Neurosurgical Treatment for Brain Metastases: Clinical Features, Operative Strategies, Recurrence and Survival

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Contents

Abstract

Brain metastases are a frequent complication of cancer arising in up to 15 % of patients with systemic malignancies. Symptoms and findings are highly dependent on the location and size of the lesion. The diagnostic method of choice is magnetic resonance imaging before and after the administration of contrast material. The initial and essential therapeutic step is complete surgical resection of the lesion in order to (1) erase intracranial space-occupying lesions and (2) gain adequate tissue for histological diagnosis. Resection is usually followed by whole brain radiation therapy and/or radiosurgery.

Bone metastases are far less common than brain metastases. They may affect the calvaria or the skull base. The standard treatment is also surgical resection followed by bone plasty.

Dural metastases are also infrequent. They are an important differential diagnosis of meningioma when they arise as a solid mass. When they manifest as subdural fluid collection, they can mimick chronic subdural hematoma.

Introduction

The Incidence of Metastasis

Distant metastasis is the leading cause of death in cancer patients. The property to form distant metastases is a characteristic feature of malignant tumors. Distant metastasis requires a specialized subset of tumor cells that can migrate from the

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primary site, invade the bloodstream, survive in the blood vessel, extrude the vessel and migrate to the distant site and, finally, proliferate at the distant site. This multistep process has been named the metastatic cascade (Mina and Sledge 2011).

It is more than 120 years ago that Stephen Paget (1889) showed, based on autopsy findings, that "the distribution of secondary growths is not a matter of chance" (Paget 1889). Today we know that the type of cancer spread is influenced by vascular anatomy and molecular properties of the metastatic cells as well as the host tissue (Liotta and Kohn 2001). As a result, specific cancer types show a predilection to metastazise to certain organs.

The Brain as a Special Environment

The brain is an organ where unwanted movement, namely metastatic cell movement, is highly restricted. The brain lacks significant diffusion channels, it has no significant extracellular matrix and no lymphatic system. The brain tissue contains an extensive capillary bed and it is separated from the blood stream via the blood–brain barrier – hereby excluding many chemotherapeutic agents from targeting cancer cells inside the brain parenchyma (Puduvalli 2001). Thus, cells which are able to migrate to and proliferate into the brain parenchyma must have specific abilities which should also be "visible" in their genetic expression profile (Beasley and Toms 2011).

Following this hypothesis, Yoneda and colleages have inserted human breast cancer cells into mice. As a result, multiple metastases to different organs were formed. The study group then harvested only the brain metastases and inoculated them again into other mice. After several passages these cells exclusively formed brain metastases (Yoneda et al. 2001). Based on this model, we have shown that these "trained" cells have acquired specific molecular properties different from the original "parental" cells, namely overexpression of matrix-metallo-proteinases 1 and 9. Functionally, these factors were associated with cell invasion and migration (Stark et al. 2007). Further factors being differentially expressed in brain-seeking breast cancer cells are vascular factors as TIE-1 and endoglin as well as members of the metastasis-suppressor gene family (Stark et al. 2010).

Maybe due to the fact that the brain is a "special, uncomfortable place" for distant metastases, it is usually affected in an advanced stage of disease. This is also true for other sites of metastastic growths in the neurocranium: bone and dural metastases. Both sites are far less common than intraparenchymal (brain) metastases and are discussed at the end of this chapter.

Brain Metastases

Epidemiology and Definitions

Intraparenchymal "brain" metastases are a common complication of cancer arising in approximately 15 % of all patients with malignancies (Sperduto et al. 2010). The incidence is rising due to the increasing senescence of the population, higher detection rates, and improved treatment of primary tumors (Al-Shamy and Sawaya 2009; Siu et al. 2011). The three most common solid tumors of the human body that cause brain metastases are lung cancer, breast cancer and malignant melanoma. Further frequent primary lesions are colorectal and renal cancer. Among our surgical series of 309 patients with solid cancer brain metastases, the tumor origin was as followed: lung cancer: 49.8 %, breast cancer: 15.2 %, urogenital cancer: 11.0 %, colorectal cancer: 8.4 %, malignant melanoma: 7.1 %, others: 8.4 % (Stark et al. 2011).

When brain metastases are diagnosed, most patients are in an advanced stage of disease. However, in 15 % of patients brain metastases are detected as the first sign of malignant disease and in up to 10 % of patients no primary tumor is found at initial presentation (Al-Shamy and Sawaya 2009; Wesseling et al. 2007). This is especially the case in lung cancer patients. According to our experience in 309 patients, the rate of patients where cancer was detected by the occurrence of brain metastases depending on the primary tumor was as followed: non small

cell lung cancer 50.4 %; malignant melanoma 15.0 %, renal cancer 5.9 %; breast cancer 2.1 %; colorectal cancer 0 % (Stark et al. 2011).

By definition, the term "solitary" brain metastasis refers to one single intracranial lesion without evidence of extracranial metastases. "Singular" brain metastasis refers to one single brain lesion in the presence of extracranial metastases. Usually, the term "multiple" brain metastases refers to a number of at least three intracranial metastases.

Patient History and Physical Examination

Symptoms and findings are highly dependent on the location of the lesion and its size. They may be specific for the location (hemiparesis, aphasia, cranial nerve involvement, visual disturbance) or unspecific (headache/nausea/vomiting, vertigo). According to our experience, the most common initial symptoms in patients with brain metastases are hemiparesis (21 %), headache/nausea/vomiting (17 %), ataxia (16 %), cranial nerve impairement (10 %), aphasia (9 %), vertigo (9 %), and seizures (7 %) (Stark et al. 2011).

According to the expendable growths of brain metastases, Neurological deficits may originate from tumor-caused compression of neural structures and/or from the peritumoral edema. This, mostly finger-like edema, is a characteristic feature of brain metastases and may be significant even in patients with small metastases. Deficits may exclusively being caused by the edema, which can be reduced by corticosteroids and decreases significantly after resection of the lesion.

In most cases, symptoms evolve over days to weeks. However, intratumoral bleeding may lead to stroke-like appearance of symptoms. Metastases from melanoma and renal cancer show a predominance to bleed.

According to the fact that brain metastases compress the adjacent brain instead of infiltrating it, the vast majority of patients shows improvement of performance after surgical removal of the lesion (Stark et al. 2011). This is in contrast to patients with primary brain tumors, namely glioblastoma, where infiltration and destruction of the neighbouring brain is present.

Clinical examination should also evaluate the extent of the primary tumor and extracranial metastases, if known. The overall patient performance is a reliable prognostic factor and should therefore be noticed, mostly according to the Karnofsky Performance Score (KPS) (Karnofsky and Burchenal 1949).

Diagnostic Workup

Magnetic resonance imaging (MRI) before and after the administration of contrast material is the diagnostic method of choice when brain metastases are suspected. MRI can (1) accurately show the anatomical location of the lesion, most often at the gray-/white matter interface, (2) differentiate between the lesion itself and the peritumoral edema, (3) estimate the number of metastases down to a diameter of less than one millimeter and (4) detect complications of metastases such as intratumoral bleeding, ifiltration of the dura, hydrocephalus due to compression of CSF pathways and meningeosis carcinomatosa (Osborn et al. 2010).

Brain metastases appear in MRI studies mostly as circumscribed, contrast enhancing solid, cystic or mixed solid/cystic lesions. The peritumoral edema can be well shown in T2 images and in fluid attenuated inversion recovery (FLAIR), where the cerebrospinal fluid signal is suppressed and interstitial edema is pronounced. Figure 26.1 shows characteristic appearance of an exemplary brain metastasis in MRI and CT.

In cases of tumor location in or adjacent to eloquent neural structures, additional diagnostic workup can be useful. Functional MRI can visualize brain regions with increased metabolism during patient action, such as speech or movement. As a consequence, in tumors located closely to speech or motor areas, functional MRI may give additional information of the functional localization of eleoquent brain areas. This is also very useful in left-handed patients where the functional speech area may be on the left or on

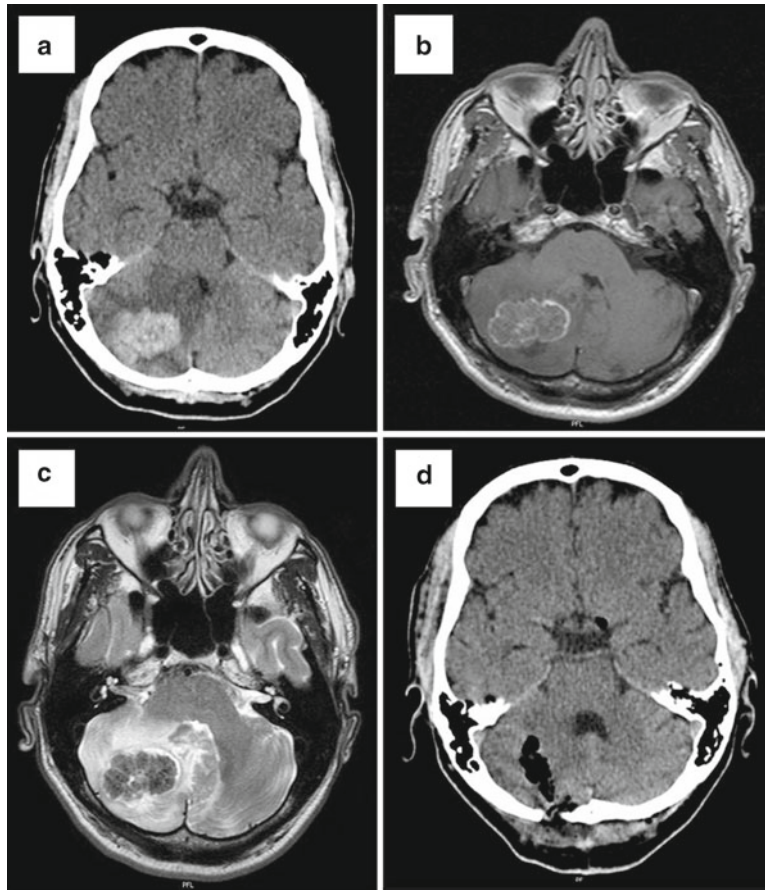

Fig. 26.1 66-year old patient with the history of colorectal cancer who presented with vertigo and dysarthry. (**a**) native CT shows a dense mass in the right cerebellar hemisphere with surrounding edema towards the fourth ventricle (*arrow*). (**b**) T1-weighted MRI after contrast administration shows the same lesion as solid, contrastenhancing mass. (**c**) T2-weighted MRI shows the lesion and highlights the hyperintense peritumoral edema (*arrows*). (**d**) Post-operative CT shows the resection cavity while the fourth ventricle is now, after the removal of the space-occupying lesion, expanded to normal size (*arrow*).

the right or on both sides of the cerebrum. Fiber tracking MRI detects diffusion movement in neural tracts. It is useful in patients with metastases located nearby or even compressing the pyramidal tract or other white matter tracts.

The most important differential diagnoses of brain metastases are glioblastoma and brain abscess. Notably, both lesions can also be multiple. Even in patients with known cancer establishment of a histological diagnosis is often advisable in order to apply adequate treatment. In contrast to brain abscess, brain metastases usually show no restriction on diffusion weighted images. Further differential diagnoses are demyelinating diseases and cerebral infarction (Osborn et al. 2010).

In case of emergency presentation, often a computed tomography scan (CT) is performed. In native CT, the lesion may be hyper-, iso- or hypodense to the brain parenchyma depending on the solid, cystic, necrotic or hemorrhagic nature. More or less surrounding edema is noticed and mass effect may be identified. The patient history of cancer usually is the key to diagnosis. MRI should be followed to adequately approximate the nature of the lesion and show anatomical details.

CT might also be useful in addition to MRI when involvement of the bone is suspected. It is essential in metastases of the skull base. Additionally, CT of the cervical spine is advisable in patients with suspected bone metastasis in order to prevent positioning damage during the operation.

Treatment of Brain Metastasis

The decision whether patients should undergo surgical resection always needs careful evaluation of the individual case and informed consent of the patient. If possible, the patient`s family should be included in the decision process.

The mainstay of treatment for patients with brain metastases is complete surgical excision of the lesion. Surgery is able to (1) erase the space-occupying lesion and therefore relief the patients symptoms and, in most of the cases, improve neurological function (Stark et al. 2011). (2) Surgery enables histological examination of the tumor tissue which is essentially required for adequate adjuvant treatment. According to advances in operative techniques and neuroanesthesia, surgical complications nowadays can be reduced to a minimum and surgical procedures can be applied to a rising amount of patients including patients of advanced age (Al-Shamy and Sawaya 2009; Siu et al. 2011).

The Indication for Surgery

To date, surgery is generally warranted under the following conditions assuming that the metastases are accessible and the primary tumor is under control or unknown.

1. In solitary or singular brain metastasis, either symptomatic or not, surgical treatment is regarded as the standard treatment option. The benefitial role of resection in addition to whole brain radiation therapy has been well documented since the early 1990s (Patchell et al. 1990; Vecht et al. 1993).
2. Life threatening lesions require immediate surgery. This is the case in large lesions causing mass effect, finally leading to tentorial herniation. It is also an important issue in infratentorial tumors causing obstruction of the aqueduct resulting in acute, life-threatening hydrocephalus.
3. The diagnosis is uncertain (cancer of unkown primary, CUP). Tumor resection, or biopsy in cases where tumor removal would cause unacceptable neurological deficits, enables accurate histopathological diagnosis. Remarkably, the rate of histopathological "surprises" in cases with suspected brain metastases based on clinical observations is in the range of 11 % (Al-Shamy and Sawaya 2009).

In contrast to patients with singular metastases, prospective randomized trials are lacking for the treatment of patients with multiple metastases. However, according to the recent literature and our own experience it seems appropriate to resect all lesions if technically feasible (Al-Shamy and Sawaya 2009; Siu et al. 2011). We tend to remove up to 3, maybe 4 lesions in 1–2 operations during one anesthesia in these cases. If needed, the patients head position is changed in between.

As a consequence of increasing senescence of the population, the amount of elderly patients with brain metastases is rising. There is actually no reason to generally exclude elderly patients from surgical treatment. In a systematic review, we have found that survival in patients over the age of 65, in contrast to younger individuals, is affected by the number of metastases (<=3 vs. >3) and the presence of co-morbidities. In younger patients the presence of extracranial metastases was significantly associated with reduced survival. In both groups, as expected, favorable patient performance was associated with prolonged survival (Stark et al. 2011).

The role of histopathological diagnosis in neurooncology cannot be overestimated. Modern imaging techniques can approximate the diagnosis but they can, at least up to now, not prove it. Only histopathological examination based on paraffin sections can. It is essential to obtain enough tissue for diagnosis and store it adequately. Further material might be stored in liquid nitrogen or −80° freezers for genetic testing.

Surgical Technique

Pre-operative preparation for craniotomy requires patient consent to operation and anesthesia as well as MRI before and after contrast administration. CT might be added if bone erosion is suspected, it is essential in cases with skull base involvement. MRI or CT slides are prepared for neuronavigation. Besides laboratory blood examination, we perform chest X-ray and electrocardiogram in every patient over the age of 40 years on a routine basis.

Intraoperatively, rigid head fixation is needed to prevent patient movement during the operation. All intracranial tumor operations are carried out under the microscope with a magnification of 6–40 fold. Neuronavigation is routinely applied for minimizing the access to the tumor and for resection control in large metastatic lesions which, in the end, is benefitial for the patient (Tan and Black 2007). Neuronavigation represents a 3D-computer model based on a pre-operative CT or MRI scan that is intraoperatively available. The surgeon can check the position of a pointer held to (for craniotomy planning) or into (for detection of small lesions and resection control) the patient`s head in reference to the computer model. A limitation of this technique is the fact that the intracranial structures move after opening of the skull and resection of intracranial tissue. This incidence is called brain shift.

After craniotomy, the bone flap and the dura can be inspected for possible tumor infiltration. Superficial lesions are sometimes, though not always, visible through the cortex. In deep-seated small lesions neuronavigation is extremely helpful in minimizing the access through the sulcus or the brain parenchyma. After the lesion is accessed, it is debulked before the border can be dissected in order to prevent damage to the adjacent brain. Cyst fluid can be punctured, leading to additional reduction of space-occupation. The first tumor tissue removed can be used for frozen sections for further approximation of the diagnosis. After dissection of the tumor/brain interface the metastasis is removed, either in toto, or piece by piece. Resection should be complete to reduce the risk of local recurrence. After meticulous hemostasis of the resection cavity, the dura is closed in a watertight fashion. This is important since post-operative CSF fistula is a major source of peri-operative morbidity and a significant risk factor for infection. Following dural closure, the bone flap is replaced and fixed and the wound is closed. To our experience, a wound drainage can be omitted in most of the cases. Figure 26.2 shows pre-operative MRI and intra-operative microscopic images of a superficially located brain metastasis.

Post-operative care

It is essential to mobilize the patient early after the operation in order to prevent thrombosis and pneumonia. In this situation, specially trained physiotherapists can effectively contribute to favorable patient performance and outcome. Depending on the medical system, the hospital stay is usually in the range of 3–7 days. The sutures are removed the 7th–10th postoperative day. Patients can wash their hair 24 h thereafter.

After obtaining the definite histopathological diagnosis based on paraffin sections further therapeutic steps can be planned (radiotherapy, chemotherapy, combined approaches).

Medical and Adjuvant Treatment

Medical treatment for brain metastases constitutes in the application of corticosteroids which can stabilize the blood–brain barrier and therefore reduced peritumoral edema. Corticosteroids are mandatory in the perioperative phase in order to prevent further brain swelling. Postoperatively, the peritumoral edema decreases and corticosteroids can be reduced.

Whole Brain Radiation Therapy

Whole brain radiation therapy in addition to surgical excision has been shown to reduce local and distant recurrence but it does not prolong survival (Al-Shamy and Sawaya 2009).

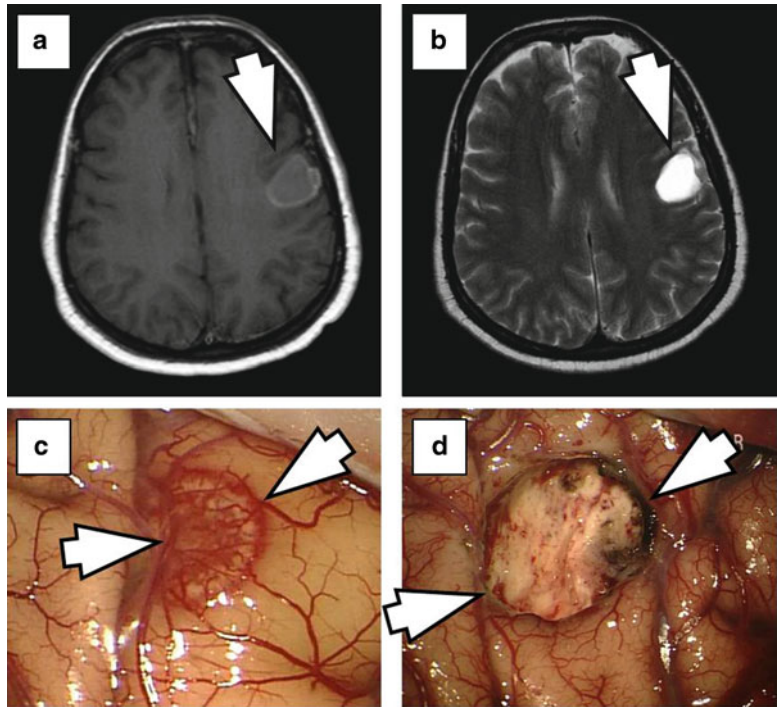

Fig. 26.2 55-year old patient with known breast cancer who presented with aphasia. (**a**) T1-weighted MRI after contrast administration shows a cystic ring-like contrast enhancing left temporo-parietal lesion (*arrow*). (**b**) T2-weighted MRI demonstrates cyst fluid inside the lesion (*arrow*). (**c**) Intra-operatively, after opening the dura, the lesion is visible through the cortex (*arrows*). (**d**) Intra-operative imaging after microsurgical resection shows the resection cavity.

The combination of whole brain radiation therapy and stereotactic radiosurgery can also not prolong survival but again improve local control when compared to radiosurgery alone. This observation has been made in a series including 132 patients with 1–4 metastases (Aoyama et al. 2006).

Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) refers to the (usually) single time application of small collimated beams of ionizing radiation to an ill-defined intracranial mass. The most often used techniques are Gamma Knife Surgery (multiple cobalt sources) or LINAC (linear accelerator). SRS can be applied on an ambulatory basis. The technique is limited by the size of metastases of up to only 3 cm diameter.

The role of SRS as adjuvant treatment following open resection is currently under examination. In a retrospective study including 47 patients who underwent stereotactic radiosurgery (Gammy Knife) to the resection cavity after complete removal of brain metastases as well as to synchronous or metachronous metastases, Jagannathan et al. saw effective local tumor control. Herein, whole brain radiation was reserved for patients with small numbers of metastases and favorable performance, finally applied in 10/47 patients (Jagannathan et al. 2009).

SRS has also been evaluated as single treatment option for small metastases (<=3 cm in diameter) instead of surgical resection. Overall, there is a growing body of evidence that surgery is superior to SRS in these circumstances (Al-Shamy and Sawaya 2009).

Procedure in Patients with Cancer of Unkown Primary

In cases of cancer of unknown primary (CUP) gaining tumor tissue is essential for histopathological diagnosis. Histopathology can give first information concerning the underlying tumor (adenocarcinoma versus squamous cell carcinoma). Using special immunohistochemical markers, such as certain cytokeratins, the primary tumor can be targeted more precisely (Drlicek et al. 2004). In our series, 93 patients (30.1 %) presented with brain metastases as first sign of malignant disease (the far most of the patients suffered from lung cancer, see above). In a total of 8 patients (2.6 %) the primary tumor remained unknown even after diagnostic workup during the perioperative period (Stark et al. 2011).

Valuable clinical diagnostic steps are chest X-ray, computed tomography of the thorax and abdomen, ultrasound of the abdomen, and endoscopy of the gastrointestinal tract. In women, gynecological examination may give valuable clues as well as examination of the skin for detection of melanoma. In cases where melanoma is suspected and examination of the skin is normal, ophthalmological examination might be useful for detection of choroid melanoma of the orbit.

Chemotherapy

Brain metastases in general are hard to treat by systemic chemotherapy due to the presence of the blood–brain barrier. So, chemotherapy in patients with brain metastases is usually directed to the primary tumor as well as systemic metastases. As an exception, it is the standard initial treatment in certain tumor types as choriocarcinoma and gern cell tumors (Al-Shamy and Sawaya 2009).

Post-operative Follow-Up and Survival

We recommend an observation interval of clinical re-examination and MRI before and after contrast material application every 3 months. This time interval seems adequate in the light of brain metastases progression and helps identify recurrence before it gets clinically symptomatic in most cases.

Median survival of patients with brain metastases overall is less than 1 year. However, recent evidence suggests a complex relationship between prognosis and tumor type as well as prognosis and patient age. In a retrospective database analysis including over 4,000 patients treated during a 22-year interval, Sperduto and colleages have found prognostic factors specific for the primary tumor. Herein, patient age had only prognostic impact in lung cancer whereas patient performance had prognostic impact in lung cancer, melanoma, renal cell cancer and breast cancer. The number of brain metastases was relevant in lung cancer, melanoma and renal cancer but not in breast cancer patients (Sperduto et al. 2010).

In our retrospective series of 309 patients, we found age-dependent impact of prognostic factors. Herein, the incidence of extracranial metastases, complete resection of all metastases and re-craniotomy was only significantly associated to survival in patients >= 65 years. In contrast, co-morbidities and the number of brain metastases <=3 was exclusively associated to survival in patients >65 years (Stark et al. 2011).

Brain Metastases Recurrence

Brain metastases recurrence is traditionally defined as re-manifestation at the site of resection or elsewhere in the brain. In older series, its occurrence is reported in the range of 50 % of patients. According to technical advances (surgical techniques, WBRT, SRS), this incidence might be lower today. According to new data, the recurrence rate at the site of resection can be estimated to 10–15 % and is hereby comparable with the local control rate of stereotactic radiosurgery (Siu et al. 2011).

Re-craniotomy has been shown to prolong survival and improve quality of life in younger patients with favorable performance (Arbit et al.

1995; Al-Shamy and Sawaya 2009; Bindal et al. 1995). Surgery furthermore enables histological examination hereby differentiating between tumor recurrence and radiation necrosis.

In our own series, we performed re-craniotomy for recurrence in 43/309 patients (13.9 %). Herein, re-craniotomy was an independent prognostic factor in patients <= 65 years of age (Stark et al. 2011).

Leptomeningeal Metastasis

Leptomeningeal metastasis (leptomeningeal carcinomatosis, neoplastic meningitis) refers to the metastatic dissemination of tumor cells to the subarachnoid space and the leptomeninges. Its incidence is in the range of 5–15 % of all cancer patients (Walbert and Groves 2010). It might occur along with solid brain metastases or without it. Leptomeningeal carcinomatosis almost always occurs in an advanced stage of disease and it is associated with a poor prognosis. MRI shows contrast-enhancing thickening of the dura, cytology of the subarachnoid space shows malignant cells. Leptomeningeal dissemination is most common in patients with lung and breast cancer, melanoma and lymphoma. Treatment options include intrathecal chemotherapy via a CSF reservoir. The reservoir can also be punctured when hydrocephalus is present which is a common complication of leptomeningeal metastasis (Grewal et al. 2012).

Dural Metastases

Hematogenous metastatic spread to the intracranial dura is found in up to 9 % of cancer autopsies. Although, it is rarely clinically diagnosed (Nayak et al. 2009). Dural metastasis may manifest as solid dura-based lesions mimicking meningioma or as a subdural fluid accumulation mimicking subdural hematoma. Therefore, in patients with subdural fluid collection and the history of cancer, subdural fluid should be sent for cytological examination (Stark and Mehdorn 2004).

In patients with solid growing dural metastases, CT is essential to show erosion of the calvaria or skull base. Only surgical resection has been shown to improve survival. Intraoperatively, the skin and the bone flap must be large enough to enable dural plasty and, if the bone is infiltrated, cranioplasty. In some cases the tumor growths through the bone. Then, the galea aponeurotica may be infiltrated and must then be excised. The brain tissue is infiltrated in as many as 34 % of the cases (Nayak et al. 2009).

Bone Metastases

Hematogenous bone metastases might involve the calvaria or the skull base. Despite the fact that bone metastases can be caused by virtually all malignant primary tumors, breast cancer is the far most common malignancy to cause hematogenous metastasis to the skull (Bontoux et al. 1998). Most lesions stay asymptomatic. Symptomatic lesions cause local swelling, sometimes accompanied by local pain. Rarely, neurological deficits are present at the time of diagnosis of bone lesions. Large lesions may compress the dural sinuses. Skull base metastases may cause cranial nerve impairment and/or exophthalmia when the orbit is involved (Constans and Donzelli 1981; Stark et al. 2003).

Bone erosion is best visualized on CT scan while MRI is superior to CT in detecting dural invasion which is important for operative planning. Surgery is indicated in case of (1) a neurological deficit and/or (2) massive destruction of the bone, (3) a painful mass, (4) solitary metastasis or (5) confirmation of the diagnosis is requested (Stark et al. 2003).

The operative strategy in hematogenous metastases of the calvaria is to resect the lesion leaving an intact bony rim. The defect is replaced by bone cement. The dura, if affected, is excised and replaced, too. A wound drain is mandatory.

In skull base lesions, complete removal can seldomly be achieved without damaging cranial nerves or vascular structures. In cases of large skull base metastases, combined approaches with

tumor biopsy/partial removal followed by radiotherapy should be discussed. Post-operative follow-up is identical to patients with brain metastases. Bone metastases grow very slowly, although, these patients are at high risk for developing intraparenchymal metastases.

Conclusion

In conclusion, intraparenchymal "brain" metastases are a frequent complication of systemic cancer. Surgery should be considered anytime if possible. Far less frequently symptomatic metastatic locations at the neurocranium are the dura and the bone. Both are also treated by surgery. Adjuvant treatment consists in radiotherapy whereas chemotherapy is limited and if applied, it is directed mainly to the systemic manifestation of the disease. Leptomeningeal carcinomatosis is a diffuse tumor cell dissemination along the leptomeninges occurring exclusively in late-stage cancer patients. The placement of a burr hole reservoir enables intrathecal chemotherapy, and, if indicated, CSF release for the treatment of hydrocephalus.

References

Al-Shamy G, Sawaya R (2009) Management of brain metastases: the indispensable role of surgery. J Neurooncol 92:275–282

Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, Kenjyo M, Oya N, Hirota S, Shioura H, Kunieda E, Inomata T, Hayakawa K, Katoh N, Kobashi G (2006) Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 295:2483–2491

Arbit E, Wroński M, Burt M, Galicich JH (1995) The treatment of patients with recurrent brain metastases. A retrospective analysis of 109 patients with nonsmall cell lung cancer. Cancer 76:765–773

Beasley KD, Toms SA (2011) The molecular pathobiology of metastasis to the brain: a review. Neurosurg Clin N Am 22:7–14

Bindal RK, Sawaya R, Leavens ME, Hess KR, Taylor SH (1995) Reoperation for recurrent metastatic brain tumors. J Neurosurg 83:600–604

Bontoux D, Plazanet F, Azais I (1998) Distribution of bone metastases of cancers. A scintigraphic study of 376 cases. Bull Acad Natl Med 182:997–1008

Constans JP, Donzelli R (1981) Surgical features of cranial metastases. Surg Neurol 15:35–38

Drlicek M, Bodenteich A, Urbanits S, Grisold W (2004) Immunohistochemical panel of antibodies in the diagnosis of brain metastases of the unknown primary. Pathol Res Pract 200:727–734

Grewal J, Saria MG, Kesari S (2012) Novel approaches to treating leptomeningeal metastases. J Neurooncol 106:225–234

Jagannathan J, Yen CP, Ray DK, Schlesinger D, Oskouian RJ, Pouratian N, Shaffrey ME, Larner J, Sheehan JP (2009) Gamma Knife radiosurgery to the surgical cavity following resection of brain metastases. J Neurosurg 111:431–438

Karnofsky DA, Burchenal JH (1949) Evaluation of chemotherapeutic agents. In: Macleod CM (ed) Columbia Press, New York, pp 191–205

Liotta LA, Kohn EC (2001) The microenvironment of the tumour-host interface. Nature 411:375–379

Mina LA, Sledge GW Jr (2011) Rethinking the metastatic cascade as a therapeutic target. Nat Rev Clin Oncol 8:325–332

Nayak L, Abrey LE, Iwamoto FM (2009) Intracranial dural metastases. Cancer 115:1947–1953

Osborn AG, Salzman KL, Barkovich AJ (eds) (2010) Salt Lake City. Diagnostic imaging: brain, 2nd edn. Amirsys

Paget S (1889) The distribution of secondary growths in cancer of the breast. Lancet 1:571–573

Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, Markesbery WR, Macdonald JS, Young B (1990) A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 322:494–500

Puduvalli VK (2001) Brain metastases: biology and the role of the brain microenvironment. Curr Oncol Rep 3:467–475

Siu TL, Jeffree RL, Fuller JW (2011) Current strategies in the surgical management of cerebral metastases: an evidence-based review. J Clin Neurosci 18:1429–1434

Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, Bhatt A, Jensen AW, Brown PD, Shih H, Kirkpatrick J, Schwer A, Gaspar LE, Fiveash JB, Chiang V, Knisely J, Sperduto CM, Mehta M (2010) Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys 77:655–661

Stark AM, Mehdorn HM (2004) Images in neuro-oncology: dural metastases. J Neurooncol 68:11

Stark AM, Eichmann T, Mehdorn HM (2003) Skull metastases – clinical features, differential diagnosis and review of the literature. Surg Neurol 60:219–225

Stark AM, Anuszkiewicz B, Mentlein R, Yoneda T, Mehdorn HM, Held-Feindt J (2007) Differential expression of matrix metalloproteinases in brain- and bone-seeking clones of metastatic MDA-MB-231 breast cancer cells. J Neurooncol 81:39–48

Stark AM, Mentlein R, Mehdorn HM, Held-Feindt J (2010) Genetisches Profil von Hirn- und Knochen-selektiven MDA-MB-231 Klonen. Chirurg Forum 39:19–21

Stark AM, Stöhring C, Hedderich J, Held-Feindt J, Mehdorn HM (2011) Surgical treatment for brain metastases: prognostic factors and survival in 309 patients with regard to patient age. J Clin Neurosci 18:34–38

Tan TC, Black PM (2007) Image-guided craniotomy for cerebral metastases: techniques and outcomes. Neurosurgery 61(1 Suppl):349–356

Vecht CJ, Haaxma-Reiche H, Noordijk EM, Padberg GW, Voormolen JH, Hoekstra FH, Tans JT, Lambooij N, Metsaars JA, Wattendorff AR (1993) Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? Ann Neurol 33:583–590

Walbert T, Groves MD (2010) Known and emerging biomarkers of leptomeningeal metastasis and its response to treatment. Future Oncol 6:287–297

Wesseling P, von Deimling A, Aldape KD (2007) Metastatic tumours of the CNS. In: Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (eds) WHO classification of tumours of the central nervous system. IARC Press, Lyon, pp 248–251

Yoneda T, Williams PJ, Hiraga T, Niewolna M, Nishimura R (2001) A bone-seeking clone exhibits different biological properties from the MDA-MB-231 parental human breast cancer cells and a brain-seeking clone in vivo and in vitro. J Bone Miner Res 16:1486–1495