disease (i.e., two or three brain metastases), as long as the patient's systemic disease is stable, either with or without chemotherapy *(Table 2)*. For smaller metastases that are no larger than 3 cm in diameter, radiosurgery results in local tumor control at a rate comparable to resection (89–93% at 12 months), as was found in a prospective, randomized trial (27). The larger the tumor, however, the higher the risk that radiosurgery will cause symptomatic brain edema or medically intractable radionecrosis (6–17%) (e19, e20). For patients with a larger volume of metastatic tumor, hypofractionated stereotactic radiotherapy or radiosurgery is better tolerated and also yields considerable local tumor control (ca. 86% at 12 months) (e21).

The relative utility and risk profiles of radiation and resection for larger metastases (> 3 cm) have not been studied in any prospective, randomized trial to date. The international guidelines therefore favor surgery for (symptomatic) lesions of diameter greater than 3 cm with mass effect, particularly if located in the posterior fossa *(Figure)* (4, 5). A randomized phase III trial has shown that postoperative stereotactic irradiation of the tumor bed improves local tumor control (hazard ratio 0.46, [0.2; 0.9]) (28). Cystic metastases in functionally relevant areas, can be treated with minimally invasive stereotactic cyst puncture followed by tumor irradiation (e22, e23).

The role of resection for multiple brain metastases

30–50% of patients with brain metastases have more than one metastasis (2, e1). There have not been any randomized, prospective trials of surgical resection in this situation *(Table 2)* (29). Resecting a clinically dominant metastasis can stabilize the patient's condition and lessen the need for steroids, which may be

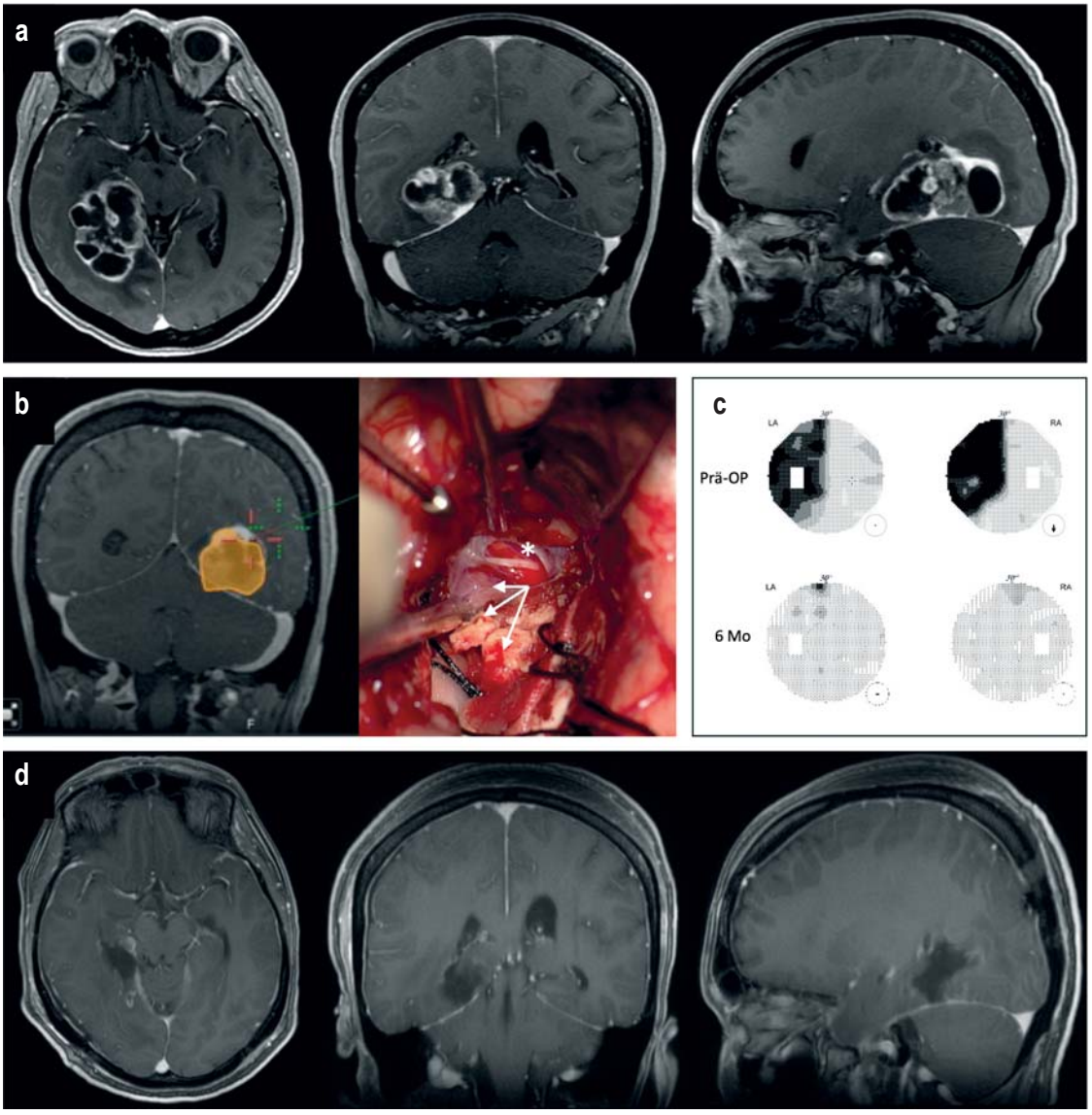

Figure: Microsurgical resection of a symptomatic solitary brain metastasis in a 64-year-old woman with breast cancer who presented with progressive dizziness, visual disturbances, and diplopia.
a) There is a large right temporo-occipital mass involving the optic radiation and compressing the midbrain. b) Intraoperative neuronavigation (left) and photographic documentation (right) of tumor tissue (arrows) and of the trochlear nerve (asterisk) after midbrain decompression. c) Visual field examinations: a homonymous hemianopsia that was present before surgery (above) has fully resolved by the time of the follow-up examination at six months (below). d) Early postoperative MRI (within 72 hours of surgery) shows no residual tumor tissue.

relevant in the context of multimodal treatment, e.g., in combination with single-session radiosurgery, whole-brain radiation (now only rarely considered to be indicated), or newer types of pharmacotherapy, including immune checkpoint inhibitors (4, 5, 29, 30, 31) *(eFigure 2)*. In the absence of data from prospective trials, decisions regarding combined treatment for patients with multiple brain metastases are taken on a case-by-case basis and should be critically evaluated by an interdisciplinary tumor board (32). With a variety of targeted therapies for brain metastases now being developed, there is a need for prospective, tumor- and target-specific trials so that the diagnostic and therapeutic value of neurosurgical intervention in these patients can be more precisely defined.

The role of resection for recurrent metastases and radionecrosis

Local recurrence of a metastasis does not have the same implications for treatment as a new metastasis arising at a different site. The decision whether to operate on a local recurrence must be made individually in the light of all prior treatments and the patient's systemic disease status. No prospective, randomized trials have been performed on the resection of local recurrences of metastases. Retrospective studies have shown that

favorable prognostic factors include good clinical status, a longer time since previous treatment at the same site, and breast cancer as the primary tumor (33, 34, e24).

The detection of a recurrent a brain metastasis poses a diagnostic challenge: oncologic follow-up is based on MRI imaging, which cannot definitively distinguish a local tumor recurrence from post-therapeutic changes (so-called pseudoprogression) or from symptomatic radiation necrosis. In fact, the risk of radionecrosis after single-session stereotactic irradiation (depending on the radiation dose and the treatment volume) is 12–20%. Moreover, radionecrosis can occur at any time from 10 to 36 months after treatment (9). Positron emission tomography (PET) with amino acid tracers, when it is available, enables greater differential-diagnostic specificity (35, e25), but generally does not obviate the need for histopathological examination, preferably by biopsy (29). Histopathology is also needed if changes in the molecular profile of the tumor, compared to the primary tumor from which it is derived, might affect the therapeutic strategy (4). In the future, new approaches such as liquid biopsy from cerebrospinal fluid or peripheral blood may yield important differential diagnostic information (e26).

Surgical treatments for leptomeningeal tumor seeding

About 5% of all patients with solid tumors develop leptomeningeal tumor seeding (4). In this situation, the median overall survival across entities is only approximately 4 months (36). Therapeutic options include systemic and/or intrathecal drug therapy as well as cranial irradiation down to the C2 level. The implantation of a ventricular catheter connected to a subcutaneous Ommaya or Rickham reservoir seems to enable a more homogeneous distribution of drugs in the CSF space compared to repeated lumbar punctures and is associated with a median survival time of 5.2 months in retrospective studies; the risks accompanying repeated lumbar punctures are thereby avoided as well (37). When needed, CSF can be obtained repeatedly by puncture of the reservoir in order to monitor the response to treatment over time.

Ventriculoperitoneal shunting: symptom control in patients with hydrocephalus

Two-thirds of patients with leptomeningeal tumor seeding develop a CSF circulation disturbance leading to hydrocephalus (e27, e28). The implantation of a ventriculoperitoneal shunt yields adequate symptom control in more than 90% of cases, with an associated improvement in the quality of life, enabling further treatment if indicated (38, e29). The periprocedural morbidity of shunt implantation is slightly higher (4–10%) in this situation than in patients without malignant tumors (39). In two retrospective series of 37 and 59 patients, shunt malfunctions necessitating revision arose in 8% an 13% of cases; peritoneal seeding, though occasionally feared, was not demonstrable in any case (38, 39). In summary, neurosurgical intervention can be helpful as a palliative measure in patient with leptomeningeal tumor seeding.

The role of neurosurgery in clinical window-of-opportunity studies

Valuable pharmacokinetic information can be obtained during neurosurgical procedures for the resection of brain metastases, e.g., information on the achievable levels of systemically administered drugs within tumor tissue (so-called window-of-opportunity studies) (40). Aside from the measurement of drug concentrations, the surgical specimen can be subjected to further study in the laboratory, e.g., concerning drug binding to molecular target structures and the biological effects of drugs on tumor tissue and normal tissue (pharmacodynamics).

Conclusion

Brain metastases are an increasingly common problem and neurosurgery remains a key component of their multidisciplinary treatment, all the more so after the recent introduction of immuno-oncological and targeted therapies. The spectrum of neurosurgical procedures also includes minimally invasive ones, such as the placement of catheter systems for the palliative treatment of patients with leptomeningeal tumor cell seeding. The scientific evidence for these statements is of poor quality (level IV) in the absence of controlled, prospective trials. In the future, multicenter databases with long-term follow-up may yield more detailed information on the utility of neurosurgical intervention. Moreover, window-of-opportunity studies using neurosurgical tissue specimens may yield important information on pharmacokinetics and pharmacodynamics that can serve as a basis for the implementation of new therapeutic options.

Conflict of interest statement

JP.S. has received lecture honoraria from Seagen, Roche, and MedUpdate. He is a member of the advisory boards of Roche, Boehringer-Ingelheim, Seagen, and Novocure and of the council of the Neuro-Oncology Working Group of the German Cancer Society.

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References

1. Cagney DN, Martin AM, Catalano PJ, et al.: Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. Neuro Oncol 2017; 19: 1511–21.
2. Lamba N, Wen PY, Aizer AA: Epidemiology of brain metastases and leptomeningeal disease. Neuro Oncol 2021; 23: 1447–56.
3. Steindl A, Brunner TJ, Heimbach K, et al.: Changing characteristics, treatment approaches and survival of patients with brain metastasis: data from six thousand and thirty-one individuals over an observation period of 30 years. Eur J Cancer 2022; 162: 170–81.
4. Le Rhun E, Guckenberger M, Smits M, et al.: EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol 2021; 32: 1332–47.

5. Vogelbaum MA, Brown PD, Messersmith H, et al.: Treatment for brain metastases: ASCO-SNO-ASTRO guideline. J Clin Oncol 2022; 40: 492–516.
6. Karschnia P, Le Rhun E, Vogelbaum MA, et al.: The evolving role of neurosurgery for central nervous system metastases in the era of personalized cancer therapy. Eur J Cancer 2021; 156: 93–108.
7. López Vázquez M, Du W, Kanaya N, Kitamura Y, Shah K: Next-generation immunotherapies for brain metastatic cancers. Trends Cancer 2021; 7: 809–22.
8. Chukwueke UN, Brastianos PK: Sequencing brain metastases and opportunities for targeted therapies. Pharmacogenomics 2017; 18: 585–94.
9. Lee D, Riestenberg RA, Haskell-Mendoza A, Bloch O: Brain metastasis recurrence versus radiation necrosis: evaluation and treatment. Neurosurg Clin N Am 2020; 31: 575–87.
10. Le Rhun E, Wolpert F, Fialek M, et al.: Response assessment and outcome of combining immunotherapy and radiosurgery for brain metastasis from malignant melanoma. ESMO Open 2020; 5: e000763.
11. Katzendobler S, Do A, Weller J, et al.: Diagnostic yield and complication rate of stereotactic biopsies in precision medicine of gliomas. Front Neurol 2022; 13: 822362.
12. Tan AC, Bagley SJ, Wen PY, et al.: Systematic review of combinations of targeted or immunotherapy in advanced solid tumors. J Immunother Cancer 2021; 9: e002459.
13. Brastianos PK, Carter SL, Santagata S, et al.: Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets. Cancer Discov 2015; 5: 1164–77.
14. Sperduto PW, Mesko S, Li J, et al.: Survival in patients with brain metastases: summary report on the updated diagnosis-specific graded prognostic assessment and definition of the eligibility quotient. J Clin Oncol 2020; 38: 3773–84.
15. Steindl A, Yadavalli S, Gruber KA, et al.: Neurological symptom burden impacts survival prognosis in patients with newly diagnosed non-small cell lung cancer brain metastases. Cancer 2020; 126: 4341–52.
16. Lamba N, Kearney RB, Catalano PJ, et al.: Population-based estimates of survival among elderly patients with brain metastases. Neuro Oncol 2021; 23: 661–76.
17. Schödel P, Jünger ST, Wittersheim M, et al.: Surgical resection of symptomatic brain metastases improves the clinical status and facilitates further treatment. Cancer Med 2020; 9: 7503–10.
18. Gupta S, Dawood H, Giantini Larsen A, et al.: Surgical and peri-operative considerations for brain metastases. Front Oncol 2021; 11: 662943.
19. Berghoff AS, Rajky O, Winkler F, et al.: Invasion patterns in brain metastases of solid cancers. Neuro Oncol 2013; 15: 1664–72.
20. Kamp MA, Rapp M, Slotty PJ, et al.: Incidence of local in-brain progression after supramarginal resection of cerebral metastases. Acta Neurochir (Wien) 2015; 157: 905–10; discussion 10–1.
21. Patel AJ, Suki D, Hatiboglu MA, Rao VY, Fox BD, Sawaya R: Impact of surgical methodology on the complication rate and functional outcome of patients with a single brain metastasis. J Neurosurg 2015; 122: 1132–43.
22. Tewarie IA, Jessurun CAC, Hulsbergen AFC, Smith TR, Mekary RA, Broekman MLD: Leptomeningeal disease in neurosurgical brain metastases patients: a systematic review and meta-analysis. Neurooncol Adv 2021; 3: vdab162.
23. Nguyen TK, Sahgal A, Detsky J, et al.: Predictors of leptomeningeal disease following hypofractionated stereotactic radiotherapy for intact and resected brain metastases. Neuro Oncol 2020; 22: 84–93.
24. Prabhu RS, Turner BE, Asher AL, et al.: A multi-institutional analysis of presentation and outcomes for leptomeningeal disease recurrence after surgical resection and radiosurgery for brain metastases. Neuro Oncol 2019; 21: 1049–59.
25. Kiesel B, Prihoda R, Borkovec M, et al.: Postoperative magnetic resonance imaging after surgery of brain metastases: analysis of extent of resection and potential risk factors for incomplete resection. World Neurosurg 2020; 143: e365-e73.
26. Sanmillan JL, Fernández-Coello A, Fernández-Conejero I, Plans G, Gabarrós A: Functional approach using intraoperative brain mapping and neurophysiological monitoring for the surgical treatment of brain metastases in the central region. J Neurosurg 2017; 126: 698–707.
27. Muacevic A, Wowra B, Siefert A, Tonn JC, Steiger HJ, Kreth FW: Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single metastases to the brain: a randomized controlled multicentre phase III trial. J Neurooncol 2008; 87: 299–307.
28. Mahajan A, Ahmed S, McAleer MF, et al.: Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. Lancet Oncol 2017; 18: 1040–8.
29. Ene CI, Ferguson SD: Surgical management of brain metastasis: challenges and nuances. Front Oncol 2022; 12: 847110.
30. Alvarez-Breckenridge C, Giobbie-Hurder A, Gill CM, et al.: Upfront surgical resection of melanoma brain metastases provides a bridge toward immunotherapy-mediated systemic control. Oncologist 2019; 24: 671–9.
31. Petrelli F, Signorelli D, Ghidini M, et al.: Association of steroids use with survival in patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. Cancers (Basel) 2020; 12: 546.
32. Bodensohn R, Kaempfel AL, Fleischmann DF, et al.: Simultaneous stereotactic radiosurgery of multiple brain metastases using single-isocenter dynamic conformal arc therapy: a prospective monocentric registry trial. Strahlenther Onkol 2021; 197: 601–13.
33. Mitsuya K, Nakasu Y, Hayashi N, et al.: Retrospective analysis of salvage surgery for local progression of brain metastasis previously treated with stereotactic irradiation: diagnostic contribution, functional outcome, and prognostic factors. BMC Cancer 2020; 20: 331.
34. Hessler N, Jünger ST, Meissner AK, Kocher M, Goldbrunner R, Grau S: Recurrent brain metastases: the role of resection of in a comprehensive multidisciplinary treatment setting. BMC Cancer 2022; 22: 275.
35. Galldiks N, Langen KJ, Albert NL, et al.: PET imaging in patients with brain metastasis-report of the RANO/PET group. Neuro Oncol 2019; 21: 585–95.
36. Beauchesne P: Intrathecal chemotherapy for treatment of leptomeningeal dissemination of metastatic tumours. Lancet Oncol 2010; 11: 871–9.
37. Montes de Oca Delgado M, Cacho Díaz B, Santos Zambrano J, et al.: The comparative treatment of intraventricular chemotherapy by ommaya reservoir vs. lumbar puncture in patients with leptomeningeal carcinomatosis. Front Oncol 2018; 8: 509.
38. Omuro AM, Lallana EC, Bilsky MH, DeAngelis LM: Ventriculoperitoneal shunt in patients with leptomeningeal metastasis. Neurology 2005; 64: 1625–7.
39. Nigim F, Critchlow JF, Kasper EM: Role of ventriculoperitoneal shunting in patients with neoplasms of the central nervous system: an analysis of 59 cases. Mol Clin Oncol 2015; 3: 1381–6.
40. Vogelbaum MA, Krivosheya D, Borghei-Razavi H, et al.: Phase 0 and window of opportunity clinical trial design in neuro-oncology: A RANO Review. Neuro Oncol 2020; 22: 1568–79.

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► **Supplemantary material**
eReferences, eFigures:
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Supplementary material to:

Neurosurgical Interventions for Cerebral Metastases of Solid Tumors

by Niklas Thon, Philipp Karschnia, Louisa von Baumgarten, Maximilian Niyazi, Joachim P. Steinbach, and Jörg-Christian Tonn

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eReferences

e1. Ostrom QT, Wright CH, Barnholtz-Sloan JS: Brain metastases: epidemiology. Handb Clin Neurol 2018; 149: 27–42.

e2. Berghoff AS, Schur S, Füreder LM, et al.: Descriptive statistical analysis of a real life cohort of 2419 patients with brain metastases of solid cancers. ESMO Open 2016; 1: e000024.

e3. Kromer C, Xu J, Ostrom QT, et al.: Estimating the annual frequency of synchronous brain metastasis in the United States 2010–2013: a population-based study. J Neurooncol 2017; 134: 55–64.

e4. Kaul D, Berghoff AS, Grosu AL, Lucas CW, Guckenberger M: Focal radiotherapy of brain metastases in combination with immunotherapy and targeted drug therapy. Dtsch Arztebl Int 2021; 118: 759–66.

e5. Soffietti R, Abacioglu U, Baumert B, et al.: Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO). Neuro Oncol 2017; 19: 162–74.

e6. Brastianos PK, Carter SL, Santagata S, et al.: Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets. Cancer Discov 2015; 5: 1164–77.

e7. Okada H, Weller M, Huang R, et al.: Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. Lancet Oncol 2015; 16: e534-e42.

e8. Riche M, Amelot A, Peyre M, Capelle L, Carpentier A, Mathon B: Complications after frame-based stereotactic brain biopsy: a systematic review. Neurosurg Rev 2021; 44: 301–7.

e9. Karlsson B, Ericson K, Kihlström L, Grane P: Tumor seeding following stereotactic biopsy of brain metastases. Report of two cases. J Neurosurg 1997; 87: 327–30.

e10. Pinggera D, Kvitsaridtze I, Stockhammer G, et al.: Serious tumor seeding after brainstem biopsy and its treatment-a case report and review of the literature. Acta Neurochir (Wien) 2017; 159: 751–4.

e11. Berghoff AS, Bartsch R, Wöhrer A, et al.: Predictive molecular markers in metastases to the central nervous system: recent advances and future avenues. Acta Neuropathol 2014; 128: 879–91.

e12. Duchnowska R, Dziadziuszko R, Trojanowski T, et al.: Conversion of epidermal growth factor receptor 2 and hormone receptor expression in breast cancer metastases to the brain. Breast Cancer Res 2012; 14: R119.

e13. Riveiro-Falkenbach E, Villanueva CA, Garrido MC, et al.: Intra- and inter-tumoral homogeneity of BRAF(V600E) mutations in melanoma tumors. J Invest Dermatol 2015; 135: 3078–85.

e14. Clark AJ, Butowski NA, Chang SM, et al.: Impact of bevacizumab chemotherapy on craniotomy wound healing. J Neurosurg 2011; 114: 1609–16.

e15. Schipmann S, Akalin E, Doods J, Ewelt C, Stummer W, Suero Molina E: When the infection hits the wound: matched case-control study in a neurosurgical patient collective including systematic literature review and risk factors analysis. World Neurosurg 2016; 95: 178–89.

e16. Yoo H, Kim YZ, Nam BH, et al.: Reduced local recurrence of a single brain metastasis through microscopic total resection. J Neurosurg 2009; 110: 730–6.

e17. Lee CH, Kim DG, Kim JW, et al.: The role of surgical resection in the management of brain metastasis: a 17-year longitudinal study. Acta Neurochir (Wien) 2013; 155: 389–97.

e18. Proescholdt M, Jünger ST, Schödel P, et al.: Brain metastases in elderly patients—the role of surgery in the context of systemic treatment. Brain Sci 2021; 11: 123.

e19. Shaw E, Scott C, Souhami L, et al.: Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90–05. Int J Radiat Oncol Biol Phys 2000; 47: 291–8.

e20. Minniti G, Clarke E, Lanzetta G, et al.: Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis. Radiat Oncol 2011; 6: 48.

e21. Lehrer EJ, Peterson JL, Zaorsky NG, et al.: Single versus multifraction stereotactic radiosurgery for large brain metastases: an international meta-analysis of 24 trials. Int J Radiat Oncol Biol Phys 2019; 103: 618–30.

e22. Lee SR, Oh JY, Kim SH: Gamma knife radiosurgery for cystic brain metastases. Br J Neurosurg 2016; 30: 43–8.

e23. Wang H, Liu X, Jiang X, et al.: Cystic brain metastases had slower speed of tumor shrinkage but similar prognosis compared with solid tumors that underwent radiosurgery treatment. Cancer Manag Res 2019; 11: 1753–63.

e24. Schackert G, Schmiedel K, Lindner C, Leimert M, Kirsch M: Surgery of recurrent brain metastases: retrospective analysis of 67 patients. Acta Neurochir (Wien) 2013; 155: 1823–32.

e25. Galldiks N, Abdulla DSY, Scheffler M, et al.: Treatment monitoring of immunotherapy and targeted therapy using (18)F-FET PET in patients with melanoma and lung cancer brain metastases: initial experiences. J Nucl Med 2021; 62: 464–70.

e26. Soler DC, Kerstetter-Fogle A, Elder T, et al.: A liquid biopsy to assess brain tumor recurrence: presence of circulating Mo-MDSC and CD14+ VNN2+ myeloid cells as biomarkers that distinguish brain metastasis from radiation necrosis following stereotactic radiosurgery. Neurosurgery 2020; 88: E67–e72.

e27. Chamberlain MC, Kormanik PA: Prognostic significance of 111indium-DTPA CSF flow studies in leptomeningeal metastases. Neurology 1996; 46: 1674–7.

e28. Mason WP, Yeh SD, DeAngelis LM: 111Indium-diethylenetriamine pentaacetic acid cerebrospinal fluid flow studies predict distribution of intrathecally administered chemotherapy and outcome in patients with leptomeningeal metastases. Neurology 1998; 50: 438–44.

e29. Kim HS, Park JB, Gwak HS, Kwon JW, Shin SH, Yoo H: Clinical outcome of cerebrospinal fluid shunts in patients with leptomeningeal carcinomatosis. World J Surg Oncol 2019; 17: 59.

e30. Roos DE, Smith JG, Stephens SW: Radiosurgery versus surgery, both with adjuvant whole brain radiotherapy, for solitary brain metastases: a randomised controlled trial. Clin Oncol (R Coll Radiol) 2011; 23: 646–51.

e31. Mintz AH, Kestle J, Rathbone MP, et al.: A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. Cancer 1996; 78: 1470–6.

e32. Vecht CJ, Haaxma-Reiche H, Noordijk EM, et al.: Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? Ann Neurol 1993; 33: 583–90.

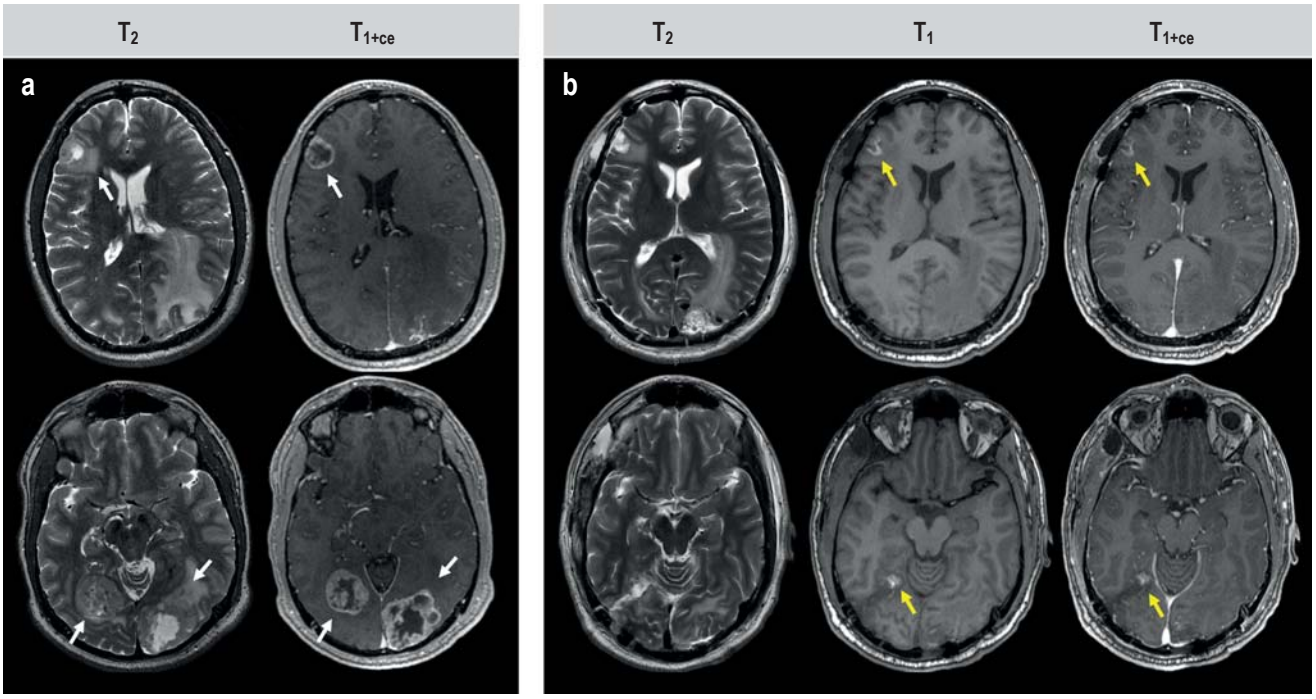
e33. Patchell RA, Tibbs PA, Walsh JW, et al.: A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 1990; 322: 494–500.

e34. Aftahy AK, Barz M, Lange N, et al.: The impact of postoperative tumor burden on patients with brain metastases. Front Oncol 2022; 12: 869764.

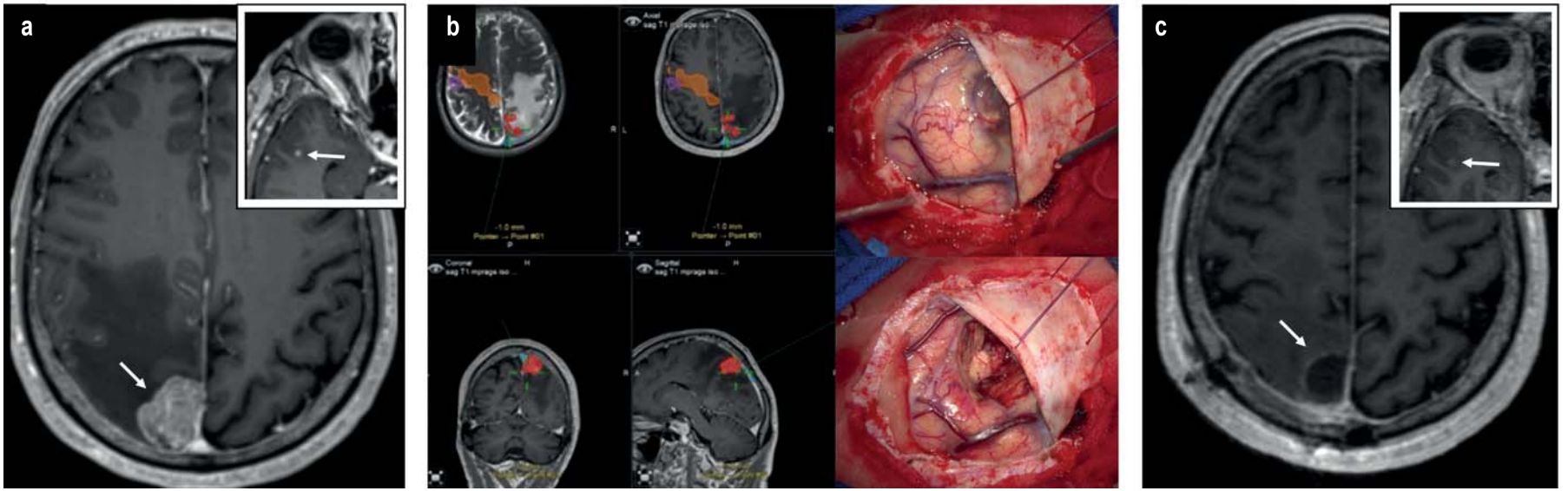
e35. Junger ST, Reinecke D, Meissner AK, Goldbrunner R, Grau S: Resection of symptomatic non-small cell lung cancer brain metastasis in the setting of multiple brain metastases. J Neurosurg 2021: 1–7.

e36. Paek SH, Audu PB, Sperling MR, Cho J, Andrews DW: Reevaluation of surgery for the treatment of brain metastases: review of 208 patients with single or multiple brain metastases treated at one institution with modern neurosurgical techniques. Neurosurgery 2005; 56: 1021–34; discussion—34.

e37. Bindal RK, Sawaya R, Leavens ME, Lee JJ: Surgical treatment of multiple brain metastases. J Neurosurg 1993; 79: 210–6.



eFigure 1: The microsurgical resection of multiple symptomatic brain metastases
A 48-year-old man with colon cancer presented with progressive visual disturbances.
a) The preoperative MRI shows multiple brain metastases (arrows) in the occipital lobes and elsewhere. b) The postoperative follow-up MRI, obtained within 72 hours of surgery, confirms total resection of the metastases; the patient's vision was markedly improved.



eFigure 2: Combined surgery and radiotherapy in a 72-year-old man with melanoma who presented with two brain metastases: a) a right parietal metastasis with marked perifocal edema and left hemiparesis (motor strength 4 out of 5) and a right temporal metastasis measuring 4 mm in diameter (inset). b) Neuronavigation (left) and intraoperative photo documentation both before and after (top/bottom right) complete resection of the parietal metastasis (arrows). c) MRI follow-up six weeks after stereotactic irradiation of the resection cavity according to the VMAT scheme (total dose 25 Gy, in 5 fractions of 5 Gy each) and single-session radiosurgery of the temporal metastasis (1 x 20 Gy at the 80% isodose), followed by immunotherapy as directed by a dermato-oncologist. VMAT, volumetric intensity-modulated arc therapy.

Questions on the article in issue 10/2023:

Neurosurgical Interventions for Cerebral Metastases of Solid Tumors

cme plus

The submission deadline is 9 March 2024. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

What is the most common primary tumor of brain metastases?

a) breast cancer
b) lung cancer
c) melanoma
d) ovarian cancer
e) cervical cancer

Question 2

What Karnofsky performance score is generally considered necessary to qualify a patient for the resection of brain metastases?

a) < 30%
b) < 10%
c) < 60%
d) ≥ 50%
e) ≥ 70%

Question 3

What examination should be performed to assess the extent of resection of a brain metastasis?

a) lumbar puncture after at least 12 hours
b) MRI within 72 hours
c) CT at 48 hours
d) ultrasound at 24 hours
e) EEG at 36 hours

Question 4

Approximately what percentage of patients with solid tumors develop leptomeningeal tumor seeding?

a) 1%
b) 5%
c) 10%
d) 15%
e) 25%

Question 5

What problem (also described in the text) arises in two out of three patients with leptomeningeal tumor seeding?

a) epilepsy
b) meningitis
c) hydrocephalus
d) encephalitis
e) strabismus

Question 6

According to international guidelines, at what size (diameter) is surgery preferable to radiosurgery for the treatment of a symptomatic, space-occupying brain metastasis, especially if located in the posterior cranial fossa?

a) > 0.3 cm
b) > 2 cm
c) > 3 cm
d) > 5 cm
e) > 7 cm

Question 7

As described in the text, what is a potentially effective treatment for a cystic metastasis in a functionally relevant area of the brain?

(a) chemotherapy followed by irradiation
(b) surgical cyst removal followed by irradiation
(c) radiotherapy followed by chemotherapy
(d) minimally invasive stereotactic puncture followed by radiotherapy
(e) surgical cyst removal followed by chemotherapy

Question 8

What is the risk of radionecrosis after single-session stereotactic irradiation?

a) 0.2–0.8%
b) 1–2%
c) 5–8%
d) 12–20%
e) 30–40%

Question 9

Which of the following mutations, if present in an extracranial primary tumor, is almost certainly present in the associated brain metastasis as well?

a) BRAF in melanoma
b) HER-2 in breast cancer
c) EGFR in non-small-cell lung cancer
d) BRCA1 in breast cancer
e) MYD88 in lymphoma

Question 10

Approximately what percentage of brain metastases have clinically relevant mutations that are not found in the primary tumor?

a) 5%
b) 12%
c) 23%
d) 32%
e) 53%