Intracranial metastases: therapeutic options

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Pathophysiology
Metastatic spread of tumour cells detached from systemic tumours into the central nervous system occurs hematogenously since lymphatic drainage is absent in the brain. Little is known about the precise mechanisms of tumour cell attachment in the brain and local progression of micrometastasis into clinically symptomatic tumours or into lesions visible on modern imaging techniques, such as magnetic resonance imaging (MRI).

Intensive research activities are focused on these pathophysiological mechanisms [1]. It is known that metastases are able to produce and secrete angiogenic substances enabling these tumours to become vascularized and to open the blood–brain barrier locally.

Different tumour entities reveal a different tendency to metastasise intracerebrally independently of their incidence. Therefore, the relative incidence of intracerebral metastases does not correlate with the systemic incidence of tumours. Metastases of breast cancer, lung cancer and malignant melanoma are common.

Some tumours, even when systemic metastases are a common phenomenon, are almost never found intracranially, as is the case in prostate cancer. Even inside the intracerebral compartment different locations of metastatic preferences exist. Metastases from kidney cancer for instance, arising from highly vascularized kidney parenchyma, are more often found in the well vascularized choroids plexus of the lateral ventricle than in other brain areas.

Epidemiology
Brain metastases are a common complication of systemic cancers. At autopsy, one-quarter of patients dying from cancer have intracranial metastases. Metastases are the most common intracerebral malignancy; resulting in 20–40% of all intracranial tumours [2]. The most common primary tumours causing brain metastases in adults are lung cancer, breast cancer, melanoma, renal cancer and colorectal cancer, with a peak age group of 55–65 years. Brain metastases can appear at any time in the course of a systemic cancer; most often they are metachronous, but may occur synchronously or even prior to diagnosis of the primary tumour. In general, all solid tumours are able to spread into the central nervous system and rare cerebral metastases (sarcomas, seminomas, etc.) may occur. Typically, brain metastases develop 6 months to 2 years after diagnosis and are usually associated with progressive systemic disease.

By definition, solitary brain metastasis is distinguished from singular brain metastasis.

- A solitary brain metastasis is defined as the only known metastasis of a tumour in the whole body which happens to be localised in the central nervous system.
- A singular brain metastasis is defined as a single cerebral metastasis with additional metastases in other organ systems.

Symptoms
Most brain metastases are detected because of unspecific symptoms depending on size, number and localisation of metastatic lesions. Symptoms usually evolve over a few weeks. Most common are headache, mental and behavioural changes (often first detected by family members), defects of higher cortical functions—such as impaired comprehension, reading, calculation—field cuts and difficulty performing motor function tasks, such as eating or dressing. Acute and more rare symptoms, including seizures (10–15%) or intratumoral bleeding (10%), are more common in metastatic melanoma. In general, seizures suggest more extensive disease with multiple metastases and/or leptomeningeal spread.

A thorough physical examination and history is useful to determine the extent of disease, the possible primary tumour in patients with primary brain metastasis and to assess the patient’s prognosis with the Karnofsky performance score as a robust predictor of survival and functional quality of life.

In our institutional series of 244 patients with cerebral metastasis, the most common initial symptom was headache (21.3%), followed by seizures (14.8%) and speech disturbance (11.9%) (M. Westphal, O. Heese, unpublished data).

An important, and potentially fatal, initial symptom is the subacute or acute rise of intracranial pressure due to blockage of cerebrospinal fluid (CSF) flow by otherwise asymptomatic metastases in the posterior fossa leading to obstructive hydrocephalus making emergency treatment necessary (Figure 1).

Diagnostic procedures
The imaging method of choice and the only necessary test for brain metastases is MRI. Although the scan cannot unequivocally differentiate metastases from other lesions, certain abnormalities suggest metastatic disease. Metastases are usually spherical or quasispherical and are well demarcated from the adjacent brain tissue. They are usually found at grey-white matter junctions in watershed areas of the brain [3]. The metastatic lesion is hyperintense on T1-weighted images after gadolinium injection. T2-weighted images and FLAIR-sequences demonstrate the surrounding oedema. With computed tomography one-half of the patients were classified as having singular brain metastases. Mag-
Magnetic resonance imaging reveals that 65–80% of brain metastases are multiple. Differential diagnosis includes abscesses, primary brain tumours, CNS lymphomas, demyelinating lesions or inflammations. If there is sufficient uncertainty in diagnosis, a biopsy is warranted. Eleven per cent of patients who were initially thought to have a single brain metastasis turned out to have a different diagnosis after biopsy [4]. In general, appearance of multiple lesions is highly suspicious of cerebral metastases, as differential diagnosis multiples gliomas, multiples lymphomas or multiples abscesses have to be considered. The latter can be found in patients suffering from immunosuppression or with an open foramen ovale (Figures 2 and 3).

Laboratory tests are of limited value. Tumour markers should be ordered as appropriate according to the known or suspected primary cancer, e.g. α-fetoprotein (AFP) or human chorionic gonadotropin (HCG) in non-seminomatous germ-cell tumours. Cytological analysis of CSF is useful to exclude or establish leptomeningeal involvement.

Median survival of untreated patients is ~1 month, 2 months if corticosteroids are added, 4–6 months after whole-brain irradiation [5] and 8–10 months if surgery or radiosurgery is utilised [4, 6]. In addition, survival is superior with a higher Karnofsky score (>70), age <65 years, controlled primary tumour and in the absence of extracranial metastases.

**Therapy**

Therapy of brain metastases is a complex and interdisciplinary approach where close cooperation between medical oncologists, medical radiation oncologists, neurosurgeons and anaesthesiologists is essential. A systematic and interdisciplinary initial diagnostic work-up is required to identify patients eligible for improved modes of therapy. Specific treatment strategies depend on the number and location of metastases, Karnofsky performance status, age and patient’s overall health status.

**Figure 1.** Right cerebellar metastasis of a breast cancer with resulting occlusive hydrocephalus and brain stem compression, requiring immediate operation due to vital threat. Magnetic resonance imaging in T1 sequence with contrast.

**Figure 2.** Flow chart of diagnostic work-up.
neurosurgeons and radiation oncologists is needed. Management consists of both symptomatic and definitive therapies. Symptomatic therapy includes corticosteroids for the treatment of peritumoural oedema and anticonvulsants for the control of seizures. Definitive treatment includes surgery, radiotherapy and chemotherapy directed at eradicating the tumour cells.

Symptomatic therapy
Only patients with brain metastases presenting with seizures should be treated with anticonvulsants; if possible, in the form of monotherapy utilising phenytoin or carbamazepine [7]. Possible exceptions are patients with brain metastases in areas with high epileptogenicity, patients with multiple melanoma metastases [8] and patients with both brain and leptomeningeal metastases [9]. These patients have a higher possibility of seizures and may benefit from prophylactic anticonvulsant therapy. There are no clear rules as to when anticonvulsants should be stopped in patients with documented seizures.

Dexamethasone, which acts by reducing the permeability of tumour capillaries [10], is the corticosteroid most commonly used to reduce oedema, as it has fewer mineralocorticoid effects and lower levels of protein binding than prednisone. Clinical improvement can usually be seen within 2 days, while neuroimaging may not show a decrease in oedema for up to 1 week [10]. The conventional starting dose is high (10–32 mg) followed by 4 mg four times daily, although there is some evidence that lower doses (4–8 mg/day) may be as effective [11]. The twice daily schedule is more rational because of the long half-life of dexamethasone (24–36 h). Once the patient is clinically stable, a slow taper should be initiated with the aim of establishing the lowest effective dose (e.g. taper 2 mg every 5–7 days). In patients with a history of gastric problems, we use a prophylactic proton pump inhibitor (omeprazole) or H2 blocker. Sometimes in immunocompromised patients receiving dexamethasone >4 mg daily Candida prophylaxis and Pneumocystis carinii prophylaxis with TMP-SMX (trimethoprim–sulfamethoxazol) on weekends is used. It should be kept in mind that phenytoin induces hepatic metabolism of dexamethasone and significantly reduces half-life and bioavailability [12]. Conversely dexamethasone may also reduce phenytoin levels (measurement of plasma level necessary).

Definitive therapy
The optimal combination of definitive treatment options for each patient depends on careful evaluation of numerous factors, including localisation, size and number of brain metastases; patient age, general condition and Karnofsky performance status; extent of systemic cancer as well as the tumour’s response to past therapy and possible future treatment options.

Systemic chemotherapy
The definitive role of chemotherapy in the treatment of patients with brain metastases has not been defined. Traditionally it had been assumed that the blood–brain barrier prevented chemotherapeutic agents from entering the CNS. However, there is evidence that the blood–brain barrier is in fact partially disrupted in brain metastasis [13]. This suggests that the disappointing response of brain metastases to chemotherapy may be caused by other factors, such as an intrinsic resistance of the tumours. The lack of adequate randomised trials makes it difficult to draw definitive conclusions about the precise role of chemotherapy.

Lung cancer
The objective response rate of brain metastases from small-cell lung cancer (SCLC) without prior therapy is about 70–80%, with a median survival of ~8 months. The duration of response and response rate are lower in previously treated SCLC with CNS metastases (around 40%). The European Organisation for Research and Treatment of Cancer (EORTC) conducted a phase III trial comparing single-agent chemotherapy (teniposide) with the same chemotherapy combined with whole-brain radiation in SCLC with CNS metastases. The improvement in tumour response rate

Figure 3. Differential diagnosis of a left frontal cystic lesion. Metastasis of a breast cancer with (A) space occupying surrounding oedema [magnetic resonance imaging (MRI) in fluid attenuated inversion recovery (FLAIR) sequence] and (B) contrast enhancing rim and central necrosis (MRI in T1 with contrast). (C) Left frontal abscess (computed tomography with contrast).
(57% versus 22%; \( P < 0.001 \)), as well as time to progression in the brain, was statistically significant following the addition of whole-brain irradiation [14].

For non-small-cell lung cancer (NSCLC), multiple drug regimens have shown an overall response rate of 8–10%. The Italian Oncology Group for Clinical Research observed a 30% response rate in previously untreated patients with brain metastases from NSCLC followed by a median time to progression of 4 months and median survival of 8 months [15]. Two trials were conducted utilising temozolamide, either alone or in combination, with whole-brain irradiation. Dardoufas et al. [16] started with single-agent temozolamide (60 mg/m\(^2\) per day for 2 weeks), followed by radiotherapy (30 Gy + 6–9 Gy boost) and six cycles of adjuvant temozolamide (200 mg/m\(^2\) for 5 days every 28 days). The response rate was 55% in all patients after six cycles and 86% in 11 patients with lung cancer. Antonadou et al. [17] randomly assigned patients to whole-brain irradiation or temozolamide plus whole-brain irradiation. The response rate was 66% versus 96% in favour of the combination. These results merit further studies using this combination.

**Breast cancer**

Since 1970, patients with metastatic breast cancer have been treated with chemotherapy. In the largest series to date, Rosner et al. [18] treated 100 breast cancer patients with CNS metastases with several first-line chemotherapy regimens. The overall response rate of this nonrandomized trial was 50% [10% complete response (CR), 40% partial response (PR)] and 9% showed stable disease (SD). Median duration of remission was 7–10 months. The Italian Oncology Group for Clinical Research treated 56 patients with brain metastases from breast cancer with the combination of cisplatin and etoposide for a maximum of six cycles, and observed 13% CR, 26% PR and 21% SD, resulting in a 1-year survival of 31% [15]. Several other small series have reported responses to a variety of regimens [19–21].

**Testicular cancer**

Patients with testicular cancer who present with brain metastases at initial diagnosis have a high response rate to cisplatin-based chemotherapy with a 5-year survival rate of 45%. Central nervous system metastases after initial chemotherapy have a lower response rate of 12%. Survival in this group is effectively increased with surgery and radiotherapy if there is an isolated recurrence in the CNS [22].

**Leptomeningeal metastases**

Two different clinical types of leptomeningeal metastases from solid tumours exist: (i) local infiltration; and (ii) dissemination of tumour cells throughout the neuraxis by the flow of the CSF (neoplastic meningitis, carcinomatous meningitis). Carcinomatous meningitis is clinically less common than brain metastasis or spinal cord compression, and has dire consequences for both quality of life and overall survival of patients with solid tumours. It occurs in about 5% of all adult cancer patients, but autopsies may double this number. If leukaemia and lymphoma are excluded, most cases are due to breast cancer, lung cancer and melanoma.

Leptomeningeal spread can be diagnosed by cytological examination of CSF or by MRI. The criteria for treatment choice are as controversial as the role of intrathecal chemotherapy (ITC) [23]. We include, in addition to dexamethasone, ITC usually with methotrexate (plus dexamethasone) and/or cytosine arabinoside. Sometimes following intrathecal therapy with methotrexate, eight applications of folinic acid 6 mg are prescribed orally every 6 h. Intrathecal application is performed twice a week including cytology of CSF. Following CR consolidation therapy includes weekly therapy for 4 weeks, followed by intrathecal therapy every other week for 3 months. In remaining CR intrathecal therapy is performed for 1 year every 6 weeks. Ongoing trials are evaluating sustained-release cytarabine for carcinoma and lymphoma with leptomeningeal spread.

For evolving lesions of the spinal cord, radiotherapy of the neuronal axis with 20 Gy should be discussed, while keeping in mind the possible complications of this approach and the life expectancy of the patient.

**Local therapy**

In general, the local treatment of asymptomatic cerebral metastases should be started if systemic tumour disease is controlled, life expectancy is greater than 3 months and the Karnofsky score is at least 60. The indication of surgery or radiosurgery should not depend on technical feasibility, but with the aim of improving quality of life.

**Radiation therapy**

**Stereotactic biopsy and whole-brain radiation therapy**

In a previously published series of 891 patients, treated between 1985 and 2000 with diagnostic stereotactic biopsy and whole-brain radiation, the mean survival of the whole patient population was 3.4 months [24]. Dividing the group into subgroups according to a method called recursive partition analysis (RPA, Gaspar), the best group with a solitary cerebral metastasis showed a mean survival of 13.5 months. Various studies revealed that young age, single cerebral metastasis and high Karnofsky score are beneficial factors.

Whole-brain radiation is performed differently in various centres. The applied dose and fraction varies between 10 fractions of 3 Gy with a total dose of 30 Gy [25] to 50 Gy total dose in 2 Gy fractions [24], or 20 fractions of 2 Gy with a total dose of 40 Gy [26].

**Radiosurgery with or without whole-brain radiation therapy**

Radiosurgery is a radiation protocol with stereotactically applied high dose focussed external radiation usually as a single dose. In general, a maximum of four lesions seem to be technically feasible in one session. The maximum diameter of metastasis suitable for radiosurgical treatment ranges between 3 and 4 cm, and the maximum radiation dose used ranges between 10 and 25 Gy. Either a gamma knife or a linear accelerator (Linac, X-Knife) are used.

In a retrospective study, the additional benefit of whole-brain irradiation to radiosurgery was studied. Out of a cohort of 983
patients, 569 were investigated [26]. The study revealed no significant difference with regard to survival whether whole-brain irradiation was added to radiosurgery or not. Therefore radiosurgery alone for cerebral metastasis seems to be an adequate treatment option if the above mentioned criteria are fulfilled [26].

Surgery

Surgical resection of cerebral metastasis is an effective and well-established method to control the disease. A resection in toto is preferable. One major benefit of surgical resection of a metastasis is the fast resolution of the surrounding oedema (Figure 4).

Due to multidisciplinary treatment protocols of brain metastases, a combination of surgical resection and radiosurgery for multiple lesions is sometimes used. A direct comparison revealed a faster resolution of perifocal oedema at the resection site in contrast to the radiated area. A recently published paper in which radiosurgery was evaluated for its tumour control potency revealed not only a prolonged time to oedema resolution, but, in addition, a local recurrence rate of ~50% [27].

The only randomised study in which surgery was evaluated in addition to whole-brain irradiation in patients with a single brain metastasis revealed a mean survival of 40 weeks for those receiving surgery and whole-brain radiation in contrast to a mean survival of 15 weeks for those receiving whole-brain radiation alone. Therefore, the benefit of surgical resection in these circumstances is well documented [4]. In addition, the local recurrence rate was 20% in a combined protocol of radiation and surgery and 52% in the radiation alone group. Even more striking in the study was the influence of the Karnofsky score on the outcome. Patients with a Karnofsky score >70 showed a survival of 38 weeks with the combined protocol versus 8 weeks with radiation alone, revealing a highly statistically significant benefit of surgery in combination with radiation (P 0.005). Even though the above mentioned study was conducted before radiosurgery was done, routinely the actual radiosurgery studies showed that surgical resection, if feasible, is superior with regard to tumour control.

Therefore, a surgical resection should be performed if the cerebral metastasis is easily accessible, if a strong surrounding oedema causes neurological deficits, when a metastases has major cystic components or if fast relief of secondary complications is the goal, as for example in the resolution of acute hydrocephalus due to metastases in the posterior fossa (Figure 1). Even though systematic studies are still lacking, it can be hypothesised that complete tumour resection leads to better control of seizures compared with radiosurgery since cerebral irritation of necrotic tumour tissue is absent.

In a patient group in which tumour resection or radiosurgery in combination with whole-brain radiation is performed and a recurrence occurs, a re-operation is indicated if the Karnofsky score is

Figure 4. Right frontal metastasis of a thyroid cancer. (A, B and C) Small lesion with massive perifocal oedema reaching the motor cortex. (D) Complete resolution of the oedema after surgical resection. Magnetic resonance imaging in T1 sequence with contrast.
good and no other therapeutic options are available. Mean survival after re-operation is 8.6 months, compared with 2.8 months without re-operation [4]. This difference in survival seems logical since only patients with well controlled systemic disease will survive until a local cerebral recurrence will occur and will therefore profit from a second operation. As a combined therapeutic approach in cases of large cystic lesions in eloquent areas, aspiration of the cyst and placement of a Rickham reservoir, in order to reduce the total volume for a subsequent radiosurgical procedure, may be indicated (Figure 5).

Conclusions
In conclusion, the approach to brain metastases and meningeal spread should be based on an assessment of prognostic variables. After the classification of patients into favourable, intermediate and unfavourable prognosis groups, the precise role of surgery, radiotherapy, radiosurgery and chemotherapy can be defined after appropriate symptomatic medical management. The approach will vary from aggressive treatment, starting with chemotherapy, followed by surgery and/or radiotherapy for patients with newly diagnosed germ-cell tumours, to primary surgery followed by irradiation in patients with unknown primary, or hospice care in patients with melanoma and systemic unresectable metastases following initial chemotherapy.

References